THE SUBSTANCE ABUSE HANDBOOK

THE SUBSTANCE ABUSE HANDBOOK

SECOND EDITION

Pedro Ruiz, M.D.

Professor and Executive Vice-Chair
Director of Clinical Programs
Department of Psychiatry and Behavioral Sciences
Miller School of Medicine, University of Miami
Miami, Florida

Eric C. Strain, M.D.

Professor
Director, Johns Hopkins Center for Substance
Abuse Treatment and Research
Medical Director, Behavioral Pharmacology Research Unit
Johns Hopkins University School of Medicine
Baltimore, Maryland

Wolters Kluwer
Health

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Julie Goolsby
Senior Product Development Editor: Kristina Oberle
Production Project Manager: Bridgett Dougherty
Senior Manufacturing Manager: Beth Welsh
Design Coordinator: Holly McLaughlin
Production Services: S4Carlisle Publishing Services

Two Commerce Square
2001 Market Street
Philadelphia, PA 19103 USA
www.LWW.com

1st edition, © 2007 by Lippincott Williams & Wilkins

Printed in China

Library of Congress Cataloging-in-Publication Data

The substance abuse handbook / editor, Pedro Ruiz, Eric C. Strain. — Second edition.
p. ; cm.
Companion to: Lowinson and Ruiz's substance abuse : a comprehensive textbook / editors, Pedro Ruiz, Eric C. Strain. 5th ed. c2011.
Includes bibliographical references and index.
ISBN 978-1-4511-9196-7 (paperback)
I. Ruiz, Pedro, 1936- II. Strain, Eric C. III. Lowinson and Ruiz's substance abuse.
[DNLM: 1. Substance-Related Disorders. 2. Behavior, Addictive. WM 270]
RC564.15
616.86—dc23

2013044532

10 9 8 7 6 5 4 3 2 1

PREFACE

In 2007, we conceived, created, and published the first edition of *The Substance Abuse Handbook* as a practical companion book to the fourth edition of *Substance Abuse: A Comprehensive Textbook*, published by Lippincott Williams and Wilkins in 2005. At that time, it was clear to us that mental health professionals working in the field of addiction, primary care practitioners, addiction counselors, students, residents, and trainees at large needed a clinically oriented handbook that focused on the most essential aspects of addictive disorders and their treatment. Our goals were very ambitious. In creating and publishing the first edition of *The Substance Abuse Handbook*, we, together with Wolters Kluwer Health/Lippincott Williams and Wilkins, offered the field authoritative, clinically oriented information on the topic of substance use, abuse, and dependence, with an emphasis on diagnosis, treatment, and prevention. Our goal was to provide short and focused reviews on the nature of substance abuse as well as each type of drug that is abused, chapters that addressed comorbidities and other related disorders, and also information about treatment approaches. In addition, we also wanted to create a handbook that could be useful to all disciplines involved, directly or indirectly, in the addiction field.

We were very pleased that the first edition of this Handbook was very well received throughout the field and by a wide variety of practitioners—reflecting, in part, the multidisciplinary nature of those who treat persons with addictions. Over the ensuing years the addiction field has continued to change and evolve. At the present time, we are better able to understand the biological, psychological, behavioral, and sociocultural aspects of addictive disorders and conditions associated with substance use. New treatment approaches and different modes of intervention have continued to be tested, shown to be effective, and brought into clinical practice—helping people who suffer from addictive disorders. These advances in our understanding of addictions, as well as new methods of intervention and treatment, have stimulated us to produce the second edition of *The Substance Abuse Handbook* as a practical and relevant companion to the fifth edition of *Lowinson and Ruiz's Substance Abuse: A Comprehensive Textbook*, also published by Wolters Kluwer Health/Lippincott Williams and Wilkins in 2011.

This second edition of *The Substance Abuse Handbook* follows the general outline and format of the latest edition of the Comprehensive Textbook, and addresses those topic areas that we thought were particularly useful in a more abbreviated version of that larger book. As is always the case, the interested reader should be aware that the field is constantly evolving, and that the current Handbook's material should be balanced by familiarity with timely literature on the nature of addictive disorders and their treatment. That said, our hope is that this book will provide a useful resource that provides more condensed information about substance use disorders. Our target audience continues to be all who treat persons with substance abuse disorder. We hope you will find this book a useful resource in your daily practice.

Finally, we want to take this opportunity to thank and express our appreciation to the persons who assisted us and made possible the publication of the second edition of *The Substance Abuse Handbook*. We first thank the expert authors and colleagues who helped and collaborated with us in the production of the fifth edition of *Lowinson and Ruiz's Substance Abuse: A Comprehensive Textbook*; second, we thank the editorial staff of Wolters Kluwer Health/ Lippincott Williams and Wilkins. Third, we recognize our staff who worked very hard in making this handbook a reality. Fourth, we show appreciation for our family members who supported us during this academic and clinical project: our spouses, Angela Ruiz and Grace Serafini, as well as our children and grandchildren. Finally, and most important, we extend our deepest gratitude to the patients who have suffered from addictive disorders and conditions; these patients stimulated us to work harder in this area of the medical field. They certainly deserve the best outcomes of our efforts.

Pedro Ruiz, M.D.
Eric C. Strain, M.D.

CONTENTS

Section 1

Etiologic Factors

1 Etiology

Etiology

The reasons persons start and then continue to use a drug can be quite complex, and it is likely that no two persons have quite the same constellation of reasons for starting and then becoming addicted to a substance. However, certain vulnerabilities to drug experimentation and subsequent addiction have been identified—including the genetic propensity of the person, the biologic and behavioral effects of a drug, and the social circumstances to use and availability.

Etiology and Genetics

Alcohol

Numerous studies have found that rates of alcoholism are substantially higher in relatives of alcoholics than in relatives of nonalcoholics, with children of alcoholics demonstrating a four- to fivefold increased risk of developing the disorder. Relative to controls without alcohol dependence, the siblings of alcohol-dependent probands have elevated rates of the disorder.

Studies have found that allelic variants of aldehyde dehydrogenase (ALDH) genes play an important role in influencing the metabolism of alcohol, and polymorphisms are associated with the risk of developing alcohol dependence. Individuals with the ALDH 2*2 variant typically experience aversive responses (e.g., facial flushing, tachycardia, headache, hypotension) to alcohol consumption as a result of the accumulation of acetaldehyde. Studies have demonstrated the protective effect of ALDH 2*2 gene carriers from developing alcohol dependence.

Neurotransmitter Systems

The dopaminergic system is involved in the reinforcing effects of drugs of abuse. There is evidence to implicate the D2 dopamine receptor (DRD2) gene in alcoholism as well as other substance use disorders (SUDs). γ-aminobutyric acid (GABA) receptor genes, which encode the GABAa and GABAb receptors that bind GABA, have also been identified as promising candidate genes for alcoholism.

Two main alleles of the serotonin transporter–linked polymorphic region (5-HTTLPR) of the SLC6A4-1 gene have either 14 short (S) or 16 long (L) copies of a 22 base-pair imperfect repeat. The L allele increases transcriptional activity of the 5-HTT gene, which results in increased production of 5-HTT and more rapid reuptake of serotonin. It is thought that more

rapid reuptake, associated with the L allele, results in a lower level of this neurotransmitter and potentially decreased alcohol effects.

The μ-opioid receptor (MOR) OPRM1 plays a central role in the rewarding process of alcohol, opioids, and other substances of abuse. One of the most widely studied polymorphisms of the OPRM1 gene is the A118G variant. Individuals with one copy of the Asp40 allele have been found to have a greater response to the effects of alcohol than those who were homozygous for the Asn40 allele.

Nicotine

Taken together, results of several twin studies indicate there is a significant genetic influence on the development and continuation of cigarette smoking. It appears that approximately 50% of the initiation of smoking behavior is genetically influenced, while persistence of smoking and amount smoked have approximately a 70% genetic contribution.

Neurotransmitter Systems

Both past and current cigarette smokers were found to have higher prevalence of the A1 allele of the DRD2 than did nonsmoking controls. Moreover, the prevalence of the A1 allele increased progressively from nonsmokers to past smokers to active smokers.

Cytochrome P450 Enzyme System

CYP2B6 polymorphisms also appear to influence smoking behaviors; smokers of European ancestry who have the CYP2B6*6 genotype have been found to have higher rates of relapse when trying to quit than those with other cytochrome P450 genotypes.

Cocaine

Cocaine inhibits the reuptake of dopamine and other monoamines via its blockade effects at monoamine transporters, resulting in an acute accumulation of extracellular dopamine in the synaptic cleft. There is relatively limited information available about genetic variants affecting dopamine transporter function and cocaine dependence. The DRD3 gene may play a modest role in the susceptibility to cocaine dependence. Allelic variants in the DRD2 gene have also been associated with cocaine dependence.

Opioids

Opioids that are misused primarily act as MOR agonists. The MOR is a transmembrane G-protein–coupled receptor consisting of seven subunits. A polymorphism at position 118 (A118G) of the μ receptor gene has been found that changes the receptor's ability to bind opioid ligands, especially endogenous β-endorphin. The 118G allele has been associated with opioid addiction in certain populations, although not all studies have been able to find such an association.

Cannabinoids

Family studies have reported that the use, abuse of, and dependence on cannabis seem to aggregate in families. For cannabis use, estimates of heritability range from 0.17% to 0.67%. The most important cannabinoid-related candidate genes for SUDs are CNR1 and CNR2, corresponding to the receptor proteins (CB1 and CB2) they encode. Some studies have found evidence for associations among single-nucleotide polymorphisms (SNPs) in CNR1 and vulnerabilities to SUDs.

Etiology and Neurobiology

Although different classes of abused drugs have different mechanisms of action, there are several striking similarities in terms of the brain circuits modified by repeated exposure to these drugs. Thus, the reinforcing effects of all drugs of abuse are due to actions in the limbic system. Limbic nuclei including the amygdala, hippocampus, and medial prefrontal cortex (mPFC) send major glutamatergic efferent projections to the nucleus accumbens, which is broadly subdivided into limbic and motor subregions known as the shell and core, respectively. The nucleus accumbens sends two main GABAergic efferents to the ventral pallidum and ventral tegmental area (VTA), both of which send GABAergic projections to the medial dorsal thalamus. This limbic circuit is closed via glutamatergic projections from the medial dorsal thalamus to the mPFC. Dopaminergic axons from the VTA innervate the nucleus accumbens, amygdala, hippocampus, mPFC, and ventral pallidum, and changes in dopaminergic transmission in these nuclei play a critical role in modulating the flow of information through the limbic nuclei comprising this neuronal network. An overwhelming body of evidence indicates that increased dopamine neurotransmission contributes significantly to the reinforcing efficacy of drugs.

Psychostimulants

Dopamine and Stimulants

Although the psychostimulants bind to all of the biogenic amine transporters with high affinity, the reinforcing potency of psychostimulants, particularly cocaine, is correlated with their affinity at dopamine but not serotonin or norepinephrine transporters. Data show that increased dopamine transmission plays a critical role in psychostimulant reinforcement. Enhanced dopamine transmission in the nucleus accumbens is important for the initiation and maintenance of psychostimulant self-administration behavior.

The five dopamine receptors were classified as D1-like (D1 and D5) or D2-like (D2, D3, and D4) on the basis of pharmacology and sequence homology. Results show that both D1-like and D2-like dopamine receptors are critically involved in psychostimulant reinforcement.

Norepinephrine, Serotonin, and Stimulants

Although increased norepinephrine transmission may be involved in the discriminative stimulus effects of cocaine as well as the reinstatement of cocaine seeking, norepinephrine does not appear to play a significant role in cocaine reinforcement. The role of serotonin in cocaine reinforcement remains unclear. To the extent that norepinephrine and serotonin influence cocaine reinforcement, they appear to do so by modulating mesolimbic dopamine.

Glutamate and Stimulants

Repeated exposure to cocaine influences the expression of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and *N*-Methyl-D-aspartate (NMDA) receptor subunit protein. These studies indicate that after a period of forced abstinence following repeated exposure to cocaine, there is increased expression of AMPA and NMDA receptor subunits in the nucleus accumbens. Evidence suggests that the trafficking of AMPA receptors to and from synapses in the nucleus accumbens plays a critical role in cocaine-induced behavioral and neuronal plasticity. Modulation of AMPA and NMDA receptor–mediated glutamate transmission influences psychostimulant self-administration.

Opiates

Opioid receptors are G-protein–coupled receptors that can form homodimeric as well as heterodimeric protein complexes with other opioid receptors or nonopioid receptors. Stimulation of MORs is mainly responsible for the reinforcing effects of morphine-like opiates, although δ-opioid receptors may also contribute to opiate reinforcement. MORs are widely distributed throughout the central nervous system (CNS). Opiates reduce membrane excitability and subsequently slow cell firing by activating a variety of potassium channels in the plasma membrane of cells in brain regions that send afferents to the VTA (including the nucleus accumbens, ventral pallidum, prefrontal cortex, and amygdala).

Dopamine and Opiates

Opiates exert their effects in the VTA and accumbens through both dopamine-dependent and dopamine-independent mechanisms. The reinforcing effect of opioids self-administered into the nucleus accumbens appears to result from either direct inhibition of GABAergic accumbal projection neurons or inhibition of excitatory neurotransmitter release from glutamatergic terminals within the accumbens. A substantial literature suggests that self-administration of opiates directly into the VTA relies on the activation of the mesoaccumbens dopamine system. Only a very small percentage of dopaminergic neurons in the VTA express MORs. Stimulation of MORs in the VTA inhibits GABA release, which disinhibits dopaminergic neurons, resulting in increased extracellular dopamine levels in the nucleus accumbens.

Ethanol

Ethanol positively modulates $GABA_A$ receptors, inhibits NMDA and kainate glutamate receptors, inhibits N- and P/Q-type calcium channels, has both inhibitory and excitatory effects at nicotinic acetylcholine receptors, enhances the activity of calcium-activated potassium channels, and modulates inwardly rectifying potassium channels.

Ethanol and Dopamine

A number of studies suggest that ethanol increases extracellular dopamine levels in the nucleus accumbens by increasing the firing rate of dopaminergic neurons in the VTA rather than an effect in the nucleus accumbens itself. There are several potential mechanisms whereby ethanol might influence the firing rate of dopaminergic neurons, including effects on potassium channels and $GABA_A$ receptors in the VTA. D1-like and D2-like dopamine receptor agonists and antagonists modify ethanol self-administration behavior.

GABA, Opiates, Serotonin, Cannabinoids, and Ethanol Self-Administration

Ethanol potentiates GABA-induced hyperpolarization either through $GABA_A$ receptors or by directly stimulating chloride channel opening. GABAergic terminals synapsing on dopaminergic neurons in the VTA have been implicated in the acute rewarding effects of ethanol, and $GABA_B$ receptors appear to play a critical role in this process. The opioid system also mediates ethanol self-administration behavior. The endogenous opioids β-endorphin and enkephalins play a critical role in the reinforcing effects of ethanol. Opioid receptor agonists increase ethanol self-administration behavior at low doses and decrease ethanol self-administration at high doses. Serotonergic efferents from the dorsal raphe nucleus to the nucleus accumbens also play a critical role in the reinforcing effects of ethanol. Paradoxically, 5-hydroxytryptamine (5-HT) receptor agonists and antagonists have both been shown to increase and decrease ethanol self-administration behavior.

Cannabinoids

Endocannabinoids are not stored in vesicles but, instead, are synthesized and released in an activity-dependent manner. In the CNS, endocannabinoids act as retrograde messengers that are released from a postsynaptic neuron and subsequently inhibit the release of classical neurotransmitters from presynaptic terminals via the stimulation of presynaptic CB1 receptors.

Although systemic administration of Δ^9-THC or CB1 receptor agonists increases extracellular accumbal dopamine levels, particularly in the accumbens shell, CB1 receptors are not found on dopaminergic terminals or cell bodies. It seems likely that stimulation of CB1 receptors on GABAergic terminals in the VTA disinhibits dopaminergic neuronal activity, resulting in increased dopamine release in the nucleus accumbens.

Nicotine

Twelve nicotinic receptor subunits have been identified in the brain; these are heterogenous cation channels that are typically composed of combinations of five α and β subunits.

Nicotine and Dopamine

In the VTA, nicotinic receptors are found on dopaminergic cell bodies and glutamatergic terminals, as well as GABAergic cell bodies and terminals. In the nucleus accumbens, nicotinic receptors are localized on presynaptic dopamine terminals as well as presynaptic GABAergic and glutamatergic terminals. Systemic administration of nicotine increases extracellular dopamine in the nucleus accumbens.

Nicotinic receptor antagonists attenuate nicotine self-administration and blunt nicotine-induced increases in accumbal dopamine levels. Activation of the mesoaccumbal dopamine system appears to contribute significantly to nicotine reinforcement. D1-like or D2-like dopamine receptor antagonists administered systemically attenuate nicotine self-administration.

Nicotine, GABA, and Glutamate

The prolonged stimulation of dopaminergic neuronal activity in the VTA following nicotine exposure is due to decreases in GABAergic and increases in glutamatergic transmission. Infusion of $GABA_A$- or $GABA_B$-receptor agonists directly into the VTA reduces nicotine self-administration behavior and suggests that GABAergic mechanisms are involved in mediating the reinforcing efficacy of nicotine. Nicotine-induced decreases in VTA GABA transmission appear to disinhibit dopaminergic neuronal activity, which in turn promotes the reinforcing effects of nicotine. Glutamate has also been demonstrated to play a critical role in mediating the reinforcing effects of nicotine. Decreasing glutamatergic transmission may reduce the reinforcing effects of nicotine. Glutamate activation and GABA inhibition appear to act concurrently to activate dopamine cells in the VTA, following nicotine self-administration.

Etiology and Psychological Factors

The interplay of cultural, social, familial, and individual predispositions, neurobiology, and genetic factors, though frequent, is apparently not sufficient for reliably determining substance use conditions. The effect sizes of psychological and social factors in determining substance abuse are modest. Further, once SUDs 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.

Personality and Personality Disorders

The concept of the "addictive personality" frequently relates to long-standing and generalizable traits that involve inability to control indulgences. This popular term, though descriptive, has little empirical support. By contrast, research into long-standing psychological and personality "traits" or styles shared by individuals with substance abuse shows a good deal of support for common characteristics, specifically sensation seeking, delay discounting, and other components of impulsivity.

In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a representative national sample of 43,093 individuals, those who met criteria for any personality disorder were 1.8 to 3.3 times more likely to be comorbid for drug abuse or drug dependence than those who did not meet personality disorder criteria, respectively. Individuals with antisocial personality disorder were 2.5 times more likely than those without antisocial personality disorder to also meet criteria for drug abuse and dependence.

Affective Disorders

Aspects of bipolar disorder share behavioral features with SUDs, including problems in inhibiting impulses and excessive time spent on sensation seeking. About one third of comorbid individuals report that SUDs preceded onset of their bipolar disorder. Among individuals whose bipolar disorder onset was earlier than or concurrent with onset of substance abuse disorders, a more unstable and severe course of bipolar disorder is noted. Compared with those who are not depressed, having a major depressive disorder doubles the odds of meeting the criteria for a SUD.

Thought Disorders

Individuals living with schizophrenia have one of the highest rates of comorbidities with SUDs. In a probability sample, 47% of respondents with schizophrenia also met criteria for lifetime diagnoses of substance abuse.

Anxiety Disorders/Posttraumatic Stress Disorder

Compared with individuals without an anxiety disorder, individuals with an anxiety disorder are more likely to meet criteria of alcohol dependence and any drug dependence. Posttraumatic stress disorder (PTSD) is prevalent in alcohol and drug-abusing populations. Individuals with PTSD frequently report using substances to reduce anxiety and to block reexperiencing the traumatic event.

Attention-Deficit Hyperactivity Disorder

Among adults with SUDs, about one in five has attention-deficit hyperactivity disorder (ADHD) diagnoses. Individuals diagnosed with ADHD as children who matured into adults with SUDs carry substantial genetic predisposition for both disorders. A meta-analysis suggested that treatment for ADHD with a psychostimulant had no deleterious effects on subsequent development of a SUD, and may have even extended a protective effect for children who received treatment.

Impulsivity

A central psychological characteristic shared by many individuals with substance abuse and dependence involves a significant and principal deficit of inhibiting impulses linked to

using substance. Several examples of impulsive cognitive style have been noted in individuals with substance abuse, including delay discounting (discounting the value of rewards that may be more valuable, but more distant, in favor of lower value rewards that are immediately available). One important component of impulsivity that can contribute to establishment of a SUD is sensation seeking. Drug use compromises impulse inhibition and contributes to continued substance use, particularly for those who have made efforts to quit using substances.

Etiology and Social Factors

Violence and Aggression

Among individuals with substance abuse, especially those who have multiple treatment and incarceration experiences, there exists a high prevalence of comorbid violence and aggression. As expected, alcohol has a strong and consistent link to violence and aggression, with associations between these variables becoming most apparent as severity of alcohol use disorders increases.

Violence and aggression that occurs within the context of a close interpersonal relationship, intimate partner violence (IPV), is a form of violence that frequently co-occurs with abuse of alcohol and other drugs. Not all aggression is physical, however. Among those predisposed and who engage in heavy drinking episodes, use cocaine, and experience depressive symptoms, psychological aggression is very common. Although males remain statistically more likely to be the perpetrator, the prevalence of females as perpetrators in IPV is increasing.

Childhood Adversity, Family Factors, and Life Stress

Individuals with substance abuse commonly cite a range of early experiences with childhood adversities, including parental substance abuse, family violence, physical and sexual abuse, and poverty. Individuals with SUDs commonly mention more than one childhood adversity. Adults commonly cope with stressful life events by turning to tobacco, alcohol, or other drugs to reduce psychological discomfort that accompanies stressful life events. Yet it appears relatively uncommon for even severe life stressors to be an independent major contributor to establishing a SUD or worsening an existing one.

Social Attachment

Development of substance abuse is less frequent in individuals who have strong social attachments to their families and their culture, including the institutions within the culture. Among adolescents, poor family attachment, poor school attachment, involvement with friends who use drugs, and a student's own use of drugs are predictors of a SUD.

Etiology and Behavioral Aspects of Substance Abuse

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 reinforcers, increase the probability that a person will repeat a behavior in the future. An extensive body of

experimental research suggests that drug addiction is also operant behavior that is maintained by its consequences. Operant conditioning includes four basic elements: an antecedent stimulus, a response, a consequence, and a contingency that specifies the relationship between the other three elements. In a typical laboratory arrangement with a rat as an experimental subject, the antecedent stimulus might be a green light, the response a lever press, and the consequence a food pellet. The contingency might specify that each lever press emitted when the green light is illuminated will produce a food pellet, and that lever presses emitted when the green light is not illuminated will not produce food pellets. If this contingency produces an increase in the frequency of the lever pressing, the food pellets are called reinforcers, and the process is called reinforcement. With sufficient exposure to the contingency, lever presses can become common in the presence of the illuminated green light and rare when the green light is not illuminated. If, as a result of the contingency, lever pressing becomes more common when the green light is on than when it is off, then the green light is called a discriminative stimulus. The process whereby discriminative stimuli come to alter the probability of responding is called stimulus discrimination.

Laboratory Models of Drug Addiction

The Reinforcer

Nonhumans and humans will self-administer most commonly abused drugs. If responding is maintained at higher rates when a reinforcer is presented contingent on responding than when it is presented independent of responding, it provides firm evidence that the responding is maintained by reinforcement, and is not simply a product of the direct pharmacologic effects of the drug. Studies in humans have demonstrated reinforcement by a number of drugs of abuse.

Immediacy and magnitude of reinforcement are two factors that seem particularly important in modulating drug reinforcement. Increasing the delay between response and reinforcer typically diminishes reinforcement effects. In drug reinforcement, the magnitude of reinforcement can be increased by increasing the dose of the drug. Very high doses of some drugs can have aversive effects, or can lead to satiation, or performance impairment, which can affect measures of drug reinforcement. However, assessments that mitigate those effects typically show that higher drug doses are more effective reinforcers than lower doses.

The Discriminative Stimulus

In the lives of drug users, certain environmental events seem to serve as triggers that prompt drug seeking and drug use. These stimuli or events probably acquired their "triggering" function in large part through operant conditioning. The availability of money, for example, frequently sets the occasion for a chain of drug seeking behaviors that leads to drug use and drug reinforcement. Thus, the money in the example may come to serve as a discriminative stimulus, whose presence increases the probability of drug seeking and drug taking.

From an operant perspective, a drug that has a reinforcing function (as a consequence) can also acquire a discriminative function (as an antecedent). In drug self-administration sessions, as in other studies of operant reinforcement, the reinforcer is presented contingent on responding on given trials, but it also precedes responding on subsequent trials. Through this arrangement, reinforcers can acquire discriminative functions for subsequent responding.

Drug-Seeking Response

In general, drug self-administration varies as a function of the effort or price required to procure the drug. In laboratory studies with nonhuman subjects and sometimes with human

subjects, this phenomenon is investigated by modulating the number of responses required for each drug administration. While the precise relationship between consumption and response requirement can differ as a function of a variety of conditions, consumption of a particular reinforcer generally decreases as the number of responses required for reinforcement increases.

If the number of responses required for reinforcement is increased progressively, subjects will typically reach a response requirement where they stop responding to drug. The point at which a particular subject stops responding is called a breaking point and has been used widely as a measure of the strength of a reinforcer.

Punishment

When an event is presented contingent on a behavior and that contingency decreases the future probability of that behavior, the event is called a punisher, and the process is called punishment. For example, an early study examined the effects of punishment on cocaine self-administration in rhesus monkeys. That study showed that cocaine self-administration was decreased when brief electric shocks were administered along with cocaine administrations contingent on lever pressing.

Reinforcement of Alternative Behaviors

Drug users engage in behaviors to obtain and use drugs; but they also eat, sleep, talk, work, and play, all under the control of different reinforcers. Organisms continually make choices between reinforcers, and distribute their behavior accordingly. Research, primarily conducted in nonhuman subjects, has shown that organisms distribute their behaviors among available alternatives in ways that increase, and possibly maximize, their overall rate of reinforcement. Controlled laboratory studies in which subjects have multiple response options have shown that, in general, the relative rate of responding for any response option is equal to the relative rate of reinforcement obtained for that option.

Operant Modulation of Drug Use in Clinical Populations

Laboratory research shows that drug self-administration can be viewed as operant behavior that is maintained by drug reinforcement and modifiable by the same range of environmental events that affect other operant behavior. Importantly, clinical research on the effects of environmental interventions provides additional support that drug addiction is operant behavior and sensitive to its consequences. Two types of environmental interventions are particularly informative: (1) interventions that increase the price of a drug and (2) abstinence reinforcement interventions that provide nondrug reinforcement contingent on drug abstinence.

For example, population level analyses of the effects on price on cigarette smoking have shown that increases in prices can decrease cigarette smoking. Researchers have also studied the effectiveness of interventions that arrange for the direct reinforcement of drug abstinence. Under these procedures, patients receive a desirable consequence contingent on providing biologic evidence of drug abstinence (e.g., drug-free urine samples). These procedures have proven to be among the most effective behavioral or psychosocial treatments for drug addiction. Some of the clearest data come from research on voucher-based abstinence reinforcement. A meta-analysis showed that voucher-based abstinence reinforcement has effectively promoted abstinence from cocaine, opiates, opiates and cocaine, polydrug use, marijuana, and cigarette smoking.

Etiology and Sociocultural Factors

Social Groups: Family, Peer Group, School, Workplace

Family interactions may serve as protective or risk factors for drug use. Youth's first drug-related discussions and/or modeling of use occurs through the parental and older siblings' perceptions and behaviors. Examples of predictive factors for drug use include conflict-ridden versus warm family interactions, quality and quantity of family time a child experiences, as well as parental monitoring of child's activities.

Friends and peer affiliation can inhibit or promote drug use behaviors. Group members are influenced to act consistently to gain or maintain acceptance by other group members. Affiliation with deviant peer groups increases the likelihood that one will experiment with drugs as group members offer drugs to each other and role-model drug use.

The school environment may be conducive to drug experimentation or may promote delay in exposure to drugs. Large community surveys concur that for men and women of all ages, an increased risk of alcohol use and illicit drug disorders is associated with dropping out of high school or leaving college early. Strategies based on inducing fear or providing information about the adverse effects of drugs have been found to be largely ineffective. An alternate approach is a value-based model aimed at producing more global attitudinal changes, including enhanced self-esteem without addressing drug use specifically.

Employment is also related to the prevalence of substance use. Unemployment is associated with a higher risk for alcoholism, and so are "blue-collar" occupations and lower socioeconomic status (SES). This association may be a cause or a result of substance use. Stressful work circumstances have been associated with high levels of alcohol intake. The prevention of problem drinking in the workplace can be achieved by effective controls of the work environment. In safety-sensitive situations, a program of urine monitoring of illegal substances can ensure the safe handling of vehicles and machines.

Larger Social Structures

Chaotic areas may be more heavily exposed to social disobedience. Access to more prosocial activities (i.e., community centers or movie theaters) is typically limited. Abandoned, dilapidated buildings and enclosed public spaces may result in greater incidence of drug exposures as one of the local gang activities.

The association between these adverse conditions and drug abuse is complex and can be a two-way process, that is, low status leading to drug abuse or drug abuse resulting in a downward socioeconomic drift. Low socioeconomic conditions, often in densely populated areas, are often twinned with sparse community remedial resources or may increase the exposure to drug-related criminal activity. Disadvantaged conditions reduce the impact of the family or social fabrics. Conversely, individuals of higher SES may be able to financially afford large quantities of drugs, resulting in significant physical damage prior to a descent in social status.

Individual drug use is influenced by the local ease of distribution, access, and acquisition of drugs. Areas of drug production (i.e., cannabis or opium fields), manufacturing (i.e., cocaine or heroin creation), and distribution routes equally tend to be regions at high risk for abuse.

Culturally shaped life habits or rituals, normative structures, and expectations as well as beliefs about drug use and its effects may all affect drug use initiation and maintenance. Cross-culturally, a defining characteristic of the transition from drug use to abuse appears to be the ability to carry or not to carry a culturally specific role. These roles may vary by gender or ethnicity. Sex-role expectations within one's environment and differential stigma associated with

use may affect drug prevalence or self-disclosure. Ethnicity also plays a role as a predictor or protective factor for drug use. Ethnic pride may also be a strong direct protective factor among disadvantaged groups.

Acculturation has been defined as the processes whereby immigrants change their behavior and attitudes toward those of the host society. The degree to which newly exposed individuals adopt a culture may inhibit or promote drug use depending on the culture they are from and the norms of the new culture. In studying the complex role of acculturation, it is also important to recognize that family dynamics, socioeconomic factors up to poverty levels, ethnocultural characteristics, and the role of religion, among others, have their direct and/or indirect influences in the frequency, amount, and types of drugs used and/or abused among the different ethnic groups.

Increasingly, the sociocultural influence of the media affects the initiation and experimentation to drug use. Media advertisement can affect an individual's preferences and behavioral options toward drug use. The World Wide Web is a trove of wide-ranging information about drugs. The impact of the Internet on various demographic groups remains to be systematically investigated.

Management Implications and Their Challenges

Social Preventive Strategies

There are many examples of evidence-based interventions targeting social units. Prevention programs include early childhood education, social support for parents, and skills acquisition in parent–child communication, crisis management, and resource networking. Drug education programming in schools relies on a number of mediating agents of change. These include a mix of beliefs and skills. Mediating beliefs include the perceived prevalence of drug use and its acceptability among peers, the consequences of use, and the potential incongruence with other future aspirations. Mediating skills include the ability to resist pressure, goal setting, and prosocial alternatives as well as stress management, self-esteem, and social skills.

High-profile media campaigns "against drugs" abound, many of dubious effectiveness. Mass media campaigns targeted at youths that appear to exert the strongest effect on drug misuse depict dramatic true consequences; appeal to sensation-seeking youths through fast-paced and exciting material; take an activism stance, including correction of normative misperceptions; and offer greater autonomy from nondrug lifestyles.

Conclusion

The etiology of substance use is multifactorial and includes aspects of availability, personal vulnerability (e.g., genetics, neurobiology), and potential psychiatric comorbidity (e.g., depression). Social and cultural factors can be both protective and permissive in the experimentation of use.

Suggested Readings

Agrawal A, Lynskey MT. Are there genetic influences on addiction: evidence from family, adoption and twin studies. *Addiction*. 2008;103(7):1069–1081.

Castro FG, Garfinkle J. Critical issues in the development of culturally relevant substance abuse treatments for specific minority groups. *Alcohol Clin Exp Res*. 2003;27(8):1381–1388.

Conner KR, Pinquart M, Holbrook AP. Meta-analysis of depression and substance use and impairment among cocaine users. *Drug Alcohol Depend*. 2008;98:13–23.

Ducci F, Goldman D. Genetic approaches to addiction: genes and alcohol. *Addiction*. 2008;103(9):1414–1428.
Dutra L, Stathopoulou G, Basden SL, et al. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry*. 2008;165(2):179–187.
Koob GF. Neurobiological substrates for the dark side of compulsivity in addiction. *Neuropharmacology*. 2009;56(suppl 1):18–31.
Room R. Taking account of cultural and societal influences on substance use diagnoses and criteria. *Addiction*. 2006;101(suppl 1):31–39.
Silverman K, Higgins ST, Brooner RK, et al. Sustained cocaine abstinence in methadone maintenance patients through voucher-based reinforcement therapy. *Arch Gen Psychiatry*. 1996;53(5):409–415.
Swann AC. The strong relationship between bipolar and substance-use disorder: mechanisms and treatment implications. *Ann N Y Acad Sci*. 2010;1187:276–293.
Volkow ND, Fowler JS, Wang GJ, et al. Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology*. 2009;56(suppl 1):3–8.

2 Epidemiology

The United States

There are several surveys that assess substance abuse in the United States. The National Survey on Drug Use and Health (NSDUH) has been the leading source for information on the incidence and prevalence of alcohol, tobacco, and other drug abuses (ATOD). The University of Michigan has annually conducted Monitoring the Future (MTF), a primary source for data on ATOD use by secondary school students. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) sponsors the National Alcohol Survey (NAS) and also the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). The Centers for Disease Control and Prevention (CDC) provides data on alcohol and tobacco abuse via the Behavioral Risk Factor Surveillance System (BRFSS) and the Youth Risk Behavior Survey (YRBS). The Drug Abuse Warning Network (DAWN) reports drug-related emergency visits from hospitals. Lastly, the Community Epidemiology Work Group (CEWG) conducts surveillance in 21 major metropolitan areas.

Sociodemographic Factors

According to the NSDUH, in 2011, among those aged 12 to 17, 10.8% of males and 9.3% of females were current users of illicit drugs (defined as use in the past month). Among 18- to 25-year-olds, 25.6% of males and 17.2% of females reported past-month use, and of those 26 and older, only 8.5% of men and 4.4% of women did so. About 24.3% of males (12 and older) smoked cigarettes in the past month compared to 19.9% of females, while 39.4% of men and 19.0% of women reported binge or heavy alcohol use. Rates of illicit drug use in the past month in 2011 for persons aged 12 and older were 3.8% for Asians, 8.4% for Hispanics, 8.7% for Whites, 10.0% for Blacks, and 13.4% for American and Alaskan Natives.

Substance abuse or dependence among individuals involved in the criminal justice system, incarcerated or otherwise, is more than four times that of the general population. In 2004, 53% of state and 45% of federal inmates met DSM-IV criteria for abuse or dependence. Some 32% of state and 26% of federal prisoners in 2004 had used a psychoactive drug at the time they committed their crimes. Drug offenders accounted for 24.9% of federal prisoners in 1980 and 52.2% in 1990, their numbers increased to 60.7% in 1994 and 1995 and declined to 54.1% in 2004. In state prisons in 2007, drug offenders represented 19.5% of the total population and 15.4% of White prisoners, compared to 22.5% of Black and 21.3% of Hispanic prisoners.

Current drug use consistently reaches a peak in late adolescence and young adulthood and then declines markedly. In 2011, past-month use of any illicit drug was 2.7% for persons aged 12, 6.8% for those aged 14, 15.9% for those aged 16, and 22.4% for those aged 18. For persons aged 26 to 29, rates decline to 14.9% and for those aged 35 to 39 to 8.2%. Current drug use

continues to decline further with age, to 6.0% for those 55 to 59, 2.7% for those 60 to 64, and 1.0% for those 65 and older.

Employment status is a significant predictor of past-month illicit drug use and is related to age. In 2011, for unemployed persons aged 18 or older, the rate of past-month use was 17.2%, but 8.0% for those employed full-time and 11.6% for those employed part-time. However, some occupational environments involve factors that increase the risk of substance misuse. Notably, physicians and other medical workers have historically higher rates and/or different patterns of substance abuse.

Comorbidity

Mental Health

Since the 1990s, there has been growing interest in the comorbidity of drug-use disorders with each other and with psychiatric syndromes, such as depression, antisocial personality disorder, generalized anxiety disorder, and mood disorders. In 2007, among people with drug abuse or dependence aged 18 or older, past-month use of alcohol or illicit drugs was 8.8% among those who had a major depressive episode in the past year, compared with 2.1% who had not. For alcohol alone, past-month use was reported by 17% of those who had a major depressive episode in the past year, compared with 7% who had not.

HIV and HCV

Since the advent of human immunodeficiency virus (HIV) in the early 1980s, men who have unprotected sex with men (MSM) have accounted for the vast majority of cases; the next largest group consists of injection drug users (IDUs) and their mostly female sexual partners. HIV incidence has declined markedly from the late 1980s. Although HIV has increased slightly among MSM since the 1990s, it has continued to decline among IDUs. Of the estimated annual incidence of HIV between 2003 and 2006, approximately 56% were MSM, 11% were IDUs, and 3% were both MSM and IDUs. Since the late 1990s, HIV incidence among IDUs has dropped 80%, likely because of the growth of syringe exchange programs (SEPs), expanded access to treatment, availability of syringes, and education/awareness programs of needle sharing and cleaning.

The vast majority of hepatitis C virus (HCV) cases in the United States are from IDUs. HCV incidence peaked in the mid- to late 1990s and then declined substantially from 5.2 cases per 100,000 population in 1995 to 0.5 in 2007 among the age group that historically had the highest rates of infection (25 to 39 years). Still, the prevalence of chronic HCV in 2007 was substantial, with approximately 3.2 million persons infected, largely among those aged 40 to 49, most of whom were likely infected through needle use in the 1970s and 1980s.

Substances

Alcohol Alcohol is the most commonly used psychoactive substance in the United States. NSDUH reported that 55.1% of Americans aged 26 and older were current alcohol users in 2011, with 21.6% of those over 26 reporting binge drinking and 5.7% reporting heavy drinking. About 22.3% of Whites reported binge use and 6.4% reported heavy use; 20.1% of Blacks reported binge drinking and 6.4% heavy drinking. American and Alaskan Natives had the highest proportion of binge and heavy use: 23.0% are binge users and 12.5% are heavy users. Hispanics show a higher proportion of binge and heavy alcohol use than do Whites and Blacks: 23.5% reported binging and 4.6% heavy use. Asians have the lowest proportion of all groups: only 10.2% reported an episode of binging and 1.3% heavy use.

Underage drinking is a continuing concern, even though past-month alcohol use among those aged 12 to 17 has dropped from 17.6% in 2002 to 13.3% in 2011. MTF shows steady but

significant declines over the past 10 years in past-month alcohol use (28% of 8th, 10th, and 12th graders combined in 2008) and having been drunk in the past month (14.9%). However, trend analysis data from six NASs between 1979 and 2005 suggest that although mean values of drinking measures have declined for those older than 26, there has been an increase both in alcohol volume and drinking days among those aged 18 to 25, indicating the possibility of a sustained increase in future U.S. alcohol consumption.

In the past 30 years, there has been a substantial decline in the number of social drinkers arrested for driving under the influence (DUI). DUI rates in the past year reflect, in part, the relationship between drinking behavior and age: 7.8% for the 16- to 17-year-old group, 18.3% for the 18 to 20 group, and 25.8% for the 21 to 25 group. For the 26- to 29-year-old group, the rate declined to 20.1%. Overall, for Americans aged 12 and older, past-year DUI declined modestly but significantly from 2002 (14.2%) to 2008 (12.7%).

NSDUH annual estimates of Americans with substance abuse or dependence have remained stable between 2002 and 2011 at just above 20 million. The vast majority—roughly 16.7 million—abuse or are dependent on alcohol alone; 2.6 million abuse or are dependent on both alcohol and illicit drugs. Binge drinkers were far more likely to use an illicit drug (13.9%) than nonbinge past-month alcohol users (3.8%). Adolescents and young adults who were past-month alcohol users were far more likely than older age groups to have used illicit drugs. The illicit drug used most frequently in concurrence with alcohol was marijuana (4.8%), followed by cocaine (0.06%) and pain relievers (0.04%).

Marijuana Since the 1970s, marijuana has been by far the most commonly used illicit drug. In 2011, of Americans aged 12 or older, 41.9% had tried marijuana at least once, 11.5% had used in the past year, and 7.0% or 18.1 million in the past month. The rate of past-month marijuana use in youths aged 12 to 17 had increased through the 1990s, declined from 8.2% in 2002 to 6.8% in 2005, but was back up to 7.9% in 2011. However, in 2011 only 1.6% of Americans were estimated to have marijuana dependence or abuse, representing a slight decline from 1.8% in 2002. SAMHSA's Treatment Episode Data Set (TEDS) reports that primary treatment admissions for marijuana use increased from 11.7% of all admissions in 1996 to 15.8% in 2007. Nationally, between 1996 and 2006, the rate of marijuana-user admissions increased from 91 to 120 per 100,000 population aged 12 and older.

Tobacco Rates of current cigarette use have been declining, especially since the late 1990s, with the continued expansion of legal prohibitions, higher taxes, and increasingly negative attitudes toward smokers and smoking. Between 2002 and 2011, past-month American cigarette smokers declined from 26% to 22.1% (56.8 million). Most smokers begin in adolescence and, after a decline through most of the 1980s, current cigarette use among teenagers and young adults began to increase and peaked in the mid-1990s. Still, the declines in this age group are greater than the overall decline. Between 1996 and 2008, current smoking has declined substantially among 8th graders (67%) and 10th graders (60%), and a cohort effect seems to explain the more modest 44% decline among 12th graders.

Heroin and Other Opioids Only 0.1% of Americans aged 12 and older have reported past-month heroin use between 2002 and 2011. Among 12th graders, the annual prevalence of heroin use between 1975 and 1979 fell from 1% to 0.5% and then remained steady until the early 1990s, peaking at 1.5% in 2000. Since then, annual prevalence among 12th graders has declined, fluctuating slightly, to 0.9% in 2007 and 0.7% in 2008. Since the early 2000s, most parts of the country have reported growing nonprescription use of pharmaceutical opioids such as oxycodone (OxyContin) and hydrocodone (Vicodin). Between 2002 and 2011, previous-year illicit use of pharmaceutical pain relievers has fluctuated (and was 4.7% and 4.3%, respectively). Past-year OxyContin use has remained steady at 0.5% to 0.6% since 2004.

Cocaine Between 2002 and 2007, the prevalence of past-month use of cocaine hydrochloride by Americans aged 12 and older has remained stable, hovering at 0.9% in 2002, 0.8% in 2004, 1% in 2006, and 0.5% in 2011. Relatively few Americans used crack in the past month: 0.2% in 2002, 0.3% in 2005, and 0.1% in 2011. Despite low overall rates of use, the majority of drug-related emergency room visits involved cocaine, with Blacks and Whites accounting for roughly equal numbers. Among cocaine abusers, crack remains predominant across 11 CEWG areas in 2008, when between 56% and 95% of cocaine treatment admissions were crack smokers.

Club Drugs Since the 1980s, drugs such as MDMA, GHB, and ketamine have been referred to as club drugs because they have been associated with dance parties and nightclubbing. Past-month ecstasy use among Americans aged 12 and older dropped slightly but significantly from 0.3% in 2002 to 0.2% in 2003 through 2007. In 2008, 2.9% of 8th, 10th, and 12th graders had used ecstasy at least once and 0.9% and 1.2% had used GHB and ketamine, respectively. Ecstasy use dropped in this group from a peak of 2.4% in 2002 to 1.2% in 2008.

Methamphetamine In the early 1990s, concern grew about the expectation that methamphetamine would move eastward. Through the late 1990s, both methamphetamine-related emergency room visits and treatment admissions increased, although these numbers began to decline overall. The number of Americans aged 12 and older who used methamphetamine nonmedically in the past year changed little from 1999 (0.5%) to 2004 (0.6%). There were relatively low rates of methamphetamine use between 2002 and 2005 by Americans aged 12 and older, both for annual use (0.7% in 2002 and 0.5% in 2005) and past-month use (0.3% in 2002 and 0.2% in 2005). Previous-month use has remained stable, with 0.2% of those 12 and older using in the past month in 2011.

Pharmaceutical Stimulants The nonmedical use of pharmaceutical stimulant drugs such as amphetamine (Adderall) and methylphenidate (Ritalin) has been a growing concern. Pharmaceutical stimulant use peaked in 1996, when 4.8% of 8th, 10th, and 12th graders combined used them in the past 30 days, but their use declined to 3.9% in 2003 and 2.6% in 2008. In contrast to these rates of use, more high schoolers perceive these drugs as easily available. In 2008, 12.8% of 8th graders, along with 32% of 10th graders and 47.9% of 12th graders, said the drug was "fairly" or "very" easy to obtain. The higher rate among 12th graders is curious in light of their high rates of disapproval: 87.2% disapprove of using amphetamine once or twice and 94.2% disapprove of its regular use.

Among college students and their age peers, amphetamine use also increased through the 1990s, with college students having lower rates. Even so, in the 1990s and 2000s, rates for college students, their noncollege age peers, and 12th graders were substantially lower than in the 1980s. In the 2000s, use among 12th graders and the noncollege group declined, while annual use among college students increased to 7.2% in 2001 and remained stable at 6.9% in 2007. College students vastly overestimate the levels of nonmedical use of pharmaceutical drugs among their peers, as they also do with alcohol and other substances.

Drug Abuse and Treatment

In 2011, 20.6 million Americans aged 12 and older were classified with substance dependence or abuse in the past year (based on DSM-IV), a number that has remained relatively stable since 2002. Roughly 16.7 million were dependent on or abusing alcohol only, 3.9 million illicit drugs only, and 2.6 million both alcohol and illicit drugs. In 2011, men were almost twice as likely (10.4%) as women (5.7%) to report past-year abuse or dependence. Past-year dependence or abuse changes with age: in 2011, 4.6% of the 12 to 17 age group and 7.5% of the 18 to 25 group had abuse or dependence problems; in the 26 and older group, only 1.4% had such problems.

In 2007, 7.5 million Americans aged 12 or older needed treatment for an illicit drug problem but only 1.3 million (17.8%) received it at a specialty facility, leaving 6.2 million in need of treatment. In 2007, 2.7 million people received treatment for a problem with alcohol or an illicit drug in the past year at a rehabilitation facility. Less than 2.2 million of the people who received treatment in 2007 did so in self-help groups. These figures changed little between 2002 and 2007. According to the combined 2004 to 2007 NSDUH data, 35.9% of those who tried to get treatment failed because of lack of funds or health coverage.

From 1996 to 2006, roughly 40% of TEDS treatment admissions were not in the labor force and 30% were unemployed. Well over half the admissions during this period were between the ages of 25 and 44; roughly 70% were men, and about 60% of all admissions were White, while Blacks comprised 25.7% in 1996 and 21.3% in 2006.

Five substances represented 96% of TEDS admissions in 2007: alcohol (40%); opiates, primarily heroin (19%); marijuana/hashish (16%); cocaine (13%); and stimulants, primarily methamphetamine (8%). Between 1996 and 2006, 40% of admissions were for problems with both alcohol and an illicit drug. Primary admission for treatment of alcohol alone dropped to 40% from 51% in 1996. Although 58.1% of primary heroin admissions were self-referrals, 14.2% came through the criminal justice system; in contrast, for primary marijuana admissions, 56.9% came through the criminal justice system and 14.8% were self-referrals.

In 2007, 213,000 Americans were dependent on or abusing heroin. From 1996 to 2006, heroin treatment admissions increased 10%; however, the number receiving medication-assisted therapy decreased by 22%, and in 2007 only 29.1% received methadone or buprenorphine. This is noteworthy, considering not only the growing emphasis on pharmacological treatment for addiction but also, by the mid-2000s, the easing of regulations governing methadone buprenorphine, meant to encourage greater use of these treatments for heroin addiction, especially in physicians' offices.

Europe

The principal source of information regarding trends of European drug problems is the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). It provides decision-makers and professionals, institutions, and other organizations involved in drug-related interventions with evidence-based information to support the drug debate and decisions at both political and technical levels. The EMCDDA produces annual reports on the drug situation in Europe, including data about drug trafficking, estimation of consumption, and information about treatment requests and availability. To develop a European overview of drug prevalence, the EMCDDA coordinates a network of National Focal Points (NFPs) set up in the 27 EU Member States, Norway, the European Commission, and candidate countries. Together, these information collection and exchange points form Reitox, the European Information Network on Drugs and Drug Addiction. Given the national or regional level of the system of data collection, combining and comparing reported drug prevalence is problematic.

This section uses treatment demand as a measure of drug use in Europe. It is the best filter to make meaningful comparisons between different use-groups and to describe longitudinal trends. Nevertheless, treatment demand may correspond to a different rate of actual problematic drug use, depending on the availability and accessibility of treatment, the level of information about treatment options in the general population, and not least the legal consequences of enrolling into treatment. An important restriction applied in EMCDDA reports is the case definition, which includes only people entering treatment for drug use. Therefore EMCDDA data do not necessarily include clients in continued treatment from previous years. Moreover,

it should be considered that treatment demand data come from each country with varying degrees of national coverage (from 24% to 100% of treatment units covered).

Finally, the EMCDDA definition of "problem drug use" as a key indicator of drug use epidemics is "injecting drug use or long duration/regular use of opioids, cocaine and/or amphetamines." Such a definition omits noninjectable drug use, at any stage, but does include prescribed opioid use, provided that the opioids are prescribed on a regular basis.

Pattern of Substance Treatment Demand

In Europe, primary heroin use rose from 108,000 (persons) in 2002 (63% of all treatment episodes) to 129,000 in 2007 (52%); primary cocaine use rose from 22,000 (13%) to 47,000 (19%); and primary cannabis use from 27,000 (16%) to 50,000 (20%). Stimulants other than cocaine accounted for 15,000 cases of primary problem drug use in 2002 (9%) and 20,000 (8%) in 2007. Among new clients entering treatment, heroin use rose slightly from 36,000 (48%) in 2002 to 38,000 (34%) in 2007, while cocaine use increased sharply from 13,000 (17%) to 28,000 (25%) and cannabis from 18,829 (25%) to 34,312 (31%). There was a smaller increase for stimulants other than cocaine, from 8,000 (10%) to 10,000 (9%).

Primary heroin treatment demand increased in number but decreased as a rate of all treatment demand (+20% from 2002 to 2007), because of the absolute and relative rise of treatment demand for cocaine (+135%), cannabis (+85%), and other stimulants (+33%). The trend is more evident among new clients (+5% for heroin, +115% for cocaine, +82% for cannabis, and +25% for other stimulants). The rise in emerging use, as calculated by the ratio between new client numbers in 2002 and 2007, was twice as much for cocaine than for heroin.

Alcohol

The EMCDDA report features alcohol as a secondary substance; however, no European data about alcohol treatment episodes are presented. For licit substances such as alcohol, estimates of abuse and addiction epidemiology are problematic. In fact, alcohol use may be regular and heavy, but this pattern of use does not necessarily equate with addiction, whereas such a relationship is often presumed with illicit drugs such as heroin.

Increasing alcohol abuse, such as recurrent episodes of heavy drinking, was reported in most countries across the late 1990s, among both men and women. More recently, no uniform course can be observed. By 2006, approximately 5% of male and 2% of female drinkers report negative consequences of habitual drinking on their job or study performance. A significant rate of premature deaths and disability is related to alcohol, at least as a contributing risk factor for the cause of death or accident (12% in men and 2% in women).

Opiates

In most European countries supplying data, between 50% and 80% of all treatment demand (about 387,000 persons for 24 countries in 2006) is related to opioids as the primary drugs; in the remaining countries the proportion varies between 1% and 40%. Opioids are infrequently reported as a secondary drug (11% to 13%), and are generally less frequent among clients entering their first treatment episode (40%). As a rule, treatment demand related to opioid use has been increasing in recent years. Data from nine countries show that opioids are the most frequent primary drug of abuse among clients who are already in treatment (59%) but account for only 40% of clients entering treatment for the first time in their lives.

Injecting drug use is not as frequent as one may presume: 63% of all opioid users applying for, or currently receiving, treatment reported injecting opioids at the time of treatment entry. Percentages vary between 25% and over 80% across different countries. Some countries, such as Ukraine, report higher percentages such as 97%. Among those entering treatment for the

first time, the percentage of opioid injectors is generally lower and decreased from 43% to 35% between 2003 and 2006, although there has been a more recent reprise up to 42%.

The mean age of patients entering outpatient treatment for primary opiate use is 33 years and has been increasing since 2003. Men outnumber women by 3.5 to 1. Among those who develop opioid-related problems and apply for treatment later in life, opioid use is likely to start before the age of 25, and unlikely to start after 25 years. An average time interval of 7 to 9 years stands between first use of opioids and first contact with drug treatment.

Cannabis

The rate of treatment requests for a primary cannabis-related drug problem rose to 12% of all clients, and 30% of all new clients, in 2002. Although rates varied across different countries, cannabis appeared to be an increasing problem in all European countries for the 1996 to 2002 period. In 2007 primary cannabis-related demands were 20% of all cases and 28% of new cases.

The peculiarity of cannabis-related treatment demand is the high prevalence of compulsory treatment or nonspontaneous treatment requests, such as in the case of treatment requests to avoid jail or other legal consequences. According to EMCDDA in several countries, cannabis users, regardless of a thorough assessment of their possible addictive state, are referred to treatment programs for implicitly supposed problematic cannabis use, thus confusing a legal option with a medical condition of cannabis abuse/dependence. In fact, the majority of presumed abusers, about two thirds, do not use cannabis on a regular basis (less than daily), and in half of those cases consumption is actually infrequent (once a week or less often). In 2007, 24% of clients were classified as occasional users, or had not been using the substance during the last month. As such, the reason for cannabis-related treatment seeking does not always appear related to intensive cannabis use.

Stimulants

In Europe, cocaine was the primary drug in 17% of treatment-seeking drug users in 2007, and the secondary drug in 18% of cases. The rate among new clients is higher (22%) and has been increasing in recent years (on the whole, 19% of cases were cocaine related at some level). Spain, in particular, has experienced an increasing rate of primary and secondary cocaine-related treatment demand (over 40% and over 60%, respectively). Most countries report a higher prevalence of primary cocaine use among new clients than among all clients, indicating a generally increasing trend in problematic cocaine use. Intravenous use is rare (6%) and does not seem to be increasing.

The rate of cocaine- and amphetamine-related problems appears to be inversely related, which may suggest that these two stimulants are seen as equivalent to each other, alternatively dominating each territory's market. Crack cocaine use is limited to some urban areas and is rather uncommon (at any level in 2% of all treatment requests).

Treatment for primary amphetamine use is usually below 5%, although some countries have rates of 25% to 35%, notably Sweden (34%) and Finland (Helsinki, 23%). In treatment settings, problematic methamphetamine use is predominantly via injection. MDMA treatment requests are relatively rare (0.5% down to irrelevant numbers for most countries, a few countries reporting up to 4%). As a rule, MDMA problem users applying for treatment are polydrug abusers, mostly of alcohol, cannabis, or other stimulants.

Polydrug Abuse

As many as 57% of clients reported at least one secondary drug used (33% one drug, 20% two, 4% three or more). Clients entering treatment for the first time are more likely to be polyabusers, except for first-time heroin treatment clients. The lowest rate of polyabuse is among cannabis clients (43%), while crack cocaine abusers report the highest (69%). This latter

category, however, corresponds to a very small proportion of all clients receiving treatment in most European countries. The list of secondary drugs reported by polydrug users includes cocaine (32%), alcohol (40%), cannabis (27%), and other stimulants (11%). The involvement of cocaine in polyabuse patterns plausibly increases the weight of this drug in the course and outcome of treatment for primary drug abuse pictures such as heroin.

Cannabis polyabuse accounts for most cannabis-related treatment demands (85%), with cannabis predominantly being the secondary substance of abuse. Most featured combinations are with alcohol, cocaine, or both. Primary cocaine users in treatment report 63% of polyabuse, mainly alcohol (42%), cannabis (28%), and heroin (17%).

Opiate clients often engage in polyabuse during the relapsing course of their disease: as such, the likelihood of polyabuse is higher among reentering clients or those who have been in treatment for some time. A Swedish study reported a history of hospitalization due to alcohol-related problems in one out of three heroin addicts entering methadone treatment. An Irish study reported a rate of 56% of alcohol polyabuse among methadone patients.

Benzodiazepine use is also frequent, although to a variable extent (11% to 70%). Cocaine polyabuse in methadone maintenance is also common, and seems to mirror the estimated trend of use in the general population. Cocaine polyabusers during methadone treatment are also likely to report alcohol abuse.

Gender Differences

Male-to-female sex ratios show male predominance in all age groups and across all countries. A relatively higher rate of females is found among very young and older clients (<15 and >45), which suggests a lowering trend for sex ratios in the future, at least for clients who will stay in long-term treatment or display the usual addictive pattern of recurrent relapse and subsequent reentering into treatment. The relatively higher proportion of females within the over-45 age group may suggest a gender-specific feature, either the concentration of late-onset drug abuse among women or the higher rate of long-term treatment adherence for females, especially within standard maintenance treatments (i.e., opiate addiction).

Drug-related deaths have been a predominantly male phenomenon. However, recent data show that the incidences of drug-related deaths have not been decreasing by the same rate in the two sexes (half as much among women). Factors affecting drug-related deaths do not seem to have the same impact among women as among men.

Infectious Diseases

In the epidemiologic study of addictive diseases, infectious diseases, especially HIV, HCV, and hepatitis B virus (HBV), can be regarded as behavioral indicators of drug abuse and treatment outcome. Likewise, prevention strategies and responses to drug-related infectious disease should be founded on a synergy between core addiction treatment and harm reduction, particularly for those initially resistant to treatment.

At the beginning of the 1990s, over 90% of AIDS cases among drug users were registered in 3 out of the 12 current European community countries: France, Italy, and Spain, which accounted for less than 50% of the current European community population. Countries with a low prevalence and relatively stable incidence were those for which the introduction of methadone treatment dates back to the 1980s or late 1970s. Thus, despite territorial contiguity and membership to a common economic system, the differential impact of HIV infection among high-risk categories such as IDU was directly related to the differential availability of treatment.

Among countries with a more recent history of opioid addiction epidemics, the Russian Federation shows a higher prevalence and incidence rate of HIV infection among injecting drug users. The prevalence rate of officially registered cases of drug addiction in Russia leaped

from about 60/100,000 in 1997 to 241/100,000 by the end of 2003. The vast majority of cases correspond to opioid addiction (133.1/10,000 in 1999 and 210.9/10,000 in 2004). The majority of HIV-infected people in Russia are aged between 20 and 29, and one third are women, mostly within the 15 to 25 age range (25% in the 15 to 20 age group and 50% in the 20 to 30 age group). Up to 80% of people with HIV infection are IDUs with variable patterns of use and have had at least occasional experience of sex trading for money. As much as 60% of viral hepatitis B and 90% of hepatitis C are due to injecting drug use.

Treatment

In general, treatment is provided mostly in outpatient settings. Some countries continue to offer no specific treatment approaches for opioid addiction, although agonist treatment is available. It appears that broad-spectrum treatments are increasing in those countries. Further, the provision of agonist treatment does not appear to depend on the duration of the opioid use epidemic: countries with decades of experience such as England and Germany show coverage rates similar to those observed with newcomers such as Croatia, Italy, and the Czech Republic. In some territories, profiles of drug users entering treatment are changing in a way that suggests improvement in the outreach to problem drug users.

The involvement of general practitioners (GPs) in the treatment of heroin addiction is somewhat surprising in some countries. On the one hand, in some countries GPs are the primary treatment provider, representing about 80% in France and 90% in Germany. Such a status should correspond to the capillary spread of specific knowledge about heroin addiction and mental disorders. On the other hand, some countries that are theoretically enabled to provide GP-based methadone treatment fail to do so, or do it exceptionally, as in the case of Italy. Although the feasibility of GP-based methadone maintenance has been documented both in Germany and in Italy, other factors seem to influence such diverging national situations.

Convergence upon overlapping targets may be considered when harm reduction and specific treatment interventions share the same therapeutic components and goals. Opioid agonists, the primary option for the specific treatment of heroin addiction, may also serve as a harm-reduction approach, as long as harm reduction is conceived as a means to act upon the same disease, although at a low-threshold level. From a treatment point of view, what is specifically targeted at treating addiction is also likely to function as an effective form of harm reduction.

Drug-Related Crime

Data are available regarding drug law offences. However, the interrelationship of drug use, pathologic drug use (i.e., addiction), and involvement in criminal behavior is complex. Specific indicators of drug addiction (as opposed to drug use) are missing from the EMCDDA reports, which makes it difficult to identify addiction-related criminal records from drug law offences and general crime committed by nonaddicted individuals. Further, drug use data from prison populations also fail to discriminate between addicts and recreational users.

According to various reports to the Italian parliament (from 1986 to 2002), the number of addicts in jail increased from about 6,000 in 1986 to about 15,000 in 2002. The rate of addicts in treatment at the time of arrest rose from below 5% in 1986 to above 20% in 1989, congruent with the greater availability of methadone programs throughout the territory. The 2002 trend continues. Thus, the spread of methadone treatment in the wider community has not directly translated into a reduction in criminal behavior, although the increased number of clients receiving methadone, and the classification criteria used, may explain the apparent rise in the number of addicts being incarcerated.

Drug-Related Deaths

The EMCDDA data permit the monitoring of the incidence of drug-related deaths, poisonings, or overdoses in several European countries. Overall, drug-related deaths have been stable since the early 1990s, although variability of incidence exists between different countries. As a general rule, the age of drug-related deaths has been increasing over the years. While in some countries drug-related deaths have remained relatively stable, in others there have been changes over time. In Poland, the mean age of drug-related deaths has increased from around 40 years in the middle of 1990s to above 45 years by 2006. In Bulgaria, the mean age of death was approximately 45 years in the early 1990s and has fallen to 30 by 2007. Data suggest that there has been a decrease in deaths due to acute drug intoxication throughout the 1990s up to 2005.

Conclusion

Epidemiological data are not uniform across Europe. Across Europe, many clinicians remain unfamiliar about the methodology of evaluation of diagnostic interventions; their degree of reliability, efficacy; the safety of therapeutic interventions; and other features of clinical epidemiology. The culture of evaluation is, however, essential to interpret the large body of available research data and to provide evidence-based treatment and best practice. Therefore, it is critically important to promote the transition from clinical epidemiology to etiologic epidemiology and workforce development.

Suggested Readings

Compton WM, Thomas YF, Stinson FS, et al. Prevalence, correlates, disability, and comorbidity of *DSM-IV* drug abuse and dependence in the United States: results from the national epidemiological survey on alcohol and related conditions. *Arch Gen Psychiatry*. 2007;64:566–576.

Grant B, Dawson D. Introduction to the National Epidemiological Survey on Alcohol and Related Conditions. *Alcohol Res Health*. 2006;29:74–78.

Hasin DS, Stinson FS, Ogburn E, et al. Prevalence, correlates, disability, and comorbidity of *DSM-IV* alcohol abuse and dependence in the United States: results from the National Epidemiological Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*. 2007;64:830–842.

Kozlov AA, Perelygin VV, Rohlina ML, et al. Heroin dependence in the Russian Federation: the current situation. *Heroin Addict Relat Clin Probl*. 2006;8(1):11–24.

Maremmani I, Pacini M, Lubrano S, et al. Harm reduction and specific treatments for heroin addiction. Different approaches or levels of intervention? An illness-centred perspective. *Heroin Addict Relat Clin Probl*. 2002;4(3):5–11.

Michelazzi A, Vecchiet F, Leprini R, et al. GPs' office based Metadone Maintenance Treatment in Trieste, Italy. Therapeutic efficacy and predictors of clinical response. *Heroin Addict Relat Clin Probl*. 2008;10(2):27–38.

Office of Applied Studies. *Results from the 2011 National Survey on Drug Use and Health*. Rockville, MD: Department of Health and Human Services; 2012.

Penka S, Heimann H, Heinz A, et al. Explanatory models of addictive behaviour among native German, Russian-German, and Turkish youth. *Eur Psychiatry*. 2008;23(suppl 1):36–42.

Strang J, Sheridan J, Hunt C, et al. The prescribing of methadone and other opioids to addicts: national survey of GPs in England and Wales. *Br J Gen Pract*. 2005;55(515):444–451.

Swendsen J, Anthony J, Conway K, et al. Improving targets for the prevention of drug use disorders: sociodemographic predictors of transitions across drug use stages in the national comorbidity survey replication. *Prev Med.* 2008;47:629–634.

3 Evaluation and Diagnosis

The clinical assessment process requires different components to generate a treatment plan. These components can include the patient's self-report (which can be collected through the patient interview, as well as through screening tests), collateral reports and records (e.g., via family members, prior treatment records), results from an examination of the patient (e.g., for signs of substance use), and laboratory assessments. Although all of these may not be readily available to the clinician, the final evaluation and generation of a diagnosis and treatment plan are based upon a synthesis of these sources of data.

Screening Instruments and Structured Interviews

There are a number of screening instruments and structured interviews that can be used in the process of assessing the patient with a suspected or known substance use disorder (SUD). Screening instruments are often distinguished by assessing alcohol versus other drug use, and can be conceptualized as self-reports versus those administered by a clinician. A commonly used screening instrument for alcohol use that is typically administered by a clinician is four questions often referred to by the acronym CAGE (questions that ask about the need to *C*ut down on drinking, people *A*nnoying the person by criticizing their drinking, feeling *G*uilt about drinking, and needing an *E*ye-opener drink in the morning). Other commonly used instruments that assess alcohol use include the AUDIT (the Alcohol Use Disorder Identification Test, which is 10 questions about alcohol use) and the MAST (Michigan Alcoholism Screening Test, which is 24 questions that can be answered in a paper form or can be asked of the person). Similar to the MAST, there is a DAST (Drug Abuse Screening Test, which consists of 20 items) that can be used to screen for drug use. Other instruments include the Addictive Behaviors Questionnaire (ABQ), the Alcohol Dependence Scale (ADS), the Cannabis Abuse Screening Test (CAST), the Drug Attitude Inventory (DAI), the Fagerstrom Test for Nicotine Dependence, the Global Appraisal of Individual Needs (GAIN), the NIDA (National Institute on Drug Abuse) Quick Screen, the Problem-Oriented Screening Instrument for Teenagers (POSIT), and the Substance Abuse Subtle Screening Inventory (SASSI). By no means is this an exhaustive list of such instruments, and some lists of screening instruments for addictive disorders have numbered over 200 questionnaires.

There are fewer structured interviews for SUDs, and most such interviews tend to be comprehensive assessments for all psychiatric disorders. Three such interviews worth noting are the Structured Clinical Interview for DSM-IV (SCID), the Mini International Neuropsychiatric Interview (MINI), and the Addiction Severity Index (ASI). The first two instruments (SCID,

MINI) produce diagnoses and are probably more commonly used in research setting. However, familiarity with their wording can help guide a clinician in phrasing interview questions for unstructured assessments. The ASI is a well-established interview that does not produce diagnoses but does provide quantitative assessments (e.g., the number of days out of the past 30 that the person has used a drug, had legal problems, had problems with their family); these can be useful baseline assessments for a person entering treatment, and can also be useful for tracking treatment response over time.

Using the Assessment for Severity-Based Problem Prioritization

Combining multiple questions into an index or scale, with clearly defined cut points for marking severity and clinical decisions, helps generate more reliable, valid, and useful information. Clinicians often do this intuitively: recognizing that although one symptom or problem might be a red flag, greater priority needs to be given to areas where there is a pattern of recent problems, multiple symptoms, high prevalence, or impaired functioning.

The GAIN is an example of a clinical assessment that is widely used and known for its effective use of scales and indices. It is based on a measurement model that combines classical scales and summative indices. Indices (also known as formative or summative measures) are counts of problems that may not have the same cause but still add up to predict outcomes of interest. The GAIN arranges several scales and indices into a hierarchical system that gives clinicians and researchers information about overall severity. It also has scales representing the main dimensions of variation (substance use, internal distress, external behavior problems, crime/violence) and clinically oriented subscales within each, for problems like dependence, depression, anxiety, attention-deficit hyperactivity disorder, and conduct disorder. These in turn are made up of face-valid individual items that address salient issues like suicidal thoughts. A notable advantage of using scales and indices is that many individual questions have slightly different meanings for key subgroups (e.g., by gender, race, age, sexual orientation, geography), but these differences average out when looking at the pattern across multiple items. It should be noted that many of these properties are not unique to the GAIN; there are actually compendiums of other scales, indices, and multiple domain assessment batteries available.

Treatment and Problem History as an Indicator of Severity

The needs assessment should help treatment providers look not only at the presence of a particular problem but also at the patient's treatment history and the severity of the reported problems. In assessing placement and treatment needs, the clinician will need to consider both problem severity and treatment. The response to treatment (whether positive, neutral, or negative) can be one of the most clinically significant pieces of information in deciding what to do next. Understanding past treatment requires consideration of the recency of the problem, the extent to which the patient complied with treatment recommendations, the speed with which the problem returned (if it dissipated), and the willingness of the patient to try again.

Clinicians can do this kind of evaluation for the overall need for substance abuse treatment as well as for related life domains (e.g., withdrawal problems and treatment history, physical health, emotional and behavioral health, readiness for change and motivational interventions,

relapse potential and relapse prevention interventions, and recovery environment factors). In each case, there is a continuum of problem severity and treatment history.

Patient Placement Criteria

The clinical assessment provides data that can then be used to plan treatment. The American Society of Addiction Medicine's (ASAM) Patient Placement Criteria (PPC) outlines six treatment planning dimensions that should be considered when assessing a patient for admission, continued stay, or discharge from any level of care. Those dimensions are (1) acute alcohol or drug intoxication or withdrawal potential; (2) biomedical conditions and complications; (3) emotional, behavioral, or cognitive conditions and complications; (4) readiness to change; (5) relapse, continued use, and continued problem potential; and (6) recovery environment. These PPC can then be used to help guide the appropriate level of initial and ongoing service for the patient: level 0.5 (early intervention); level I (outpatient treatment); level II (intensive outpatient treatment/partial hospitalization); level III (residential/intensive inpatient treatment); level IV (medically managed intensive inpatient treatment); and opioid maintenance therapy (which is not characterized with a level).

Diagnostic Laboratory Testing

Comprehensive drug testing is important for the evaluation and selection of appropriate treatment. Testing is also important after drug abusers are identified. Treatment strategies are intimately connected to frequent urinalyses to monitor recovering addicts. Negative results support the success of treatment, while positive results alert providers to relapses.

The testing of five drugs, selected by the Department of Health and Human Services/Substance Abuse and Mental Health Services Administration (DHHS/SAMHSA), is required for accreditation by their National Laboratory Certification Program (NLCP). Panel I testing includes amphetamines, cannabinoids, cocaine, opioids, and PCP (usually referred to as the SAMHSA-5). Panel II represents other commonly abused drugs, such as barbiturates, benzodiazepines, methadone, oxycodone, methylenedioxymethamphetamine (MDMA), methylenedioxyamphetamine (MDA), and ethanol. Interestingly, some powerful hallucinogens are seldom routinely tested. LSD, psilocybin, and ketamine are listed in Panel III with club drugs and other designer drugs.

Tests Available

Urine samples are most commonly sent for a "routine drug screen." But oral fluid (saliva) testing is becoming more popular. Providers assume that a comprehensive drug test detects all abused drugs. Thin-layer chromatography (TLC), mostly used in the past, is not sensitive enough to detect drugs such as marijuana, PCP, LSD, psilocybin, mescaline, and fentanyl, among others. Thus, a negative drug screen may mean that the test menu does not contain the drug(s) of interest, the test cutoff is too high, and/or there is no evidence of drugs commonly detected by the method used. Low-level abuse of drugs is not likely to be detected; therefore, "false negatives" are a possible result. More sensitive enzyme immunoassays (EIA) have replaced TLC as an initial screening procedure. EIA, enzyme-linked immunoadsorbent assay (ELISA), fluorescent polarization immunoassay (FPIA), and radioimmunoassay (RIA) are routinely used for initial drug screening in serum, urine, oral fluid, sweat, and hair.

Screening for an unknown drug can be performed by capillary gas–liquid chromatography (GLC). In a single GLC analysis, more than 25 drugs can be identified. This system is advantageous when there is no clue to the identity of the substance. However, GLC, LC-MS, and GC-MS are all time-consuming, labor-intensive, and usually expensive. EIA procedures are easily adaptable for high-volume automated screening of drugs.

Analytic Methodologies

Alcohol

The addictive chemical substance in all alcoholic beverages is ethanol or ethyl alcohol. Ethanol is present in beer (3.2% to 4.5%), wine (7.11% to 14%), and distilled beverages (40% to 75%). Assuming an average of 0.02 g% blood alcohol increase per drink, a 170-lb subject must ingest about four drinks of 12 oz beer, 4 oz wine, or 1.5 oz whiskey in 1 hour to reach the ethanol level of 0.08 g/100 mL blood or 80 mg/100 mL blood. The illegal limit to operate an automobile in most states is 0.08 g%.

Ethanol is one of the few drugs for which its blood levels correlate relatively well to levels of intoxication or impairment, although large individual variations do exist because of tolerance and genetic variations. Ethanol is analyzed by means of enzymatic assays or GLC methods. If ethanol analysis is performed by means of a breathalyzer, or on blood or urine by one of the chemical or enzymatic assays, the results are reliable for general use. Some states allow breathalyzer results in driving-while-intoxicated cases and driving accidents to determine legal impairment. In forensic cases, results should be confirmed with a blood specimen by using a GLC analysis. Ethanol measurement must be requested in addition to a drug screen because alcohol testing is not performed routinely by most laboratories.

Alcohol biomarkers can be useful, objective indicators of outcome measures of interventions for alcohol abuse, screening tests, and a means of confirming abstinence. Indirect biomarkers include blood chemistry analytes that demonstrate the harmful effects of alcohol (e.g., γ-glutamyltransferase, alanine aminotransferase, aspartate aminotransferase, and carbohydrate-deficient transferrin). Direct alcohol biomarkers are metabolites of alcohol (e.g., ethyl glucuronide [EtG] and ethyl sulfate [EtS]).

Enzyme Immunoassays and Enzyme-Linked Immunoadsorbent Assays

Immunoassays for drug detection use antibodies to seek out specific drugs in biofluids. In samples containing one or more drugs, competition exists for available antibody-binding sites. The presence or absence of specific drugs is determined by the percent binding. The specificity and sensitivity of the antibodies to a given drug differ depending on the particular drug assay and the assay manufacturer. Immunoassay can be very specific; however, compounds structurally similar to the drug of interest (i.e., metabolites or structural congeners) often cross-react. Interaction of the antibody with a drug and its metabolites increases the sensitivity of the assay.

EIA, ELISA, and FPIA are commonly used for drug-abuse screening because no complicated extraction is required and the system lends itself to automation. EIA with specific antibodies is sensitive for most drugs and detects low drug and metabolite concentrations in biofluids. ELISA offers greater sensitivity than some other screening assays. The sensitivity and specificity of ELISA are valuable to the clinician. A variety of biologic samples, such as urine, serum/plasma/blood, and oral fluid (saliva), are applicable to ELISA.

Comparative studies in the scientific literature support oral fluid as an excellent alternative to urine and blood for the identification of drug abuse. Because oral fluid collection is convenient, noninvasive, fast, and observable, sample adulteration is not likely to occur.

On-Site Screening Immunoassays

The increased prevalence of drug use and abuse has prompted the development of new drug screening technology that produces results in as little time as 5 minutes. These tests are designed to be performed on-site and are particularly useful for preemployment screening, random testing, probable cause workplace testing, and accident-related injuries. Visually interpreted immunoassays do not require complex instrumentation and no special technical skills. These kits are particularly effective because there is no calibration, instrument maintenance, or downtime. Most kits have built-in quality control zones in each panel, which ensures reagent integrity, sample validity checks, and sufficient sample size. Lastly, most on-site devices have an extended shelf life at room temperature.

On-site screening kits have demonstrated greater than 97% agreement with confirmatory tests such as GC-MS. However, these kits provide only preliminary test results. A more specific alternate chemical method must be used to confirm presumptive positive screening results. GC-MS and LC-MS are the most specific confirmation methods.

Gas–Liquid Chromatography (CLC) and Gas Chromatography-Mass Spectrometry (GC-MS)

GLC is an analytic technique that separates molecules by migration. Long glass or metal tubing called columns are packed or coated with stationary materials of variable polarity. The extracted analyte is carried through the column to the detector by a steady flow of heated gas. The detector responds to the vaporized drugs. This response is graphically recorded and quantified, and is proportional to the amount of drug or metabolite present in the sample.

Indisputable evidence can be obtained by using the mass spectroscopy (MS) detector, which identifies substances by gas chromatography separation and mass fragmentation patterns. Not all bonds in molecules are of equal strength. In the MS detector, electron beam bombardment breaks weak molecular bonds. The exact mass and quantity of the molecular fragments or breakage products are measured by the mass detector. The breakage of molecules results in a fragmentation pattern unique for a specific drug. The fragments occur in specific ratios to one another. Therefore, MS with either GC or LC separation is the most reliable and most definitive procedure in analytic chemistry for drug identification.

The sensitivity of GLC for most drugs is in the nanogram range, but with special detectors some compounds can be measured at picogram levels. GLC and GC-MS can also be used quantitatively, which provides additional information helpful for clinical interpretation. Tandem mass spectrometry (MS-MS) offers even greater sensitivity than GC-MS or LC-MS alone. MS-MS provides a confirmation procedure for the even more sensitive screening methods and is used at very low drug concentrations common in alternate matrices, such as oral fluids, sweat, and hair analyses.

HPLC is used especially for drugs that are polar or not volatile and cannot be made volatile by derivatization. Some of these drugs and glucuronidated metabolites are not amenable for analysis by GC or GC-MS. Examples of drugs or drug groups for which HPLC is the choice of analysis are the benzodiazepines, tricyclic antidepressants, and acetaminophen, among others.

Choice of Body Fluids and Time of Sample Collection

When drug-abuse detection is the goal, the following questions should be asked: (a) How long does the suspected drug stay in the body, or what is its biologic half-life? (b) How fast and how extensively is the drug biotransformed? On the basis of the rate of biotransformation, should one look for the drug itself or its metabolite(s)? (c) Which body fluid is best for analysis, and what is the major route of excretion? Intravenous use or smoking of drugs provides nearly instantaneous absorption into the bloodstream. Metabolism, tissue distribution, and excretion of the drug and/

or metabolites into urine occur depending on the rate of the aforementioned processes. Oral use of drugs will result in slower absorption, but greater first-pass metabolism in the liver.

The collection of urine specimens must be supervised to ensure donor identity and to guarantee the integrity of the specimen. It is not unusual to receive someone else's urine or a highly diluted sample when collection is not supervised. Also, the laboratory tests for pH, specific gravity, and creatinine levels assure that the sample is not adulterated. As a rule, first morning urine samples are more concentrated; therefore, drugs are easier to detect in those samples than in more diluted daily samples. The decision to use blood or urine must be based on the purpose of the test and the suspected drug's pharmacokinetic, metabolic, and excretion characteristics.

Interpretation of Results

Psychoactivity of most drugs lasts only a few hours, while urinalysis can detect some drugs and/or metabolites for days or even weeks. Thus, the presence of a drug (or metabolite) in urine is only an indication of prior exposure, not a proof of intoxication or impairment at the time of sample collection. Laboratory data and corroborating drug-induced behavior must be interpreted by experts in psychopharmacology and toxicology with experience in drug biotransformation and pharmacokinetics.

Drug analysis reports, either positive or negative, may raise questions about the meaning of the results. The usual questions are as follows: (a) What method was used? (b) Did the laboratory analyze only for the drug, or the metabolite, or both? (c) What is the "cutoff" value for the assay? (d) Was the sample time close enough to the suspected drug exposure?

False-negative results occur more easily than false-positive results, mainly because once a test is screened negative, it is usually not tested further. If the screening method was EIA, the cutoff may have been set too high, in which case, drugs present below the cutoff concentration are reported negative. It is imperative to know the cutoff for each drug tested and, for diagnostic purposes, ask for any drug presence above the blank and below the cutoff. Another possibility for false negatives is that the sample was taken too long after the last drug exposure. Whatever the case may be, if the suspicion of drug use is strong, the clinician must repeat testing and ask the laboratory for a more sensitive cutoff level. False-positive results can also occur especially in the screening process. Most common are the so-called cross-reactivity issues.

Clinical Drug Testing

Clinical drug testing has three components: emergency toxicology, rehabilitation toxicology, and diagnostic toxicology. Each has slightly different goals and requirements. Emergency toxicology requires quick analysis, responding to critical situations in overdose cases. Sometimes the clinical symptoms or the leftover drug is a sufficient clue to the laboratory for which drug to test. In rehabilitation programs, drug testing is of foremost importance. Identified ex–drug abusers need to know that the therapist or the counselor knows objectively that they are in good standing or in danger of relapsing to drug use. In this situation, drug-abuse testing is a deterrent and an important component of the treatment process. Urine testing is the most common; however, oral fluid testing is also becoming popular in drug-treatment clinics. When direct observation of urine collection is not possible or collection of urine is difficult because the donor has renal disease or a shy bladder, oral fluid is an appropriate alternative. Finally, diagnostic drugs of abuse identification is another important testing with a slightly different goal. Denial is typical of drug abusers. Therefore, astute physicians are frequently testing their patients for drug use or abuse.

Forensic Drug Testing

Forensic or legal drug testing has three components: workplace testing, postmortem testing (medical examiner), and criminal justice (correctional and parole) testing.

Workplace testing is performed on subjects at their place of employment. Many industries and governmental agencies mandate testing of individuals performing critical duties. These places of employment have strict drug policies in place, informing employees that drug abuse is not tolerated and that tests are performed to protect the public interest. The different types of tests performed are preemployment, for cause, and random drug testing. Positive tests can result in loss of job or job opportunity. The consequences of workplace testing are very serious and often disputed. People's livelihoods depend on laboratory results; therefore, sufficient safeguards must be built into the system to provide assurance that the results are reliable. In forensic testing, the usual procedure is screening with an automated immunoassay analyzer (i.e., EIA, ELISA, and FPIA) and confirmation of positive screening tests by GC-MS, LC-MS, or MS-MS for additional sensitivity.

Other forms of forensic drug testing requiring "litigation documentation" are medicolegal cases and postmortem analysis of body fluids for the presence of drugs, alcohol, and poisons. Currently, very strict rules and regulations govern workplace testing. More rigorous and complete chain-of-evidence documentation and more accurate methods are required in medicolegal and postmortem testing.

Another area of drug testing is in correctional institutions and testing in the prison system. It is not unusual to find that drug abuse continues in prisons. Consequently, correctional facilities have adopted a drug-abuse testing policy in prisons and also during parole. Although the consequences of testing are potentially punitive, testing of inmates in many states requires only screening without confirmation of positive results.

Testing Drugs in Oral Fluid

In the past, blood and urine samples were preferred for drug detection, until analytic methods, especially LC-MS-MS, increased sensitivity to a desired level. This advancement opened up the possibility for oral fluid as an alternative specimen for drug detection. There are several advantages for using oral fluid for drug screening: (a) collection of specimens is noninvasive and easily observable by the collector, (b) the introduction of LC as an analytic instrument negates the often difficult and time-consuming extraction and cleanup steps needed for GC and GC-MS analyses, (c) the sensitivity of LC-MS-MS permits identification and quantitation of drugs in relatively small oral fluid samples, and (d) water-soluble drugs, conjugated drugs, and metabolites can be easily recovered from the oral fluid without extraction.

However, there are also limitations for using oral fluid for drug detection. (a) Often the collected sample is either inadequate or too small for further analysis and confirmation, if needed. (b) The detection time of drugs or metabolites in oral fluids is about the same as in blood, but shorter than in urine. Many different oral fluid collectors are available; when compared to each other some are better for some drugs or drug classes than for others. That they are not uniformly effective for some drugs may cause contradictory results just from the choice of collector used.

Conclusively, properly validated oral fluid testing performed in certified laboratories provides a reasonable opportunity for screening and confirmation of recent drug use. However, urine specimens still provide longer detection times and larger sample volumes for further analysis and confirmation, if requested.

Testing Drugs in Sweat and Hair

Because the amount of sweat produced is dependent on environmental temperatures, routine sweat collection is difficult because of a large variation in the rate of sweat production and lack of adequate standardizations. However, cocaine, morphine, nicotine, amphetamine, ethanol, and other drugs have been identified in sweat. A "sweat patch" resembles an adhesive bandage and is applied to the skin for a period of days to weeks. Sweat is absorbed and concentrated on the cellulose pad, which is then removed and tested for drug content.

Testing for drugs in hair is an alternate method to the drug-abuse detection technology. Because of the very low concentrations of drugs incorporated in hair, very sensitive methodology must be used. Screening is performed by RIA with ultrasensitive antibodies, or by ELISA, with confirmation by GC-MS, GC-MS-MS, or LC-MS-MS. Representatives from virtually all abused drug classes have been detected in hair. Drugs can enter the hair in various ways: (a) diffusion from blood into the hair follicle and hair cells with subsequent binding to hair strands; (b) excretion in sweat, which bathes hair follicles and hair strands; (c) excretion in oily secretions into the hair follicle and onto the skin surface; and (d) entry from the environment. Two controversial issues in hair drug testing are the possibility of environmental contamination that may result in false-positive test results and the difficult interpretation of dose-to-time relationships. In spite of some controversial aspects of hair testing, this technique is being used on an increasingly broad scale in a variety of circumstances. This technology may be used to estimate the long-term drug-abuse habit of the patient who is in denial. It is expected that this type of comparison would be more effective than urine testing because urine provides a historical record of only 2 to 4 days under most circumstances.

Ethical Considerations

Legitimate need for drug-abuse testing in the clinical setting is indisputable. Denial makes identification of drug abuse difficult; therefore, testing is necessary both for identifying drug abusers and for monitoring of treatment outcome. Drug testing in the workplace and in sports is more controversial because positive test results may be used in termination of long-time employees or refusal to hire new ones.

Private companies believe that it is their right to establish drug- and alcohol-free workplaces and sport arenas. The opposition believes that one is ill-advised to terminate individuals for a single positive test result, even when it is confirmed by forensically acceptable procedures. A testing program is reasonable when a chance for rehabilitation is also offered. Probationary periods provide an opportunity to stop using drugs through treatment or self-help programs. Employee assistance programs, which refer employees to drug counseling, are available in larger companies and governmental organizations.

It is important that this powerful tool—drug testing—be used judiciously as a means of early detection, rehabilitation, and prevention. Test results must be interpreted only by individuals who understand drugs of abuse medically and pharmacologically. Improper testing or improper interpretation of drug testing data must be prevented.

Summary of Drug Testing

As long as illegal drug use is prevalent in our society, drug-abuse testing will have an important clinical and forensic role. Testing in the clinical setting aids the physician who treats subjects with psychiatric signs and symptoms secondary to drug abuse, monitors treatment outcome, and handles serious overdose cases. Drug testing in the forensic setting will be used for workplace testing and monitoring of parolees convicted of drug-related charges.

Civil rights must be respected to protect the innocent. Testing must follow strict security and chain-of-custody procedures to ensure anonymity and prevent sample mix-up during testing. The reliability of testing procedures is of foremost importance. Good laboratories institute internal open, blind, and external quality control systems to assure high quality of testing. Reliability depends on three major factors: well-qualified and well-trained laboratory personnel, state-of-the-art instrumentation, and logical organization of the testing laboratory.

Nationally recognized agencies protect the rights of government-mandated testing programs by assuring proper procedures in forensic drug testing. The DHHS/SAMHSA administers its National Laboratory Certification Program (NLCP). Similarly, the College of American Pathologists (CAP) runs its Forensic Toxicology Inspection and Proficiency Program. In

addition, numerous state and city regulatory agencies inspect and certify drug-testing laboratories. Good laboratories are easily identified by having current certificates of qualification (COQ) issued by national and/or local regulatory agencies.

Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), is the diagnostic classification system developed by the American Psychiatric Association. The International Classification of Disease, 10th revision (ICD-10), is the system used by the World Health Organization. The substance use disorders sections of previous iterations of each classification system differed significantly from each other, although many of the concepts they contained were similar. As a result, considerable efforts were made to make these two systems as similar as possible.

Overview

Psychiatric disorders attributable to abusable substances are of two general types: (a) disorders related to the pattern and/or consequences of substance use itself (i.e., Substance Use Disorder [SUD] in DSM-5; dependence, abuse in DSM-IV-TR [TR: text revision]; and harmful use in ICD-10) and (b) disorders produced by the pharmacologic effects of the substances themselves (i.e., intoxication, withdrawal, and substance-induced mental disorders).

DSM-IV-TR provided generic criteria sets that were used to diagnose abuse and dependence on most psychoactive substances (with some exceptions). Abuse was essentially a less severe form of problematic substance use compared to dependence. The use of the term "dependence" in DSM-IV-TR was problematic, as it caused confusion between the concepts of a syndrome of dependence (as laid out in DSM-IV-TR) and physical dependence (which was an element in the diagnosis of syndromic dependence, but which was neither necessary nor sufficient for the diagnosis). In an effort to address these issues, DSM-5 essentially merged the abuse and dependence criteria sets into one category (SUD), with the exception that the criterion regarding legal problems (from the abuse diagnosis) was dropped and a criterion regarding craving was added. In general, SUD diagnoses have 11 elements, and a diagnosis of a SUD requires a minimum of 2 criteria.

There are several other notable changes with DSM-5. DSM-IV-TR has a common set of criteria for abuse and dependence (the criteria were not specific for a particular substance), whereas DSM-5 now has specific sets of criteria for each particular drug's SUD (i.e., there is a specific set for alcohol SUD, cannabis SUD, etc.). In general, the items are similar across drug categories. There also are some new diagnoses—most notably, caffeine withdrawal and cannabis withdrawal—and there are some other changes in categories (e.g., nicotine dependence is now tobacco use disorder, cocaine and amphetamines are now in a single-stimulant use category).

Compared to ICD-10, DSM-5 continues to provide a more detailed descriptive text for each of the diagnostic categories. ICD-10 also has a "harmful use" category, which is not included in DSM-5. However, each classification system is founded on the Edwards and Gross definition of the alcohol dependence syndrome, a concept that was originally developed from working with individuals having problems with alcohol but later expanded to all abusable substances.

DSM-5 SUD Severity Codes and Course Modifiers

DSM-5 includes severity codes and course modifiers for SUD. The severity codes provide three levels (mild, moderate, severe) based on the number of criteria that the person fulfills for the current diagnosis of a SUD (2 to 3, 4 to 5, 6 or more, respectively), and do not vary

between drug classes. In addition, each SUD diagnosis has the option of specifying whether the person is in early or sustained remission (3 to 12 months versus more than 12 months, respectively), and whether the person is in a contained environment. For selected diagnoses, there is also the option to note that the person is on maintenance therapy (e.g., for an opioid or tobacco SUD).

ICD-10 Dependence Course Modifiers

The course modifiers for ICD are similar but not identical to those found in DSM-5 and are as follows: currently abstinent; currently abstinent, but in a protected environment (e.g., hospital, therapeutic community, prison); currently on a clinically supervised maintenance or replacement regime (controlled dependence) (e.g., with methadone, nicotine gum, or nicotine patch); currently abstinent, but receiving treatment with aversive or blocking drugs (e.g., naltrexone or disulfiram); currently using the substance (active dependence); continuous use; and episodic use (dipsomania).

Substance-Induced Disorders

Diagnostic criteria for intoxication and withdrawal syndromes for each category of drug (for which there is a DSM-5-recognized intoxication and/or withdrawal syndrome) are included in the criteria for that drug's particular SUD. As noted earlier, caffeine and cannabis now have criteria sets for withdrawal syndromes (unlike in DSM-IV-TR); hallucinogens (including PCP) and inhalants do not have withdrawal syndromes in DSM-5. All drug categories except tobacco have intoxication diagnoses in DSM-5.

DSM-5 also has a number of substance-related diagnoses. These include sleep- and anxiety-related disorders, as well as affective disorders (depressive, bipolar), psychotic, sexual, neurocognitive, and obsessive-compulsive disorders, as well as delirium. Not all drug categories are associated with such drug-induced disorders, and these may be associated with intoxication and/or withdrawal. Information on these is contained in other sections of DSM-5, and is only cross-referenced in the section on substance use disorders.

Other Features of DSM-5

DSM-IV-TR included a category for polysubstance use; this has been dropped from DSM-5. It would seem appropriate to include such patients in the "other (or unknown)" drug use category, if necessary. Finally, DSM-5 now includes gambling disorder in the section Substance-Related and Addictive Disorders. Gambling disorder has a criteria set that is similar to the one used for most of the drug-related SUD diagnoses, although the gambling disorder set has only 9 (rather than 11) criteria.

Conclusion

The evaluation of the patient is based on an assessment of the patient's self-reports, instruments that provide data regarding the patient's drug use (including structured interviews and questionnaires), records from others, and collateral reports. In addition, testing of biologic fluids (most commonly urine, but saliva, sweat, hair, and blood may all be of value) helps in assessing the patient, as well as in monitoring progress in treatment. The decision regarding treatment placement can be aided by guides such as ASAM's PPC. The final diagnosis for the patient typically will use the DSM criteria, or may use ICD. The DSM-5 criteria for substance-related

disorders have several changes relative to the criteria provided in DSM-IV-TR, and the clinician should be familiar with these changes—especially as they become more ingrained in clinical practice.

Suggested Readings

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

American Society of Addiction Medicine (ASAM). *Patient Placement Criteria for the Treatment for Substance-Related Disorders*. 2nd ed. Chevy Chase, MD: American Society of Addiction Medicine; 2001.

Bosker WM, Huestis MA. Oral fluid testing for drugs of abuse. *Clin Chem*. 2009;55(11):1910–1931.

Cone EJ, Huestis MA. Interpretation of oral fluid tests for drugs of abuse. *Ann N Y Acad*. 2007;1098:51–103.

Crouch DJ, Hersch RK, Cook RF, et al. A field evaluation of five on-site testing devices. *J Anal Toxicol*. 2002;26:493–499.

Gallardo E, Queiroz JA. The role of alternative specimens in toxicological analysis. *Biomed Chromatogr*. 2008;22:795–821.

Hanes-Stevens L, Dennis ML, White M. *GAIN Clinical Interpretation Training Manual*. Bloomington, IL: Chestnut Health Systems; 2007.

Hanes-Stevens L, White M. Effective treatment planning for substance abuse and related disorders. *Counselor*. 2008;9:10–18.

Pragst F, Balikova MA. State of the art in hair analysis for detection of drug and alcohol abuse. *Clin Chim Acta*. 2006;370:17–49.

World Health Organization. *Tenth Revision of the International Classification of Disease (ICD-10)*. Geneva: World Health Organization; 1992.

Section 2

Substances of Abuse

4 Alcohol

Epidemiology of Alcohol Consumption

It has been estimated that approximately 2 billion people or one half of the world's adult population consume alcoholic beverages. Consumption rates are generally greater among men (55%) than among women (34%). Most alcohol is consumed by a relatively small group of consumers, with the top 30% of drinkers accounting for up to 75% of all consumption. In most Western countries, consumption rates of alcoholic beverages have remained stable, and are expected to remain that way over the next two decades. However, in countries of the South-East Asian Region and the low- to middle-income countries of the Western Pacific Region, alcohol consumption is expected to increase during the same period.

In 2000, 76.4 million people worldwide suffered from an alcohol use disorder—63.7 million were men and 12.7 million were women. The lifetime prevalence of alcohol abuse or dependence varied from as low as 4.5% in Hong Kong to a high of 22% in Korea.

In the United States, the majority (87.8%) of the adult population (>18 years old) has consumed alcohol in their lifetime. Slightly more than half (51.6%) of Americans aged 12 or older reported drinking at least once during the last month, with the majority (57.7%) male. However, among youths aged 12 to 17, the percentage of males who were current drinkers (14.2%) was similar to that of females (15.0%). Alcohol consumption in the United States is greatest among young men 18 to 25 years old; the prevalence of current drinking decreases with increasing age. The highest prevalence of drinking is found among non-Hispanic Whites, followed by Native Americans and Hispanics. The lowest prevalence is seen among non-Hispanic Blacks and Asians. College-educated individuals are almost twice as likely to be current drinkers as individuals with less than a high school education.

The National Epidemiological Survey on Alcohol and Related Conditions (NESARC) study showed that alcohol abuse or dependence, defined by the fourth edition of the DSM-IV-TR criteria, affected 8.5% of the U.S. population, with 4.7% meeting the criteria for a diagnosis of alcohol abuse and 3.8% for alcohol dependence.

Classification and Phenomenology of Alcohol Use Disorders

DSM-IV-TR and ICD-10 recognized and used similar diagnostic criteria for alcohol dependence. However, DSM-5 merged selected items from the abuse and dependence diagnoses

found in DSM-IV-TR (as well as adding a craving item), and has a single "Substance Use Diagnosis" (SUD), with 11 criteria for alcohol SUD (of which 2 are needed to qualify for a SUD). ICD-10 includes the diagnosis of harmful drinking, which is defined by alcohol consumption that causes physical and/or mental damage in the absence of alcohol dependence.

In the early phases of the disorder, generally during the individual's early and mid- twenties, the most prominent feature is daily heavy drinking or frequent binge drinking. Individuals describe a rewarding sense of euphoria and elation that immediately follows the first drinks. As heavy drinking persists, tolerance to alcohol's effects sets in, leading the individual to escalate alcohol consumption. Increased frequency and intensity of drinking may be associated with irresistible urges to drink or craving.

During an individual's early thirties, alcohol-related psychosocial problems may become prominent. Typically, the person experiences increasing days absent from work, frequent family conflicts, and other interpersonal and legal problems. Work, home, and/or motor vehicle accidents while intoxicated causing injury also become common.

From the individual's mid- to late thirties, there may be a frank loss of control over drinking that is associated with a worsening of social and work-related problems and the onset of medical complications. Attention to personal care and hygiene may deteriorate, and alcohol consumption can dominate the individual's life. Often, at this point, the individual's global level of functioning is further impaired by alcohol-induced cognitive deficits.

By the time the individual is in his or her late thirties or early forties, severe medical complications such as liver cirrhosis or chronic pancreatitis may develop, leading to visits to emergency services and hospitalizations. Efforts to stop drinking may be associated with significant symptoms of alcohol withdrawal. Continued heavy drinking often exacerbates medical complications, with potentially fatal results.

Determinants of Alcohol Consumption

Pharmacology of Alcohol: Absorption

After alcohol is ingested, absorption of alcohol from the duodenum and jejunum is greater (80%) and faster than that occurring via the stomach (20%). However, when alcohol is consumed with food, gastric emptying is slowed, and the stomach becomes the main absorption site. The amount and rate of drinking may also influence alcohol absorption. When alcohol is consumed in a single large dose rather than several smaller doses, the resulting alcohol concentration gradient is greater, potentially yielding higher peak blood alcohol concentrations. However, when alcohol-containing beverages are rapidly ingested, the irritant properties of alcohol not infrequently cause superficial erosions and hemorrhages of the mucosa, causing paralysis of the smooth muscle and reduced blood perfusion. This can reduce alcohol absorption. Other factors that influence gastric emptying and alcohol absorption include smoking, diurnal changes in blood glucose, physical activity, and medications such as ranitidine or erythromycin.

In view of the significant variability in rates of gastric emptying and in alcohol absorption, the time to achieve peak blood alcohol concentration is also highly variable. The rate of absorption can range from 14 to 130 minutes.

Pharmacology of Alcohol: Distribution

Although alcohol shows little solubility in fat, it has the ability to cross all biologic membranes. Alcohol distributes from the bloodstream into all body tissues and fluids in proportion to their relative water content. There are large variations in the proportions of body fat and body water

content in humans, so an equivalent alcohol dose per unit of body weight can yield different blood alcohol levels (BALs) in different individuals. On account of lower volumes of total body water among women and the elderly, they have a smaller volume of distribution for alcohol than men and younger individuals. Thus, women and older individuals reach greater peak BALs than men and younger individuals when given an equivalent dose of alcohol.

Pharmacology of Alcohol: Metabolism

Some alcohol consumed orally does not enter the systemic circulation, but is oxidized in the gastric mucosa by isoforms of the enzyme alcohol dehydrogenase (ADH). This first-pass metabolism appears to be important in determining alcohol toxicity since its efficiency determines alcohol bioavailability. First-pass metabolism is reduced in women and alcoholics secondary to decreased ADH activity. This may translate into increased sensitivity to alcohol and greater blood alcohol concentrations in these populations. Several drugs, including histamine 2 receptor blockers such as cimetidine or ranitidine or aspirin, decrease gastric first-pass metabolism by inhibiting gastric ADH activity. First-past metabolism also occurs in the liver.

Nearly all (i.e., 92% to 95%) of the alcohol that is ingested is metabolized in the liver by ADH. In the most common pathway, alcohol is first oxidized to acetaldehyde by a class I ADH. Subsequently, acetaldehyde is oxidized to acetate by the enzyme aldehyde dehydrogenase (ALDH), which is localized in the mitochondria. Finally, the last step in alcohol metabolism occurs when acetate is oxidized to CO_2 and water in peripheral tissues as part of the Krebs cycle.

Pharmacology of Alcohol: Elimination

Nearly 90% to 95% of ingested alcohol is eliminated as water and CO_2. A small proportion of consumed alcohol (approximately 1%) undergoes conjugation with glucuronic acid to yield ethyl glucuronide as a by-product that can be measured in urine. The remainder of the consumed alcohol (approximately 4%) is excreted unchanged in the breath, urine, and sweat. Because the amount of alcohol expelled in the breath is proportional and in equilibrium with the concentration in the pulmonary arterial blood, alcohol breath tests can be used as a means to estimate the blood alcohol concentration.

Although alcohol elimination rates vary widely, in humans the metabolic capacity to remove alcohol is approximately 170 to 240 g/day for a person with a body weight of 70 kg. This is equivalent to an average metabolic rate of about 7 to 10 g/h, which translates to about one drink per hour.

Effects of Alcohol on Neurotransmission

Alcohol enhances dopamine release by directly increasing the firing rate of dopamine cells in the ventral tegmental area (VTA). Chronic alcohol exposure and alcohol withdrawal result in neuroadaptive changes in dopaminergic transmission that in general are contrary to the acute effects of alcohol on this system.

Alcohol also has effects on the GABAergic system, which has been mainly attributed to a postsynaptic mechanism similar to that of benzodiazepines and barbiturates, compounds that allosterically enhance $GABA_A$ receptor function. However, it has been recognized that alcohol administration also enhances GABAergic inhibitory effects presynaptically by increasing GABA (γ-aminobutyric acid) release in many brain regions, including the hippocampus and the cerebellum. Chronic alcohol exposure and alcohol withdrawal in rodents and humans result in decreased GABAergic tone.

Acute administration of alcohol antagonizes NMDA (*N*-Methyl-D-aspartate) receptors, whereas chronic administration increases the density of these receptors. Chronic alcohol

exposure and withdrawal result in significant increases in glutamatergic neurotransmission mediated by NMDA receptors in the basolateral amygdala and in the nucleus accumbens (NAcc).

Alcohol administration stimulates hypothalamic synthesis, release, and binding of endogenous opioids such as β-endorphin and enkephalin to μ-opiate receptors (MOR). Disturbances in opioidergic neurotransmission have been described among alcoholic patients and their unaffected adult children. It has been hypothesized that offspring of alcoholics have an inherited or acquired deficiency in endogenous opioid activity that leads them to drink to compensate for the deficiency (opioid deficiency hypothesis). Support for the opioidergic hypothesis of alcoholism is provided by the fact that opioid antagonists reliably reduce alcohol preference and consumption in different experimental paradigms and across different animal species.

The acute administration of alcohol to rodents increases their brain concentrations of serotonin (5-HT). Direct infusion of 5-HT activates dopaminergic neurons in the VTA. In contrast, chronic exposure to alcohol reduces 5-HT concentrations in the brain, which is associated with impulsive aggression and behavioral disinhibition. Although administration of 5-HT reuptake inhibitors to alcohol-preferring rodents reduces alcohol drinking behavior, it is unclear whether these compounds specifically dampen the reinforcing effects of alcohol or produce a reduction in all consummatory behaviors.

In healthy humans and social drinkers, pharmacologic manipulation of the nicotinic cholinergic receptor with mecamylamine or varenicline appears to reduce the stimulant effects of acute alcohol administration and alcohol consumption. These findings suggest that pharmacologic treatment with compounds targeting nicotinic receptors may be a useful strategy to reduce alcohol consumption among alcoholics.

Genetics of Alcohol Dependence

Family, adoption, and twin studies strongly support the involvement of genetic factors in the etiology of alcohol dependence. Family studies have shown that there is a sevenfold risk of alcohol dependence in first-degree relatives of alcohol-dependent individuals, especially among men. However, the observation that the majority of alcohol-dependent individuals do not have an alcohol-dependent first-degree relative underscores the fact that risk of alcohol dependence is also determined by environmental factors that may interact in complex ways with genetics. Twin studies have shown that the proportion of risk attributable to genetic factors (i.e., the heritability) of alcohol dependence ranges from 0.52 to 0.64 with no significant differences between men and women.

Linkage Studies

Linkage studies of alcohol dependence have implicated a region on the long arm (q) of chromosome 4 where an ADH gene cluster has been identified. Similar findings were obtained for the phenotype of alcoholism severity on chromosome 4 in a sample of 474 Irish families and among 243 Mission Native Americans from the southwest United States.

Among African Americans, a significant linkage between alcohol dependence and markers in chromosome 10 was also reported. This region contains numerous genes potentially relevant to alcohol dependence, such as those encoding the synaptic vesicular amine transporter and the 5-HT_7 receptor. Consistent with this finding, suggestive linkages were found on chromosomes 10, 11, and 22 for a low level of response to alcohol in a predominantly European American sample of college students. This trait has been shown to predict an increased risk of alcohol dependence. Other chromosomal regions of interest are those reported on chromosomes 6, 12, 15, and 16, which showed suggestive linkages with alcoholism severity and with alcohol withdrawal symptoms among Mission Native Americans.

Candidate Gene Studies

Candidate gene studies are population-level investigations in groups of unrelated individuals, in which genetic loci that encode proteins believed to be important in the etiology of a disorder are examined. In this approach, a statistical comparison of allele or haplotype frequencies at a candidate locus is made between affected individuals and control subjects.

ALDH Genes

The influence of genetic variants encoding ADHs and ALDHs on risk of alcohol dependence in some populations is well established. *ALDH1A1* and *ALDH2* are the genes that encode ALDH1 and ALDH2. These genes have been mapped to chromosomes 9 and 12, respectively. A well-known coding variant of the *ALDH2* gene, *ALDH2*2*, encodes a substitution of lysine for glutamate at position 504. This mutation results in the coding of an ALDH2 enzyme with very little oxidizing activity (i.e., a null mutation). People with one copy of the *ALDH2*2* allele have almost no detectable ALDH2 activity in their liver, whereas people who are homozygous have no detectable activity. The inactive *ALDH2*2* variant is relatively frequent among people of Chinese, Japanese, and Korean origin but is almost absent in people of European or African descent. People with an *ALDH2*2* allele experience a typical reaction when alcohol is consumed, which is characterized by severe skin flushing, nausea, and tachycardia, owing to the rise in the blood concentration of unmetabolized acetaldehyde. It is known that subjects heterozygous for the inactive ALDH2 variant have only one-fourth the risk of alcohol dependence as those with two functional alleles.

ADH Genes

To date, there are seven known human ADH genes: *ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6,* and *ADH7*. These genes have been mapped to a small region on chromosome 4. Several mutations have been identified in the *ADH1B* and *ADH1C* genes that are differentially distributed across population groups and that produce enzymes with different pharmacokinetic properties. The differences in the amino sequence encoded by *ADH1B* and *ADH1C* translate into differential rates of alcohol oxidation by the liver.

GABAergic and Acetylcholine Receptor Genes

A variety of loci encoding proteins that play a role in GABAergic neurotransmission have been associated with alcohol dependence and related phenotypes. Initial evidence that variation in the gene encoding the muscarinic acetylcholine receptor M2 (*CHRM2*) contributes to risk of alcohol dependence has been reported.

Serotonergic Genes

Genes encoding proteins in the serotonergic system have also been targeted as candidates for alcohol dependence risk. An insertion–deletion polymorphism consisting of a repetitive sequence of base pairs in the promoter region of the serotonin transporter protein (genetic locus *SLC6A4*) has been of particular interest. Compared with the long allele, the allele with the smallest number of repeats, commonly called the short (S) allele, has lower transcriptional activity. In a meta-analysis of data from 17 studies, the presence of the S allele increased the risk of alcohol dependence by almost 20%.

Opioidergic Genes

A meta-analysis of studies focusing on the gene encoding the MOR (genetic locus *OPRM1*) failed to provide convincing evidence of an association with alcohol dependence. Some evidence suggests that an A118G polymorphism that encodes an Asn40Asp amino acid substitution

in *OPRM1* may moderate the response to treatment with the opioid antagonist naltrexone. Healthy individuals with one or two Asp40 alleles who were pretreated with naltrexone reported lower levels of alcohol craving and a greater alcohol-induced "high" than those with Asn40 homozygotes after intravenous alcohol. Naltrexone pretreatment blunted the positive response to alcohol, an effect that was stronger among individuals with the Asp40 allele.

In summary, the available evidence shows that the risk of alcohol dependence is determined by multiple genes that interact with environmental factors. Despite substantial evidence that a genetic component is operative in the development of alcoholism, the disorder is etiologically complex, with a variety of other vulnerability factors playing a substantial role.

Evaluation

Conducting a detailed, systematic evaluation of alcohol-dependent patients allows the clinician to develop an individualized plan of treatment. A complete drinking history should be obtained, including questions on typical quantity and frequency of alcohol consumption, maximal number of drinks per drinking occasion, frequency of heavy drinking episodes, history of alcohol-related problems, psychiatric symptoms and the nature of their relationship with alcohol consumption (e.g., precipitation or exacerbation), and history of medical complications.

Screening

A number of self-report screening tests have been developed to identify alcoholics and individuals at risk of alcohol problems. One of the most frequently used is the CAGE, which includes four questions: (1) Have you ever felt you ought to *cut* (the "C" in CAGE) down on your drinking? (2) Have people *annoyed* (A) you by criticizing your drinking? (3) Have you ever felt bad or *guilty* (G) about your drinking? (4) Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover, that is, an *eye-opener* (E)? A total CAGE score of 2 or greater (at least 2 of the items are endorsed as being positive) is considered highly suggestive of an alcohol use disorder.

Another commonly used screening instrument is the Alcohol Use Disorders Identification Test (AUDIT), which consists of 10 items. The AUDIT is sensitive and specific in the identification of hazardous or harmful drinkers, and can identify alcohol-dependent individuals. It can be used as the first step in a comprehensive alcohol use history. The AUDIT's cutoff score is 8 for detecting alcohol use disorders.

Psychiatric History

Given the lack of reliability in unstructured clinical diagnoses, it is recommended that clinicians use a structured or semistructured interview to conduct and report their diagnostic evaluations. If it is not possible to use a complete psychiatric interview, such as the Composite International Diagnostic Interview or the Structured Clinical Interview for DSM-IV, then the alcohol sections of these interviews can be used.

Physical Examination and Laboratory Findings

Physical Examination

The physical examination provides essential information about the presence and extent of alcohol-induced organ damage—most commonly in the GI system, the central and peripheral

nervous system, and the cardiovascular system. The clinician should be alert to acute alcohol-related signs, including alcohol withdrawal or delirium and the acute presentation of psychiatric symptoms. Other systemic or nonspecific health problems associated with alcoholism include malnutrition and vitamin deficiencies, polyneuropathy, immune suppression and infectious diseases, and trauma secondary to fights and accidents.

Laboratory Tests

Carbohydrate Deficient Transferrin The most sensitive and specific laboratory test for the identification of heavy alcohol consumption is the determination of carbohydrate deficient transferrin (CDT) concentrations in the blood. Transferrin is a globular protein that is responsible for iron transport in plasma. An increase in CDT concentration is induced by heavy drinking. CDT appears to be more specific in detecting heavy drinkers without liver disease. Generally, CDT concentrations return to normal levels after 1 to 2 weeks of abstinence from drinking. Among patients under alcohol treatment, CDT appears to detect relapse to heavy drinking more accurately than other laboratory tests do. To date, CDT is the only laboratory test approved by the FDA for the detection of heavy alcohol consumption.

γ-glutamyl-transpeptidase After the cessation of heavy drinking, the concentration of serum γ-glutamyl-transpeptidase (GGTP) gradually falls by approximately 50% within 2 weeks, usually returning to the reference range over a 6- to 8-week period. The normalization of GGTP levels may be delayed or incomplete if there is underlying alcoholic liver disease or other medical disorders. GGTP concentrations are also elevated in a variety of nonalcoholic liver diseases. Nonetheless, elevations of GGTP occur in approximately three fourths of alcoholics before there is clinical evidence of liver disease. In comparison with CDT, an abnormal GGTP level appears to be more specific in detecting alcoholics with hepatic damage secondary to heavy drinking.

Whenever possible, CDT and GGTP should be used together to detect heavy drinking. This approach has been shown to increase the likelihood of correctly identifying individuals with alcohol use disorders and may be especially useful in diagnostically complex cases.

Liver Function Tests As with GGTP, elevations of the transaminases serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) are frequently observed when heavy drinking affects the liver. However, these enzymes can also be elevated in nonalcoholic liver disease. Heavy alcohol consumption is more likely to be present when the ratio of SGPT to SGOT exceeds 1.5, whereas other liver pathologies are more commonly associated with a lower ratio.

Mean Corpuscular Volume Erythrocyte mean corpuscular volume (MCV) can also be used as an objective indicator of heavy drinking. The MCV may be most useful when used in combination with GGTP or CDT. An elevation of MCV, which is caused by folate deficiency in alcoholics, is more prominent among alcoholics who are smokers. Because there is a 2- to 4-month period of abstinence required for MCV to normalize, this marker is not an efficient indicator of relapse.

The Alcohol Breath Test and Blood Alcohol Level The alcohol breath test measures the amount of alcohol in expired air, providing an estimate of venous BAL. Although its accuracy is contingent upon the patient's cooperation in exhaling into the instrument, the alcohol breath test can be a reliable and inexpensive method to assess recent alcohol consumption. A direct venous BAL can also be obtained. A BAL greater than 150 mg/dL in a patient showing no signs of intoxication can be interpreted to reflect physiologic tolerance. In nontolerant individuals, a BAL in excess of 400 mg/dL can result in death, and 300 mg/dL indicates a need for emergency care.

Treatment

Treatment Setting

In patients with a diagnosis of alcohol dependence, it is critical to determine the severity of the disorder and whether the patient is in need of medical detoxification. Outpatient nonpharmacologic treatment is indicated when the risk of withdrawal symptoms is low; however, when the risk of withdrawal is moderate or high, outpatient or inpatient pharmacologic detoxification is indicated. Medical complications of alcoholism indicate the need for immediate admission into an inpatient treatment setting for acute stabilization. Psychosocial problems such as homelessness and/or the lack of a social support network also may warrant admission into an inpatient or residential treatment setting.

Treatment of Alcohol Withdrawal

An important initial intervention is the management of alcohol withdrawal (i.e., detoxification). There are two approaches to the management of alcohol withdrawal. One is a nonpharmacologic approach known as social detoxification, which is indicated in patients experiencing mild symptoms. Medical detoxification is indicated for patients experiencing moderate- to severe- or complicated alcohol withdrawal.

Social detoxification consists of frequent reassurance, reality orientation, monitoring of vital signs, personal attention, and general nursing care. Medical detoxification involves the use of agents that act predominantly on the GABAergic neurotransmitter system. Benzodiazepines are the drugs of first choice in the pharmacologic treatment of alcohol withdrawal. Although all benzodiazepines will control alcohol withdrawal symptoms, diazepam and chlordiazepoxide appear to have a slight advantage over compounds such as lorazepam and oxazepam in preventing seizures and delirium tremens. This effect is explained by the fact that as a result of being metabolized to long-acting compounds, diazepam and chlordiazepoxide appear to self-taper. Oxazepam and lorazepam are not oxidized to long-acting metabolites and thus carry less risk of accumulation.

The prevention, detection, and treatment of common co-occurring or complicating medical conditions in alcoholics are important clinical considerations during detoxification. Good supportive care is also essential. Administration of thiamine (50 to 100 mg by mouth or intramuscularly) and multivitamins is a low-cost, low-risk intervention for the prophylaxis and treatment of alcohol-related complications such as Wernicke–Korsakoff syndrome.

Psychosocial Treatment of Alcoholism

In both residential and outpatient settings, commonly utilized psychosocial treatments include group or individual cognitive-behavioral psychotherapies, self-help groups (e.g., AA), family therapy, and recreational and occupational therapy. Separate chapters of this handbook address these approaches, including cognitive-behavioral therapies, contingency management, Alcoholics Anonymous (AA) and other self-help programs, and family/couples therapy.

Pharmacotherapy of Alcoholism

During the past decade, the use of medications in the rehabilitation treatment of alcohol dependence has gained increasing importance. Progress in this field has been fueled by an increased understanding of specific neurotransmitter systems involved in the modulation of alcohol

consumption. A number of medications have been approved for the treatment of alcoholism (disulfiram, oral and extended release naltrexone, acamprosate), and others have shown promise in controlled trials (e.g., topiramate, ondansetron). A separate chapter in this handbook reviews pharmacotherapies for alcoholism.

Pharmacotherapy of Psychiatric Comorbidity in Alcoholics

Clinically significant anxiety, depression, insomnia, and general distress induced by chronic alcohol consumption are common complaints among alcohol-dependent patients after detoxification. Frequently, these symptoms represent a diagnostic challenge, since they are usually indistinguishable from psychiatric disorders with onset prior to the initiation of heavy drinking. Regardless of the cause, when untreated, these problems can increase the likelihood of relapse in alcoholic patients, whereas attempts to relieve emotional symptoms can translate into reduced drinking.

During the early phases of alcohol withdrawal, depressive symptoms are common; however, they tend to improve spontaneously with sustained sobriety. However, for depressive symptoms that last longer than the acute withdrawal period (which for practical purposes might best be considered 2 to 4 weeks), antidepressant treatment may be beneficial.

In view of the potential of benzodiazepines to produce dependence and CNS depressant effects when ingested concurrently with alcohol, the use of these medications for the treatment of anxiety in alcoholics is probably best avoided. Buspirone, a nonbenzodiazepine anxiolytic without sedative effects or abuse potential that does not interact with alcohol, has been shown to be effective in the treatment of anxious alcoholics.

Comorbidities and Complications of Alcohol Consumption

Alcoholism Comorbidity with Other Psychiatric Disorders

Data from a large representative community survey examining comorbidity of past-year prevalence of alcohol use disorders and other mental health problems have been provided by the NESARC survey, which examined household respondents residing in the United States using DSM-IV diagnostic criteria. This survey showed that among those in the community diagnosed with a current alcohol use problem, one-third experienced at least another axis I disorder. This prevalence rate is two times greater than the prevalence rate of psychiatric problems observed among nonalcoholic respondents. The NESARC survey also described that in comparison with those with no diagnosis of a mental illness, those with a psychiatric diagnosis had a three times greater risk of experiencing an alcohol use disorder.

NESARC found that 13.05% of persons diagnosed with an alcohol use disorder experienced a drug use disorder (OR = 9.0), whereas among persons diagnosed with drug abuse or dependence more than half (55.2%) were diagnosed with an alcohol use problem. NESARC also found more than half of the persons with an alcohol use disorder (58.2%) use tobacco, a rate two times higher than the prevalence observed for the use of this substance in the community.

In NESARC, mood disorders were diagnosed in 18.9% of alcoholics (OR = 2.6). Conversely, among individuals diagnosed with a mood disorder, 17.3% also experienced an alcohol problem. Individuals diagnosed with a mania or hypomania had the greatest risk (OR = 3.5%), with 24.0% diagnosed with a comorbid alcohol use disorder. Other mood disorders such as major depression were relatively common among alcoholics (13.7%) and were significantly associated with drinking problems.

The NESARC showed that 17.1% of persons diagnosed with alcohol abuse or dependence experienced an anxiety disorder (OR = 1.7), while in those diagnosed with an anxiety disorder, 13.0% had an alcohol use disorder. The NESARC also showed that 12.3% of individuals with an alcohol use disorder met the criteria for antisocial personality disorder (ASPD) (OR = 4.8), whereas 28.7% of persons diagnosed with ASPD also had alcohol abuse or dependence.

Alcohol Intoxication

This condition is characterized by behavioral disturbances such as aggression or inappropriate sexual behavior or psychological changes such as labile mood and impaired judgment that begin shortly after heavy drinking. Other clinical signs include slurred speech, lack of coordination, unsteady gait, nystagmus, impairment of attention and memory, and, in the most severe cases, stupor and coma. After large amounts of alcohol have been ingested, severe disturbances in consciousness and cognition can occur.

Alcohol Withdrawal

Among alcohol-dependent individuals, alcohol withdrawal occurs following a substantial reduction in drinking (among individuals who have severe physical dependence) or the abrupt cessation of alcohol consumption (in the majority of physically dependent individuals). Uncomplicated alcohol withdrawal is characterized by signs and symptoms of autonomic hyperactivity, including increased heart rate, diaphoresis, tremor, nausea, vomiting, insomnia, and anxiety. The symptoms of alcohol withdrawal generally begin 4 to 12 hours after the last drink, and symptom severity generally reaches its peak after 48 hours, subsiding after 4 to 5 days of sobriety. Less severe anxiety, insomnia, and autonomic hyperactivity may last for a few weeks, though in some cases they can persist for up to 6 months.

Approximately 10% of alcohol-dependent patients can experience episodes of alcohol withdrawal complicated by delirium and/or grand mal seizures. Alcohol withdrawal delirium (*delirium tremens*) is seen in approximately 5% of the cases. This condition is characterized by severe signs of autonomic hyperactivity accompanied by a fluctuating level of consciousness and disorientation generally occurring 36 to 72 hours after the last drink. During alcohol withdrawal, patients can also experience vivid illusions and hallucinations of an auditory, visual, or tactile nature, which can also occur in a clear sensorium. Alcohol withdrawal seizures occur in approximately 3% to 5% of cases, generally within the first 48 hours after drinking cessation. A failure or delay in instituting treatment in patients with complicated alcohol withdrawal is associated with an elevated mortality risk. Predictors of complicated alcohol withdrawal include older age, poor nutritional status, co-occurring medical or surgical conditions, a history of high tolerance to alcohol, and a history of previous episodes of delirium tremens and/or alcohol withdrawal seizures.

Alcohol-Induced Cognitive Disorders

Chronic heavy alcohol drinking can result in severe folate and thiamine deficiency, leading to severe neurocognitive problems such as Wernicke encephalopathy, which is characterized by confusion and disorientation, ataxia, nystagmus, and gaze palsies. Generally, this disorder responds promptly to thiamine repletion and sustained sobriety. If heavy drinking persists, repeated episodes of Wernicke encephalopathy can lead to a persistent alcohol-induced amnestic disorder known as Korsakoff psychosis. Although not a true psychotic disorder, a prominent characteristic of this condition is confabulation that stems from profound deficits in anterograde and retrograde memory that prevent the retention of previously learned information and/or the acquisition of new information. Despite a profound disorientation to time and place, Korsakoff patients are unaware of their deficits.

Memory deficits can be exacerbated by continued heavy drinking, resulting in (for DSM-IV) an alcohol-induced persisting dementia, or (for SM-5) substance/medication-induced major or minor neurocognitive disorder.

Alcohol-Induced Mood and Anxiety Disorders

Chronic heavy alcohol drinking can also result in mood and/or anxiety disorders, which are common (affecting up to 90% of alcoholic patients entering treatment). Alcohol-induced mood and anxiety disorders can occur during alcohol intoxication or withdrawal, and may be indistinguishable from a primary mood or anxiety disorder. Typically, the severity and duration of alcohol-induced mood and anxiety symptoms are greater than the symptoms usually attributable to alcohol withdrawal (e.g., dysphoria, insomnia, and lack of energy). However, alcohol-induced mood and anxiety symptoms generally subside fully within 2 to 4 weeks following alcohol cessation.

Given that suicide is highly prevalent among depressed and anxious alcoholics, clinicians should closely monitor the patient for emerging suicidal thoughts and/or behaviors.

Alcohol-Induced Psychotic Disorder

Hallucinations or delusions induced by chronic heavy alcohol consumption generally occur within 30 days of alcohol intoxication or a withdrawal episode. Although alcohol-induced psychosis can occur during or shortly after an episode of alcohol intoxication or delirium, hallucinations and/or delusions do not occur exclusively during the course of these conditions. However, alcohol-induced psychotic symptoms tend to subside within a few weeks of abstinence.

Alcohol-Induced Sleep Disorder

Alcohol intoxication is associated with an increase in the density of nonrapid eye movement (NREM) sleep and a reduction in the density of rapid eye movement (REM) sleep. However, chronic heavy drinking results in a reduction in NREM sleep and a rebound in REM sleep density. These effects are clinically reflected by increased wakefulness, restless sleep, and vivid dreams, or nightmares. Alcohol withdrawal is also characterized by sleep fragmentation and an increase in REM sleep. Sleep tends to improve during periods of sustained sobriety. Persistence of sleep disturbances for more than 4 weeks and/or a history of a previous sleep problem are highly suggestive of a primary sleep disorder.

Morbidity and Mortality Associated with Alcohol Use

The World Health Organization has identified heavy drinking as an important risk to global health. In 2002, 2.3 million deaths (3.7% of global mortality) were attributable to alcohol. Although there is evidence that nonhazardous drinking (which according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) consists of ≤1 drink/day for women and ≤2 drinks/day for men) protects against cardiovascular disease, this effect appears to be confined to men 45 years old or older and to postmenopausal women. Conversely, greater levels of drinking have been shown to increase mortality risk due to cardiovascular disease and other health problems. After accounting for its health protective effects and without

considering other adverse consequences, it was estimated that alcohol drinking accounts for 4.4% of the global burden of disease.

In the United States, excessive drinking is the third leading preventable cause of death. Of the alcohol-attributable deaths, 46% resulted from chronic complications such as alcoholic liver cirrhosis and pancreatitis, whereas 54% resulted from acute complications such as injury from motor vehicle crashes and violence. Overall, 72% of all alcohol-attributable deaths involved men, with 75% of these involving men aged ≥35 years. In addition to medical morbidity and mortality, heavy drinking also contributes to financial, social, and family problems. The cost of alcohol-related problems, including hospitalization and institutionalization, motor vehicle crashes, and crime more than tripled over two decades, going from $70.3 billion in 1985 to an estimated $220 billion in 2005. In 2005, this cost was greater than that associated with other health problems such as obesity ($133 billion) and cancer ($196 billion).

Suggested Readings

Arias A, Feinn R, Kranzler HR. Association of an Asn40Asp (A118G) polymorphism in the μ-opioid receptor gene with substance dependence: a meta-analysis. *Drug Alcohol Depend*. 2006;83(3):262–268

Gelernter J, Kranzler HR. Genetics of alcohol dependence. *Hum Genet*. 2009;126:91–99.

Grant BF, Stinson FS, Dawson DA, et al. Co-occurrence of 12-month alcohol and drug use disorders and personality disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*. 2004;61:361–368.

Hernandez-Avila CA, Krnazler HR. Alcohol Use Disorders. In: Ruiz P, Strain EC, eds. *Lowinson and Ruiz's Substance Abuse: A Comprehensive Textbook*. 5th edn. Philadelphia, PA: Wolters Kluwer/Lippincott Williams and Wilkens; 2011:138–160.

Kaner E, Beyer F, Dickinson H, et al. Effectiveness of brief alcohol interventions in primary care populations. *Cochrane Database Syst Rev*. 2007;2:CD004148. DOI:004110.001002/14651858.CD14654148.

Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *JAMA*. 2004;291:1887–1896.

Rehm J, Mathers C, Popova S, et al. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet*. 2009;373:2223–2233.

Vengeliene V, Bilbao A, Molander A, et al. Neuropharmacology of alcohol addiction. *Br J Pharmacol*. 2008;154:299–315.

5 Opioids

Terminology: Opioids and Opiates

The term *opiates* refers to two of the psychoactive alkaloids (morphine and codeine) that occur in opium and to the many similarly psychoactive compounds that can be derived from them (such as heroin and oxycodone). *Opioid* is a superset of *opiates*: it additionally includes fully synthetic compounds (such as methadone and fentanyl) and endogenous compounds (such as endorphins, enkephalins, and dynorphins) that share the actions and effects of opiates.

Classification of Opioids Through Their Actions at Receptors

The four known types of opioid receptor are μ, δ, κ, and nociceptin/orphanin FQ peptide (NOP) receptors. Each type is G-protein coupled, and although each has been suggested to have further subtypes, such variation seems to reflect posttranslational modifications. There are at least 20 endogenous opioid ligands, most with preferential but promiscuous affinities for receptor types.

μ receptors are preferentially activated by β-endorphin and are largely responsible for the constellation of effects classically associated with morphine-like drugs: analgesia, euphoria, cough suppression, respiratory suppression, pupillary constriction, and (via receptors in the gut) constipation. Studies of μ-knockout mice suggest that μ receptors are necessary for morphine-induced analgesia and for development of tolerance to morphine. δ receptors are preferentially activated by enkephalins. δ agonists do produce effects distinct from those of μ agonists; in laboratory animals, these include anxiolytic and antidepressant-like effects, along with proconvulsant effects and only limited efficacy for analgesia. κ receptors are preferentially activated by dynorphin A. κ agonists, such as pentazocine, cyclazocine, and salvinorin A, are not self-administered by laboratory animals; the agonists produce analgesia, but also produce a distinct profile of other effects, most notably "prodepressant" and aversive effects that presumably correspond to what human users experience as dysphoria and psychotomimesis. NOP receptors (also called opioid receptor like-1 [ORL-1] receptors) are preferentially activated by nociceptin (also called orphanin FQ). They are considered part of the family of opioid receptors owing to structural similarities, but they appear to represent a separate branch of the family, in terms of both their pharmacology and their effects when activated. NOP receptors have little or no affinity for most of the prototypical endogenous opioids

(endorphins, enkephalins, and dynorphins), analgesic opioids, or the prototypical antagonist naloxone.

Thus, the three receptor types most relevant to a classification of abused or prescribed opioids are μ, δ, and κ. But classification in these terms is often not straightforward: a given opioid can interact with all three types of receptors and be an agonist, partial agonist, or antagonist at each. This complexity is reflected in the term *mixed agonist–antagonist*, which typically describes a drug that is an agonist or partial agonist at one type of receptor while being an antagonist at another type.

Phenomenology of Use and Withdrawal, and Criteria for Opioid Use Disorders

Phenomenology of Use

A first-person description of heroin effects notes that heroin can initially be a social lubricant and euphoriant, at least for some users:

> The unglamorous truth is that it's not that pleasurable or interesting a drug—except at the beginning. . . . The first time I snorted heroin, I couldn't believe it had such bad press: I felt absolutely wonderful and consummately able to conduct all essential life activities—talk, write, listen to music. Sex, it turned out, wasn't so great, but you can't have sex all the time anyway. I liked heroin much better than alcohol and didn't notice a physical downside: my coordination was okay and nothing was blurred or confused. The high felt . . . like nothing so much as happiness itself. (A 1994 Village Voice article by A. Marlowe)

On chronic use, these positive effects become unreliable: "Sometimes you can do dope all night and function the next day; other times hours of vomiting replace the evening partying you had in mind." Eventually, the effects of heroin use may become, at best, emotionally numbing:

> What passes for interaction is so much more minimal on dope. . . . A non-drug-using friend called some of my junkie pals "holograms," as in: "they're not really there, you can't talk to them." But that's just the point; heroin may not warm a cold world, but it lowers your comfort zone to the reptilian average. Heroin loses its savor once you start seeing this numbing effect as a negative rather than an advantage. Used regularly, heroin is mainly a way of lowering one's expectations. . . . Among users, heroin is proverbially what you do when you really must organize your files or your house; it lends itself to cushioning activity that's deadening and inherently repetitious. (A 1994 Village Voice article by A. Marlowe)

Phenomenology of Withdrawal

Withdrawal from opioids produces a flu-like syndrome that is not life threatening. Abrupt discontinuation of relatively short-acting μ agonists such as heroin typically leads to onset of symptoms in 6 to 8 hours; the most prominent are yawning, watery eyes, runny nose, chills, muscle aches, nausea/vomiting, diarrhea, and fever. Eating is disrupted for approximately 7 days; sleeping is increased on the first day, but disrupted for at least 15 days; fever peaks on the third day and may persist for approximately 15 days.

Abrupt discontinuation of methadone leads to symptoms that are slower in onset (usually starting after 24 hours), longer in duration, and possibly milder. Some patients state that

methadone withdrawal (even during a taper) is at least as severe as heroin withdrawal, and there is some evidence to support this contention.

Some of the clinically observable signs of opioid withdrawal (such as increased blood pressure, increased metabolic rate, and lowered body weight) may take approximately 6 months to resolve, an observation that has been discussed in terms of a subtle "protracted abstinence syndrome" in which such signs are accompanied by dysphoria and vulnerability to relapse.

Criteria for Opioid Use Disorders

In both of the major diagnostic systems for substance use disorders (SUDs)—the DSM-5 and the ICD-10—the essential criteria are generic, applying across substances. What bears emphasis here is that, in either system, physical dependence (tolerance or withdrawal) is neither necessary nor sufficient for the diagnosis of an opioid use disorder.

DSM-5 has essentially merged the diagnoses of abuse and dependence that were found in DSM-IV, and has one diagnosis (SUD). There are 11 criteria for this diagnosis, and a person will qualify for an opioid SUD if they fulfill 2 of the 11 criteria. If the person fulfills more criteria, then they may progress from mild to moderate to severe in the diagnosis.

The ICD-10 provides for diagnoses of dependence and harmful use. The dependence diagnosis reflects mostly the same set of criteria as was used for the DSM-IV dependence diagnosis, though it also incorporates a "sense of compulsion" as one possible (not required) criterion. Interestingly, DSM-5 now includes a craving criterion in the SUD diagnosis (the one criterion that was not found in DSM-IV diagnoses of abuse or dependence). The "harmful use" diagnosis reflects patterns of use that damage physical or mental health without otherwise meeting criteria for dependence.

Determinants of Use

Receptor Activity

Among the numerous factors that determine the degree to which a given drug is abused, the most fundamental is the interaction between the drug and endogenous receptors. Upon binding to a receptor, a drug may be a *full agonist* (fully activating the receptor), a *partial agonist* (activating the receptor to a lesser degree than a full agonist), or an *antagonist* (blocking the receptor). In the presence of a full agonist, a partial agonist can produce the behavioral effects of an antagonist. Some drugs, termed *mixed agonist–antagonists*, can act at more than one receptor with differing degrees of agonist and antagonist activities. Small differences in structure can result in substantial differences in receptor activity.

Drugs that act as full agonists at the μ-opioid receptor (MOR) are more likely to be abused than those with activity at other opioid receptors. In fact, all of the most highly abused opioids are μ agonists, including morphine, heroin, hydrocodone, oxycodone, hydromorphone, fentanyl, and methadone. When administered to experienced drug users, these drugs produce positive mood effects, described as euphoria, along with a wide range of other subjective and physiologic effects such as nausea, vomiting, itching, dry mouth, and respiratory depression. With repeated administration of μ agonists, tolerance and physical dependence develop. Development of tolerance to the positive mood effects of μ agonists may play a role in the dose escalation that frequently occurs during opioid dependence. On abrupt discontinuation of μ agonist use following repeated administration, there is a characteristic abstinence syndrome.

Drugs with κ-agonist activity, such as cyclazocine, ketocyclazocine (after which the κ receptor is named), and enadoline, produce a different profile of subjective effects, including

sedation and effects described as psychotomimetic or dysphoric. Abrupt discontinuation of repeated administration of κ agonists produces an abstinence syndrome distinct from that of μ agonists. κ-agonist activity is associated with low abuse liability. In fact, although κ agonists have been investigated for analgesia and other potential benefits such as neuroprotection in ischemia, their unpleasant subjective effects have so far prevented their successful development as medications.

The group of drugs that act at multiple-opioid receptors are often referred to as the agonist–antagonist opioids. Some of these are marketed as analgesics, such as pentazocine, butorphanol, nalbuphine, and buprenorphine. These drugs can be distinguished from μ agonists such as morphine using subjective-effect questionnaires and human drug-discrimination procedures. In fact, the differences in subjective effects between prototypic μ-opioid agonists and the agonist–antagonist opioids, respectively, described as morphine-like and nalorphine-like in early work, were a partial basis for the development of the multiple-opioid-receptor theory. In general, agonist–antagonist opioids have been less abused than prototypic μ agonists, though they have been abused under some circumstances.

Buprenorphine differs from the other agonist–antagonists in having partial μ-agonist activity without κ-agonist activity; its activity at the κ receptor is as an antagonist. Buprenorphine's subjective effects are very similar to those of the full μ agonists. Without the abuse-limiting κ-agonist effects of the other agonist–antagonists, buprenorphine has some history of diversion and abuse. However, its abuse by chronic users of full μ agonists (such as heroin, oxycodone, or methadone) is naturally limited because it blocks the acute effects of full μ agonists and can thereby precipitate withdrawal in individuals who are physically dependent on them. Also, because buprenorphine is only a partial agonist at μ receptors, it is relatively unlikely to produce respiratory depression, even at high doses. However, deaths have occurred with high doses of buprenorphine, especially when it is taken in combination with benzodiazepines.

Opioid antagonists that lack agonist effects, such as the opioid antagonists naloxone, nalmefene, and naltrexone, are generally devoid of subjective effects. These drugs have little or no abuse liability.

Some opioids have additional activity at nonopioid sites, which can affect their abuse liability. Examples include tramadol, which produces analgesia through both μ-agonist activity and blockade of noradrenergic reuptake transporters, and meperidine, which has both μ-agonist and anticholinergic activities. Meperidine has a long history of abuse, sharing many subjective effects with more selective μ agonists, but it also has a distinctive profile of adverse effects that appear to limit its abuse relative to those drugs. Tramadol has not been widely abused despite its wide availability in a variety of dosage forms, perhaps because it is less potent in producing positive mood effects than in producing analgesia. Overall, opioids with selective μ-agonist activity have somewhat higher abuse liability than those with mixed actions and much higher abuse liability than those without any μ-agonist activity.

Pharmacokinetics

The abuse liability of opioids is influenced by the numerous factors that determine their bodily distribution, metabolism, and excretion. One important factor is the speed with which the drug is delivered to the CNS. In general, abuse potential is enhanced by speeding the delivery of drug to the brain, thus shortening the interval between drug administration and the perceived onset of pharmacodynamic effects. One likely reason for the popularity of heroin over morphine is that its onset is faster than that of morphine.

Although the pharmacokinetic profile of a particular opioid is largely determined by its physical/chemical attributes, the route of administration can also have a substantial impact on speed of delivery. For most drugs, the rank order for routes of administration from slowest to fastest delivery is typically as follows: oral < intranasal < intramuscular ≈ subcutaneous <<<

intravenous ≤ inhalation (e.g., smoking). Opioids that can be inhaled or injected intravenously will likely have greater liability for abuse than those that can be used only orally.

Nonpharmacological Drug-Related Factors

The abuse liability of opioids is also affected by at least two nonpharmacological factors that are nonetheless related to the drug itself: availability and formulation. The availability of heroin is not evenly distributed around the world, and rates of use and abuse can follow availability. For example, India, the largest producer of licit raw opium, also has the highest illicit opium use, attributed in part to diversion of licit opium production. Heroin trafficking from the point of production to major markets can also increase local heroin use along the route. Temporary decreases in heroin supply can decrease the rate of initiation of new heroin users.

Abuse of prescription opioids has been increasing somewhat disproportionately to the number of licit opioid prescriptions. Availability partly determines which specific opioids are abused. For example, when availability is limited to hospitals, the opportunity for abuse of even highly abusable opioids will obviously be reduced; even within hospitals, availability and opportunity play a role in rates of abuse, as evidenced by the greater prevalence of substance abuse among anesthesiologists than among other physician groups. In contrast, even the least desirable opioid may be abused if it is widely available. An example of this is the over-the-counter cough suppressant dextromethorphan, with activity at sigma and phencyclidine (PCP) receptors. Early studies of dextromethorphan showed that it did not produce morphine-like subjective effects and was not liked by experienced opioid users. Nevertheless, dextromethorphan has been abused, mostly by teenagers either specifically seeking a dissociative/hallucinogenic experience or simply seeking any intoxicating effect.

Increasing the availability of a medication with a low rate of abuse can substantially increase the incidence of abuse. For example, abuse of both fentanyl (a potent μ agonist with high abuse liability) and butorphanol (a mixed agonist–antagonist with moderate abuse liability) increased when each drug was approved for prescribed use in outpatients, despite the use of formulations that might have been expected to minimize abuse liability. In the case of fentanyl, until 1990, reports of abuse usually involved health care providers with inpatient access to the intravenous formulation. After 1990, when fentanyl became available to outpatients (in a transdermal-patch formulation), abuse spread to a much broader population, mostly individuals who were not legitimate patients. Butorphanol was an unscheduled, injectable analgesic available primarily for acute administration in hospitals with only sporadic reports of abuse until an intranasal dosage form was approved for outpatient use in 1991. Reports of overuse and physical dependence began to appear soon afterward.

Formulation changes were probably not the direct culprit in increases in fentanyl or butorphanol abuse, given that a transdermal or intranasal formulation is generally less reinforcing than an intravenous formulation. The role of formulation becomes clearer when users devise a way to self-administer a drug by a route other than that intended by the manufacturer. For example, sustained-release formulations designed to deliver a low, constant dosage of medication over an extended period should have lower abuse liability than immediate-release formulations. However, if the slow-release formulation can be defeated, making the entire contents of the product rapidly available, abuse liability can be increased. The best-known example is that of OxyContin, a time-release formulation of oxycodone hydrochloride, which abusers found that they could crush to release the medication rapidly. Abuse of OxyContin became widespread.

Formulation-based strategies have sometimes been used to decrease the abuse liability of prescription opioids. Naloxone, which is far more bioavailable when injected than when taken orally, has been added to pentazocine and buprenorphine tablets to decrease the likelihood that they will be dissolved and injected by opioid-dependent individuals. Sustained-release products that resist manipulation are also being considered. Further development of abuse-deterrent

formulations must meet criteria for both risk-benefit and cost-effectiveness. Meeting patients' pain treatment needs while suppressing illicit use is a complex problem.

Genetics

The common allelic variants of interest that can modify opioid effects occur in genes coding for a drug-clearing cell-membrane transporter (P-glycoprotein), phase I drug-metabolizing enzymes (specifically, cytochrome P450 enzymes in the liver), phase II drug-metabolizing enzymes (such as UDP-glucuronosyltransferase, which facilitates urinary excretion of drugs), and opioid receptors. These genetic differences can have implications for medical and nonmedical use of opioids. A case-control study of single-nucleotide polymorphisms at sites representing 130 candidate genes suggested small associations between heroin addiction and several variants in noncoding regions of genes for μ, δ, and κ receptors. Genetic differences like these might lead to individual differences in splice variants of opioid receptors.

Cognitive Factors

The process of social learning can apply to opioids as well as other drugs. For example, a user's first nonmedical experience with an opioid often includes nausea and vomiting, but the user may learn from experienced peers that these symptoms are an intrinsic part of a desirable experience. Thus, the phrase "pleasant sick" is among the standard clinical descriptors for opioid effects. Social learning may also play a role in defining oneself as an addict and behaving accordingly; some addicted users report that they had initially interpreted their withdrawal symptoms as flu symptoms until experienced users told them otherwise, leading them to seek more opioids for relief.

Peers and General Environmental Setting

The archetypal pusher who distributes free samples of heroin to snare nonusers is largely a myth. Ethnographic studies indicate that initiation of heroin use typically occurs with peers, is often serendipitous, and is attributed retrospectively to curiosity.

Initiation of opioid use is sometimes said to be causally related to prior use of marijuana or other drugs; this is the version of the gateway hypothesis. This hypothesis would be difficult to prove or disprove, but is not necessary to explain epidemiological data. The observations that underlie the gateway hypothesis—association and temporal sequencing of marijuana use and opioid use—can be fully accounted for incorporating only two rules: differing individual propensities to use drugs in general and temporally staggered availabilities of different drugs.

Once nonmedical opioid use is established, environmental factors seem to be prime determinants of whether it progresses to addiction or remains at the level of chipping (regular but nonproblematic, noncompulsive use). For illicit drugs in general, the likelihood of addiction, given use, increases with low educational background, low income, and minority-group membership, but the surveys from which these statistics were drawn do not disaggregate opioid addiction from other drug addiction.

Specific Opioid-Associated Cues

General aspects of the environment affect individuals' overall propensities toward opioid use, abuse, and addiction. Specific opioid-associated cues seem to contribute to ongoing use, and to lapses and relapses, among established users. It has been theorized that environmental cues associated with past use of opioids (or with opportunities to obtain opioids) induce conditioned responses that can occur long after the last use of opioids, can include withdrawal symptoms

and craving, and can play a role in relapse. Laboratory work has shown that signs and symptoms of opioid withdrawal can be induced in users by cues that have been paired with a prior experience (naloxone-precipitated withdrawal). Further work demonstrated that cues previously paired with opioid *use* could induce craving and "high-like feelings" as well as withdrawal symptoms and that each cue-induced response could occur independently of the others. The variability of the responses may hamper users' ability to recognize cue-elicited opioid seeking as a general phenomenon in daily life.

If cue-elicited craving and withdrawal do contribute to relapse, it might seem encouraging to note that they can be extinguished in a laboratory setting. Unfortunately, efforts to parlay this finding into an extinction-based treatment have been thwarted by the failure of extinction to generalize outside the environment in which it occurs.

Complications of Opioid Use and Comorbid Disorders

History and Physical Examination in Patients with Opioid Use Disorders

Like all clinical medicine, evaluation and treatment of opioid use disorders require the development of a therapeutic relationship based on trust and a two-way exchange of information. Patients with opioid use disorders should undergo all elements of a basic medical history (chief complaint, history of present illness, past medical history, medications, allergies, and review of systems). Additionally, special attention should be paid to the patient's social history; this should include a complete assessment of substance use and HIV risk factors. The medical history in patients with opioid use disorders should also include a screening for depression and anxiety and an assessment for personal safety with regard to both living situation and personal relationships.

A complete physical examination is warranted in all patients with opioid use disorders. In addition to the standard elements, the physical examination should include special attention to signs and symptoms related to opioid use and its complications.

Complications of Opioid Use

Chronic use of pure opioid analgesics does not produce frank signs of toxicity in any major bodily organ, though it may be immunosuppressant to a degree whose clinical significance is not clear. Nonetheless, chronic misuse of opioids usually has considerable medical sequelae, many of them attributable to the associated lifestyle and to the routes of administration employed.

Heroin is most often taken by sniffing, intravenous injection, or "skin popping" (subcutaneous injection); these routes are also sometimes used for other opioids (such as crushed OxyContin tablets). Each route of administration has accompanying complications. Injection can result in the entry of organisms from the skin, injection works, or perhaps the drug itself into the surrounding soft tissue and the bloodstream. This can result in a localized infection such as cellulitis, abscess, wound botulism, or necrotizing fasciitis. It can also result in more widespread systemic infection such as endocarditis and septic emboli. Injection drug users are more likely than nondrug users to be admitted to the hospital for infection.

Sniffing opioids can result in pulmonary complications, including granulomatous responses, hemoptysis from airway irritation, and emphysema. There may also be nasal irritation, chronic sinusitis, and septal perforation.

As might be expected, overdose is a common adverse event among opioid misusers. Most opioid misusers acknowledge having witnessed a nonfatal overdose, many acknowledge having witnessed a fatal one, and many also acknowledge having experienced a nonfatal overdose themselves. The mechanisms of overdose death are unclear; it has been argued that most such deaths involved synergistic effects of opioids and other drugs.

Because opioid misusers are often reluctant to summon help for peers who have overdosed in their presence, and because many also hold inaccurate beliefs about resuscitation methods, a case has been made for providing take-home naloxone with appropriate training for emergency use. Initial arguments against take-home naloxone have not been borne out in several subsequent pilot programs in different cities. In one of the programs, bystander-administered naloxone was shown to be effective when administered as a nasal spray, eliminating the risks associated with injection.

Evaluation Approaches

Tools for Screening and Evaluation

There are several tools that have been developed for screening and evaluation of drug-use disorders. These include the Addiction Severity Index (ASI), a 161-item multidimensional clinical and research instrument administered as a semistructured face-to-face interview that assesses functioning in 7 domains (medical, employment/support status, alcohol, drug, legal, family/social, and psychological); the Drug Abuse Screening Test (DAST), a 28-question self-report measure used to screen and evaluate individuals for drug abuse or dependence; the ICD-10 Symptom Checklist for Mental Disorders, a 10-question instrument that asks about symptoms associated with heroin or other opioid use; the NIDA-Modified ASSIST (Alcohol, Smoking and Substance Involvement Screening Test); and the Severity of Dependence Scale (SDS), a 5-item questionnaire that provides a total score indicating an opioid dependence severity.

Treatment Approaches

Overview of Treatment Approaches

Opioid addiction is considered a chronic relapsing disorder, and as such, its treatment is a long-term process. Detoxification (the management of opioid-withdrawal symptoms that occur when an individual discontinues use) addresses the physical component of addiction and can be an initial step in treatment. However, detoxification should be followed by long-term treatment to address the full syndrome of addiction. Maintenance therapy, when administered correctly, addresses the full syndrome by providing long-term opioid replacement and supportive psychosocial treatments. Combining several treatment modalities is more effective than giving stand-alone treatment, but no specific combination has been shown to be superior to all other possible combinations, so treatment approaches should be individualized based on the patient's needs. The best approach is the one that works for that particular patient at that particular time.

Detoxification

The goal of detoxification is safe management of withdrawal symptoms while the patient adjusts to an opioid-free state. Repeated detoxifications in the absence of subsequent treatment are neither cost-effective nor helpful. This is because detoxification addresses only the acute

physiological effects of opioid withdrawal, not the emotional, cognitive, behavioral, and social aspects of recovery. Detoxification in and of itself does not constitute treatment for opioid dependence. Rather, it should be considered a first stage of treatment, and should be followed by formal assessment, referral, and coordination of care. Use of detoxification programs is associated with increased rates of initiation of long-term treatment for addiction (including methadone maintenance and other forms of addiction treatment).

Traditional Detoxification Methods

Traditionally, opioid detoxification consisted of a methadone taper. This method has been criticized by providers and patients alike for the long duration of withdrawal symptoms associated with it. The method has been improved with the use of adjunctive medications for symptomatic relief; these include α-2 adrenergic agonists such as clonidine and lofexidine. An alternative to methadone-assisted detoxification is buprenorphine.

Comparison of Traditional Detoxification Methods

Methadone and buprenorphine have been shown to be comparable in suppressing signs and symptoms of opioid withdrawal and in their adverse-event profiles and rates of treatment completion. In a systematic review comparing buprenorphine to clonidine, buprenorphine was found more effective in decreasing signs and symptoms and was associated with greater treatment retention and fewer adverse events. When given as a stand-alone treatment for opioid withdrawal, clonidine provides considerably less reduction of subjective symptoms than of autonomic signs; given that the problematic aspect of opioid withdrawal is the distress associated with symptoms rather than any medical risk associated with autonomic signs, clonidine is probably best used as an adjunct to a methadone-assisted or buprenorphine-assisted taper.

Detoxification under Anesthesia

Detoxification under anesthesia has been promoted as a quick and painless way to achieve opioid withdrawal. However, this approach is expensive, generally not covered by insurance, carries significant medical risks, and lacks evidence of effectiveness.

Maintenance Medications

Maintenance combines pharmacologic therapy with psychosocial interventions and support services and has the greatest likelihood of success in most patients. The pharmacological therapies include methadone, buprenorphine, and naltrexone. These medications are reviewed in other chapters of this handbook.

Behavioral Therapies

Behavioral therapies encourage cessation of opioid use and teach patients to function without drugs, handle cravings, avoid drug-using people and drug-associated places, and cope with lapses and relapses. They are most effective when used in conjunction with pharmacological treatments, but when this is not possible, they are also effective alone. Behavioral treatment can include individual counseling, group or family counseling, contingency management, and cognitive-behavioral therapies, among others. Behavioral therapies are reviewed in other chapters of this handbook.

Needle Exchange

Needle-exchange programs (NEPs) are both clinically effective and cost-effective in reducing HIV, and there is no convincing evidence for unintended negative consequences (e.g., increases

in the initiation, duration, or frequency of illicit drug use or injection). Furthermore, there is evidence that NEPs might increase entry into drug-treatment programs and contact with primary health care. NEPs should be seen as an important component of an evidence-based approach to reducing the spread of HIV and other blood-borne infections.

Conclusion

Opioids, and the use and misuse of opioids, are complex. For example, opioids that could once be mentioned in the same breath as μ-preferring analgesics with differing pharmacokinetics (morphine, heroin, oxycodone, methadone) might act quite differently from each other at different μ-receptor variants, with behaviorally and therapeutically significant consequences. Newly selective agonists may disaggregate aspects of opioid-induced analgesia (for example, δ agonists may relieve allodynia without producing more general analgesia). New types of mixed or bivalent ligands, or new ways of administering antagonists (such as ultralow-dose regimens with seemingly paradoxical effects), may open new possibilities for prevention or treatment of physical dependence. At the same time, physical dependence is increasingly understood not to be the defining feature of opioid addiction. And opioid addiction is increasingly understood to be determined in large part by cognitive and sociocultural factors, despite lore that emphasizes the irresistibility of intoxication and the hellishness of withdrawal.

These insights have emerged from disciplines as remote from each other as ethnography and molecular biology, as well as the behavioral sciences that in some respects bridge the two. Continued work in all of those disciplines should increase the proportion of good outcomes from therapeutic use of opioids, and should also expand the already good range of treatments available for opioid use disorders.

Suggested Readings

Ananthan S. Opioid ligands with mixed μ/δ opioid receptor interactions: an emerging approach to novel analgesics. *AAPS J*. 2006;8(1):E118–E125.

Campbell ND. *Discovering Addiction: The Science and Politics of Substance Abuse Research*. Ann Arbor, MI: University of Michigan Press, 2007.

Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction: a clinical trial with methadone hydrochloride. *JAMA*. 1965;193:646–650.

Epstein DH, Phillips KA, Preston KL. Opioids. In: Ruiz P, Strain EC, eds. *Lowinson and Ruiz's Substance Abuse: A Comprehensive Textbook*. 5th edn. Philadelphia, PA: Wolters Kluwer/Lippincott Williams and Wilkens; 2011:161–190.

Mello NK, Mendelson JH. Buprenorphine suppresses heroin use by heroin addicts. *Science*. 1980;207(4431):657–659.

O'Brien CP, O'Brien TJ, Mintz J, et al. Conditioning of narcotic abstinence symptoms in human subjects. *Drug Alcohol Depend*. 1975;1(2):115–123.

Preston KL, Jasinski DR. Abuse liability studies of opioid agonist-antagonists in humans. *Drug Alcohol Depend*. 1991;28(1):49–82.

Rollason V, Samer C, Piguet V, et al. Pharmacogenetics of analgesics: toward the individualization of prescription. *Pharmacogenomics*. 2008;9(7):905–933.

Schuster CR, Smith BB, Jaffe JH. Drug abuse in heroin users: an experimental study of self-administration of methadone, codeine, and pentazocine. *Arch Gen Psychiatry*. 1971;24(4):359–362.

Swendsen J, Conway KP, Degenhardt L, et al. Socio-demographic risk factors for alcohol and drug dependence: the 10-year follow-up of the National Comorbidity Survey. *Addiction*. 2009;104(8):1346–1355.

6 Cocaine and Crack

Epidemiology

In the United States, current cocaine use appears to have been holding steady over most of the past decade at between 0.5% and 1.0% of Americans aged 12 years and older, with approximately 1.4% of 18- to 25-year-olds using cocaine currently (based on results from the National Survey on Drug Use and Health [NSDUH]). A consistent 20% to 25% of current cocaine users have been identified as users of crack and, although precise estimates are not currently available, most instances of frequent cocaine use and most daily or nearly daily use appear to be crack related. In 2011, the NSDUH estimated that there were 821,000 persons with cocaine abuse or dependence. Crack cocaine users represent a disproportionately high percentage—approximately 75%—of those cocaine users entering treatment.

The stable rates of overall cocaine use belie the extremely elevated rates of current use in certain subgroups. For example, over the past decade, unemployed adults have been shown to be more likely than full-time employed adults to be current users of illicit drugs, and an adult without a high school diploma has been shown to be about twice as likely to be a current user than a college graduate. Young adults in the criminal justice system (parolees or on probation) have had current illicit drug use rates as much as four times those of age-matched adults over the past 10 years. Youngsters who smoke cigarettes regularly are well documented to have rates of current illicit drug use as much as 15 times higher than that of nonsmokers, even higher if they regularly use alcoholic beverages.

Phenomenology

Most people try cocaine out of curiosity, but those who pursue it seek the unique experience of cocaine intoxication. Although chronic addicts will often relate that they never quite obtain the same subjective "highs" that they did when they first started using, there is nonetheless anecdotal evidence that the typical cocaine user experiences with reasonable consistency a combination of intense, brief pleasure and related enhancements of sensation and perception that are generally outside the scope of normal everyday human experience. Patients may develop brisk speech, strained facial expressions, darting eyes, fidgeting, and pacing. Sexual interest and sensitivity is often piqued, and some users describe the experience as akin to a "full body orgasm." The feeling of increased alertness reported subjectively with cocaine can be confirmed by electroencephalographic recordings, which show a general desynchronization of brain waves after

cocaine administration. Such desynchronization, which indicates arousal, reveals widespread involvement of the cerebral hemispheres through brainstem and thalamic relays which mediate conscious awareness, attention, and wakefulness. Despite the feeling of arousal, individuals using cocaine usually do not gain superior ability or greater knowledge. Their sense of omnipotence is a temporary delusion; they tend to misinterpret their enhanced confidence and lowered inhibitions as signs of enhanced physical or mental acuity.

In addition to the subjective experiences already mentioned, acute intoxication with moderate-to-high doses of cocaine may be associated with rambling speech, headache, transient ideas of reference, hypersensitivity to low frequency sounds, and tinnitus. There may also be frank paranoid ideation, auditory hallucinations in a clear sensorium, and tactile hallucinations ("coke bugs"), which the user usually recognizes as effects of cocaine. Visual illusions are common, but true visual hallucinations less so, and when they do occur this is usually indicative of very high or protracted dosing, often in combination with sleep deprivation. Extreme anger with threats or acting out of aggressive behavior may occur. Mood changes such as depression, suicidal ideation, irritability, anhedonia, emotional lability, or disturbances in attention and concentration are common.

Self-motivated or externally imposed abstinence in cocaine-dependent individuals may or may not be accompanied by signs of withdrawal, although cocaine rarely, if ever, produces physiologic dependence, as is common with addiction to opiates, alcohol, and barbiturates. At the extreme ends of the spectrum, cocaine withdrawal may manifest with minimal degrees of dysphoria or produce frank anhedonia with psychomotor retardation. Patients may have limited interest in the environment, limited ability to experience pleasure, and severely decreased energy.

Determinants of Use

Pharmacologic Considerations

Cocaine—benzoylmethylecgonine—is a naturally occurring crystalline alkaloid of the tropane family that also includes atropine and scopolamine. It does not exert notable anticholinergic effects. Cocaine's primary neuropharmacologic effect is to block the uptake of monoamines released into synapses of the CNS. However, cocaine also has sympathomimetic actions in peripheral tissues and quinidine-like anesthetic/type I antidysrhythmic properties. As a local anesthetic, cocaine's main effect is to block sodium channels in excitable tissues, and in high doses it can also interfere with certain potassium channels and induce a profound failure of electrical transmission in the heart and CNS, as may be seen with accidental massive overdoses (e.g., a smuggler who "bodypacks," or "bodystuffing" during a police raid).

Cocaine is a relatively small (molecular weight 303) lipophilic molecule that is well absorbed through mucous membranes and alveoli. About one-third of an oral or nasal dose of powder cocaine, and up to 95% of an inhaled dose of freebase or crack cocaine may be bioavailable. Once in the blood, it readily penetrates the blood–brain barrier. Binding of cocaine to plasma proteins is minimal, and volume of distribution is low; blood-to-plasma concentration ratios are typically close to unity. At the doses typically seen in clinical practice, ingestion of cocaine can be viewed as a multitoxic exposure because enzymatic and nonenzymatic hydrolysis produce a number of metabolites, some of which have the same or greater effects as cocaine. Active metabolites may intensify or prolong cocaine euphoria. Benzoylecgonine, a neuropharmacologically active and cardiotoxic agent, is produced rapidly by enzymatic (hepatic carboxyesterases) and nonenzymatic hydrolysis and is usually the major metabolite of cocaine, but when cocaine is smoked there may be relatively greater production of ecgonine methylester. The latter is generally considered the least toxic of the major metabolites and is formed readily by the action of butyrylcholinesterases in plasma, brain, and lung. Tiny quantities of several other metabolites

are produced to varying extents under varying conditions, but these are usually of no clinical significance. Very little cocaine is passed unchanged in the urine and stool.

The purer the drug, the greater its effects, but as a rule, pure cocaine is unavailable on the street. Cocaine is typically heavily adulterated with other substances such as mannitol, lactose, or glucose to add weight, and caffeine, lidocaine, amphetamines, quinine, or even heroin to add taste and to provide additional CNS stimulant effects. The typical concentration of cocaine in street preparations ranges from 10% to 50%; rarely, samples can contain as much as 70% cocaine.

Routes of administration that deliver drug rapidly to the brain are intensely euphoric, most rapidly addicting, and also the most sensitizing to the effects of future cocaine use. Rate of administration appears to influence the extent to which long-lasting changes in brain cell function, including expression of immediate early genes and neurotransmitter receptor populations, may occur. Generally, cocaine tends to be less addictive if the dose is small, the peak plasma levels low, the onset of activity slow, the duration of action long, and the unpleasant withdrawal effects absent or very mild. If cocaine is taken by means of chewed coca leaves, through oral ingestion, or through nasal insufflation, consequences are generally slow to develop. Intravenous (IV) cocaine use ranks high on the addiction potential scale. The onset of the IV cocaine "rush" is within 30 to 45 seconds, and the drug's effects last for 10 to 20 minutes. One hundred percent of an IV dose is delivered to the circulatory system, compared with perhaps 20% to 30% of a relatively poorly absorbed oral or intranasal dose, and peak blood levels after an injection can be more than twice those that occur following intranasal ingestion.

Cocaine in any smokable form, whether coca paste, freebase, or crack, probably has the highest addictive potential. The resulting high is intense and the onset is extremely rapid. Only 8 to 10 seconds elapse before the user experiences the high, and peak brain concentrations occur more rapidly than following IV use since the venous side of the circulation is bypassed. Crack cocaine is frequently used in combination with alcohol. As with coadministration of an opiate in the IV cocaine user, the effects of alcohol tend to blunt the undesirable effects and may prolong the high. People who simultaneously abuse cocaine and alcohol may be susceptible to heightened morbidity related to cocaethylene, a cardiotoxic metabolite that also possesses some stimulant effect. Also contributing to the high addiction potential of crack is the fact that the effects of the drug last only 5 to 10 minutes. After the high is over, the crack user feels extremely anxious and depressed. Such a rapid shift between the drug's positive and negative effects makes users immediately crave the euphoria they felt just moments before.

Neurobiology

Cocaine addiction has been described as a disease of the brain's "pleasure centers"—neural networks subserved primarily by the monoamine neurotransmitter dopamine (DA). However, recent insights have broadened the concept of pleasure center to include not only the dopaminergic connections between the brainstem and the structures of the basal forebrain (prominently including the nucleus accumbens [NAcc]), but several frontal cortical regions, and an increasingly important role for nondopaminergic neurotransmission. The latter prominently includes, but is certainly not limited to, amino acid neurotransmitters (both excitatory [glutamate] and inhibitory [γ-aminobutyric acid, GABA]), serotonin (5-HT), endogenous opioids, endocannabinoids, and proximal components of the hypothalamic–pituitary–adrenal (HPA) axis. The hippocampal formations, amygdalae, prefrontal cortex, and anterior cingulate regions—all components of the limbic system—play prominent roles in this enriched and more differentiated view of pleasure-center circuitry.

A receptor for cocaine has been identified, a high-affinity binding site on the DA transporter (DAT) in presynaptic elements of dopaminergic nerve terminals. By attaching to and reversibly inactivating these membrane-bound transport proteins, cocaine blocks the reuptake of DA when it is released and thereby produces an acute but *relatively* sustained increase in synaptic DA availability. Increased DA-receptor binding occurs as a consequence. Cocaine is not a

selective DAT blocker, however, and it is well established that it also impairs reuptake of serotonin and norepinephrine. It is interesting to note that in DAT "knockout" mice, cocaine may still induce increases in DA levels in the brain and still produce its primary reinforcing effects.

Some of the best evidence for a general theory of addiction centering on DA comes from classic experiments utilizing animal models of cocaine self-administration. Dialysis probes in the ventral tegmental area (VTA) projections that terminate within the NAcc provide direct evidence for specific roles of these structures in sensitization to cocaine's effects in self-administration paradigms. Similarly, using microdialysis in the NAcc, extracellular DA levels are found to be increased during cocaine self-administration, with behaviors directed toward attaining specific, almost optimal, DA levels. DA levels attained were dose dependent and correlated with increased cocaine intake. However, DA projections from the VTA to NAcc are certainly not the only elements involved in increasing DA neurotransmission in response to cocaine. The pleasurable effects of cocaine are probably also related to increases in DA and serotonin in the cerebral cortex through extensive mesocortical projections.

Acute administration of cocaine clearly results in increased levels of synaptic DA. However, it is superficial to imagine that brain DA levels remain elevated in the wake of repeated cocaine exposure; the opposite may be the case. Chronic exposure to cocaine may significantly alter the patterns but not the magnitude of the acute DA response to cocaine. Dopaminergic neurons appear to demonstrate tolerance and diminished responses to chronic self-administration consistent with the notion of a functional DA deficit developing over time. There is strong evidence that postsynaptic DA receptor availability (and probably the actual density of DA receptors) changes in response to prolonged, repeated exposure to cocaine.

Environmental and Social Features

In experiments involving drug-naive monkeys, individuals with lower D2-type dopamine receptor levels have heightened vulnerability to the reinforcing effects of cocaine. Similarly, nonaddict human subjects with lower levels of D2 receptors were more likely to report a euphoric response to IV methylphenidate. In contrast, subjects with higher levels of these receptors tended to state that methylphenidate not only does not appeal to them, but makes them feel awful. These type of findings are further complicated by the fact that, at least in subhuman primates, brain DA receptor levels may change according to position in a dynamic social hierarchy (up in dominant animals, down in submissive animals).

In most animal models of cocaine dependence, drug pursuit behaviors seem to be powerfully reinforcing themselves. Brain DA levels and rapidity of reinforcement are increased in self-administration paradigms compared with circumstances where the same dose of drug is administered by the experimenter. Studies have tried to separate addiction from neural adaptation by comparing volitional self-administration with passive (involuntary) drug injections. Not only does addiction develop in the former, but neurochemical changes *appear to be maximized* with self-administration models.

Pavlovian conditioned responses to environmental cues seem to be a major trigger to relapse. In autoradiographic studies in animals, and using positron emission tomography and functional magnetic resonance imaging in humans, a subject's perception of drug-related cues causes activation of limbic-connected neocortical regions. For example, the sight of drug paraphernalia or a street corner where drugs were frequently purchased might elicit powerful craving that is accompanied by increased cerebral metabolism, particularly in the orbitofrontal cortex and portions of the anterior cingulate region. In fact, these cue-sensitive changes in regional metabolism provide some of the best evidence for a critical role of neocortical structures in mediating hallmark features of full-blown addiction: anticipation and craving as preludes to relapse, even after long periods of abstinence.

In persons with established addiction to cocaine, or other psychostimulants, frontal lobe metabolism may be substantially *decreased* from baseline *during withdrawal* from a period

of binge use. This finding does not necessarily conflict with the suggestion that phasic cortical activation is essential to the behaviors leading up to relapse. Perhaps not unexpectedly, withdrawal-related hypometabolism appears to correlate with decreased dopamine receptor availability, as judged by radiotraced DA-receptor studies, consistent with the concept of a hypodopaminergic state in the chronic abuser. Unfortunately, frontal deficits may not always be reversible functional changes. Certain cognitive deficits and impairments of affect, particularly those related to impulse control and assignment of circumstance-appropriate salience to stimuli, may be permanent in some people.

Evaluation and Treatment Approaches

Initial Evaluation and Management

After establishing medical stability, the first step in treatment is, of course, to diagnose the patient's condition accurately. Importantly, the withdrawal syndrome following even heavy, frequent cocaine use may not be particularly prominent, is rarely life-threatening, and generally not the focus of the specialist in addiction medicine. It is often said that withdrawal from cocaine is primarily psychological, as opposed to the prominent physical withdrawal syndromes seen commonly with dependence on alcohol, opiates, benzodiazepines, and barbiturates. The symptoms of cocaine withdrawal syndrome are certainly of concern, however, because withdrawal-related dysphoria and intense craving increase the chances of elopement from treatment. One of the clinician's most important roles is to assure the person in withdrawal from cocaine that their symptoms are common, transitory, not usually of major medical concern, and, perhaps for some, part of the process of recovery.

Regardless of the initial (provisional) diagnosis, toxicologic analysis of body fluids should be made. Testing confirms the clinical impression and may help identify concomitant use of other drugs. Negative testing may help identify numerous other disorders that can mimic all or most of the features of cocaine intoxication, cocaine withdrawal, cocaine delirium, and cocaine delusional disorder. Laboratory testing's main value, however, is to eliminate the need to continually question the patient about current drug use and uncover occult use in the therapeutic setting. As a therapeutic relationship is established, "trust but verify" is the operative principle, and this attitude can provide a strong motivation for the patient to remain drug free. Immediately following the initial physical examination, blood and/or supervised urine samples should be collected and sent for analysis; if possible, a sample of the cocaine used by the patient should also be submitted to the laboratory; all subsequent urine collections should be supervised and taken first thing in the morning; temperature and/or specific gravity should be measured to confirm that the sample has not been adulterated.

Characterization of the patient's pattern of use is important in assessing the extent to which the patient has progressed along the path that leads from experimental or occasional use (initiation) to compulsive, often more frequent use. The severity of withdrawal symptoms may be estimated from the pattern of use, and the chronicity of use is frequently an indirect indicator of the extent to which the patient's life may be in disarray. Unlike the so-called functioning alcoholic, it is relatively rare for a regular cocaine user to maintain anything resembling functionality. Cocaine dependence is associated with either of two patterns of self-administration: episodic or daily (or almost daily) use. Cocaine use separated by 2 or more days of nonuse is considered episodic. Binges are a form of episodic use characterized by continuous high-dose use over a period of hours or days. Binges usually terminate only when cocaine supplies are depleted or the user becomes so exhausted that they "pass out." With chronic daily use, there are generally no wide fluctuations in dose on successive days; rather, it is an increase in dose over

time that indicates the development of dependence. With continuing use, there is often diminution of pleasure as a consequence of tolerance, increase in dysphoric effects, and accumulation of adverse consequences. Despite these realities, with cocaine dependence use persists or may even accelerate.

Inpatient versus Outpatient Care

For several reasons, outpatient treatment is the preferred modality of care if circumstances permit. First, as noted above, use of cocaine can usually be stopped abruptly without medical risk or major discomfort, so many cocaine abusers can be treated as outpatients. Second, the goal of treatment is always to return the patient to a normal life. Third, the cost of outpatient treatment is in general lower (although some insurance companies may refuse to pay for care delivered in the outpatient setting). Fourth, many patients—particularly women with parenting responsibilities—are more willing to accept help on an outpatient basis because it carries less of a social stigma and is less disruptive to daily life. Given the lifelong risk of relapse and the need for ongoing support, all cases of substance abuse will eventually need outpatient care, and this is perhaps the most important consideration of all. On the other hand, recommending treatment in a hospital or residential rehabilitation center clearly conveys the impression of imminent danger. When drug use is severe, or if outpatient care is not possible or has failed in the past, treatment in a hospital or residential rehabilitation center is called for. Commonly recognized indications for inpatient care include chronic cocaine use with history of multiple relapses, comorbid dependence on another drug, serious comorbid psychiatric or medical illness, or major lack of social support. An important advantage of a treatment facility is removing patients from the environment—the home, the street—that may be contributing to their drug use. Patients under round-the-clock supervision are unable (in most cases) to obtain illicit drugs. They can take daily advantage of the many types of therapy the inpatient or residential facility offers. Another advantage is that patients are available for full medical and psychiatric evaluations, which will reveal whether any coexisting problems exist. Suspected cognitive impairments and psychiatric problems in particular can only be confirmed after detoxification and substantive observation. Successful initial treatment in a residential setting may improve retention by facilitating the integration of the patient into self-help and social support networks. Indeed, inpatient or residential treatment may provide an ideal transition from active addiction to abstinence and daily meetings.

Types of Nonpharmacological Treatments

Different treatment modalities for cocaine addiction have their advocates and detractors, but some of the more durable and commonly used include the 12-step programs, cognitive-behavioral therapy (CBT), contingency management, and the matrix model. More information on the most common of these approaches can be found in other chapters of this handbook.

Pharmacologic Treatment

Reducing Brain Exposure to Ingested Cocaine

Two of the more exciting developments of recent years have the common goal of reducing brain exposure to cocaine when cocaine is ingested. Modified enzymes capable of degrading cocaine to nonactive or less toxic metabolites include genetically engineered high-activity variants of human butyrylcholinesterase, and high-activity cholinesterases derived from bacterial species. Some of these enzymes can metabolize cocaine at rates that are orders of magnitude higher than normal, and may be useful in acute treatment of massive overdoses. The so-called

immunotherapies have been designed to prevent or reduce passage of cocaine across the blood–brain barrier. The immunotherapies furthest along in development involve attachment of cocaine to larger molecules capable of stimulating an immune response, such as the inactivated cholera B toxin. In animal models, immunotherapies have reduced the behavioral reinforcement effects of cocaine, and in clinical trials some subjects have reported diminished cocaine-induced euphoria. There have been promising indicators of reduced desire to pursue further use in immunized individuals. Immunotherapies have no known direct psychoactive effects and therefore no abuse liability. However, there are several important shortcomings worth noting. First, mounting an effective immune response may take several weeks or even months. Second, given the variability in immune response and often low antibody titers, a dedicated addict may readily overcome the immune response by simply using more cocaine. Third, there have been concerns raised about the ethics of using a long-term immune response in socially vulnerable patient populations. Nevertheless, judicious use of cocaine immunotherapy in highly motivated addicts holds promise.

Agonist Therapies

The so-called agonist or replacement therapies have dominated the development of drugs for cocaine addiction over the past several decades. As a general approach, agonist therapies replace some aspect(s) of the dopaminergic reinforcement mechanisms described in preceding sections, but using drugs that for pharmacokinetic or pharmacodynamic reasons may not have the same abuse potential as cocaine. In this respect, they can be thought of as analogous to methadone or buprenorphine therapies for opiate addiction. A recurring concern with nearly all agonist therapies is that they may perpetuate psychostimulant reinforcement and hence prevent natural extinction of the core mechanisms of the addiction process. Some agonist therapies such as modafinil have produced modestly encouraging results in clinical trials, but abuse potential is a substantial concern as more is learned about effects on brain chemistry.

There are often no clear lines of demarcation that separate agonist therapies and the multifaceted agents under development for relapse prevention, but drugs that alter reuptake of dopamine or interact directly with dopamine receptors have been involved in most of the clinical trials for cocaine addiction to date. Drugs that exert selective agonist effects on D1 dopamine receptors—as opposed to D2 receptors—have been quite effective in reducing ongoing cocaine use and reinstatement of cocaine self-administration in animal models, highlighting the observation that D1 and D2 receptor systems may exert opposing effects, at least under certain conditions.

Relapse Prevention

There are a wide range of chemicals that interfere with one or more aspects of experimental cocaine self-administration and show substantial promise as relapse prevention agents. Animal models have focused on three aspects of the relapse process that realistically simulate clinical situations: relapse triggered by stressful conditions that activate the HPA axis, relapse triggered by drug-associated environmental cues, and relapse triggered by reintroduction of a "priming" dose of cocaine. Major themes include GABA receptor agonists or GABA reuptake inhibitors, certain glutamate receptor modulators, HPA axis antagonists, endocannabinoid system antagonists, and κ-opioid system agonists.

Disulfiram is a drug that has been available for decades as an adjunct in the treatment of alcoholism. It has shown some promise in relapse prevention in cocaine addiction independent of effects on alcohol consumption, but data are mixed. The purported mechanisms of action and clinical features are of considerable interest. In addition to its well-known blocking effect on aldehyde dehydrogenase, disulfiram may also inhibit dopamine B-hydroxylase, and one of its metabolites may influence NMDA-subtype glutamate receptors. Theoretically, disulfiram may have the properties of a functional DA agonist and a neuroprotectant. Several randomized, placebo-controlled clinical trials have demonstrated at least moderate effects on cocaine

use. However, in the event of a relapse to cocaine and/or alcohol, disulfiram may increase cocaine plasma level and compound the cardiovascular effects associated with increased blood acetaldehyde.

The story of *N*-acetyl cysteine provides an opportunity to discuss a novel therapeutic approach as it relates to the important role of corticofugal glutamate projections to brainstem and basal forebrain in chronic cocaine addiction. Used for decades as a mucolytic agent and antidote to acetaminophen poisoning, *N*-acetyl cysteine also appears to reverse impaired cysteine–glutamate exchange within neurons and glia. Since intact cysteine–glutamate exchange is needed to maintain normal extracellular glutamate levels (which may be low in the cocaine-addicted brain), a therapeutic effect is suggested. A key principle is that low basal glutamate levels can result in amplified responses to glutamate "signals" from corticofugal projections that are triggered by cocaine; the net result may be long-term potentiation of cocaine-associated reinforcement and relapses. Restoring low basal glutamate may offset this series of events and possibly also improve baseline cortical functioning. Pilot studies with *N*-acetyl cysteine have been promising.

Numerous glutamate system modulators, and in particular group 1 metabotropic glutamate receptor antagonists, are being tested in relapse prevention paradigms. Glutamate receptor modulators will likely play a preeminent role in addiction-related pharmaceutical discovery over the coming decade. Use of a glutamate antagonist to prevent or diminish reinforcement of cocaine-seeking behavior may seem to contradict the statements above pertaining to restoration of basal glutamate levels with *N*-acetyl cysteine. However, the chief therapeutic target is pathologic glutamate signaling, not glutamate levels per se. A major challenge will be to develop compounds with sufficient specificity so that interference with normal glutamate-dependent brain functions may be avoided.

Cochrane group meta-analyses have not found interventions involving either antiepileptic drugs or antidepressants promising enough to support their routine use in treating cocaine addiction. Clinical trials involving topiramate, an anticonvulsant that is also used in treating migraine headaches and bipolar disorder, have provided only weak evidence of a beneficial effect in cocaine addiction. Nevertheless, anticonvulsants are often used off-label with a rationale similar to that which justifies testing of novel GABA agonists and glutamate antagonists. The hope is that these drugs will dampen DA neurotransmission and thereby block cocaine reinforcement. D2 receptor antagonists, including commercially available antipsychotic agents, would seem to be a logical therapeutic approach, but clinical trials have been disappointing, and in some cases (e.g., olanzapine), clinical decompensation of cocaine addicts has been reported.

GABA-producing cells of the NAcc often coexpress or act in parallel with cells that manufacture the important κ-opioid receptor ligand dynorphin. Cortical components of the limbic system express dynorphin abundantly. Chronic cocaine use upregulates the κ-opioid receptor system, and in some experimental paradigms this appears to counteract the chemistry of reinforcement. There is some evidence from human genetic material that people possessing a "multiple-copy" version of the dynorphin gene may be less prone to develop cocaine dependence after exposure to cocaine. Dynorphin and other κ-opioid system agonists are under intensive investigation as therapeutic agents. Cannabinoid receptors are also heavily expressed throughout the limbic system, and their activation can powerfully facilitate DA release in the NAcc. The cannabinoid receptor (CB1) antagonist rimonabant can block the ability of conditioned cues to trigger reinstatement of cocaine use in experimental animals with "extinguished" drug-seeking behavior. Unfortunately, rimonabant development has halted, but the study of CB1 receptor interactions more generally is an important area of pharmaceutical development.

Drugs that may diminish the impact of stress on relapse (e.g., corticotrophin-releasing factor antagonists and orexin receptor antagonists) are another example of a therapeutic approach with great promise, but because of their broad actions on the HPA axis, currently available compounds are not likely to be tolerated long term. Short-term interventions along these lines during periods of peak vulnerability may nonetheless be appropriate, given the importance of social–environmental stress in predicting early relapse.

Comorbidities and Complications of Cocaine Abuse

Associated Psychiatric Disorders

Depending upon diagnostic criteria and methods of data acquisition, the lifetime prevalence of psychiatric comorbidity with cocaine abuse may exceed 75%. On the other hand, psychiatric symptoms and signs at the time of presentation for treatment will be exaggerated by the various manifestations of cocaine toxicity and withdrawal. The clinician must therefore be wary of overdiagnosing primary psychiatric pathology while at the same time not missing opportunities to intervene in ways that may improve long-term outcome. It is important to weigh the risk of treating newly suspected psychiatric comorbidity with psychoactive prescription drugs, potentially confounding diagnosis and patient compliance with treatment for cocaine addiction, against the risk of relapse when comorbid psychopathology goes untreated. Management philosophies and medical resources vary widely. There are no straightforward guidelines in this regard, and clinical judgment is used on a case-by-case basis. The heterogeneity inherent in this area of addiction medicine may account for poor outcomes in certain patient populations, and in others reports of positive responses to treatment that are tantalizing but difficult to replicate.

Certain conditions, particularly anxiety disorders and major depression with prominent anxiety symptoms, may drive the reinforcing effects of cocaine and increase the risk of relapse. In animal models of relapse, there are numerous well-established correlates between resumption or acceleration of use and exaggerated primary HPA responses. These may reflect increased adrenergic inputs from brain-stem centers or impaired inhibitory control of responses to stress by higher brain centers.

Some surveys of people undergoing treatment for cocaine abuse reveal that half or more meet current diagnostic criteria for mood disorders. Lifetime major depression is diagnosed in approximately 50% of patients, whereas dysthymia is diagnosed in another 25% to 50%. However, as much as 20% of cocaine abusers experience cyclothymic or bipolar disorder (manic depressive illness).

Another commonly seen condition among adult cocaine addicts is residual ADHD (attention-deficit hyperactivity disorder), occurring in up to 30% in some series. In both adolescents and adults with histories consistent with ADHD, it is often reported that cocaine ingestion may result in paradoxical relaxation comparable to the calming and focusing effects of therapeutic doses of methylphenidate and dextroamphetamine. However, these generalizations are harder to confirm in structured longitudinal studies, and destabilization of the patient with ADHD on cocaine is not uncommon. Methylphenidate has been used as a "substitution" therapy in cocaine addiction, similar to how "methadone maintenance" is used in heroin addiction. The predominant finding has been that the majority of the modest benefits attributable to methylphenidate occur in those individuals who displayed moderate-to-severe ADHD symptoms.

Chronic cocaine abusers frequently cultivate "superstitions," and may even experience feelings of suspiciousness and esoteric thinking as a source of pleasure or entertainment that can play into their systems of denial. In more extreme cases, persecutory delusions may provoke violent or aggressive behavior. Acute, subacute, and chronic paranoia are commonly seen products of cocaine abuse. In its ability to induce a state resembling functional paranoid psychosis, cocaine is similar to other central stimulants, most notably methamphetamine. Like a person with schizophrenia, a person in the throes of cocaine delirium may lose contact with reality and become confused and disoriented. When the pharmacologic effects of cocaine have worn off, the delirium usually disappears. Typically, cocaine delirium with or without frank psychotic features resolves within 3 to 5 days of cessation of use; if it persists for a longer period, or if the patient becomes increasingly difficult to manage, a reevaluation of the diagnosis is indicated and an antipsychotic medication may be considered.

Perhaps more than those with any other personality disorder, people diagnosed as having antisocial personality disorder (ASPD) are prone to use mood-altering drugs. People with this disorder are distressed, tense, unable to tolerate boredom, and agitated to the point of discomfort. Their use of drugs often removes any remaining inhibitions, increasing the risk of anger, violence, and actions that violate the rights or property of others. Because cocaine is by definition an illicit substance, use of the drug in itself constitutes a form of antisocial behavior.

The combined use of cocaine and alcohol is common, with reports of up to 90% of cocaine abusers also being concurrent ethanol abusers, and as many as 60% having lifetime diagnoses of alcoholism. Cocaethylene, the ethyl ester of benzoylecgonine, is produced abundantly when cocaine and alcohol are used together. Like cocaine, it binds to the DA transporter and increases extracellular concentrations of DA in the NAcc, but seems to have little effect on the serotonin (5-HT) transporter. While similar to cocaine in producing stimulant effects, cocaethylene is reported to have longer half-life and increased lethality, particularly increased cardiovascular morbidity. Concurrent marijuana use is also common, and may enhance the cocaine high, not only by offsetting the anxiety and agitation of cocaine intoxication but also by altering the drug's pharmacokinetics and metabolism.

Medical Complications

Cocaine use results in a frequent form of serious morbidity and mortality. However, serious medical complications, including sudden cardiac death, fatal intracranial hemorrhages, malignant hyperthermia with rhabdomyolysis, and renal failure, among others, have all been documented in association with first-time use, even of moderate doses. There are obviously wide interindividual variations in both initial response and tolerance to the effects of cocaine, and the occurrence of serious medical complications does not correlate well with plasma levels of the drug at the time of presentation for emergency care.

Cardiovascular System and Pulmonary Syndromes

By affecting the release and reuptake of epinephrine and norepinephrine, cocaine causes a shift in the blood supply from the skin and the viscera into the skeletal musculature. Oxygen levels rise, as do concentrations of sugar in the blood. Tachycardia, increased cardiac contractility (β-1 adrenergic effects), and hypertension (α-adrenergic effects) may be pronounced, and increases in myocardial oxygen demand may outstrip supply, particularly in the presence of cocaine-induced spasm of epicardial or penetrating vessels. Persistent cocaine use has also been linked to acceleration of atherosclerotic coronary artery and renal arterial disease. Apart from the consequences of cocaine-related violence, chest pain is the most common issue prompting presentation for emergency care.

Atrioventricular nodal conduction block and QT interval widening are common; premature ventricular depolarization, ventricular tachycardia degenerating to defibrillation, and asystole are not uncommon causes of death. Direct stimulation of vagal centers in the brain stem by cocaine or indirect stimulation of baroreceptor responses may also result in severe bradyarrhythmias.

Cocaine abusers often present with atypical, sometimes bizarre presentations of chest pain, and there may be unusual electrocardiographic findings, including those suggestive of "centrally mediated" ST segment elevations in more severe cases of cocaine toxicity. In addition to acute vasospasm or blood supply–demand mismatch in the setting of preexisting coronary artery disease, other causes of chest pain include in situ coronary embolism and coronary arterial dissections. Chronically developing myocardial fibrosis, inflammatory lesions, and other direct toxic effects on myocytes also occur, and these likely contribute to the development of congestive heart failure. Cocaine toxicity should always be considered until proven otherwise when a young adult presents with chest pain or signs of congestive heart failure, with

or without the presence of other risk factors. Cocaine use is also associated with acute renal failure, often in association with hyperthermia and rhabdomyolysis, and with insidious forms of chronic renal failure.

The actual incidence of myocardial infarction associated with cocaine has been controversial, but the Cocaine-Associated Chest Pain trial, the largest prospective study of its kind ever performed, indicates that the incidence may be less than 10%, according to reports from the American Heart Association. The take-home message is that atypical chest pain syndromes, including a number of noncoronary ischemic presentations, need to be considered in the differential diagnosis. Mechanisms to consider, all well documented in case reports or case series, include aortic dissection in the setting of cocaine-induced hypertension, aortic thrombosis, cardiac contusions, pneumothorax, pneumopericardium, and other forms of pulmonary barotrauma. The occurrence of frank barotrauma is infrequent but by no means uncommon, and presumably relates to vigorous insufflations, sinus of Valsalva, and abnormal ventilatory patterns in smokers, with or without ischemic necrotic changes and perforations of the bronchial passages.

Shortness of breath is thought to be the second most common cocaine-related medical symptom in emergency-care settings. It is well established that cocaine inhalation can cause or exacerbate asthma. The *crack lung* syndrome entered the medical literature in the late 1980s; people typically present with the symptoms of pneumonia: shortness of breath, atypical chest pain, high temperatures, and a negative or nonspecifically abnormal chest X-ray pattern. An eosinophilic pneumonitis may be diagnosed via bronchoscopy and biopsy, and adulterants in smoked cocaine (e.g., talc and baking soda) may be responsible for at least some of the pathology. In addition, chronic cocaine inhalation may interfere with breathing by causing telltale destruction of the nasal septum, nasal cartilage, and hard or soft palate.

Neuropathology

The spectrum of neuropathologic changes encountered in the brains of cocaine abusers is broad, but some of the most common catastrophic events include global cerebral hypoxic–ischemic insults secondary to cardiopulmonary failure, hypertensive encephalopathy, intractable seizures, thromboembolic stroke, lobar hemorrhages, and subarachnoid hemorrhages, the latter particularly in those with preexisting intracranial aneurysms or arteriovenous malformations. Accelerated atherosclerosis may occur in the cerebrovasculature just as it does in coronary, renal, and gastrointestinal vascular beds, and in some cases frank vasospasm may produce ischemic brain lesions.

Cocaine is an epileptogenic agent that can provoke generalized seizures, even after a single dose. These convulsions are typically brief and self-limited, but rare instances of status epilepticus, including difficult-to-recognize nonconvulsive status epilepticus masquerading as a toxic-metabolic encephalopathy, have been reported. Recurrent convulsions are well recognized as a poor prognostic indicator and may trigger a downward cascade, including hyperpyrexia, metabolic acidosis, and rhabdomyolysis. When a witnessed or suspected seizure occurs and there is a possibility of cocaine toxicity, then appropriate diagnostic tests, vigorous hydration, and close monitoring are called for. When interictal periods are accompanied by extreme psychomotor agitation, neuroleptics should be avoided because they all, to some extent, lower seizure threshold. IV phenytoin should also be used with caution owing to its potential to induce cardiac dysrhythmias, and in most circumstances benzodiazepenes would be the anticonvulsants of choice.

In addition to potentially reversible functional deficits in frontal brain regions, it is common to find multiple, small, often silent, "Swiss cheese" infarcts and neural change associated with cocaine and crack use.

Chronic cocaine abuse can result in dopamine disinhibition phenomena, including increased release of prolactin; in fact, hyperprolactinemia is the endocrine abnormality most often reported in clinical studies of cocaine abusers. Extrapyramidal dysfunction, including akathisia, dystonias, choreiform movements, bruxism, and a peculiar combination of stereotyped

movements and disordered gait (sometimes referred to as "crack dancing") may occur. These symptoms and signs are functionally analogous to the syndromes seen after exposure to dopamine antagonists (e.g., neuroleptics).

Cocaine potently stimulates the HPA axis. As noted previously, activation of corticotrophin-releasing factor (CRF) and increased glucocorticoid response to stressors have both been linked to acceleration of cocaine reinforcement in some animal models. By inactivating the feeding center located in the lateral hypothalamus, cocaine also supersedes the primary drive to eat, thus leading to severe loss of appetite and loss of body weight, the latter sometimes a justification for sporadic use (e.g., in people with eating disorders). Muscle wasting, often associated with low-grade elevation of CPK (creatine phosphokinase), and often without clear etiology but possibly linked with central dopamine dysregulation, is common. The cocaine user's decreased need for sleep may result from the drug's effects on regulation of brain-stem neurotransmitters, particularly 5-HT, which plays a major role as modulator of the sleep cycle.

Impact on Sexual Function and Sexuality

Many users, particularly men, claim that cocaine is an aphrodisiac. Indeed, as mentioned earlier, the feeling of sexual excitement that sometimes accompanies cocaine use may be the result of its impact on the DA system and may produce spontaneous orgasm. Nonetheless, chronic cocaine abuse causes derangements in reproductive function, and loss of interest in sex and poor sexual performance noted by chronic addicts may be related in part to increased prolactin release in the setting of a chronic hypodopaminergic state. These symptoms may persist for long periods after use of cocaine has been stopped. In women, cocaine abuse has adverse effects on reproductive function, including derangements in the menstrual-cycle function, galactorrhea, amenorrhea, and infertility. Some women who use cocaine report having greater difficulty achieving orgasm.

Infections with hepatitis B, hepatitis C, and HIV are associated with cocaine dependence as a result of promiscuous sexual behavior. HIV seropositivity seems clearly associated with crack smoking, independent of concurrent IV use. The clear association between the smoking of crack and high-risk sexual practices has been reported and linked to acceleration in the spread of the HIV virus. Other sexually transmitted diseases, hepatitis, and tuberculosis are also seen in cocaine abusers.

Cocaine, Pregnancy, and Fetal Development

One of the most troubling aspects of the cocaine epidemic is its use by pregnant women. "Crack babies" are not just a tragedy of American inner cities; reports from Australia, Europe, and South America suggest problems with cocaine abuse during pregnancies and at the time of deliveries. It is important to remember that many historical accounts likely underestimate fetal exposure. Cocaine's effects on the unborn and newborn may also be related to poor nutrition, poor hygiene, and neglect. Cocaine compromises the mother or any caregiver's ability to respond to the new baby through talking, eye contact, and tactile stimulation.

The available data pertaining to cocaine's teratogenicity and obstetric complications are very complex and sometimes conflicting. The least controversial findings involve impaired somatic growth. Gestational age at birth, birth weight, head circumference, and height are often decreased. Placental abruption, or premature separation of a normally implanted placenta, is thought to occur in approximately 1% of pregnancies in women who use cocaine, making the drug a significant cause of maternal morbidity as well as of fetal mortality. Women who use cocaine during pregnancy have a high rate of spontaneous abortion, higher than that of heroin users. Pregnancy also appears to increase a woman's susceptibility to the toxic cardiovascular effects of cocaine.

Conclusion

Treatment for cocaine addiction certainly seems to be on an upward trajectory, but preventing initiation of cocaine use should remain in the forefront, and prevention ideally begins before conception. The tragedies associated with cocaine use during pregnancy and in youth are hard to fully appreciate. While it has become fashionable to scoff at the "Just Say No" campaign of the 1980s, the prevention efforts of the U.S. federal and state governments and the Partnership for a Drug-Free America brought many of the best scientific, advertising, and marketing minds to the awesome task of "unselling" drugs. These educational programs and advertisements have helped to reduce drug use in general, but they have had an especially significant effect upon adolescents and children.

Most organizations with responsibility for drug-control policy currently advocate flexible understanding and flexible approaches to cocaine addiction/abuse. A flexible approach takes into consideration the fact that there are different phases of cocaine epidemics and that they may vary considerably on a regional basis. For example, in the rapid "infective" stages of an epidemic, initiation of use may increase exponentially as established users bring friends and associates not otherwise predisposed to use above a certain socially reinforced threshold. Interdiction operations led by law enforcement may be uniquely effective in reducing spread under these circumstances. In contrast, established users may obtain supply and perpetuate their illnesses more or less regardless of the legal and other social consequences of continuing use. Yet, these same individuals are the most in need of medical treatment and the most likely to benefit from it.

Ideally, in the earliest stages of chemical dependency, patients should have access to well-trained specialists in addiction medicine and/or addiction psychiatry. Addiction specialists are more likely to be aware of the pitfalls of early recovery, less likely to harbor judgmental attitudes, and able to appreciate that recovery is a long, hard road. Most experienced clinicians have seen examples of impressive long-term success in addition to the many failures, and the medical community now seems ready to move beyond anecdotal experience to greater participation in rationally designed, fully integrated treatment programs.

Suggested Readings

Carroll KM, Onken LS. Behavioral therapy for drug abuse. *Am J Psychiatry*. 2005;162:1452–1460.

Dutra L, Stathopoulou G, Basden SL, et al. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry*. 2008;168:179–187.

Kalivas PW. Glutamate systems in cocaine addiction. *Curr Opin Pharmacol*. 2004;4:23–29.

Kinsey BM, Jackson DC, Orson FM. Anti-drug vaccines to treat substance abuse. *Immunol Cell Biol*. 2009;87:309–314.

Nader MA, Czoty PW. PET Imaging of Dopamine D2 Receptors in monkey models of cocaine abuse: genetic predisposition versus environmental modulation. *Am J Psychiatry*. 2005;162:1473–1482.

Paczynski RP, Gold MS. Cocaine and Crack. In: Ruiz P, Strain EC, eds. *Lowinson and Ruiz's Substance Abuse: A Comprehensive Textbook*. 5th edn. Philadelphia, PA: Wolters Kluwer/Lippincott Williams and Wilkens; 2011:191–213.

Porrino LJ, Lyons D, Miller MD, et al. Metabolic mapping of the effects of cocaine during the initial phases of self-administration in the nonhuman primate. *J Neurosci*. 2002;22(17):7687–7694.

Samaha A-N, Mallet N, Ferguson SM, et al. The rate of cocaine administration alters gene regulation and behavioral plasticity: implications for addiction. *J Neurosci*. 2004;24(28):6362–6370.

Simpson DD, Joe GW, Broome KM. A national 5-year follow-up of treatment outcomes for cocaine dependence. *Arch Gen Psychiatry*. 2002;59(6):538–544.

Volkow ND, Wang G-J, Ma Y, et al. Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. *J Neurosci*. 2005;25(15):3932–3939.

7 Cannabis

Cannabis is the generic and most appropriate scientific term for the psychoactive substance(s) derived from the plant *Cannabis sativa* and used by humans to alter their consciousness or physical state. It contains over 500 distinct chemical compounds, but the one of primary interest related to substance abuse is δ-9-tetrahydrocannabinol (THC). Marijuana and hashish are the most common names for cannabis used by the general population.

Epidemiology

The National Survey on Drug Use and Health (NSDUH) indicates that cannabis is the most commonly used illicit substance in the United States, with an estimated 41% of U.S. persons aged 12 and older having used it at least once in their lifetime, 10% having used it at least once in the past year, 6% having used it at least once in the past month, and approximately 2% reported having used cannabis almost every day. These rates are similar to those seen in other developed countries, with approximately 34% of Australians and 20% of Europeans reporting lifetime use of cannabis. Among developing countries, use rates also appear to be increasing. Globally, an estimated 166 million people (4%) had used cannabis as of 2006.

Males are more likely than females to use cannabis, with 45% versus 36% reporting lifetime use and 8% versus 4% reporting past-month use. Use is most common among those 18 to 25 years old, with 28% reporting past-year use. Data from the U.S. Monitoring the Future Study indicate that 29% of 10th graders and 37% of 12th graders report having used cannabis in the past year. In the United States, an estimated 7,000 to 8,000 individuals start using cannabis each day, with the highest rates of initiation among those 12 to 25 years old.

Among ethnic groups, those who identify themselves as being multiracial (two or more races) have the highest rates of use in the past year and past month, followed by African Americans, Whites, and Hispanics. Rates of past-year and -month use among 18- to 25-year-old African Americans are lower than those of Whites, but among those aged 26 years and older, rates are higher among African Americans, accounting for the overall disparity in use.

A review of several surveys from multiple countries estimated rates of lifetime cannabis dependence at 1% to 4%. The rate of abuse or dependence in the past year among those aged 12 years and over in the United States has remained close to 2% in past years, with the rate of cannabis dependence alone being 1%. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study observed prevalence rates of lifetime and 12-month cannabis use disorder (CUD) of 8.5% and 1.5%, respectively. Although this rate of cannabis dependence may seem a minimal percentage of the population, it is more than double the dependence rate for any

other illicit drug. The high prevalence of cannabis dependence reflects the much more widespread use of cannabis relative to other illicit drugs of abuse rather than greater addictive potential.

Over the past 10 to 15 years, the prevalence of CUD has increased among adults across the United States despite stabilization of rates of use, while the rates of both cannabis use and CUD have increased among adolescents. Such increased prevalence of CUD may be a result of an increase in the potency of cannabis available (which has increased by over 60% during the past decade); this may increase its addictive potential. In addition, cannabis use is being initiated at a younger age, which is related to the risk of developing CUD.

Paralleling the rise in CUD, treatment admissions for a primary CUD have increased both in absolute numbers and as a percentage of total admissions. Cannabis ranks a close third, behind only alcohol (40%) and opiates (18%), among primary substances reported by individuals seeking treatment. Approximately 50% of all adolescents in substance abuse treatment report cannabis as their primary substance.

Administration and Phenomenology

The most commonly used form of cannabis is the dried plant material, which can be subdivided into preparations that include whole-plant material and those that only contain the unfertilized flowers of the female plant (often referred to as sinsemilla). Whole-plant cannabis typically ranges in potency from 1% to 5% THC (v/v), and sinsemilla typically ranges from 7% to 15% THC (v/v). Hashish refers to the resin of the cannabis plant, which typically contains 10% to 20% THC (v/v). Hash oil is derived from concentrated resin extract and usually contains approximately 20% THC (v/v), but may reach as high as 60% THC (v/v). During the past few decades, a steady increase in the potency of seized cannabis has been observed with mean percentage of THC concentration (v/v) increasing from 3.4% in 1990 to 8.5% in 2008, but there has been little change in the range of potency encountered.

In most instances of cannabis use, the plant material is burned and the smoke emitted from the cannabis is inhaled. Methods of smoking cannabis include the use of pipes, water pipes (bongs or hookahs), cigarette paper (joints), and the paper from hollowed-out cigars (blunts). Cannabis is also sometimes ingested orally, most often by dissolving cannabis or concentrated by-products of the cannabis plant into food (typically baked goods). More recently, devices have been developed in which cannabis is "vaporized." Following these routes of administration, THC bioavailability is approximately 18%, and cannabis intoxication typically occurs within 1 minute, reaches the peak in 15 to 30 minutes, and persists for approximately 4 hours. Following oral ingestion, THC bioavailability is approximately 6%, and intoxication occurs approximately 30 minutes after administration, peaks in 2 to 3 hours, and persists for 6 hours or longer.

There are several reliable effects of acute cannabis use. Subjectively, the user feels a euphoric effect or "high" that is typically characterized by a sense of relaxation or drowsiness and an increased propensity for laughter. Sense of perception is also affected such that time seems to slow down and many report an increased appreciation for music and other mediums of art. Potentially related to the latter effect, cannabis users tend to prefer engaging in nonverbal social activities (watching a movie or listening to music) while under the influence of cannabis. Feelings of anxiety, paranoia, fear, or panic may also be experienced. These effects most often occur in less experienced users or following use of higher-than-usual doses. In rare cases, usually involving particularly high doses, users may experience hallucinations. These effects are not life threatening, dissipate with time, and may be reduced with comfort and reassurance.

Acute administration of cannabis produces several reliable physiologic effects. The mouth becomes dry, and appetite is stimulated, which typically results in an increase in the consumption of food and drink, particularly high-calorie products. At low-to-moderate doses, cannabis

typically has antiemetic effects (reduces nausea), but can induce nausea or vomiting at higher doses or among less experienced users. Cannabis administration is associated with a significant (20% to 100%) increase in resting heart rate, a slight increase in supine blood pressure, and increased orthostatic hypotension. The increased cardiac output also causes a dilation of small blood vessels, which typically results in a redness of the eyes. Despite the magnitude of the acute effects of cannabis use on cardiovascular function, tolerance develops rapidly and chronic use is not clearly associated with significant cardiovascular health risks.

Controlled laboratory studies in which cannabis or oral THC has been administered indicate that cannabis can impair focused and divided attention, short-term and episodic memory, some types of complex cognitive processing, and some aspects of motor ability. Studies of chronic cannabis users suggest that sustained use of cannabis may impair attention, memory, and complex cognitive abilities. These effects are addressed in more detail below.

Abrupt cessation of daily or near-daily cannabis use often results in the onset of a cannabis withdrawal syndrome. Common symptoms of withdrawal include anger and aggression, anxiety, depressed mood, irritability, restlessness, sleep difficulty and strange dreams, decreased appetite, and weight loss. Chills, headaches, physical tension, sweating, stomach pain, and general physical discomfort have also been observed, but are less common. Most symptoms begin within the first 24 hours of cessation, peak within the first week, and last approximately 1 to 2 weeks. Clinical reports and survey studies suggest that cannabis withdrawal contributes to relapse among cannabis users trying to quit.

Determinants of Use

Pharmacology and Neurobiology

The defining pharmacologic constituents of the cannabis plant are a family of compounds referred to as cannabinoids. Ninety different cannabinoids have been identified in the cannabis plant, of which THC has been identified as the primary compound responsible for the psychoactive effects of cannabis. THC is metabolized into 11-hydroxytetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy-tetrahydrocannabinol (THC-COOH), which are then excreted through feces and urine. Although the subjective effects of cannabis typically last a few hours, because THC is highly lipophilic, it is rapidly absorbed and stored in fatty tissues, and the elimination half-life can extend for as long as 4 days. There is no indication that the presence or release of cannabinoids in fat stores results in perceptible intoxication in the user.

Cannabis exerts its effects on human function primarily through an endogenous cannabinoid receptor system. Two receptor subtypes (CB1 and CB2) and five endogenous ligands have been identified. The psychoactive and reinforcing effects of cannabis are primarily mediated by activation of the CB1 receptor by THC. The CB1 receptor is a presynaptic G-protein-coupled receptor, activation of which inhibits adenylyl cyclase and voltage-dependent Ca2+ channels, and activates K+ channels and mitogen-activated protein (MAP) kinase. The CB1 receptor is abundant throughout the CNS, but is expressed in the brain at the highest concentrations in the basal ganglia, cerebellum, hippocampus, and cortex.

Genetics

Genetic influences contribute to the development of CUDs. Heritable factors contribute between 30% and 80% of the total variance in risk of CUD, and genetic linkage studies of CUD and earlier stages of cannabis use (including frequency of use) further establish a genetic link to cannabis use problems.

Environment

A number of environmental factors can contribute to cannabis use and abuse. Foremost of these is cannabis availability. Cannabis is the most widely available illicit drug in the world, with a conservatively estimated 88,000 to 110,000 metric tons of cannabis cultivated each year. Several other important environmental and demographic factors predict cannabis use and CUD. The strongest and most consistent population-based predictors of cannabis use are use of other licit or illicit drugs, use of cannabis by others within one's peer network, and use of cannabis by immediate family members. Delinquent/rebellious behavior, unstable or abusive home life, low socioeconomic status, other types of psychopathology, and less perceived risk of harm associated with cannabis are also associated with increased risk of cannabis use and CUD.

Evaluation

Screening and Assessment Tools

The Cannabis Use Disorder Identification Test provides a short method for making a DSM diagnosis. Adult and adolescent versions of the Cannabis Problems Questionnaire provide a general measure of severity of cannabis-related problems. The Marijuana Screening Inventory provides assessment of cannabis patterns and identification of clinical cases requiring more in-depth assessment and intervention. The Substance Dependence Severity Scale has been validated for assessing dependence in cannabis users.

Additional measures have been developed for use in treatment evaluation research settings such as the Marijuana Problem Inventory, which provides a summary score of specific cannabis-related consequences reported by the individual. A measure of cannabis withdrawal severity, the Marijuana Withdrawal Checklist, has been developed and can provide a useful list of signs and symptoms of withdrawal as well as an overall severity score.

Biologic testing for evidence of recent cannabis use is a very useful screening and treatment outcome tool. There are multiple methods for reliable and valid urine testing for cannabis (e.g., rapid dipstick-type methods, GC–MS and EMIT). A urine toxicology test may yield a cannabis-positive result for approximately 2 to 30 days, following the last use of cannabis, depending on the cutoff level used to detect the cannabinoid metabolite, the frequency, amount and duration of cannabis use prior to testing, the activity level of the individual prior to the test, and individual differences in metabolism and rate of elimination of cannabinoids.

Psychosocial Treatment Approaches

For adults, motivational enhancement therapy (MET), cognitive-behavioral therapy (CBT), contingency management (CM), and family-based treatments have been carefully evaluated and have consistently demonstrated superior treatment outcomes (reduction of cannabis use) relative to control conditions. The cumulative findings with adults indicate that (1) each of these interventions represents a reasonable and efficacious treatment approach; (2) combining MET and CBT is probably more potent than providing MET alone; and (3) an intervention that integrates all three approaches, MET/CBT/CM, is most likely to produce positive outcomes, especially as measured by rates of cannabis abstinence. Information on each of these approaches can be found in other chapters of this handbook. Although these interventions are efficacious, many individuals do not improve substantially or achieve enduring abstinence, even with the most potent treatments.

In clinical trials of adolescents with CUD, empirical support for the efficacy of group or individual CBT and family-based treatments has emerged. Family-focused interventions take advantage of social networks that are unique to adolescents in an effort to provide a treatment intervention that extends beyond the client–therapist relationship. These generally include efforts to address and alter maladaptive family patterns that contribute to substance use, make use of resources in the school and criminal justice system, and address problems that might be associated with the child's peer network. These interventions have demonstrated promise in reducing cannabis and other substance use, but reductions in use have typically been modest, and effects on abstinence rates have been difficult to demonstrate.

Pharmacotherapy

Laboratory studies of bupropion, valproate, nefazodone, clonidine, and naltrexone have not shown robust effects that would suggest potential therapeutic efficacy, and in some cases had effects opposite to those desired. Positive laboratory findings have been observed with a few medications. The most promising of these comes from studies targeting cannabis withdrawal with the oral preparation of THC, dronabinol, a CB1 receptor agonist. In laboratory studies, dronabinol significantly reduced multiple symptoms of cannabis withdrawal compared with placebo. This effect was dose dependent, and higher doses demonstrated almost complete suppression of withdrawal effects. Dronabinol alone, however, has not been shown to reduce laboratory models of relapse or cannabis self-administration (but did show positive effects when combined with lofexidine in a laboratory model of relapse).

A limited number of laboratory studies have evaluated rimonabant, a CB1 receptor partial agonist/antagonist. In an initial study, it reduced the subjective effects of smoked cannabis by approximately 40%, but a subsequent study failed to replicate this finding. Last, preliminary findings targeting sleep difficulty, a common and significant symptom of cannabis withdrawal, reported that extended-release zolpidem, an approved hypnotic, attenuated abstinence-induced sleep disturbance as measured by polysomnography in a placebo-controlled study.

Controlled clinical trials of medications (e.g., valproate, nefazodone, bupropion, buspar) for CUD have been reported. None of these medications have shown a signal of robust efficacy, and no medications have been approved for the treatment of CUD. That said, several medications have been identified that hold some promise. Dronabinol (oral THC) appears to be the best candidate medication, and follows the agonist (substitution) therapy model that has been successful in the treatment of opioid (methadone) and nicotine (patch and gum) dependence. Controlled clinical trials are needed to determine the efficacy of dronabinol for treating CUDs. Work showing the attenuation of sleep dysfunction with zolpidem during the initial period of abstinence from cannabis is also positive, but additional research is needed to determine whether or not improved sleep translates to less overall withdrawal severity and reduced relapse.

Comorbidity

CUD and Other Drug Use Disorders

Large general population studies indicate that individuals with past-year or lifetime CUD diagnoses have high rates of alcohol use disorders, and nicotine dependence. These rates of comorbid substance use problems are greater than those observed among individuals without a CUD. Rates of substance abuse other than alcohol or nicotine are also likely to be greater among cannabis abusers, but have not been estimated independently.

Among those seeking treatment for a primary cannabis use problem, other types of substance use are also common. Studies suggest this concurrent drug use is also present among those younger than 18 years (and who have a primary CUD).

Cannabis is also the most common, illegal secondary substance used by those seeking treatment for other types of substance dependence. Among those in treatment for primary cocaine use disorders, 35% report cannabis as a secondary or tertiary substance-use problem; among primary alcohol use disorder patients, 28% report cannabis as a secondary or tertiary substance use problem; and among primary heroin abusers, 16% report cannabis as a secondary or tertiary problem.

CUD and Other Psychiatric Disorders

Studies have reported a clear association between chronic cannabis use and impaired psychological functioning. In particular, cannabis use has been associated with poorer life satisfaction, increased mental health treatment and hospitalization, higher rates of depression, anxiety disorders, suicide attempts, and conduct disorder.

Large general population studies also indicate that individuals with past-year or lifetime diagnoses of a CUD also have high rates of concurrent psychiatric disorders other than substance use disorders (SUDs). Major depressive disorder, any anxiety disorder, and bipolar I disorder appear to be the most prevalent DSM-IV Axis I disorders, and antisocial, obsessive compulsive, and paranoid are the most prevalent Axis II personality disorders among those with a past-year diagnosis of a CUD. The prevalence rates of these other psychiatric disorders are greater among those with CUD than those without.

Data are also available from clinical trials assessing concurrent psychiatric disorders among adolescents enrolled in treatment for a CUD. In the Cannabis Youth Treatment study, 33% of teens reported internalizing disorders (anxiety, depression, posttraumatic stress disorder [PTSD]) and 61% externalizing disorders (conduct disorder and attention-deficit hyperactivity disorder [ADHD]). Other clinical studies have reported similarly high rates of internalizing and externalizing disorders in the adolescent treatment population.

Cannabis is also the most common type of illicit drug used among individuals with schizophrenia and other chronic psychotic disorders, and its prevalence in this population may be even greater than those with other psychiatric diagnoses. Cannabis has been linked to cases of acute psychosis. Prevalence data on acute psychosis are limited and range from it being very rare to occurring in over 15% of cannabis users.

Causality and Other Psychiatric Disorders

Self-medication is a common explanatory hypothesis for the etiology of SUDs, including CUD, that is, persons may use the substance to self-medicate existing psychiatric disorders and symptoms. However, evidence from longitudinal studies, particularly for the relation between cannabis and mood disorders, has not supported a causal self-medication hypothesis. The types of mental-health problems associated with cannabis use in longitudinal studies, once common etiologic factors are adequately controlled for, are primarily externalizing problems such as conduct/antisocial disorder or other drug-dependence disorders. The notion that cannabis is used to "medicate" externalizing disorders is not highly tenable. Rather, the conceptualization of cannabis use and abuse as part of an externalizing syndrome that includes nondrug externalizing disorders has gathered increasing attention and support. Cannabis use, particularly early initiation of use, can be considered a risk factor for nonpsychotic mental health problems.

Whether or not cannabis use can induce acute psychosis or contribute to the development of more chronic psychotic disorders (e.g., schizophrenia) remains controversial, although data supporting such a causal relationship are emerging. Suggestive evidence for a causal relationship

between cannabis use and *acute* psychosis is primarily of two types. Clinical case reports frequent the literature with examples of patients with psychotic symptoms whose onset closely follows ingestion of cannabis. Second, experimental studies have demonstrated that cannabis administration (albeit intravenous dosing of THC) can produce psychotic-type symptoms in those without risk factors for psychotic disorders. Nonetheless, the literature linking cannabis use and acute psychosis includes only uncontrolled studies; thus, other causes of the psychosis cannot be ruled out. One could reasonably conclude that high doses of cannabis can precipitate psychosis in some individuals, but whether or not a predisposition to psychotic illness or some other baseline factor is necessary for acute psychosis to occur remains unknown.

Reviews relying on findings from longitudinal studies and laboratory studies have drawn similar conclusions regarding the relationship of cannabis use and *chronic* psychotic disorders. Suggestive but strong evidence has emerged that cannabis use can induce a psychotic disorder in at least a subpopulation of those who have other risk factors for developing psychotic symptoms or disorders. This said, one must be cognizant of the degree of risk. Most regular cannabis users do not experience psychotic symptoms or develop psychotic disorders, and cannabis cannot be designated the cause of most cases of psychosis.

Nonpsychiatric Health Effects of Cannabis

Respiratory System

Chronic cannabis smoking has the potential for respiratory consequences comparable to tobacco cigarette smoking. Of concern, a large subpopulation of cannabis users smoke a combination of cannabis and tobacco, and almost half of daily cannabis users also smoke tobacco, incurring additional risk for consequences on the respiratory system. The smoke of cannabis and tobacco contains similar respiratory toxic chemicals. Cannabis smoke can contain up to 50% more carcinogens and results in substantially greater tar deposits in the lungs than filtered tobacco cigarettes. Cannabis users smoke unfiltered material, inhale the smoke more deeply, and hold the smoke longer in their lungs than tobacco smokers.

The most significant acute effect of smoking cannabis is its action as a bronchodilator, which increases vulnerability to the smoke by decreasing airway resistance and increasing specific airway conductance. Cannabis smoking also increases absorption of carbon monoxide, resulting in elevated levels of blood carboxyhemoglobin (COHb). Increased COHb leads to reduced oxygen in the blood and impairment in oxygen release from hemoglobin that can stress a number of organs, including the heart.

Chronic cannabis smoking is clearly associated with similar processes and patterns of disease that lead to aerodigestive cancers among tobacco smokers, although a causal link to cannabis has not been definitively established. Cannabis smokers tend to smoke significantly less material per day than tobacco smokers, which may slow down the impact of cannabis on the lungs.

Immune System and Cancer

Chronic cannabis smoking appears to compromise the immune system. The immunosuppressive effect occurs in a variety of immune cells. Additional concern has been raised that THC may have direct cancer-fostering properties related to acceleration or increased replication of viruses related to certain cancers, cancer cell proliferation, and tumor growth. Note that data and arguments for a potential anti-cancer impact of cannabis have also appeared in the literature. For example, cannabidiol, a nonpsychoactive constituent of cannabis, has demonstrated tumor-reducing effects in rodents. The functional consequences (development of cancers or

other immunosuppressive-related diseases) of cannabis' effects on the suppression of the immune system in humans are not well understood. Epidemiologic, cohort, and case-control studies have yielded mixed findings regarding associated risk with head and neck, lung, oropharyngeal, and testicular cancer.

Reproductive System and Perinatal Effects

Unfortunately, research examining the effects of cannabis use on reproductive function has been sparse. Pregnant women who use cannabis expose the fetus to THC, as it is known to cross the placenta. Ten to 20% of women may use cannabis during pregnancy. Risk of major congenital anomalies does not appear to be increased by cannabis use in pregnant women. Studies have reported mixed findings regarding the effects of cannabis use during pregnancy on birth weight, length, and duration of gestation.

The effects of prenatal cannabis use on cognitive functioning appear subtle, and determining causality is difficult since genetic predispositions and multiple environmental factors cannot be ruled out. The types of impairment observed could impact behavioral and cognitive performance of various tasks. Such data indicate that concern is warranted regarding prenatal cannabis use and its effects.

Cardiovascular System

Most research examining cannabis and the cardiovascular system has focused on acute effects that occur when cannabis is ingested, and suggests a limited cardiovascular health impact. The primary acute effect is tachycardia with an observed dose-dependent increase in heart rate that diminishes when tolerance develops. Cannabis can also produce small increases in supine blood pressure and impair vascular reflexes. Note that the inhalation of carbon monoxide associated with smoking cannabis and subsequent increase in COHb in combination with tachycardia increase the work required of the heart. Although these findings show clear changes in cardiovascular functioning due to cannabis use, the effects have not been associated with short- or long-term cardiovascular or cerebrovascular injury or disease. For most healthy young cannabis smokers, the stress to the heart does not appear clinically detrimental. However, for individuals with cardiovascular or cerebrovascular disease, the additional cardiac stress may increase the risk for chest pain, heart attack, or stroke.

Brain Function and Cognitive Performance

A large literature has accumulated examining the effects of cannabis on cognitive functioning and performance. Administration of cannabis or THC increases activation in frontal, prefrontal, and paralimbic regions and the cerebellum. In chronic cannabis users, fMRI studies show alterations in the activation of brain areas involved in higher cognitive (executive) functions. Early initiation of cannabis use has been linked to a number of brain-structure abnormalities and brain function patterns during performance of cognitive tasks. This literature generally indicates that cannabis use can lead to selective cognitive impairments, although the magnitude and functional significance of such deficits are difficult to assess. The ability to organize and integrate complex information appears compromised.

Acute Use

THC-induced effects on response speed and accuracy, tracking ability, body sway, and reaction time have been observed in some studies, but not in others. As one would expect, THC dose accounts for some of the variation in findings with dose–response effects observed in some

studies, and moderately strong evidence that cannabis (THC) can impair performance on some psychomotor tasks at higher doses. Tolerance also impacts the degree of impairment from acute doses of cannabis, with regular heavy users showing less performance decrements than novice or less frequent users. Affected tasks appear to be those that require more attention, motivation, and impulse control.

The literature also indicates that acute cannabis or THC ingestion dose dependently produces adverse effects on a number of cognitive functions, which are likely moderated by cannabis use history. Effects have consistently been observed on short-term memory, particularly immediate memory and recall and retrieval, following a lapse of time. Note, however, that when retrieval cues are available, these deficits may be obviated, suggesting that adverse effects on attentional or learning processes are likely involved. Cannabis has been shown to disrupt the ability to learn novel tasks, and adversely impacts performance on divided and sustained attention tasks. Cannabis intoxication also affects the subjective perception of time.

Chronic Use

The cognitive impairments observed in acute administration studies of cannabis have also been observed when studying long-term or chronic use of cannabis. Although these chronic effects have been difficult to pinpoint and replicate because of numerous methodological difficulties in studying long-term effects, multiple reports strongly suggest that cannabis users show cognitive and behavioral performance deficits even when not under the influence of cannabis. These effects have been characterized as deficits of the attentional/executive system involving mental flexibility, working memory, learning, and sustained attention. A number of studies suggest more impairment in those who initiated cannabis use at an early age.

Functional Significance

Driving Studies using driving simulators and road tests have produced mixed results. Cannabis intoxication has been shown to adversely affect performance in emergency situations perhaps due to an increase in brake latency and worsened ability to attend to extraneous stimuli. Interestingly, cannabis use appears to decrease risk-taking behavior in simulated and on-road driving situations, perhaps suggesting some awareness of and compensation for impairment. Overall, the data from experimental and epidemiologic studies strongly suggest a positive relationship among acute cannabis use, driving performance impairments, and accidents. Although these data are not without limitations, driving under the influence of cannabis warrants caution and much concern.

Academic Achievement Although one would expect that the adverse effects of cannabis use on attentional and complex cognitive processing would have a direct influence on optimal academic performance, the extent of this influence is unknown. Cannabis use has been linked to low grade-point averages, decreased academic satisfaction, negative attitudes toward school, poor overall performance in school, and absence from school, with early cannabis use (prior to age 16) associated with dropping out of high school and failure to complete college. Studies that have statistically controlled for the multiple confounding influences have reported mixed results. Because cannabis users tend to have multiple risk factors that are associated with poor academic performance, it is difficult to demonstrate causality.

Motivation Cannabis use has long been associated with an "amotivational syndrome" reflecting lethargy, inactivity, loss of motivation, and decreased goal-directed behavior. Controlled field studies have failed to provide clear evidence of an amotivational syndrome, although this research is weakened by limitations relating to sample selection and definitions of motivation. Laboratory studies examining the effect of cannabis on work performance demonstrate what

could be termed amotivational behavior. These studies suggest that cannabis affects sensitivity to reinforcement, and that motivational effects of cannabis intoxication are determined by environmental context and contingencies. Although laboratory studies indicate that acute cannabis use can engender what appears to be less motivated behavior, the link between chronic cannabis use and an amotivational syndrome that is unrelated to acute cannabis intoxication has not been clearly established.

Special Considerations and Conclusion

Two commonly discussed issues related to cannabis, its potential for medicinal use and legalization, warrant comment. The burgeoning of science directed toward understanding of the endocannabinoid system has greatly increased optimism for the use of cannabinoids (cannabis-like compounds) as medicine. Efforts are under way to develop alternative cannabinoid medications that could reproduce the desired effects of cannabis, without the potentially problematic effects of smoked cannabis. Positive findings from studies evaluating the therapeutic potential of such cannabinoid-like compounds or from compounds that can manipulate the endogenous cannabinoid system clearly indicate growing promise of medicinal value in areas such as treatment of pain, neuromuscular and neurodegenerative disorders, eating or appetite disorders, autoimmune diseases, and other psychiatric disorders. As such, it is likely that these novel compounds that interact with the endocannabinoid system, and not smoked cannabis, will eventually be determined effective and safe for medical use. Unfortunately, such scientific advances in medicine are sometimes slowed down by certain advocates, the lay public, and legislators who are concerned that demonstrating the therapeutic potential of a class of drugs might diminish the perceived risk of a drug's addictive potential and potential for harm, and lead to increased misuse of a drug.

The issue of legalization of cannabis is tied closely to concerns about perceived harm, and concerns about increased availability of substances with potential for abuse and harm. Cannabis is the most widely used illegal substance in the United States and most other developed countries. Procannabis groups have led an ongoing effort to decriminalize or legalize cannabis use. Anti-cannabis legalization proponents raise the concerns about the psychosocial, health, and psychiatric consequences associated with cannabis misuse and addiction.

Of course, elements of the arguments proposed by both sides of the legalization debate have merit. The task of creating policy that balances protection of civil liberties and protection of the public (including children) is difficult. Currently, many U.S. states have reduced penalties for possession of small amounts of cannabis and have legislation legalizing the medical use of cannabis. At the same time, many schools and work places have adopted mandatory drug testing policies that include cannabis in the list of drugs that are not tolerated, and federal regulations remain strict.

Unfortunately, the ongoing debate over the medical use and legalization of cannabis has spawned distrust and confusion regarding the scientific data that inform our understanding of cannabis and its consequences. A reasonable perspective is to acknowledge that some level of cannabis use can and does result in harmful effects. However, while we have much to learn about the parameters of cannabis use that result in adverse consequences, a wealth of new knowledge has accumulated during the past two decades. Cannabis misuse, abuse, dependence, and withdrawal are real and relatively common phenomena with significant associated consequences that reflect a clear public health problem. In addition, scientific discoveries related to the endocannabinoid system have revealed the ubiquitous nature of cannabinoids and their complex interactions with other neurobiologic systems, suggesting multiple avenues by which they might be used to treat clinical disorders in the future.

Suggested Readings

Beardsley PM, Thomas BF, McMahon LR. Cannabinoid CB1 receptor antagonists as potential pharmacotherapies for drug abuse disorders. *Int Rev Psychiatry*. 2009;21:134–142.

Budney AJ, Hughes JR, Moore BA, et al. A review of the validity and significance of the cannabis withdrawal syndrome. *Am J Psychiatry*. 2004;161:1967–1977.

Budney AJ, Vandrey RG, Hughes JR, et al. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend*. 2007;86:22–29.

Carroll KM, Easton CJ, Nich C, et al. The use of contingency management and motivational/skills-building therapy to treat young adults with marijuana dependence. *J Consult Clin Psychol*. 2006;74:955–966.

Copeland J, Swift W. Cannabis use disorder: epidemiology and management. *Int Rev Psychiatry*. 2009;21:96–103.

Dennis M, Godley SH, Diamond G, et al. The cannabis youth treatment (CYT) study: main findings from two randomized trials. *J Subst Abuse Treat*. 2004;27:197–213.

Huestis MA, Boyd SJ, Heishman SJ, et al. Single and multiple doses of rimonabant antagonize acute effects of smoked cannabis in male cannabis users. *Psychopharmacology (Berl)*. 2007;194:505–515.

Ramaekers JG, Kauert G, Theunissen EL, et al. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *J Psychopharmacol*. 2009;23:266–277.

Sewell RA, Ranganathan M, D'Souza DC. Cannabinoids and psychosis. *Int Rev Psychiatry*. 2009;21:152–162.

Solowij N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA*. 2002;287:1123–1131.

8 Amphetamines and Other Stimulants

Amphetamine-type stimulants (ATS) fall into three main groups: amphetamine, methamphetamine, and methylphenidate. Amphetamine formulations are often prescribed for attention-deficit hyperactivity disorder (ADHD), but have high abuse potential because of their powerful effects. Methamphetamine can be synthesized from readily available chemical components and is the most commonly abused ATS. Methylphenidate formulations are the most commonly prescribed ADHD medications, although, like amphetamine formulations, they are sometimes misused. When misused, ATS are highly addictive.

While there have been surges in amphetamine use in general, the appeal of amphetamines has remained consistent among three groups: the military, athletes, and students. Amphetamines appeal to these groups primarily because of the increased energy and improved performance associated with their use.

The effects of amphetamines on military performance can fall into one of two categories: performance enhancement and performance maintenance. Performance enhancement occurs when amphetamines are thought to improve one's maximum performance level for a given task. Performance maintenance is the use of amphetamines to restore skills that may have degraded as a result of sleep deprivation or normal circadian rhythm–associated decrements. Military units and pilots who work long hours with little sleep have relied on amphetamines to perform at a high level without fulfilling their biological sleep requirements. Because of concerns about side effects of amphetamines such as hypertension and tachycardia as well as adverse reactions, including paranoia, military forces are evaluating nonamphetamine stimulant drugs such as modafinil as possible alternatives to amphetamines in combat settings.

Athletes have used amphetamines to improve performance for many years. Although evidence supporting positive effects of amphetamine or naturally occurring ephedra alkaloids on athletic performance is equivocal, ATS continue to be used because of their perceived positive effects on attention, energy, self-confidence, mood, and aggression. In the 1960s and 1970s, amphetamine use in professional football and baseball was noted to be rampant. Deaths of athletes have been attributed to amphetamine misuse by an increase in blood pressure caused by increased exercise and peripheral vasoconstriction that hampers the body's ability to cool itself, leading to heatstroke, and cardiac arrest. Amphetamines may mask the warning signs of fatigue that usually result in athletes' decreasing their effort; as a result, injury may occur. Adverse events resulting from amphetamine use led to its presence on the first list of substances banned by the International Olympic Committee in 1968.

Students and professionals also use amphetamines to increase productivity. Many students believe that amphetamines and other stimulants improve concentration, increase alertness, and assist with studying. Prescription amphetamine and methylphenidate formulations are commonly misused by this group. The National Survey on Drug Use and Health (NSDUH)

demonstrated that full-time college students aged 18 to 22 were twice as likely as their age-matched counterparts who were not full-time college students to abuse amphetamines. Students report improved academic performance stemming from an ability to work at a high level for an extended period. Along with the risk of developing dependence on these stimulants, students who use these medications in an attempt to improve performance report higher rates of binge alcohol consumption, cannabis use, and cocaine use. Students or professionals who use amphetamines and other stimulants in this context are also at increased risk for heart attack and stroke.

Epidemiology of Amphetamines: Scope of the Problem

Amphetamine misuse remains an enormous problem worldwide. The United Nations Office on Drugs and Crime (UNODC) *World Drug Report 2009* estimates that as many as 51 million people around the world regularly use amphetamines, in comparison with approximately 21 million users each of cocaine and opioids. Methamphetamine is the most widely available and most commonly misused type of amphetamine. The UNODC estimated that between 230 and 640 metric ton of ATS was manufactured in 2007. The spread of illicit manufacture to new countries each year suggests that amphetamine use disorders Amphetamine Use Disorder (AUDs) will remain a problem in the coming years.

Diversion of prescribed amphetamines is a concern. While the prevalence of AUDs has remained steady globally, amphetamine consumption and prescription rates are increasing at a proportion that suggests that diversion may be occurring. The WHO estimates that the consumption of amphetamines has more than tripled, from approximately 5 to 18 daily doses per 1,000 persons. The number of prescriptions per year, in contrast, has only doubled, from 15 to 30 million. The larger increase in consumption in comparison with the number of prescriptions suggests that prescribed amphetamines may be diverted to meet the consumption demand.

Methamphetamine dependence remains an important problem in the United States in particular. Most of the reported methamphetamine production operations occur within the United States, with the United States accounting for the majority of methamphetamine laboratories seized. Methamphetamine production laboratories are increasing in size, sophistication, and production yields, as organized crime groups see methamphetamine as a source of income. While methamphetamine use was focused primarily in the western part of the United States in the early 1990s, the problem has spread across the country in recent years. As a result, the United States has enacted several policies aimed at suppressing the production of methamphetamine by restricting access to precursor chemicals. Regulations affecting large-scale producers of methamphetamine, such as improved monitoring of bulk purchases of ephedrine and pseudoephedrine, have been beneficial by contributing to a reduction in the purity of methamphetamine available in the United States. However, policies designed to combat small-scale methamphetamine production, such as the limitation and tracking of pharmacy purchases of ephedrine and pseudoephedrine, have had little or no effect.

The prevalence of methamphetamine use in the United States has remained relatively constant since 2002. However, severity of use is increasing; the number of methamphetamine users in the past month meeting the criteria for drug abuse or dependence during the past year has been increasing. Similarly, methamphetamine users progress more quickly than cocaine users from first use to regular use to entry into substance use disorder (SUD) treatment. Despite efforts to reduce access to the chemical precursors of methamphetamine, it is likely that methamphetamine will remain accessible and inexpensive, and that public health costs associated with increased use will continue to rise.

AUDs are associated with other psychiatric disorders. Those who use methamphetamine chronically are more likely to experience psychiatric symptoms, including drug-induced psychotic symptoms that may persist over time. Treatment-seeking methamphetamine users report high rates of previous suicide attempts as well as violent behavior problems. Those who misuse stimulants are more likely to misuse other illicit drugs as well. It has been shown that the lifetime prevalence of cocaine/crack and heroin use in a representative sample of youths and young adults aged 16 to 25 who regularly use amphetamines was several times higher than the prevalence in the general population.

Psychosis resulting from amphetamine use is similar to psychoses resulting from cocaine use or other psychotic disorders such as schizophrenia. Acute amphetamine psychosis is difficult to distinguish from acute schizophrenia, with hallucinations, ideas of reference, paranoia, and agitation. Amphetamine-induced psychoses usually resolve quickly with removal of the amphetamine, while psychotic symptoms resulting from schizophrenia do not. Amphetamine psychoses may be chronic, though, with persistent psychotic symptoms even after removal of amphetamine. Others have recurrence of the psychotic state with even minimal reexposure to amphetamine. Psychotic symptoms resulting from amphetamines are treated with antipsychotic medications just like psychotic symptoms of other etiologies.

AUDs have significant public health effects as well. Clandestine in-home methamphetamine laboratories have resulted in environmental costs as well as increased pediatric deaths and emergency room visits from burns and poisoning. Fetal exposure to methamphetamine leads to multiple prenatal complications. Methamphetamine use has also been associated with higher rates of hepatitis C and HIV. AUDs are associated with criminal justice costs as well; methamphetamine use is highly predictive of violent criminal behavior and recidivism among parolees.

Determinants of Use

Pharmacology

Amphetamines activate the CNS, by increasing synaptic concentrations of the monoamines dopamine (DA), serotonin (5-hydroxytryptamine [5-HT]), and norepinephrine (NE). ATS are known as "releasers" because they bind to transporter proteins and increase monoamine levels by a transporter-mediated exchange or the disruption of neurotransmitter storage in vesicles via vesicular monoamine transporter-2 (VMAT-2). The rapid efflux of intravesicular monoamines results in high concentrations of cytosolic monoamines. High levels of intracellular monoamines reverse monoamines in the cell membrane, ultimately causing a movement of monoamines into the extracellular space.

Considerable evidence suggests that the mesocorticolimbic dopaminergic system mediates the rewarding effects of amphetamines. This system, which originates from the ventral tegmental area (VTA) of the midbrain and targets a number of limbic and cortical structures, including the nucleus accumbens (NAcc), amygdala, and prefrontal cortex, has been shown to play an essential role in stimulant reward. The noradrenergic system helps to mediate the cardiovascular effects of amphetamines, and mounting evidence also suggests that the noradrenergic system is critical in mediating amphetamine's rewarding effects in preclinical models of addiction. The noradrenergic system, together with the dopaminergic system, may also contribute to withdrawal symptoms that occur with stimulant discontinuation. Changes in mood associated with stimulants result in part from activation of the serotonergic system, but 5-HT may also play a role in modulating the rewarding effects of stimulants through its impact on the DA system.

Preclinical Target Systems

Dopaminergic

The dopaminergic system plays a critical role in mediating the reinforcing effects of amphetamines. Both D1- and D2-like receptors have been proposed to mediate acute and chronic effects of stimulants. The D1-like family of receptors, including the D1 and D5 receptors, stimulates cyclic AMP (adenosine monophosphate) formation. The D2-like family of receptors, including the D2, D3, and D4 receptors, inhibits cyclic AMP formation. The D2-like receptors also function as autoreceptors reducing DA release. As a result, agents modulating DA release have been studied in several behavioral models.

GABAergic

Dopaminergic effects are modulated by γ-aminobutyric acid (GABA) and glutamate, the main inhibitory and excitatory neurotransmitters in the brain. Dopaminergic activity is decreased by GABA and increased by glutamate, suggesting that alteration of either GABA or glutamate transmission is a possible strategy in the development of a new medication for stimulant dependence. GABA effects are mediated through two types of GABA receptors: $GABA_A$ and $GABA_B$. $GABA_A$ receptors increase chloride influx and mediate the fast inhibitory responses to GABA. In contrast, $GABA_B$ receptors, found both pre- and postsynaptically, mediate the slow inhibitory response to GABA. Thus, both $GABA_A$ and $GABA_B$ receptors are potential treatment targets for new medications for stimulant dependence. Baclofen, a $GABA_B$ agonist, has been shown to produce a dose-dependent reduction in intravenous self-administration of both methamphetamine and D-amphetamine. Similarly, baclofen also attenuates the development of both conditioned place preference and behavioral sensitization, following administration of D-amphetamine.

Glutamatergic

Glutamate acts on two varieties of highly specialized receptors: ionotropic and metabotropic receptors. *N*-Methyl-D-aspartate (NMDA), kainite, and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors are called "ionotropic" receptors because of their action as ion channels. While ionotropic glutamate receptors are widespread and mediate fast synaptic transmission, metabotropic receptors are coupled to G-proteins and mediate the slow, neuromodulatory effects of glutamate. Pharmacological antagonism of glutamate transmission has been shown to block stimulant effects in preclinical paradigms of addiction. Glutamatergic drugs that act on the VTA block stimulant sensitization and reward. Consistent with these findings, riluzole, which decreases glutamate release, has been used in several preclinical paradigms to underscore the role of glutamate in amphetamine addiction. It blocks amphetamine-induced conditioned place preference, moderately attenuates amphetamine-induced locomotion, and attenuates the expression of amphetamine-induced behavioral sensitization. Although preclinical evidence for sensitization may outweigh research in humans currently, sensitization to amphetamine may be important clinically. Chronic amphetamine use may make it more difficult to maintain abstinence, increase the likelihood of amphetamine-induced psychosis, and worsen prognosis. These behavioral findings are supported by cellular studies demonstrating riluzole's effectiveness in blocking DA release in the striatum and other brain areas involved in dependence.

Adrenergic

Noradrenergic axons project widely throughout the brain and the noradrenergic system contributes to an array of psychological processes, including affective regulation, learning, memory, sleep, and reinforcement, as well as physiological responses, including regulation of heart rate and blood pressure. These functions are mediated by α- and β-adrenergic receptors and

their subtypes. Preclinical studies have demonstrated that adrenergic receptors are critical in the development of amphetamine dependence. Pretreatment with the α_1-antagonist prazosin has been shown to reduce the acute locomotor effects of D-amphetamine in rats, and concomitant administration of prazosin and the 5-HT_{2A} antagonist SR46349B produces a complete blockade of these effects along with the development of behavioral sensitization. The α_{2A}-antagonist atipamezole attenuated both locomotor hyperactivity and behavioral sensitization following D-amphetamine administration. Similarly, treatment with a β-antagonist timolol prevented the development of behavioral sensitization to amphetamines in rats. These studies suggest that α- and β-adrenergic antagonists may have promise as medications for amphetamine dependence.

Serotonergic

Neurons containing 5-HT project from the raphe nuclei to nigrostriatal and mesolimbic neurons containing DA, prompting study of the relationship of 5-HT to DA-mediated amphetamine effects. Multiple preclinical models have demonstrated the role of serotonergic neurons in amphetamine self-administration, indicating that 5-HT may attenuate the reinforcing effects of methamphetamine. Tricyclic antidepressants (TCAs), which affect monoamine reuptake and have anticholinergic activity as well, restore hypoactive intracranial self-stimulation in rats exposed to chronic amphetamine administration. Acute injection of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), attenuates the self-administration of D-amphetamine in rats. Other studies have built upon these findings to investigate the relationship between serotonergic and noradrenergic systems. Both the α_1-antagonist prazosin and the 5-HT_{2B} antagonist SR46349B attenuate the development of amphetamine-induced behavioral sensitization. Repeated administration of D-amphetamine produced a hyperactivity of NE and 5-HT neurons that was blocked by antagonist pretreatment, suggesting an uncoupling of NE and 5-HT that occurs with chronic amphetamine dependence administration. Studies also suggest that reduced serotonergic neurotransmission may contribute to amphetamine withdrawal states. In rats, the SSRI paroxetine, combined with the 5-HT_{1A} antagonist p-MPPI, attenuated the reward deficit associated with amphetamine withdrawal. These findings suggest that the serotonergic system, by modulating both amphetamine reinforcement and withdrawal, may prove to be a promising target for new amphetamine-dependence treatments.

Cannabinoid

Evidence linking the endocannabinoid system to the reward circuit has encouraged the study of the effects of this system on amphetamine-induced behaviors. A link between the cannabinoid and dopaminergic systems is suggested by the induction of sensitization to amphetamine-induced hyperlocomotion by Δ^9-tetrahydrocannabinol, the psychoactive ingredient of marijuana. Similarly, the cannabinoid CB1 receptor antagonist SR14176A blocked the reinstatement of methamphetamine-seeking behavior induced by drug-priming and drug-associated cues. Another CB1 receptor antagonist, AM251, was shown to attenuate amphetamine-induced behavioral sensitization. These findings suggest that cannabinoid antagonists may be developed as potential medications for amphetamine dependence.

Acetylcholinergic

Nicotinic and muscarinic cholinergic receptor types mediate acetylcholinergic effects. While few studies have examined a possible role for cholinergic receptors in treatments for amphetamine dependence, some studies have yielded promising results. Systemic nicotine and donepezil, an acetylcholinesterase inhibitor, attenuated the reinstatement of methamphetamine-seeking behavior. Additional experiments using muscarinic and nicotinic antagonists indicated that donepezil's effects were mediated by the nicotinic, not muscarinic, receptors. Lobeline, a nicotine agonist that decreases DA release via inhibition of VMAT-2, also attenuates intravenous self-administration in rats. Additionally, lobeline reduces the DA-releasing effects of methamphetamine, suggesting

that lobeline has unique properties at the DAT and VMAT-2. These studies suggest that nicotinic receptors may be promising targets for the treatment of amphetamine addiction.

Opioid

Opioid and dopaminergic neurons interact in the VTA, substantia nigra, striatum, and limbic areas of the brain. In addition, the endogenous opioid release following acute administration of amphetamines suggests a functional connectivity between dopaminergic and the opioid system. This connectivity has been illustrated in multiple behavioral studies as well. The opioid antagonist naloxone attenuated the locomotor response to amphetamine as well as the corresponding increase in extracellular DA. Similarly, pretreatment with naloxone decreased methamphetamine-induced conditioned place preference. Naltrexone, a nonselective opioid antagonist, attenuated methamphetamine-induced behavioral sensitization, and also inhibited reinstatement of drug-seeking behavior by methamphetamine-associated cues. It is important to note, however, that naltrexone did not affect reinstatement induced by priming with methamphetamine, and earlier work has already documented that naltrexone has no effect on methamphetamine self-administration, although another study showed that naltrexone attenuated reinstatement of amphetamine self-administration.

Nitrergic

Nitric oxide (NO) is a lipid-soluble, short-lived second messenger that plays a role in diverse functions, including learning and memory, neurotransmitter release, and cell death. NO serves as a second messenger for NMDA receptors and is released by neuronal nitric oxide synthase (nNOS), following NMDA-type glutamate receptor activation. Several studies have supported the role of NO in mediating the psychomotor sensitization and reinforcing effects of stimulants. Pretreatment with 7-nitroindazole, an NOS inhibitor previously shown to attenuate signs of opioid withdrawal, attenuated the development of methamphetamine-induced behavioral sensitization in mice. Acute minocycline treatment attenuated amphetamine-induced psychomotor activity and striatal (DA) release in rats. Consistent with these findings, a recent positron emission tomography imaging study in monkeys demonstrated that minocycline treatment protected against methamphetamine-induced neurotoxicity by attenuating the reduction of DAT in the striatum of monkeys pretreated with methamphetamine. The mechanism by which minocycline interacts with dopaminergic and glutamatergic neurotransmission has not been clarified, but it may be due to minocycline's capacity to inhibit inducible NOS and the resultant inhibition of NO release.

Pharmacodynamic Effects

Amphetamines have a long duration of action. They produce an initial "rush" of euphoria, heightened alertness, increased energy, decreased appetite, and intensified emotions. Euphoria may be experienced in as little as 5 minutes with intravenous or smoked amphetamine and lasts 8 to 12 hours. Amphetamine half-lives range from 4 to 5 hours for methamphetamine to 7 to 31 hours for amphetamine. Amphetamines, therefore, produce powerful, long-lasting effects that many people find appealing.

Not all effects of amphetamines are desirable, however. Acute adverse effects of amphetamines include insomnia, restlessness, hyperthermia, and even seizures. In addition to abuse and dependence, chronic use can result in agitation, paranoia, mood disturbances, psychosis, and cognitive impairment. After prolonged use of amphetamines, some users experience unpleasant physical side effects or a withdrawal syndrome marked by depression, irritability, anxiety, fatigue, and aggression. Unpleasant withdrawal symptoms during the initial days of abstinence from chronic amphetamine use can contribute to relapse or even suicidal ideation. The potential for abuse and the side-effect profile of ATS underscore the prescribing clinician's responsibility to educate patients about these medicines.

Amphetamines as Medications

Clinical Indications

Amphetamines and ATS have proven to be effective treatments in a variety of clinical situations. They are FDA approved as pharmacotherapy for ADHD and narcolepsy. ATS such as methylphenidate, mixed amphetamine salts, dextroamphetamine, and lisdexamfetamine are first-line treatments for ADHD. Amphetamines can also be used to augment antidepressant medications in treatment-resistant depression. Other uses of ATS include treatment of symptoms associated with traumatic brain injury and stroke. There is also evidence supporting the use of ATS as treatment for HIV-related neuropsychiatric symptoms. Use of ATS for weight loss is not encouraged by physicians largely because of the potential for dependence.

Amphetamines as Drugs of Abuse

Evaluation and Treatment Approaches

Behavioral Interventions for Amphetamine Dependence

Trials of behavioral interventions for amphetamine dependence have produced promising results warranting further study. Both cognitive behavioral therapy (CBT) and contingency management (CM) have been shown to reduce methamphetamine use. CBT involves examining learning processes in order to reduce amphetamine use. The patient receiving CBT becomes skilled at recognizing situations associated with use, avoiding them when possible, or coping with them when necessary. CM provides tangible incentives like money-based vouchers or prizes, based on objective measures of drug abstinence. Several clinical trials suggest that CM has promise as a behavioral intervention for amphetamine dependence. CM, using voucher-based reinforcers, has been shown to improve treatment retention and increase periods of continuous abstinence when compared with control conditions (such as CBT and treatment as usual) in studies of methamphetamine-dependent patients.

Pharmacotherapy

Despite promising results from preclinical studies, clinical studies have not produced reliably efficacious medication treatments for amphetamine dependence. Translation of preclinical models for amphetamine dependence into effective treatments has proven difficult, and the positive signals seen in animals have, for the most part, not been reproduced in humans. In addition, the inability to develop effective pharmacotherapies for amphetamine dependence makes it difficult to assess the validity of preclinical models. Thus far, randomized controlled trials (RCTs) of multiple classes of medications have generated inconclusive results. The classes of medications evaluated in these trials were influenced, perhaps, by previous trials of medications studied for cocaine dependence.

Antidepressants Antidepressants, including SSRIs and TCAs, have been studied as potential pharmacotherapies for amphetamine dependence for two important reasons. First, preclinical studies of amphetamine self-administration suggest that medications blocking the reuptake of 5-HT may attenuate the reinforcing effects of amphetamine. Second, blockade of the 5-HT and NE reuptake can combat some of the depressive symptoms experienced in amphetamine withdrawal such as depressed mood, fatigue, and anhedonia, which may lead to relapse. Other

medications with effects on 5-HT, NE, and DA have been studied as well. Although antidepressants have not been shown to be efficacious as medications for cocaine dependence, several studies evaluating this class as treatments for amphetamine dependence have been done.

Unfortunately, trials of both SSRIs and TCAs have had limited success in identifying an effective medication for amphetamine dependence. The SSRIs fluoxetine, paroxetine, and sertraline failed to distinguish themselves from placebo as treatments for methamphetamine use. Antidepressants with mild stimulant properties have been studied as well. Amineptine, a DA reuptake inhibitor, alleviated symptoms of depressed mood, decreased energy, increased appetite, and craving for sleep in patients experiencing amphetamine withdrawal. Bupropion, a DA and NE reuptake inhibitor, has been shown to be safe in methamphetamine users, but was no more effective than placebo in two studies whose primary outcomes were proportion of subjects having a methamphetamine-free week. Post hoc analyses, however, suggest that bupropion may be effective as a treatment for methamphetamine dependence in at least a subgroup of men using low-to-moderate amounts of methamphetamine. The monoamine oxidase B inhibitor selegiline has been shown to be safe for use as a treatment for methamphetamine dependence, but it produced minimal changes in the subjective responses of subjects to methamphetamine. Serotonergic antagonists have also been examined; mirtazapine, a 5-HT_2 and 5-HT_3 antagonist, was shown to be more effective than treatment as usual for methamphetamine withdrawal, and ondansetron, a 5-HT_3 blocker (but not an antidepressant), has been shown thus far to be safe as a treatment for methamphetamine dependence.

GABA Enhancers Clinical trials of GABAergic agents have provided preliminary evidence that such medications may be useful in the treatment of amphetamine dependence. In a 16-week, randomized, placebo-controlled, double-blind trial, neither gabapentin, a GABA-transaminase inhibitor, nor the $GABA_B$ agonist baclofen produced significant differences relative to placebo on standard treatment outcome measures. Post hoc analyses, however, showed a significant treatment effect for baclofen versus placebo in a subgroup that was highly compliant in taking study medication. Another GABA-transaminase inhibitor, γ vinyl-GABA (GVG), was shown to be a safe treatment for methamphetamine dependence in an open-label, 9-week safety study. In a separate placebo-controlled study, GVG did not alter amphetamine levels or cardiovascular effects of amphetamine, nor did it attenuate the positive subjective effects of methamphetamine in non–treatment-seeking methamphetamine-dependent volunteers. Thus, further investigations of these medications, or longer acting or more potent GABA agents, have the potential to identify an effective treatment for amphetamine dependence.

Antipsychotics Atypical antipsychotic medications have been investigated as treatments for methamphetamine dependence in part due to the effects of DA and, to a lesser extent, 5-HT on amphetamines. Medications with dopaminergic and serotonergic function, such as risperidone and aripiprazole, have been shown to block some of the behavioral effects of amphetamines that contribute to their abuse. A 4-week open-label trial demonstrated that treatment with risperidone produced significant reductions in episodes of methamphetamine use and psychiatric symptoms. A human laboratory study of the D2 and 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist aripiprazole demonstrated moderate reductions in abstinence-related and cue-induced methamphetamine craving. These studies provide a basis for additional investigations of medications with dopaminergic and serotonergic action for amphetamine dependence.

Calcium Channel Blockers Dopamine's role in the rewarding effects of stimulants has led to the study of medications that modulate midbrain DA systems. The ability of calcium channel blockers to attenuate cocaine-induced DA output in the striatum has led to investigation of this class of medications in models of amphetamine dependence. The calcium channel blocker isradipine, for example, has been shown in preclinical studies to suppress amphetamine-induced

conditioned place preference and locomotor activity in rats. Two clinical studies have followed this promising preclinical finding. Isradipine attenuated some of the subjective effects of and craving for D-methamphetamine in a human laboratory study. However, a double-blind, randomized, placebo-controlled trial of another calcium channel blocker, amlodipine, did not produce positive results. Eight weeks of amlodipine treatment was not significantly different from placebo on measures methamphetamine use, depressive symptoms, and craving.

Stimulant-like Medication Another strategy for treating stimulant dependence is to employ medications that produce some of the same positive effects as the stimulant being abused. Modafinil, for example, is a wakefulness-promoting agent that is approved by the FDA for the treatment of narcolepsy. It has some pharmacological effects similar to amphetamines, such as increases in heart rate and blood pressure, but it is marketed as having less abuse potential than amphetamines. A small open-label trial has reported preliminary findings on modafinil as a pharmacotherapy for methamphetamine withdrawal. Treatment with modafinil attenuated subjective and observer-reported withdrawal severity when compared with treatment as usual. The NE transporter inhibitor atomoxetine's effects on acute physiological and subjective responses to D-amphetamine in healthy volunteers were evaluated in another study, and were found to attenuate some of the standard physiological responses to amphetamine and some of the positive subjective effects as well.

Agonist Pharmacotherapy Another therapeutic approach, the replacement of amphetamine with agonist pharmacotherapy, has not been studied extensively, perhaps due to the lack of an established agonist pharmacotherapy for cocaine dependence. Several studies of amphetamine substitution, using retrospective and uncontrolled designs, describe promising results. In a randomized, controlled trial of amphetamine substitution treatment for methamphetamine use, the treatment group that received dextroamphetamine improved on several outcome measures, but failed to distinguish itself from the control group that received only counseling.

Genetic Mechanisms Underlying Differences in Amphetamine Response among Animals

Although progress has been made in the development of psychotherapeutic and pharmacological treatments of amphetamine dependence, the efficacy of available treatments is limited. One possible explanation for the lack of success of these treatments is the heterogeneity of populations dependent on amphetamine. This heterogeneity likely results from a variety of factors, including genetics and psychosocial factors such as addiction severity, treatment history, and chronicity of use. Genotypes, the specific composition of genes coding for the phenotype, may offer information about patients' potential response to treatment.

Preclinical work has supported the concept of functional polymorphisms. Animals with risk of polymorphisms display increased amphetamine effects compared with wild-type (WT) organisms, while those with protective polymorphisms show decreased amphetamine effects compared with WT organisms. Knockout mice lacking the DAT demonstrate a decreased locomotor response to amphetamine; this locomotion is decreased in a dose-dependent manner by the SSRI fluoxetine as well. In an investigation targeting the DA second messenger pathway, a quantitative trait locus (QTL) for methamphetamine-induced activity was identified in a region of chromosome 15 containing the casein kinase 1 epsilon gene (Csnk1e). The casein kinase 1 gene positively regulates the activity of dopamine-and-cAMP-regulated-phosphoprotein-32 kDa (DARPP-32), a prominent component of the dopaminergic second messenger pathway that regulates the locomotor response to stimulants. A 10-fold difference in the expression of this gene in the high-activity mouse line compared with the low-activity line was shown. Investigators have identified an expression QTL that comaps to both the QTL for methamphetamine-induced activity and physical location of Csnk1e

in the mouse genome, suggesting that this expression locus is responsible for differences in methamphetamine-induced activity. Mice without the α_{2A}-adrenoreceptor exhibit greater acute amphetamine-induced hyperactivity after administration of D-amphetamine than WT mice. However, the knockout mice display less amphetamine-induced hyperactivity after repeated administration of D-amphetamine than WT mice. These findings point to a complex interaction of α_{2A}-adrenoreceptor subtypes in the regulation of amphetamine-induced hyperactivity and the development of behavioral sensitization to repeated amphetamine administration.

Human Gene Polymorphisms and Associations with Amphetamine Dependence

Pharmacogenetics may be a useful tool in the development of treatments for amphetamine dependence by helping to individualize therapies. Progress made in using functional polymorphisms to inform treatment in other SUDs and studies employing these polymorphisms in relation to amphetamine dependence continue to be described. Several studies have documented genetic effects on the subjective responses to amphetamine. Studies also describe vulnerability to adverse drug effects, such as psychosis resulting from amphetamine use.

Conclusion

Around the world, people continue to abuse amphetamines, often with significant negative consequences. Amphetamine dependence can be associated with great personal and societal costs. While there are currently no effective pharmacotherapies for amphetamine dependence, strides are being made in multiple areas of research directed toward this goal. Although progress has been made in the development of behavioral treatments for amphetamine dependence, the need for effective medications has propelled exciting preclinical and clinical research. Pharmacogenetics research appears to be a promising new approach that may speed the development of treatments for amphetamine dependence. Ultimately, genotypic information may allow clinicians to tailor treatment to each individual through consideration of polymorphisms affecting treatment response. Effective pharmacotherapies may become integral components of successful comprehensive treatment strategies for amphetamine dependence.

Suggested Readings

Durell TM, Kroutil LA, Crits-Christoph P, et al. Prevalence of nonmedical methamphetamine use in the United States. *Subst Abuse Treat Prev Policy*. 2008;3:19.

Grabowski J, Shearer J, Merrill J, et al. Agonist-like, replacement pharmacotherapy for stimulant abuse and dependence. *Addict Behav*. 2004;29:1439–1464.

Ng B, O'Brien A. Beyond ADHD and narcolepsy: psychostimulants in general psychiatry. *Adv Psychiatric Treat*. 2009;15:297–305.

Palmer AA, Verbitsky M, Suresh R, et al. Gene expression differences in mice divergently selected for methamphetamine sensitivity. *Mamm Genome*. 2005;16:291–305.

Rawson RA, Marinelli-Casey P, Anglin MD, et al. A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. *Addiction*. 2004;99:708–717.

Rawson RA, McCann MJ, Flammino F, et al. A comparison of contingency management and cognitive-behavioral approaches for stimulant-dependent individuals. *Addiction*. 2006;101:267–274.

Scott JC, Woods SP, Matt GE, et al. Neurocognitive effects of methamphetamine: a critical review and meta-analysis. *Neuropsychol Rev.* 2007;17:275–297.

Shoptaw SJ, Kao U, Ling W. Treatment for amphetamine psychosis. *Cochrane Database Syst Rev.* 2009;1:CD003026.

Swanson JM, Volkow ND. Increasing use of stimulants warns of potential abuse. *Nature*. 2008;453:586.

9 Sedative–Hypnotics

In the early 1900s, barbital and phenobarbital were the first barbiturates introduced into medical practice. The barbiturates are still used in modern medicine. Meprobamate was introduced in 1955 and the benzodiazepine chlordiazepoxide in 1957. Meprobamate was widely prescribed as an antianxiety agent, but its use declined as practitioners found that it was more likely than barbiturates to lead to a withdrawal syndrome on discontinuation, which was often severe in nature and associated with seizures. Chlordiazepoxide and other benzodiazepines became the dominant antianxiety agents and hypnotics with established efficacy and less risk of lethal overdose or drug interactions. The use and availability of other sedative–hypnotics such as chloral hydrate, ethchlorvynol, glutethimide, and methyprylon also declined, because they were more toxic and less effective than the benzodiazepines. Newly developed nonbenzodiazepine hypnotics, commonly referred to as the "Z-drugs," were introduced in the 1990s. These include zopiclone, eszopiclone, zolpidem, and zaleplon. The Z-drugs are associated with abuse liability, dosage escalation above recommended levels, and associated toxicity, including seizures and a withdrawal syndrome. On the other hand, some studies suggest a low risk for tolerance, physical dependence, and rebound insomnia when Z-drugs are administered in therapeutic doses. Another type of sedative–hypnotic is γ-hydroxybutyrate (GHB). In the United States, GHB is marketed as Xyrem and approved by the FDA for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy. Its abuse liability is equivalent to ethanol and flunitrazepam.

Epidemiology

Clinicians remain divided about appropriate prescribing practices for benzodiazepines. On the one hand, there is a substantial database suggesting that abuse of benzodiazepines is not a significant health problem. Supporting this position are the results of the National Survey of Drug Use and Health (NSDUH), which has shown that sedatives: (1) are rarely the first drug abused by an individual, (2) have the low rates of abuse compared to other commonly misused drugs, (3) are rarely responsible for initiation of a treatment episode, and (4) are very rarely the specific drug used when initiating illicit drug use. Benzodiazepines are not often the primary drug of abuse leading to treatment, and when they are involved it is usually in combination with other drugs such as marijuana, opioids, and alcohol.

Other survey data and expert reports show that the number of U.S. prescriptions for benzodiazepines has steadily declined from a peak in 1973. As expected, the "Z-drugs" have increased numbers of U.S. prescriptions, but remain at relatively modest levels. Only about 1% of the U.S. population takes prescription benzodiazepines for longer than 1 year, which is consistent with European studies reporting 1 year of medical use of 1.7% and 6-month use of

approximately 3%. Long-term medical use is more common among the elderly, women, and individuals with chronic health problems or psychological disorders.

The highest rates of use and misuse occur in patients with comorbid addictions. Approximately 15% to 20% of alcoholics presenting for treatment are also taking benzodiazepines. Methadone patients can also have high rates of urine samples positive for nonprescribed benzodiazepines. About 30% of psychiatric patients are prescribed benzodiazepines, most commonly those with a long duration of illness, affective disorders, and who are frequent users of medical services. Anxiety disorder patients, as a group, do not misuse benzodiazepines, and tend to decrease the dose over time. Benzodiazepine prescriptions for anxiety disorders have declined, supplanted by the use of selective serotonin (5-HT) reuptake inhibitors as a first-line treatment in anxiety. Patients with chronic pain also tend to use prescribed benzodiazepines in higher amounts than the general population.

Comorbidities and Complications of Use

The toxicities of benzodiazepines and barbiturates differ more in severity than in the pattern of adverse consequences. All agents are CNS depressants, which at low doses produce sedation and at the highest doses may result in obtundation, coma, and death. At typical initial therapeutic doses, problems with oversedation, motor impairment, slowed cognition, and amnesia may occur. At higher therapeutic doses, slurred speech, ataxia, and impaired gag reflex may be observed. As a general rule when doses are kept within a therapeutic range, tolerance to many of these adverse effects occurs. Some studies have found that long-term benzodiazepine treatment does not impair cognitive function while others have seen persistent problems in learning, psychomotor function, concentration, and motor skills. Elderly patients may be at risk for both cognitive difficulties and falls, although it is unclear whether these drugs present greater risks to the elderly than other sedative agents. Cognitive impairment is likely to persist in the elderly although most patients do not recognize it or feel that it does not impair their daily functioning. There have been several reports of Z-drug-related amnesia associated with sleepwalking and odd nighttime behavior, such as driving, eating, shopping, and hallucinations.

Early studies suggested that there was a risk of cleft palate when benzodiazepines were prescribed during pregnancy, but at present the best evidence indicates that monotherapy with a benzodiazepine during pregnancy is not associated with major congenital anomalies. Sedative–hypnotics administered during pregnancy may lead to a withdrawal syndrome in newborns or the floppy baby syndrome, in which the neonate has low APGAR scores, poor sucking, poor reflexes, hypotonia, and apnea. Congenital abnormalities resulting from barbiturates are difficult to distinguish from those associated with other anticonvulsants because phenobarbital is usually not given as a monotherapy. When phenobarbital is given alone or in combination with other anticonvulsants, higher rates of major malformations are reported compared to mothers with a history of epilepsy who took no anticonvulsants during pregnancy.

Overview of Determinants of Abuse

Among the commonly used sedative–hypnotics, barbiturates produce the greatest pleasant mood alterations, although others (e.g., flunitrazepam, GHB) may be similar. Among the benzodiazepines, there are differences in the ability to induce mood enhancement. The most common explanation is that drugs with a rapid onset of action, followed by a rapid termination of single-dose effects, are associated with higher abuse liability. It is unlikely that pharmacokinetics explains the acute mood effects of benzodiazepines entirely; we know that binding to subtypes

of the α subunit of the GABA (γ-aminobutyric acid) receptor may influence a variety of actions, including sedation, anxiety, memory, anticonvulsant, and perhaps hedonic effects. With respect to acute euphoric effects, immediate-release alprazolam and flunitrazepam are consistently rated by experienced substance abusers as producing a high that they like. This is consistent with clinical experience, but any sedative–hypnotic may be abused by high-risk individuals.

Tolerance to barbiturates and benzodiazepines is well established. Some evidence suggests that temazepam and the Z-drug eszopiclone are not associated with the development of tolerance to their hypnotic effect and have low risk of rebound insomnia when the drugs are discontinued. With respect to treatment of anxiety, patients develop rapid tolerance to sedative effects, incomplete tolerance to impairment of coordination, memory, and muscle-relaxant effects, and little or no tolerance to antianxiety effects. In the treatment of seizures with clonazepam, partial tolerance develops. Clinicians should discuss the issue of tolerance with all patients, and caution them against unauthorized increases in dose or abrupt discontinuation of the medication. Information about the withdrawal syndrome and the risks of dependence on all sedative–hypnotics should be discussed prior to initiating therapy.

Benzodiazepines

Pharmacology

$GABA_A$ receptors act as the primary mediator of inhibition of neurotransmission in the mammalian brain. The $GABA_A$ receptor systems play a major role in mediating the actions of most of the sedative–hypnotic agents in current use. $GABA_A$ receptors are ligand-gated chloride channels that are commonly formed by five subunits. The subunit composition of these receptors, in conjunction with their precise location in the neuronal tissues, determines their functional and pharmacologic properties. Nineteen types of $GABA_A$ subunits have been identified and can be divided into seven distinct families. The α, β, δ, and λ families combine to form the receptors that are the primary targets of the sedative–hypnotic agents. There are six members of the α family (α_1 to α_6), four members of the β family, and three of the λ family. The subunit composition of $GABA_A$ receptors in the brain most frequently consists of two α subunits and two β subunits that exist in association with a γ or δ subunit. Receptors with the $\alpha_1\beta_2\gamma_2$ mix of subunits occur with the greatest frequency in the brain.

GABA binds at the interface between the α and β subunits of the $GABA_A$ receptors. Benzodiazepines bind at the interface of α and γ subunits. Binding of GABA to the $GABA_A$ receptor opens a chloride channel, which results in most instances in hyperpolarization of the neuron. The binding of benzodiazepine produces an allosteric modification in the GABA binding site. This modification usually leads to an increase in the frequency of the opening of the chloride channel.

$GABA_A$ receptors that are sensitive to the benzodiazepines contain α subunits 1, 2, 3, or 5, combined with two β subunits and a γ subunit. $GABA_A$ receptors containing the α_4 and α_6 subunits may be insensitive to the effects of benzodiazepines. This may be of significance because the α_4 and α_6 subunits in combination with δ subunit may localize primarily in extrasynaptic regions of the neuron, and may consequently act to regulate the tonic inhibitory as opposed to the synaptic phasic inhibitory effects of GABA. There is now increasing evidence that tonic currents play a major role in controlling neuronal excitability. The ability of drugs to interact with receptors that regulate tonic currents may determine the extent to which they can influence seizures, sleep, and other brain activity.

Data from animal studies suggest that $GABA_A$ receptors containing different types of the α subunit appear to mediate distinct behavioral effects of benzodiazepines and other benzodiazepine receptor agonists. Receptors containing the α_1 subunit have been implicated in the

production of sedation, amnesia, antiseizure effects, and ataxia. The presence of the α_2 and α_3 subunits is associated with the anxiolytic and muscle relaxant-inducing effects of the benzodiazepine receptor agonists. The behavioral effects of benzodiazepine agonist stimulation of the α_5 subunit containing receptors remain to be elucidated. However, it has been shown that learning and memory functions appear to be enhanced in animals missing the α_5 subunit suggesting that benzodiazepine might produce impairment of cognition by interacting with receptors that have this subunit.

Determinants of Abuse

Abuse liability of benzodiazepines has been assessed in animal models, human laboratory studies, and surveys of substance abusers, patients, and the general population. In general, all of these models consistently show that the benzodiazepines have a moderate potential for abuse that is substantially lower than that of methaqualone, barbiturates, and older sedative–hypnotics, such as chloral hydrate. Among the benzodiazepines themselves, the preponderance of evidence suggests that flunitrazepam, diazepam, lorazepam, alprazolam, and triazolam have higher abuse potential than chlordiazepoxide or oxazepam. It is unclear whether these research findings have practical clinical significance because the abuse of this class of drugs depends more on patient characteristics than benzodiazepine-induced acute subjective effects.

Several mechanisms have been implicated in the development of tolerance to the benzodiazepines. Exposure to benzodiazepines leads to uncoupling between the benzodiazepine and GABA receptor sites, that is, there is a decrease in the allosteric interactions between these sites. This, in part, may be the result of the internalization of $GABA_A$ receptors originally located on the surface of neurons.

Chronic treatment with benzodiazepines may result in the modification of the subunit composition of brain $GABA_A$ receptors. In addition to effects on $GABA_A$ receptor systems, chronic benzodiazepine exposure alters the activity of other systems that are involved in the regulation of neuronal activity. Prolonged exposure to benzodiazepines may lead to the upregulation of L-type high voltage–gated calcium-channel subunits, and voltage-gated channel currents are increased during chronic benzodiazepine treatment. Prolonged treatment with benzodiazepines also alters the activity of amino-3-hydroxy-5-methyl-4-isoxazole (AMPA), which mediates the effects of the excitatory neurotransmitter glutamate. Chronic benzodiazepine exposure also increases hippocampal AMPA receptor currents and AMPA receptor binding sites. These increases are correlated with increases in anxiety during benzodiazepine withdrawal.

Most benzodiazepines undergo rapid and extensive absorption after being administered orally. The highly lipophilic benzodiazepines, such as diazepam, readily cross the blood–brain barrier to exert their effects in the brain, but then may quickly redistribute into other tissues. The onset of action of less lipophilic agents, such as lorazepam, may be somewhat delayed.

Most of the benzodiazepines in use undergo biotransformation in the liver in reactions catalyzed by a variety of cytochrome P450 enzymes. Because a variety of drugs can alter the activity of the cytochrome P450 enzymes, the pharmacokinetic properties of the benzodiazepines that undergo hepatic metabolism have the potential of being involved in adverse drug–drug interactions. There is also a possibility that impairment of liver function as may occur in aging or a number of hepatic disorders may place patients at risk for developing benzodiazepine toxicity.

Benzodiazepines and their metabolites are frequently conjugated with glucuronide prior to their being excreted in the urine. Lorazepam and oxazepam only undergo glucuronidation prior to being excreted. These drugs offer the advantage being unlikely to interact with other drugs and of being safer to use in individuals with compromised hepatic function.

Alprazolam, midazolam, and triazolam are hydroxylated prior to being conjugated with glucuronide. In addition to hydroxylation benzodiazepine metabolites may also be the product of demethylation and nitroreduction. Clonazepam undergoes nitroreduction, catalyzed by

CYP 3A4 to form inactive metabolites. Some of the older benzodiazepines, including chlordiazepoxide, diazepam, and flurazepam, may be transformed into a variety of active metabolites that may greatly extend the duration of action of these drugs. Diazepam, for example, is converted to nordazepam, which has a half-life of between 50 and 180 hours.

Z-Drugs

Several nonbenzodiazepine drugs have been developed that share many of the pharmacologic actions of the benzodiazepines. These agents include zopiclone and its S-enantiomer, eszopiclone, zolpidem, and zaleplon. Although these agents do not form a single specific class of drugs, for convenience this group of drugs can be designated as being the "Z-drugs." These drugs are able to induce sleep at doses that produce lower levels of residual sedation and residual functional impairment in cognitive and psychomotor tasks versus barbiturate or benzodiazepine hypnotic agents. As compared to the barbiturates and the benzodiazepines, the Z-drugs do not produce marked undesirable changes in sleep architecture. In addition to sedative–hypnotic effects, these drugs have amnesic effects, anticonvulsant actions, anxiolytic activity, motor-impairing effects, and muscle relaxant effects. The Z-drugs show less pronounced amnesic and antianxiety effects than do the benzodiazepines.

Zaleplon and zolpidem may produce alterations in vision that may include altered color perception, pulsating of light, and room spinning. Common adverse effects associated with the use of zolpidem include headache, somnolence, dizziness, and nausea, and may produce hallucinations when administered with 5-HT reuptake inhibitors. Eszopiclone and zopiclone, in addition to sedation, may produce dry mouth and a metallic taste. Complex behaviors during sleep including sleepwalking, driving, eating, and cooking have been reported to occur in patients being treated with Z-drugs.

Pharmacology

The Z-drugs may activate the benzodiazepine receptor site located on the $GABA_A$ receptor complex. The actions of these drugs are antagonized by the administration of the benzodiazepine receptor antagonist flumazenil. Eszopiclone, zopiclone, and zolpidem have been demonstrated to bind in the region of the benzodiazepine binding site, but they may differ with respect to precisely which amino acid residues within this site are essential for their activity.

The Z-drugs all potentiate GABA-mediated currents in neurons containing $GABA_A$ receptors. This action produces an increase in chloride ion conductance. Binding studies, however, suggest that these agents may differ in their affinity for $GABA_A$ receptors with different α subunit compositions than do the benzodiazepines. Like the benzodiazepines, the Z-drugs have a low affinity for $GABA_A$ receptors that contain the α_4 and α_6 subunits. Zolpidem is between 5 and 10 times more selective for α_1-containing $GABA_A$ receptors than it is for α_2- and α_3-containing receptors, while having extremely low selectivity for receptors containing the α_5 subunit. Zaleplon has two- to threefold greater selectivity for α_1-containing receptors as compared to those having α_2 and α_3 subunits. This drug has minimal actions on $GABA_A$ receptors that have α_5 subunits. In contrast to zolpidem and zaleplon, zopiclone has almost equal selectivity for α_1- and α_5-containing receptors, while having between four and eight times less selectivity for those receptors with α_2 and α_3. Compared to benzodiazepines, then, the Z-drugs have modest degree of selectivity for receptors containing α_1 subunits as compared to those with α_2 or α_3 subunits.

Animal studies indicate that zolpidem and, to a lesser degree, zaleplon have greater potency as hypnotic agents than as muscle relaxants. Zopiclone, in contrast, produces its hypnotic and muscle relaxant effects at similar doses. The modest differences in the selectivity of the Z-drugs

for $GABA_A$ receptors containing α_1 subunits may not be great enough to completely explain the minimal residual adverse effects seen after these agents have been used to treat insomnia.

The pharmacokinetic properties of the Z-drugs may be one of the factors that explain the lower incidence of residual adverse effects that are associated with their use. The elimination half-life of zolpidem is approximately 2 hours while that of zaleplon is 1 hour. Eszopiclone has comparatively longer half-life of 4 hours, which can reach up to 7 hours in elderly individuals. Both zolpidem and zaleplon are metabolized in the liver into inactive metabolites. Zopiclone is metabolized to *N*-oxide zopiclone and desmethylzopiclone. The *N*-oxide metabolite has some activity. The oxide metabolite of eszopiclone, (*S*)-zopiclone-*N*-oxide, does not bind to $GABA_A$ receptors while the (*S*)-desmethylzopiclone metabolite of this drug may have anxiolytic effects.

Because zopiclone and eszopiclone are more slowly eliminated than are zolpidem or zaleplon, they can help to maintain sleep throughout the night. Zopiclone has been shown to produce psychomotor impairment 7 hours following its administration. A sustained-release formulation of zolpidem is marketed; it is designed to allow patients to maintain sleep throughout the night.

Determinants of Abuse

There are a number of case reports of Z-drug-related abuse and dependence. In many instances, extremely high doses of drugs may be self-administered. Doses of zolpidem in cases of abuse are often in the range of hundreds of milligrams being administered daily. This is in comparison with a therapeutic dose of zolpidem of about 10 mg daily.

Many individuals who misuse zolpidem have reported using the drug not for its sedative effects, but rather for its anxiolytic, euphoric, or stimulant effects. Human laboratory studies of the effects of Z-drugs indicate that these drugs may produce stimulus effects that present some risk for abuse. In social drinkers, zolpidem administration increased ratings of drug liking, but did not elevate scores on a scale that is sensitive to drug-induced euphoria. The drug-liking effects of zolpidem in these subjects were not found to be additive with those of alcohol. Subjects with a history of sedative abuse reported greater liking of triazolam and zolpidem than placebo. In subjects with a history of alcohol and drug abuse, higher doses of zolpidem produced elevations in scores for drug-liking and good effects. Zolpidem administration also resulted in elevations in rating of drug high and good effects in healthy subjects, who found triazolam and pentobarbital to have similar stimulus effects to those of zolpidem.

The results of several studies suggest that the risk for the development of tolerance, physical dependence, and withdrawal is low when therapeutic doses of the Z-drugs are used to treat insomnia. Several studies also indicate that no rebound insomnia was observed after discontinuation of the Z-drugs. In contrast, there are some studies that indicate that modest increases in anxiety and reduced sleep were observed in subjects treated with immediate-release formulations of zaleplon, zopiclone, or zolpidem. This has also been observed in individuals being treated with a sustained-release formulation of zolpidem. Overall, results from sleep trials suggest that dependence and withdrawal may not be problematic for patients being treated for insomnia with therapeutic doses of Z-drugs.

Animal studies have been conducted to determine whether Z-drugs can produce physical dependence with prolonged administration of these agents. Chronic administration of zolpidem did not result in physical dependence in mice. In monkeys, the discontinuation of chronic zopiclone administration resulted in symptoms of withdrawal, including apprehension, hyperirritability, and motor impairment. Flumazenil-induced withdrawal from zolpidem produced withdrawal signs that included tremor, jerk, and rigid posture that were moderate in severity in baboons.

Several case reports have been published that suggest that problems of dependence and withdrawal may occur in humans receiving Z-drugs. Seizures have been observed after the discontinuation of zolpidem in individuals using extremely high doses of this agent, as have other signs of withdrawal, including tremor, agitation, and anxiety.

Barbiturates

Barbiturates are barbituric acid derivatives. Prior to the introduction of the benzodiazepines, the barbiturates were extensively used as sedative–hypnotic agents. They also have been administered for their anticonvulsant effects and as anesthetic agents. The therapeutic indices of the barbiturates are comparatively low and toxic reactions, sometimes resulting in death, were frequent occurrences associated with the use of these agents. The use of these drugs is associated with a high risk of abuse and forms of dependence that can lead to severe, sometimes lethal, episodes of withdrawal.

As with the benzodiazepines, barbiturates have been used in the treatment of insomnia, seizure disorders, and anxiety disorders and to produce sedation and to induce anesthesia. Barbiturates with short to intermediate ranges of duration of action, that is, from 3 to 12 hours, including amobarbital, butabarbital, pentobarbital, and secobarbital, are currently used as sedative–hypnotic agents. Butalbital is used as a sedative component of antimigraine combination agents that also contain caffeine and either aspirin or acetaminophen. Long-acting, less lipophilic barbiturates such as mephobarbital and phenobarbital are used primarily as anticonvulsant agents. The highly lipophilic, ultrashort-acting barbiturates methohexital and thiopental are used in the induction of anesthesia.

The barbiturates produce depression of CNS activity that can range from sedation to sleep, anesthesia, and finally coma. These agents are not selective in their actions, and their antianxiety effects are not separable from their other depressant effects. The barbiturates will reduce slow wave and REM (rapid eye movement) sleep. Respiratory depression produced by the barbiturates, often in combination with other CNS depressants, may be a major contributory factor to death in cases of barbiturate overdoses.

Adverse effects of the barbiturates include sedation and disruption of motor coordination. In some patients, for example, in elderly individuals, the administration of a barbiturate may lead to the appearance of paradoxical excitement. Allergic reactions may occur in some patients receiving barbiturates, and exfolative dermatitis may sometimes be caused by phenobarbital.

Chronic barbiturate intoxication may produce somnolence, confusion, ataxia, nystagmus, coarse tremor, and emotional instability. Severe barbiturate toxicity may lead to coma and respiratory depression. Respiratory depression can cause respiratory acidosis and cerebral hypoxia. Fatal complication of barbiturate toxicity may include pulmonary complications such as pulmonary edema and renal failure.

Pharmacology

With respect to their actions at the $GABA_A$ receptor complex, low concentrations of barbiturates act as positive allosteric modulators of GABA action at the receptor. At higher concentrations, the barbiturates may directly activate the $GABA_A$ receptor. Millimolar concentrations of barbiturates appear to block the $GABA_A$ receptor. The extent of activation of the $GABA_A$ receptor system by barbiturates is dependent on the subunit composition of the receptor. The type α subunit contained in the $GABA_A$ receptor may be a major determinant of the degree of receptor activation by barbiturates. For example, pentobarbital produces greater potentiation of the effects of GABA in receptors containing the α_6 as compared to the α_1 subunit. The maximum direct effect of this drug on $GABA_A$ receptors was greatest in those receptors with α_6 as compared with those containing α_2 or α_5 subunits. In contrast to the benzodiazepines, pentobarbital also strongly activates $GABA_A$ receptors containing the α_4 subunit.

Actions of the barbiturates may not be limited to their effects on $GABA_A$ receptors. Ionotropic glutamate receptors may be subject to inhibition produced by barbiturate administration. Thiopental may decrease the activity of NMDA (*N*-Methyl-D-aspartate) excitatory

glutamate receptors, while phenobarbital appears to be ineffective in blocking the effects of NMDA. Thiopental and pentobarbital when administered may have inhibitory actions on AMPA receptors.

Barbiturates have inhibitory effects on voltage-gated calcium ion channels. This effect may lead to the inhibition of the stimulated release of noradrenaline and dopamine produced by thiopental, pentobarbital, and phenobarbital. Pentobarbital may also block calcium-dependent release of other neurotransmitters, including GABA, glutamate, and acetylcholine.

The barbiturates are inactivated by hepatic metabolism, with oxidation being an important step in the biotransformation of most of these drugs. Approximately, 25% of a dose of phenobarbital is excreted in the urine in unchanged form. Phenobarbital and other barbiturates induce cytochrome P450 enzymes in the liver. Cytochrome enzymes induced by phenobarbital exposure include CYP2B6, CYP2C9, and CYP3A4. Consequently, the chronic administration of phenobarbital has the potential to reduce the plasma concentrations of a large number of drugs.

Determinants of Abuse

In the laboratory setting the positive effects of pentobarbital have been shown to be greater than those of benzodiazepines. Healthy subjects rated a 100-mg dose of pentobarbital as producing greater "high" and "good effects" than placebo. This occurred in conjunction with larger pentobarbital-induced increases in ratings of drowsiness, sleepiness, and performance impairment.

Long-term use of the barbiturates can result in physical dependence characterized by a severe, sometimes life-threatening, withdrawal syndrome. Delirium and seizures may appear during withdrawal. Withdrawal can be a problem for seizure patients who have discontinued treatment with phenobarbital. Migraine patients receiving butalbital containing combination drugs for extended periods of time are also at risk of developing withdrawal symptoms, which can include the onset of generalized seizures.

Tolerance to the barbiturates may result from both pharmacokinetic and pharmacodynamic factors. The ability of barbiturates, such as phenobarbital, to induce hepatic metabolic enzymes may lead to an increase in the rate of their own elimination, thus producing "pharmacokinetic" tolerance. Chronic exposure to pentobarbital can lead to the decrease in the interaction between the barbiturate and GABA recognition sites producing pharmacodynamic tolerance.

γ-Hydroxybutyrate (Oxybate)

GHB is a short-chain fatty acid that is found in both the brain and peripheral tissues. Endogenous GHB may act as either a neurotransmitter or a neuromodulator. Synthetic GHB is used as a therapeutic agent and as a drug of abuse.

GHB is approved in the United States for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy patients. This drug is used in Europe in the management of alcohol dependence and withdrawal. GHB has been abused, often in nightclub settings, sometimes in combination with other "club" drugs.

GHB was available in the 1980s and early 1990s as a natural supplement, but is now classified as a controlled substance in the United States. Other designations for GHB include γ-hydroxybutyric acid, 4-hydroxybutanoic acid, and oxybate. The sodium salt of oxybate is marketed under the trade name Xyrem. GHB is called a variety of street names, including "G," GHB, Georgia Home Boy, Grievous Bodily Harm, "liquid ecstasy," and "liquid X." Precursors of GHB, γ-butyrolactone and 1,4-butanediol may be used as substitutes for GHB,

because they can produce the same range of effects. This may sometimes occur when products sold as GHB contain precursors of this drug.

Exogenously administered GHB undergoes rapid absorption from the gastrointestinal tract and then readily crosses the blood–brain barrier. This agent can cause sedation and induce sleep, and at higher doses produce anesthesia. Subjects who abuse GHB report that this drug can cause euphoria, disinhibition, and increased libido. Other pharmacologic effects of this agent include impairment of motor coordination.

GHB has a low therapeutic index. Toxic doses of GHB can produce coma, respiratory depression, myoclonus, seizures, bradycardia, and death. Respiratory depression, pulmonary edema, and positional asphyxia may be contributory factors to death resulting from GHB. Intoxication with GHB frequently occurs while other abused substances are being used, such as ethanol, that act synergistically to enhance the toxicity of GHB.

Pharmacology

In the brain, GHB is the product of the transformation of succinic semialdehyde, a GABA metabolite with the conversion reaction being mediated by the enzyme semialdehyde reductase. GABA is converted into succinic semialdehyde by the enzyme GABA transaminase. This reaction is reversible and succinic semialdehyde can then undergo biotransformation into GABA. The precise physiologic role of endogenous GHB remains unclear. Specific high-affinity binding sites have been found in the brain for this substance, including in hippocampus, cortex, and thalamus. Selective GHB receptors have been isolated and cloned. They appear to be orphan G-protein-coupled receptors. The behavioral effects of activation of selective GHB receptors remain to be elucidated.

GHB acts as a partial agonist at $GABA_B$ receptors. Millimolar concentrations of GHB are required to activate these receptors. Consequently, the activity of GHB at the $GABA_B$ receptor is of most relevance to its actions when it is exogenously administered. Behavioral manifestations of GHB-induced sedation include decreased locomotor activity, catalepsy, and loss of righting reflex. The administration of $GABA_B$ antagonists can block these effects.

GHB is readily absorbed when administered orally. Peak concentrations of this drug are attained in less than an hour following oral ingestion. The primary route of metabolism of GHB is oxidation to succinic semialdehyde by succinic semialdehyde dehydrogenase. GHB is rapidly eliminated with its half-life being in the range of 20 to 40 minutes. The rapid elimination of this compound makes it difficult to detect its use by utilizing chemical assays. Also, as a consequence of its short half-life, rapid reversal of the effects of GHB may occur, with rapid transitions from a state of unconsciousness to being alert in users being seen following ingestion of a large dose of this compound.

γ-Butyrolactone and 1,4-butanediol are biotransformed in humans into GHB. Both of these agents have been abused. Circulating lactonases mediate the conversion of γ-butyrolactone into GHB. Alcohol dehydrogenase and aldehyde dehydrogenase catalyze the conversion of 1,4-butanediol into GHB. Concurrent use of ethanol with 1,4-butanediol may result in competition between these compounds for alcohol dehydrogenase.

Determinants of Abuse

GHB is self-administered by rodents, but has not been consistently self-administered by monkeys. Clearer evidence of the high likelihood of GHB being abused is provided by human laboratory studies. In the human laboratory setting, GHB administration leads to responses that include elevated ratings of drug-liking and good effects in both abusers of sedative–hypnotics and GHB club users. The positive effects of GHB were at least comparable to those of ethanol and flunitrazepam in club users. In contrast to these two other agents, GHB also produced

bad effects including dizziness, confusion, and dysphoria. Sedative–hypnotic users also indicated experiencing nausea and other symptoms of gastrointestinal distress after the ingestion of GHB. GHB also produced impairments in memory function and psychomotor performance.

Tolerance to the sedative effects of GHB and signs of dependence during discontinuation of this agent were not observed in subjects receiving therapeutic doses of this drug. Case reports indicate that daily administration of high doses of either GHB (in the range of 20 g/day) or γ-butyrolactone may produce physical dependence.

Conclusion

Barbiturates have been used to treat a variety of disorders but possess the highest abuse liability of the sedative–hypnotics presently in common medical use. Their low therapeutic index poses high risks of toxicity, including lethal overdoses and severe withdrawal syndromes. In contrast, benzodiazepines are characterized by large margins of safety, and are associated with moderate levels of risk for abuse and dependence, particularly in certain substance-using populations. Toxicity and rates of abuse for benzodiazepines are dramatically less than the barbiturates. The Z-drugs appear to be an incremental advance over the benzodiazepines with regard to the safety of their use in the treatment of insomnia. There seems to be some, but comparatively lower, risk of the development of problems related to abuse and dependence with these agents than the benzodiazepines. GHB produces subjective effects that are similar to those produced by other sedative–hypnotic agents. It is interesting that the effects of GHB appear not be mediated by the $GABA_A$ receptor complex. With respect to its abuse liability, there is clear reason for concern regarding misuse because it produces positive stimulus effects that are at least equal to those of flunitrazepam and ethanol.

Suggested Readings

Belelli D, Harrison NL, Maguire J, et al. Extrasynaptic GABAA receptors: form, pharmacology, and function. *J Neurosci*. 2009;29(41):12757–12763.

Carter LP, Richards BD, Mintzer MZ, et al. Relative abuse liability of GHB in humans: a comparison of psychomotor, subjective, and cognitive effects of supratherapeutic doses of triazolam, pentobarbital, and GHB. *Neuropsychopharmacology*. 2006;31(11):2537–2551.

Collinson N, Kuenzi FM, Jarolimek W, et al. Enhanced learning and memory and altered GABAergic synaptic transmission in mice lacking the alpha 5 subunit of the GABAA receptor. *J Neurosci*. 2002;22(13):5572–5580.

Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet*. 2004;43(4):227–238.

Goodwin AK, Griffiths RR, Brown PR, et al. Chronic intragastric administration of gamma-butyrolactone produces physical dependence in baboons. *Psychopharmacology (Berl)*. 2006;189(1):71–82.

Hair PI, McCormack PL, Curran MP. Eszopiclone: a review of its use in the treatment of insomnia. *Drugs*. 2008;68(10):1415–1434.

Krystal AD, Erman M, Zammit GK, et al. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. *Sleep*. 2008;31(1):79–90.

Rush CR, Baker RW, Wright K. Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. *Psychopharmacology (Berl)*. 1999;144(3):220–233.

Sanger DJ. The pharmacology and mechanisms of action of new generation, non-benzodiazepine hypnotic agents. *CNS Drugs*. 2004;18(suppl 1):9–15 (discussion 41, 43–45).

Snead OC III, Gibson KM. γ-hydroxybutyric acid. *N Engl J Med*. 2005;352(26):2721–2732.

10 Hallucinogens

This chapter focuses on the major current and past hallucinogens: the prototype ergot hallucinogen lysergic acid diethylamide (LSD); other indolealkylamines such as psilocybin, psilocin, and dimethyltryptamine (DMT); and the phenethylamines, including mescaline and dimethoxymethylamphetamine (DOM). Cannabis, phencyclidine (PCP), and designer drugs such as methylenedioxymethamphetamine (MDMA or ecstasy), which are sometimes classified as hallucinogens, are covered elsewhere in this book.

The term *hallucinogen* means "producer of hallucinations." A hallucination is defined as a profound distortion in the perception of reality, frequently described as a sensory experience of something that is not there. Many drugs, when taken in sufficient quantity, can cause auditory and/or visual hallucinations. Such hallucinations can be present as part of a delirium, accompanied by disturbances in judgment, orientation, intellect, memory, emotion, and level of consciousness (e.g., organic brain syndrome). Delirium also can result from drug withdrawal (e.g., sedative–hypnotic withdrawal or delirium tremens in alcohol). However, "hallucinogen" generally refers to compounds that alter consciousness without producing delirium, sedation, excessive stimulation, or intellectual or memory impairment as prominent effects. This label is actually inaccurate because true LSD-induced "hallucinations" are rare; what are commonly seen are illusory phenomena. An illusion is a perceptual distortion of an actual stimulus in the environment: to see someone's face seeming to be melting is an illusion, whereas to see a melting face when no face is present is a hallucination. There are a variety of widely accepted synonyms for the hallucinogens, including the term psychedelic. The term psychotomimetic, meaning "a producer of psychosis," also has been widely used.

History

To a large degree, the attention to drug abuse that began in the United States in the mid-1960s and continues today initially came from concern over the use of hallucinogens, particularly LSD. In the early 1960s, Timothy Leary, then a young psychology instructor at Harvard, began experimenting with hallucinogens, particularly LSD. He claimed that LSD provided instant happiness, enhanced creativity in art and music, facilitated problem-solving ability in school and at work, increased self-awareness, and might be useful as an adjunct to psychotherapy. Leary popularized this on college campuses, coining the phrase "turn on, tune in, drop out." When he was not reappointed to the faculty at Harvard, he became a highly publicized, self-proclaimed martyr to his cause, and his followers began to proselytize for LSD. Leary's advocates organized their lifestyle around LSD and developed a subculture of fellow LSD users who shared

this common interest. Furthermore, they would not use other classes of drugs; they would not smoke tobacco, use amphetamine or amphetamine-like psychostimulants or barbiturates, or even drink alcohol. Thus, very little polydrug abuse occurred among these LSD users.

The lay press repeatedly "discovered" LSD and, in effect, advertised the LSD experience. As publicity increased, subcultures experimenting with LSD began to emerge in many east and west coast cities. Other hallucinogenic compounds, such as mescaline and psilocybin, began to be taken as well, although LSD remained the most widely used hallucinogen in view of its ready availability on the street. Musicians, rock music, the hippie lifestyle, and "flower children" were loosely joined with Leary's philosophy. There were highly publicized festivals celebrating LSD, such as "The Summer of Love" in the Haight-Ashbury district of San Francisco. Later, its use began to increase in all socioeconomic groups, particularly among middle-class and affluent youth. Moreover, many of these individuals also became active in various protest movements, speaking out against such government policies as the war in Vietnam, and about other national issues, such as civil rights. About this time, various adverse reactions to LSD (and other hallucinogens) began to be reported from medical centers around the country. The whole phenomenon continued to be widely publicized, and in many cases sensationalized, by the press. The populace reacted with anxiety and fear, worrying that many of the young would soon become "acidheads."

Many of the LSD users eventually became involved in polydrug abuse, using other drugs besides hallucinogens. This included the extensive use of marijuana, hashish, and, in some cases, methamphetamine or even heroin. Various "street" substances, whose identity was frequently unknown, as well as combinations of drugs were consumed. In addition, in the search for new drugs with different and improved characteristics, such as more or less euphoria, hallucinogenic activity or stimulant properties, longer or shorter duration of action, literally hundreds of so-called designer drugs were synthesized (e.g., DOM, MDMA, DMT). Concern about drug abuse rose to the point of becoming perceived as one of the nation's most pressing problems, along with the economy and the war in Vietnam. The nation geared up to declare the "war on drugs," and the national drug abuse effort expanded from a relatively small research-oriented program under the National Institute of Mental Health (NIMH) to the then newly created National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Eventually, a new "superagency," the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), was established to oversee NIDA, NIAAA, and NIMH. ADAMHA subsequently merged into the National Institutes of Health (NIH), only to be dissolved in later years. Yet, these NIH institutes; the Drug Enforcement Agency (DEA); the Bureau of Alcohol, Tobacco, and Firearms (BATF); the Office of the National Drug Control Policy (ONDCP); and local law-enforcement agencies continue to be involved in the "war on drugs."

By the mid-1960s, more than 1,000 articles on LSD had appeared in the medical literature. Sandoz Laboratories stopped distributing the drug in late 1966 because of the reported adverse reactions and the resulting public outcry. At that time, all of the existing supplies of LSD were turned over to the government, which was to make the drug available for legitimate and highly controlled research; however, research on humans was essentially discontinued. Although some of the hallucinogens originally were developed and studied for use in chemical warfare, the results of these experiments remain classified. Today, LSD, along with heroin, marijuana, and other psychoactive drugs, remains classified as a Schedule I drug according to the Comprehensive Drug Abuse Prevention and Control Act of 1970. Legally, LSD is regarded as having no currently accepted medical use in the United States, a high potential for abuse, and to be unsafe even when administered by a physician. Nevertheless, "black-market" LSD remains widely available on the street. The therapeutic potential of LSD as an adjunct to psychotherapy, in the management of the dying patient, and in the treatment of alcoholism and neuropsychiatric illness such as obsessive–compulsive disorder, remains unresolved, but there has been a resurgence of interest in carrying out hallucinogen research in humans.

Epidemiology

The available epidemiologic data on the use of hallucinogens center on the use of LSD and primarily come from the Monitoring the Future (MTF) studies. Many studies have lumped hallucinogens and "club drugs" (e.g., MDMA) together, making the data very difficult to interpret. The use of LSD peaked in 1995 among college students and young adults and in 1996 among 8th, 10th, and 12th graders, after which it gradually declined, then dropped sharply in 2002. This might have been due to, at least in part, the closing of a major LSD lab by the DEA. In 2008, 4% of 12th graders reported lifetime use of LSD, whereas approximately 20% of adults aged 29 to 30 reported lifetime use. Among White, African American, and Hispanic 12th graders, Whites have the highest rate of LSD use. In 2008, approximately 28% of 12th graders indicated that LSD was fairly easy or very easy to get. More than 85% of 12th graders disapproved of trying LSD once or twice, but only 34% felt trying LSD presented a risk.

Phenomenology

In the 1960s, LSD was used primarily by those interested in its ability to alter perceptual experiences (sight, sound, taste, and feeling states). Much attention was paid to *set*, the expectation of what the drug experience would be like, and *setting*, the environment in which the drug was used. The early drug missionaries promulgated the erroneous notion that only good LSD "trips" would result if the prospective user established a number of preconditions before his or her drug experience. The preconditions relating to set included being relaxed and largely stress- or anxiety free; having no major resentment or anger and no recent arguments at home, school, or work; and freeing up several days, often an entire weekend, for the drug experience and its aftermath. The preconditions relating to setting included having a close friend present as a sitter or guide for the experience; being in quiet, comfortable surroundings, particularly outdoors, or sitting on soft, thick carpeting; listening to pleasant sounds or music; and reading reassuring passages. In more recent years, users often attend concerts, dances ("raves"), or films (particularly psychedelic or brightly colored ones) during the drug experience. Use is rarely more than once weekly because tolerance to LSD and other hallucinogens occurs so rapidly.

Chemical Classification

Indolealkylamines

All of the indole-type hallucinogens have structural similarities to the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]), suggesting that their mechanism of action could involve the alteration of serotonergic neurotransmission.

Lysergic Acid Derivatives

Lysergic acid is one of the constituents of the ergot fungus that grows on rye. Inadvertently baked into bread, ergot intake has been associated with profound mental changes. Because the presence of the diethylamide group is a prerequisite for hallucinogenic activity, it is not clear whether these reported epidemics were actually caused by ergot in the bread, or by some other related substances or (psychological) phenomena. LSD was first synthesized by Hofmann in 1938; as the 25th compound made in this series of experiments on ergot derivatives, the drug was

designated as "LSD-25." In 1943, Hofmann accidentally ingested some of the compound and soon had the first LSD "trip" on a famous bicycle ride home from his laboratory. The seeds of the morning glory (*Ipomoea*) contain lysergic acid derivatives, particularly lysergic acid amide. Although they are packaged commercially, many varieties have been treated with insecticides, fungicides, and other toxic chemicals.

Substituted Tryptamines

Psilocybin and psilocin occur naturally in a variety of mushrooms that have hallucinogenic properties. The most publicized is the Mexican or "magic" mushroom, *Psilocybe mexicana*, which contains both psilocybin and psilocin, as do some of the other *Psilocybe* and *Conocybe* species. DMT, although found in the psychoactive ayahuasca, is usually produced synthetically.

Substituted Phenethylamines

The substituted phenethylamine-type hallucinogens are structurally related to the catecholamine neurotransmitters dopamine, norepinephrine, and epinephrine.

Mescaline

Mescaline is a naturally occurring hallucinogen present in the peyote cactus (*Lophophora williamsii* or *Anhalonium lewinii*), which is found in southwestern United States and northern Mexico. Peyote has been used by the Indians in these areas in highly structured tribal religious rituals for hundreds of years.

Phenylisopropylamines

The phenylisopropylamine hallucinogens DOM (or STP, from "serenity, tranquility, and peace"), MDA (methylenedioxyamphetamine or "Eve"), and MDMA (or ecstasy) are synthetic compounds and are structurally similar to mescaline as well as the psychostimulant amphetamine. They have inaccurately been called "psychotomimetic amphetamines," and are sometimes referred to as "stimulant hallucinogens." It should be pointed out that literally hundreds of analogs of the aforementioned compounds have been synthesized and are sometimes found on the street, the so-called designer drugs.

Acute Effects

The overall psychological effects of many of the hallucinogens are quite similar; however, the rate of onset, duration of action, and absolute intensity of the effects differ among the drugs. Moreover, the various hallucinogens vary widely in potency and the slope of the dose–response curve. Thus, some of the apparent qualitative differences among hallucinogens may be partly a result of the amount of drug ingested relative to its specific dose–response characteristics. LSD is one of the most potent hallucinogens known, with behavioral effects occurring in some individuals after doses as low as 20 μg. In the past, typical street doses ranged from 50 to 300 μg; however, some anecdotal evidence indicates that today's street LSD contains only 20 to 80 μg (although doses reported on the street are often inaccurate). Because of its high potency, LSD can be applied to paper blotters or the backs of postage stamps. The absorption of LSD from the gastrointestinal tract occurs rapidly, with drug diffusion to all tissues, including the brain. The onset of psychological and behavioral effects occurs approximately 60 minutes after oral administration and peaks 2 to 4 hours after administration, with a gradual return to the predrug state in 10 to 12 hours.

The first 4 hours are sometimes called a "trip." The subjective effects of LSD are dramatic and can be divided into somatic (dizziness, paresthesias, weakness, and tremor), perceptual

(altered visual sense and changes in hearing), and psychic (changes in mood, dream-like feelings, altered time sense, and depersonalization). The somatic symptoms usually occur first. Later, visual alterations are marked and sounds are intensified. Visual distortions and illusory phenomena occur, but true hallucinations are rare. Dream-like imagery may develop when the eyes are closed, and afterimages are prolonged. Sensory input becomes mixed together, and synesthesia ("seeing" smells, "hearing" colors) is commonly reported. Touch is magnified and time is markedly distorted. Feelings of attainment of true insight are common, as is the experience of delusional ideation. Separating one object from another and self from environment becomes difficult, and depersonalization can develop. Emotions become intensified, and extreme lability may be observed, with rapid and extreme changes in affect. Several emotional feelings may occur at the same time. Performance on tests involving attention, concentration, and motivation is impaired. Several hours later, subjects sometimes feel that the drug is no longer active, but later they recognize that at that time they had paranoid thoughts and ideas of reference. This is a regular, but little publicized, aftereffect that finally dissipates 10 to 12 hours after the dose. From 12 to 24 hours after the trip, there may be some slight letdown or a feeling of fatigue. There is no immediate craving to take more drug to relieve this boredom; one trip usually produces "satiation" for some time. Memory for the events that occurred during the trip is quite clear.

Effects produced by DMT are similar to those produced by LSD, but DMT is inactive after oral administration and must be injected, sniffed, or smoked. It has a rapid onset, almost immediately after intravenous administration, and a short duration of action, about 30 minutes. Because of its short duration of action, DMT was once known as the "businessman's LSD" (i.e., one could have a psychedelic experience during the lunch hour and be back at work in the afternoon). However, the sudden and rapid onset of a period of altered perceptions that soon terminates is disconcerting to some. DMT has never been a widely, steadily available or popular drug on the streets. The effects of ayahuasca, a psychoactive beverage that contains DMT, last about 4 hours. In contrast to DMT, a very slow onset and a long duration (longer than 24 hours) of effects are reported for DOM. Mescaline is approximately two to three orders of magnitude less potent than LSD, and its effects last about 6 to 10 hours, whereas the effects of psilocybin last about 2 hours.

The hallucinogens also possess significant autonomic activity. LSD produces marked pupillary dilation, hyperreflexia, increases in blood pressure and body temperature, tremor, piloerection, and tachycardia. Some of these autonomic effects of the hallucinogens are variable and might be partly a result of the anxiety state of the user. DMT and ayahuasca also increase heart rate, pupil diameter, and body temperature. LSD can cause nausea, and nausea and vomiting are especially noteworthy after the ingestion of mescaline or peyote. The hallucinogens also alter neuroendocrine function. For example, in humans, DMT elevates plasma levels of adrenocorticotropic hormone (ACTH), cortisol, and prolactin. Similarly, the hallucinogen 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) increases plasma glucocorticoids in the rat.

Effects of Chronic Use

A high degree of tolerance to the behavioral effects of LSD develops after repeated administration. Such behavioral tolerance develops very rapidly, after only several days of daily administration, and tolerance is also lost rapidly after the individual user stops taking the drug for several days. Because of this rapid development of tolerance, LSD users usually typically limit themselves the use of taking the drug to once or twice weekly. Cross-tolerance develops between LSD and other hallucinogens, such as mescaline and psilocybin, suggesting a similar mechanism of action. However, cross-tolerance does not develop to other classes of

psychotropic agents that are thought to have different underlying mechanisms of action, such as amphetamine, PCP, and marijuana. It should be pointed out that little tolerance develops to the various autonomic effects produced by the hallucinogens. There is no withdrawal syndrome after the cessation of the chronic administration of the hallucinogens.

Mechanisms of Action

Hallucinogenic drugs interact with multiple neurotransmitter systems, and the mechanisms of action to evoke their physiologic and psychological effects are complex. However, the ability of LSD and other hallucinogens to alter serotonin neurotransmission is of critical importance. Many hallucinogens, including LSD, were identified to be structurally similar to serotonin and LSD acted upon serotonergic systems within the CNS. LSD increases the levels of serotonin in rat brain, but decreased the levels of serotonin metabolites, whereas the nonhallucinogenic analog bromo-LSD fails to have the same effects. But bromo-LSD does not produce hallucinatory phenomena, suggesting that the hallucinogenic effects of LSD might be caused by LSD-induced decreases in serotonin turnover (synthesis and release) in the brain. Other evidence supports the interaction of hallucinogens with serotonergic systems: (a) the chronic administration of monoamine oxidase inhibitors decreases the density of serotonin receptors and reduces the behavioral effects of LSD, and (b) treatments that decreased brain levels of serotonin (e.g., lesions, reserpine, parachloroamphetamine, or other neurotoxins), upregulated postsynaptic serotonin receptors, and increased the behavioral effects of LSD.

Serotonin released from nerve terminals is available to interact with multiple receptors that transduce serotonin actions in the brain and periphery. Early studies demonstrated that LSD blocked the contractile effects of serotonin in isolated smooth muscle preparations, suggesting that LSD might produce its psychic effects by having similar antagonist activity at central serotonergic synapses. However, the LSD analog bromo-LSD was identified as a potent peripheral serotonin antagonist that did not evoke an LSD-like psychopharmacologic profile. Thus, the mechanism of the hallucinogenic activity of LSD could not be explained solely by its direct serotonergic antagonist activity. Rather, evidence accumulated rapidly to support an agonist-like action for LSD and other hallucinogens at serotonin receptors in the brain. It is important to note that serotonin acts at multiple receptor subtypes found in the brain and periphery. These receptors have been identified and grouped into seven families (5-HT_1R to 5-HT_7R) according to their structural and functional characteristics, including 13 distinct G-protein coupled receptors, coupled to various effector systems, and two subtypes of the 5-HT_3R, which is a pentameric ligand-gated ion channel.

LSD binds to most serotonin receptor subtypes, except 5-HT_3R and 5-HT_4R; however, its affinity for most of these receptors is too low to predict receptor activation at the brain levels achieved after ingestion of psychoactive doses. The receptors thought to contribute predominantly to its effects include the 5-HT_{1A}R, 5-HT_{2A}R, 5-HT_{2C}R, 5-HT_{5A}R, and 5-HT_6R. LSD inhibits the firing of serotonergic neurons in the dorsal raphe nucleus, most likely by interacting with presynaptic autoreceptors, termed the 5-HT_{1A}R. Other indole-type hallucinogens, such as psilocin and DMT, also produce this effect. However, strong evidence refutes a direct linkage between the presynaptic effects of LSD and its hallucinogenic activity: (a) phenethylamine hallucinogens, such as mescaline, do not have the same inhibitory effects on the firing of serotonergic neurons; (b) there is no correlation between the activity of drugs at the presynaptic 5-HT_{1A}R and their hallucinogenic activity; and (c) tolerance does not develop to the effects of the hallucinogens on neuronal firing, but behavioral tolerance rapidly develops after the repeated administration of hallucinogens. These findings suggest that interactions with the presynaptic 5-HT_{1A}R cannot be the sole mechanism of action of the hallucinogens, and other factors must be involved.

Both indole- and phenethylamine-type hallucinogens bind with varying affinities to the three members of the serotonin 5-HT_2R, which is composed of the 5-HT_{2A}R, 5-HT_{2B}R, and 5-HT_{2C}R; its actions at these receptors are characterized as either full or partial agonists. There is compelling evidence that an agonist action at the 5-HT_{2A}R is a key component underlying the mechanisms of action of the hallucinogens. For example, (a) there are very high correlations between the binding affinities of both indolealkylamine- and phenethylamine-type hallucinogens for the 5-HT_{2A}R and their hallucinogenic activity in humans and their potency in behavioral studies in laboratory animals; (b) the chronic administration of LSD, but not the nonhallucinogenic analog bromo-LSD, decreases the density of 5-HT_{2A}R, an effect associated with the development of tolerance to the behavioral effects of LSD; and (c) preclinical studies found that many of the effects of hallucinogens are blocked by 5-HT_{2A}R antagonists.

Even though the interaction of hallucinogens with the 5-HT_{2A}R appears to be critical, other serotonergic receptor subtypes might also be involved. For example, interactions with the closely related 5-HT_{2C}R (formerly called 5-HT_{1C}R) might contribute to the psychoactive effects of hallucinogens. Although apparently not critical for hallucinogenic activity, interactions with presynaptic 5-HT_{1A}R might contribute to the effects of some hallucinogens. LSD has been reported to act as an agonist at the 5-HT_5R (5-HT_{5A}R and 5-HT_{5B}R) and 5-HT_6R; however, a full appreciation of how these receptors contribute to the myriad of effects of hallucinogens awaits a full characterization of the receptors. The differential interactions of the various hallucinogens with numerous sites and systems might underlie the qualitative differences between the subjective experiences of the class of hallucinogenic drugs. However, the commonality of interactions with 5-HT_{2A}R suggests that drugs that possess 5-HT_{2A}R antagonist activity might be useful in blocking the behavioral effects of the hallucinogens in humans.

Adverse Reactions

Acute Adverse Reactions

Social factors, media presentations, and public fear have all shaped perceptions of the effects of LSD and other hallucinogens. A person's reaction to the effects of a drug may be felt to be either a pleasant or an unpleasant experience; a perceptual distortion or illusion may cause intense anxiety in one user and be a pleasant and amusing interlude for another user. Individuals who place a premium on self-control, advance planning, and impulse restriction may do particularly poorly on LSD. Traumatic and stressful external events can precipitate an adverse reaction (e.g., being arrested and read one's rights in the middle of a pleasant experience may precipitate an anxiety reaction). Predictions of who will have an acute (or other) adverse reaction are unreliable, and the occurrence of multiple previous pleasurable LSD experiences renders no immunity from an adverse reaction. Adverse reactions have occurred after doses of LSD as low as 40 µg, and no adverse effects have been observed in some individuals after ingesting 2,000 µg, although in general the hallucinogenic effects are dose dependent. Thus, acute adverse behavioral reactions are generally not dose related, but a function of personal predisposition, setting, and circumstance. Because of the perceptual distortions (and subsequent deficits in judgment), there is always the risk of self-destructive behavior. Some of the adverse reactions that occur after ingesting hallucinogens can be caused by other contaminants in the product, such as strychnine, PCP, or amphetamine. Once commonly reported by medical facilities, acute adverse LSD reactions are rarely seen today, yet the drug remains in use. Moreover, the paucity of users seeking emergency medical treatment may reflect increased knowledge of how to deal with such situations on the part of the "drug-using community," a decrease in the doses of LSD

currently used compared with those used in the past, and the availability of drugs to reduce the adverse effects (e.g., benzodiazepines for anxiety reactions).

Acute anxiety or panic reactions, the so-called "bad trip," are the most commonly reported acute adverse reactions. They usually wear off before medical intervention is sought; most LSD is metabolized and excreted within 24 hours, and acute panic reactions usually subside within this time frame. Depression with suicidal ideation can occur several days after LSD use. Paranoid ideation, "hallucinations," and a confusional state (organic brain syndrome) are other commonly reported acute adverse reactions. Initially, it was thought that LSD could replicate the signs and symptoms of schizophrenia in some subjects, and the induction of such a model psychosis could be used to study and potentially find a cure for this major psychiatric illness. These hopes did not materialize, as major differences have been found between hallucinogen-induced psychosis and the schizophrenic state.

The differential diagnosis between LSD psychosis and paranoid schizophrenia is an important distinction to be made clinically, particularly because patients, who in fact are paranoid, now often complain of being poisoned with LSD. A history of prior mental illness, a psychiatric examination that reveals the absence of an intact or observing ego, and auditory (rather than visual) hallucinations all suggest schizophrenia. Other drug-induced psychoses, including those from psychostimulants or PCP, must be ruled out. An organic brain syndrome in general speaks against LSD, especially when obtunded consciousness is present. Toxicologic analysis of body fluids can be helpful in making the ultimate diagnosis, but supportive treatment must not be withheld. Atropine poisoning can be differentiated by the presence of prominent anticholinergic effects such as dry mouth and blurred vision. Patients with amphetamine psychosis often fail to differentiate their perceptual distortions from reality, whereas LSD users are aware of the difference.

In terms of adverse physiologic effects, LSD has a very high therapeutic index. The lethal dose in humans has not been determined, and fatalities that have been reported are usually secondary to perceptual distortions with resultant accidental death (e.g., "flying" off a roof, merging with an oncoming automobile on the freeway). Posterior reversible encephalopathy syndrome with accompanying seizures occurred after ingesting LSD. Although LSD has prominent effects on the serotonin system, there is no evidence of association of its use with the serotonin syndrome, a potentially life-threatening reaction to some serotonergic drugs. DMT and ayahuasca have been reported to be relatively safe.

Treatment of Acute Adverse Reactions

Treatment of the acute adverse reactions to hallucinogens must first be directed toward preventing the patient from physically harming self or others. Anxiety can be handled by means of interpersonal support and reassurance. Psychotherapeutic intervention consists of reassurance, placing the patient in a quiet room, and avoidance of physical intrusion until the patient begins to calm down. The use of a benzodiazepine, such as lorazepam, can also be effective. The oral route can be used for administering such medication in mildly agitated patients; however, it can be difficult to convince severely agitated and/or paranoid patients to swallow a pill, in which case parenteral administration might be necessary. Severely agitated patients who fail to respond to a benzodiazepine may be given a neuroleptic agent. Caution must be used in administering neuroleptics because they can lower the seizure threshold and elicit seizures, especially if the hallucinogen has been cut with an agent that has convulsant activity, such as strychnine. Phenothiazine-type antipsychotics, such as chlorpromazine, given orally or intramuscularly can end an LSD trip and are effective in treating LSD-induced psychosis. Because anticholinergic crises can develop with chlorpromazine in combination with other drugs with anticholinergic activity (PCP and DOM), haloperidol is a safer therapeutic choice when the true nature of the drug ingested is unknown. It has been suggested that a combination of intramuscular haloperidol and lorazepam is particularly effective in treating acute adverse reactions. Theoretically,

selective 5-HT_{2A}R antagonists should block the effects of hallucinogens; however, other drugs with significant 5-HT_{2A}R antagonist activity such as atypical antipsychotics (e.g., olanzapine and risperidone) might also be effective.

Long-Term Adverse Effects

There is no generally accepted evidence of brain cell damage, chromosomal abnormalities, or teratogenic effects after the use of the indole-type hallucinogens and mescaline. Chronic adverse reactions include psychoses, depressive reactions, acting out, paranoid states, and flashbacks. The use of LSD has been found to coincide with the onset of depression, suggesting its possible role in the etiology of some depression in the young. Flashbacks are a well-publicized adverse reaction that can occur after taking hallucinogens. They now have been renamed "hallucinogen persisting perception disorder." Only a small proportion of LSD and other hallucinogenic users experience flashbacks. They can occur spontaneously a number of weeks or months after the original drug experience, appear not to be dose related, and can develop after a single exposure to the drug. During a flashback, the original drug experience is recreated completely with perceptual and reality distortion. Even a previously pleasant drug experience may be accompanied by anxiety when the person realizes that he or she has no control over its recurrence. In time, flashbacks decrease in intensity, frequency, and duration (although initially they usually last only a few seconds), whether treated or not. Flashbacks may or may not be precipitated by stressors or the subsequent use of other psychoactive drugs, such as psilocybin or marijuana. The administration of selective serotonin reuptake inhibitor antidepressants and risperidone is reported to initiate or exacerbate flashbacks in individuals with a history of LSD use. Flashbacks can usually be handled with psychotherapy. An anxiolytic or neuroleptic may be indicated, but probably is as much for the reassurance of the therapist as for the patient. Various pharmacologic agents, such as clonidine or clonazepam, or drug combinations (e.g., fluoxetine and olanzapine), have been found to be useful in the treatment of flashbacks. The exact mechanism underlying this phenomenon remains obscure. Individuals with flashbacks have a high lifetime incidence of affective disorder when compared with non–LSD-abusing substance abusers. LSD users have long-term changes in visual function. For example, a visual disturbance consisting of prolonged afterimages (palinopsia) has been found in individuals several years after the last reported use of LSD. Such changes in visual function might underlie flashbacks.

Psychosis can develop and persist after hallucinogen use, but it remains unclear whether hallucinogen use can "cause" long-term psychosis, or if it has a role in precipitating the onset of illness. For example, hallucinogens may have a variety of effects in a person who is genetically predisposed to schizophrenia: they may cause the psychosis to manifest at an earlier age, they may produce a psychosis that would have remained dormant if drugs had not been used, or they may cause relapse in a person who has previously suffered a psychotic disorder. Although there is some evidence that prolonged psychotic reactions tend to occur in individuals with poor premorbid adjustment, a history of psychiatric illness and/or repeated use of hallucinogens, severe and prolonged illness has been reported in individuals without such a history.

There are few, if any, long-term neuropsychological deficits attributable to hallucinogen use. Chronic personality changes with a shift in attitudes and evidence of magical thinking can occur after the use of hallucinogens. There is always the risk that such thinking can lead to destructive behavior, in acute as well as chronic reactions. The effects of the chronic use of LSD must be differentiated from the effects of personality disorders, particularly in those who use a variety of drugs in polydrug abuse patterns. In some individuals with well-integrated personalities and with no previous psychiatric history, chronic personality changes have resulted from repeated LSD use. Personality changes that result from LSD use can occur after a single experience, unlike other classes of drugs (except PCP, perhaps). In addition, the hallucinogenic drugs interact in a variety of nonspecific ways with the personality, which may particularly impair the developing adolescent. The suggestibility that may come from many experiences with

LSD may be reinforced by the social values of a particular subculture in which the drug is used. Treatment of chronic hallucinogen abuse can include psychotherapy on a long-term basis to determine what needs are being fulfilled by the use of the drug for this particular person. Twelve-step meetings might also be useful for reinforcement of the decision to remain abstinent.

Drug Interactions

Drug interactions involving the hallucinogens do not appear to be an important source of adverse reactions. There are reports that the effects of LSD are reduced after the chronic administration of monoamine oxidase inhibitors or selective serotonin reuptake inhibitor antidepressants, such as fluoxetine, whereas the effects of LSD are increased after the chronic administration of lithium or tricyclic antidepressants.

Conclusion

The hallucinogens represent a diverse group of drugs that have often been given significant and at times dramatic characterizations by the popular press and culture. Despite what at times has been a cultural bias, there has been interest in the study of these drugs in terms of their mechanism of action as well as their potential therapeutic use. The effects of hallucinogens on the serotonin system suggests they may both serve as pharmacologic probes for better understanding of this receptor system and provide insights into the effects of the serotonin system in human experience.

Suggested Readings

Carstairs SD, Cantrell FL. Peyote and mescaline exposures: a 12-year review of a statewide poison center database. *Clin Toxicol*. 2010;48:350–353.

Glennon RA. Do classical hallucinogens act as 5-HT_2 agonists or antagonists? *Neuropsychopharmacology*. 1990;3:509–517.

Gouzoulis-Mayfrank E, Schreckenberger M, Sabri O, et al. Neurometabolic effects of psilocybin, 3,4-methylene-dio-xyethylamphetamine (MDE) and *d*-methamphetamine in healthy volunteers. *Neuropsychopharmacology*. 1999;20:565–581.

Gouzoulis-Mayfrank, Heekeren K, Neukirch A, et al. Psychological effects of (s)-ketamine and N,N-dimethyltryptamine (DMT): a double-blind, cross-over study in healthy volunteers. *Pharmacopsychiatry*. 2005;38:301–311.

Griffiths RR, Richards WA, McCann U, et al. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl)*. 2006;187:268–283.

Halpern JH, Pope HG Jr. Hallucinogen persisting perception disorder: what do we know after 50 years? *Drug Alcohol Depend*. 2003;69:109–119.

Halpern JH, Pope HG Jr. Hallucinogens on the Internet: a vast new source of underground drug information. *Am J Psychiatry*. 2001;158:481–483.

Riba J, Rodriguez-Fornells A, Urbano G, et al. Subjective effects and tolerability of the South American psychoactive beverage ayahuasca in healthy volunteers. *Psychopharmacology (Berl)*. 2001;154:85–95.

Sessa B. Is it time to revisit the role of psychedelic drugs in enhancing human creativity? *J Psychopharmacol*. 2008;22:821–827.

Vollenweider FX, Vontobel P, Hell D, et al. 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in man—a PET study with [^{11}C]raclopride. *Neuropsychopharmacology*. 1999;20:424–433.

11 PCP, MDMA, and Designer Drugs

Certain drugs of abuse do not fall under any readily categorized drug class. Among these are phencyclidine (phenylcyclohexylpiperidine, PCP) and 3,4-methylenedioxymethamphetamine (MDMA), which are both sometimes referred to as "designer drugs" because they are manufactured in a chemical laboratory, rather than being derived from natural substances.

PCP

History

The original chemistry that led to the development of PCP took place in 1926. However, it took approximately an additional 30 years for PCP's anesthetic properties to be noted, initially in animals. In 1953, it was patented by Parke-Davis under the trade name of Sernyl in a research program targeting general anesthetics. Initial studies were promising and described the development of complete analgesia without respiratory or cardiovascular depression within a few minutes following intravenous administration of a relatively low dose. However, at higher doses that were necessary to achieve full surgical levels of anesthesia, undesirable adverse reactions were noted, including the requirement of pentobarbital for control of an "excited state."

Other early experiments involving the use of PCP for general anesthesia in humans also reported untoward side effects, including the development of apparent trance-like ecstatic states during anesthesia, and hallucinations, visual distortions, dizziness, slurred speech, and manic behavior upon emergence from anesthesia. According to some reports, nearly half of the patients who received PCP for anesthesia went on to develop psychotic reactions, some of which persisted for more than a week after surgery. Qualitatively similar, but less severe adverse effects were seen following administration of lower doses of PCP. The trance-like states that occurred in patients undergoing anesthesia with PCP, without full loss of consciousness, led to its classification as a "dissociative" anesthetic, along with the related compounds, cyclohexamine and ketamine.

Despite early promise and potential advantages over traditional general anesthetics, PCP's adverse effects and long half-life in the human body made it unsuitable for medical applications, and it was removed from the market in 1965. In 1967, it was given the trade name *Sernylan* and marketed as a veterinary anesthetic, but was again discontinued. Ironically, the ability of PCP to produce hallucinations and an altered sense of consciousness appeared to fuel, rather than deter, the first PCP epidemic in the 1970s.

Psychopharmacology

The existence of PCP receptors in the brain of rats was first demonstrated in 1979. Subsequent research in the 1980s demonstrated that PCP's primary mechanism of action was as a potent inhibitor of neurotransmission mediated by *N*-methyl-D-aspartate (NMDA) receptors, one of several receptor sites for the excitatory amino acid, glutamate. At 10-fold higher dosages, PCP also blocks presynaptic monoamine reuptake, resulting in increased synaptic levels of dopamine (DA), norepinephrine, and serotonin. Although activity at NMDA receptors occurs at much lower dosages than required to influence monoaminergic activity, monoaminergic inhibition may be achieved at doses abused recreationally that lead to intoxication. At levels of extreme intoxication, PCP blocks sodium and potassium channels and can interact with cholinergic, opiate, and γ-aminobutyric acid (GABA)/benzodiazepine receptors. These interactions are minor and not likely to occur at doses typically used in recreational settings.

PCP is highly lipid soluble and is primarily metabolized through hepatic pathways. It is stored in fatty body tissues, and it is believed that mobilization of fat stores of PCP is responsible for waxing and waning states of intoxication that can last for weeks, "flashbacks," and persistent positive urine toxicology tests that persist days to weeks after PCP ingestion. Hepatic recirculation of PCP may also explain fluctuating levels of intoxication seen following PCP use.

The behavioral effects of PCP are dose related but highly variable among individuals. Lower doses of PCP typically lead to a giddy euphoria that resembles alcohol intoxication, although anxiety, paranoia, and emotional outbursts can be seen. Higher dosages can lead to dysarthria, ataxia, increased deep tendon reflexes, decreased pain sensation, tachycardia, hypertension, and, as previously mentioned, altered perception. Malignant hyperthermia after PCP intoxication has been reported, and PCP intoxication can progress to stupor and coma. PCP is one of only a few drugs that can cause vertical nystagmus (horizontal nystagmus can also occur); the combination of nystagmus and hypertension in an otherwise healthy young adult should alert the physician to the possibility of PCP intoxication.

PCP-induced psychosis has been put forth as a model for schizophrenia, and a number of authors have hypothesized, based on clinical experience and available epidemiologic evidence, that individuals with previous psychiatric problems who use PCP are at the highest risk for developing persistent psychotic symptoms following PCP use.

Epidemiology

PCP is sold as tablets, capsules, or as white or colored powder. It is odorless and water soluble. It is often misrepresented as being more expensive substances (e.g., lysergic acid diethylamide, tetrahydrocannabinol, mescaline, and cocaine) and is often used to lace inferior batches of other drugs (e.g., marijuana). There are literally hundreds of street names for PCP, but commonly used names include angel dust, killer weed, PeaCe Pill, ozone, wack, and power fuel. Because of the large number of names for PCP and the fact that it is often used as an adulterant of other illicit substances, many people are unaware that they have used PCP. Epidemiologic data, therefore, are obtained using a variety of methods, including reports from emergency room visits, deaths, drug-abuse treatment facilities, and national surveys.

Using these sources for data, it has been suggested that there was an epidemic of PCP use between 1973 and 1979 and again, perhaps, between 1981 and 1984. Although there are regional differences in the mode of ingestion, in more than 85% of the cases, PCP is smoked, followed by inhalation or oral ingestion. Less than 2% of individuals use PCP intravenously. Usually, smoked PCP is in conjunction with marijuana, tobacco, or parsley. Individuals report developing a tolerance to PCP, with experienced users needing higher dosages of PCP to achieve the same effect.

Current Trends in PCP Use

According to recent data from the National Survey on Drug Use and Health (NSDUH), 48,000 individuals in the United States over the age of 12 initiated use of PCP during 2011. This is significantly lower than the numbers in 2002, 2003, and 2004, when the number of new users of PCP were estimated to be 123,000, 105,000, and 106,000, respectively. To put this number in perspective, the number of new users of marijuana in 2011 was estimated at 2.6 million, and new users of MDMA were estimated at 922,000. An estimated 6,103,000 individuals reported that they had used PCP at some point during their life in 2011, with approximately 119,000 individuals having used PCP within the past year. These numbers are not significantly different from those reported in 2010.

Neurotoxicity

It has been reported that single doses of PCP and related compounds (MK-801 and ketamine) led to neuronal damage of cortical neurons in rats. In particular, neurons located in layers III and IV of the posterior cingulate and retrosplenial cortices have been observed to have abnormal cytoplasmic vacuolization that was directly correlated with the potency of noncompetitive NMDA blockade. Other studies indicate that PCP induces neuronal degeneration in a variety of cerebrocortical and limbic regions, although the mechanism of degeneration is not well understood. It is also not known whether PCP-induced neuronal injury is related to lasting psychiatric and cognitive changes that have been reported in some PCP users.

MDMA

History

MDMA (sometimes also known as "ecstasy") was synthesized and patented by Merck in 1914, but was never used for commercial purposes. Although it is an amphetamine analog, it is also structurally related to mescaline, the classic hallucinogen. MDMA received little attention from the pharmaceutical or scientific communities until the 1970s. In 1985, the Drug Enforcement Administration (DEA) in the United States moved to severely restrict MDMA use by placing it on Schedule I of controlled substances. The DEA indicated that their decision was based on reports that recreational use of MDMA was on the rise, as well as concerns that MDMA might pose a public health threat, since a closely related congener of MDMA, 3,4-methylenedioxyamphetamine (MDA), had recently been found to produce toxic effects on brain serotonin neurons in rodents. The DEA also argued that MDMA had no medical utility, a statement that was disputed by a number of mental health specialists who asserted that it had utility in psychotherapeutic settings.

At roughly the same time that the DEA placed MDMA on Schedule I, MDMA's popularity was increasing on college campuses. Interestingly, this increase in popularity took place despite growing preclinical evidence that MDMA, like MDA, had the potential to damage brain serotonin neurons.

Psychopharmacology

The most prominent acute pharmacologic effect of MDMA is calcium-independent release of brain serotonin (5-HT) from brain serotonin neurons via vesicular and plasma membrane monoamine transporters. To a lesser degree, MDMA also induces release of DA. Like other amphetamines, the most prominent effects of MDMA are mediated indirectly, via release of

monoamines, rather than by directly interacting with monoaminergic receptors. This primary indirect action of MDMA is in contrast to hallucinogenic amphetamines that act primarily by activating serotonergic receptors.

Although MDMA's primary effects are indirect, it does bind to several postsynaptic receptor sites. These include, in order of affinity, the 5-HT_{2A} receptor, the α-2 adrenergic receptor, the 5-HT_2 receptor, the histamine H_1 receptor, and the muscarinic M_1 receptor. Binding at other 5-HT and adrenergic receptors, DA receptors, opioid receptors, and benzodiazepine receptors only occurs at very high concentrations.

As might be predicted by its acute pharmacologic effects, in animals MDMA administration leads to typical signs of sympathomimetic stimulation. However, some behavioral studies suggest that MDMA can be distinguished from typical stimulants. In drug discrimination studies, MDMA substitutes for D-amphetamine in rats, pigeons, and monkeys trained to discriminate D-amphetamine from saline. Results from testing with hallucinogens are less clear-cut. In particular, MDMA does not substitute for the hallucinogen DOB (dimethoxybromamphetamine), but does substitute with the α-ethyl derivative of the hallucinogen DOM (dimethoxymethylamphetamine), as well as the α-ethyl derivative α-methyltryptamine. Several animal models suggest that MDMA has abuse liability. In particular, both baboons and monkeys self-administer MDMA. Further, in intracranial self-stimulation models, MDMA consistently lowers the threshold for rewarding electrical stimulation delivered via electrodes stereotaxically implanted in the medial forebrain bundle region.

Knowledge regarding the behavioral effects of MDMA in humans has been derived from both retrospective clinical reports and reports from research subjects who receive MDMA in controlled research settings. As might be anticipated by MDMA's acute pharmacology and behavioral effects in animals, both sources indicate that, as in animals, MDMA has prominent acute stimulant effects. In addition, human MDMA users also report effects that are commonly associated with hallucinogens. Shortly after drug ingestion, stimulant effects of MDMA that have been reported include increased heart rate and blood pressure, increased core body temperature, dry mouth, decreased appetite, increased alertness, decreased speech fluency, jaw clenching, increased sleep latency, and altered sleep architecture. Associated with these physiologic effects of MDMA is an increased sense of well-being and, occasionally, euphoria. Most MDMA users do not report hallucinations, but often report increased emotional sensitiveness, a feeling of "oneness," depersonalization or sense that certain body parts are "other," derealization, and altered time perception. There continues to be interest by some mental health practitioners in the utility of MDMA as a potential psychotherapeutic adjunct.

Epidemiology

The best epidemiologic data on MDMA use in the United States is derived from the Monitoring the Future (MTF) Survey, which has measured trends in drug use among 8th, 10th, and 12th graders since 1975, and the NSDUH, which measures trends in drug use among individuals who are 12 years and older. According to MTF data, MDMA use peaked among adolescents in 2001 and has been relatively stable since 2006. Although use of MDMA is not currently rising, the perceived risk associated with MDMA use has been in decline in recent years, which is considered a concern. In 2009, 4.3% of high school seniors reported having used MDMA in the past year, with 3.7% and 1.3% of 10th and 8th graders reporting past-year use.

The NSDUH data indicate that in 2011, an estimated 544,000 individuals (0.2% of the population) in the United States over the age of 12 had used MDMA in the month prior to the survey. Past-year use of MDMA decreased from 1.0% (2.9 million) to 0.9% (2.4 million persons) between 2010 and 2011. Approximately 922,000 Americans used MDMA for the first time in 2011, which is a slight (nonsignificant) decrease from the 949,000 first-time users reported in 2010 (and a decrease from the 1.1 million first-time users in 2009).

Toxicity

Toxic effects of MDMA are, in large part, an exaggeration of acute pharmacologic actions and can include anxiety, agitation, confusion, insomnia, nausea, and palpitations. More serious adverse effects include potentially fatal malignant hypertension, severe hyperthermia, cardiac arrhythmias, myocardial infarction, strokes (both ischemic and hemorrhagic), cerebral edema, and seizures. Less well-understood adverse effects of MDMA that have been reported are the development of a syndrome of inappropriate antidiuretic hormone secretion, marked elevation in serum creatine kinase in the absence of muscle injury, and persistent neuropsychiatric complications.

Neurotoxicity

In addition to its use as a recreational drug, MDMA is also a well-documented brain serotonin (5-HT) neurotoxin in animals. In particular, MDMA causes dose-related reductions of brain serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations, the density of 5-HT uptake sites, and the activity of tryptophan hydroxylase. Neurochemical deficits, which have been documented up to 7 years after drug administration in nonhuman primates, are associated with a loss of 5-HT axon terminals, as measured using immunocytochemical methods, indicating that they are related to a distal axotomy. Although MDMA-induced 5-HT neurotoxicity is dose related, even single oral dosages that produce plasma levels on the order of those seen following human recreational use have been shown to produce neurotoxic injury.

There are also significant data indicating that some humans who use MDMA, like animals with documented MDMA-induced 5-HT lesions, develop a persistent reduction in brain 5-HT axonal markers. The duration of these lesions and their functional consequences are still a matter of debate, but it has been hypothesized that the MDMA-induced 5-HT neurotoxicity may underlie cognitive and sleep abnormalities that have been documented in abstinent MDMA users.

Miscellaneous Designer Drugs

As noted previously, designer drugs are drugs that are synthesized making minor modifications to the chemical structure of an existing drug. The goal of this enterprise is to circumvent laws (e.g., create a substance that is not illegal or scheduled) or to save money (create more potent or cheaper analogs of an existing, expensive product). In an effort to prevent the legal distribution and sale of "look-alike" designer drugs, the U.S. government amended the Controlled Substances Act in 1986 to include the Controlled Substances Analogues Enforcement Act. This law states that a substance is classified as illegal if it is "substantially similar" to the chemical structure of an already controlled substance in Schedule I or II. Despite this action, there is sufficient ambiguity in the definition of "substantially similar" that some argue that the law is imprecise and essentially useless.

As might be concluded by the definition of designer drugs, the possibilities for such compounds are virtually endless. Indeed, in a classic book about "designer" phenethylamine analogs, Alexander Shulgin and Ann Shulgin describe the synthesis and subjective effects of 179 designer drugs, including MDMA.

In addition to MDMA and related compounds, the most important designer compounds in terms of public health and substance abuse have been drugs that have been used as substitutes for opiates. α-methylfentanyl, also known as China White, was first manufactured in clandestine laboratories in Orange County, California, in 1979, and was the first synthetically produced fentanyl; it resulted in at least 15 overdose deaths. Over the next 5 years, at least 3 other analogs were identified in street-drug samples and in the bodily fluids of overdose victims: α-methylacetylfentanyl, 3-methylfentanyl, and parafluorofentanyl. In 1988, 3-methylfentanyl was identified in 16 unintentional overdose deaths in Allegheny County, Pennsylvania.

Designer analogs of meperidine (marketed as Demerol) have also appeared periodically in the illicit drug market. Two meperidine analogs that have appeared on the streets include MPPP (1-methyl-4-phenyl-4-propionoxypiperidine) and PEPAP (1-[2-phenylethyl]-4-acetyloxypiperdine). In 1983, there was an unusual outbreak of parkinsonism among young intravenous heroin abusers in California. These cases were reminiscent of an earlier similar case that had been identified at the National Institutes of Health (NIH) campus in Bethesda, Maryland. It was subsequently determined that the illicitly manufactured MPPP was tainted with 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP), a potent neurotoxin that destroys DA-containing cells in the pars compacta of the substantia nigra, the chief site of pathology in Parkinson's disease. These cases underscore the potential disastrous results from even minor modifications to the chemical structure of drugs with known safety and efficacy profiles.

Conclusion

MDMA and PCP are illicit drugs that have the potential to damage brain cells, in addition to their risks as drugs of abuse. The functional consequences of MDMA- and PCP-induced neurotoxicity are not fully understood but may include lasting cognitive disturbance. Although other "designer drugs" are not used by large percentages of the population, they periodically appear in the drug market, particularly during periods when the parent drug is scarce or expensive. In the case of designer opioids, deaths from unintentional overdose related to increased drug potency, and the development of parkinsonism related to drug contamination, underscore the fact that even minor chemical modifications to a drug structure can lead to profound pharmacologic and toxicologic changes.

Suggested Readings

Bouso JC, Doblin R, Farré M, et al. MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder. *J Psychoactive Drugs*. 2008;40(3):225–236.

Buchert R, Thomasius R, Nebeling B, et al. Long-term effects of "ecstasy" use on serotonin transporters of the brain investigated by PET. *J Nucl Med*. 2009;44:375–384.

Green AR, Mechan AO, Elliott JM, et al. The pharmacology and clinical pharmacology of 3,4-methylene dioxymethamphetamine (MDMA, "ecstasy"). *Pharmacol Rev*. 2003;55(3):463–508.

Johanson CE, Kilbey M, Gatchalian K, et al. Discriminative stimulus effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans trained to discriminate among D-amphetamine, metachlorophenylpiperazine and placebo. *Drug Alcohol Depend*. 2006;81(1):27–36.

Kalechstein AD, De La Garza R II, Mahoney JJ III, et al. MDMA use and neurocognition: a meta-analytic review. *Psychopharmacology (Berl)*. 2007;189(4):531–537.

McCann UD, Szabo Z, Seckin E, et al. Quantitative PET studies of the serotonin transporter in MDMA users and controls using [11C]McN5652 and [11C]DASB. *Neuropsychopharmacology*. 2005;30(9):1741–1750.

McCann UD, Szabo Z, Vranesic M, et al. Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (+/−)3,4-methylenedioxymethamphetamine ("ecstasy") users: relationship to cognitive performance. *Psychopharmacology (Berl)*. 2008;200(3):439–450.

Reneman L, Lavalaye J, Schmand B, et al. Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings. *Arch Gen Psychiatry*. 2001;58:901–906.

Ricaurte GA, McCann UD. Recognition and management of complications of new recreational drug use. *Lancet*. 2005;365(9477):2137–2145.

Vollenweider FX, Gamma A, Liechti M, et al. Psychological and cardiovascular effects and short-term sequelae of MDMA ("Ecstasy") in MDMA-naïve healthy volunteers. *Neuropsychopharmacology*. 1998;19:241–251.

12 Inhalants

Volatile substances are ubiquitous and varied. Thus, inhalant abuse includes a variety of drug-using behaviors that cannot be easily classified by their pharmacology or toxicology but are grouped based on their primary mode of administration. Other substances can be inhaled (e.g., tobacco, marijuana, and even heroin or crack). Natural vaporization of these latter substances is not the primary mode of administration; therefore, they do not fall into the "inhalant" classification of abused drugs. The available products containing volatile solvent mixtures, gaseous products, and aerosols that are inhalable are variable from one region to another within the United States and throughout the world and over time. These products include a variety of chemical mixtures that can be found everywhere: in industry, in the workplace, and in the home.

DSM-5 Inhalant Use Disorder (IUD)

Unlike DSM-IV-TR, in which patients could be diagnosed with either Abuse or Dependence on a substance, DSM-5 has essentially combined the criteria for Abuse and Dependence into a single diagnosis, Substance Use Disorder (SUD). There are 10 items used to make an inhalant SUD diagnosis, and a patient needs to have only two of these to qualify for this diagnosis. In addition, DSM-5 includes several other related disorders (e.g., inhalant use–related delirium, psychotic disorder). The utility of the changes in DSM-5, and especially the conceptualization of SUD (rather than Abuse or Dependence), remains to be determined.

Epidemiology

Substance Abuse and Mental Health Services Administration (SAMHSA) has provided yearly data on the lifetime prevalence of various groups of inhalants for mind-altering purposes for several years. In 2007, inhalation of aerosol sprays, nitrous oxide (N_2O), and toluene- or butane- or propane-containing products were the most prevalent forms of "lifetime use" of inhalants for 12- to 17-year-olds. In younger children, use of spray paint, glue/toluene, gas/lighter fluid, and correction fluid was highest. By age 14, these agents plus other sprays, lighter gas, nitrites, and thinner were becoming more prevalent. By age 16, N_2O was nearly as popular. There is a great concern about the inhalation of gases/solvents by younger age groups (e.g., seventh and

eighth graders) because of their lack of understanding of the problem, both what is meant by "getting high" and the resulting consequences of this use.

The 2011 U.S. National Survey on Drug Use and Health (NSDUH) found that 8.0% of persons 12 years of age and older had used an inhalant at some time in their life; however, only 0.2% had used one in the past month. Inhalant use is more common in the young, according to NSDUH. In 2011, 1.0% of 12- to 13-year-olds had used an inhalant in the past month, while only 0.3% of 21- to 25-year-olds had used an inhalant in the past month. For persons 35 years and older, this percentage dropped to 0.1%.

Few studies of the natural history of IUDs have been conducted. One study reported that 19% of persons who initiated inhalant use in the NESARC (National Epidemiologic Survey on Alcohol and Related Conditions) study went on to develop a DSM-IV Inhalant Use Disorder (i.e., Abuse or Dependence). Most of these transitions were to inhalant abuse rather than to inhalant dependence, and the risk of transition was substantially greater in the first year, following initiation of inhalant use and low thereafter. The presence of a mood or anxiety disorder or alcohol use disorder antedating initiation of inhalant use predicted significantly elevated risk of IUD, whereas being married lowered the risk of the onset of IUDs.

Adolescents

Relatively few studies have examined the prevalence of IUDs in national samples of adolescents. One study examined the prevalence of IUDs in 36,850 12- to 17-year-olds who participated in the 2000 to 2001 National Household Survey on Drug Abuse. Overall, 0.4% of adolescents aged 12 to 17 years met past-year inhalant abuse or dependence criteria. Alternatively, 10.6% of past-year inhalant users met past-year inhalant abuse or dependence criteria. Similar figures were reported for 15- to 24-year-olds participating in the National Comorbidity Survey (NESARC); 8% of participants reported inhalant use, the proportion of overall respondents (N = 8,098) with a history of inhalant dependence was 0.6%, and the proportion of inhalant users with a lifetime history of dependence was 8%.

Adults

Drawing upon data from the 2002 to 2003 administrations of the NSDUH, it has been estimated that approximately 10% of U.S. adults had used inhalants and that 4.8% of this group had used inhalants within the prior year. Among past-year inhalant users, approximately 8% met criteria for past-year IUDs. Among participants aged 15 to 54 in the NESARC, the proportion of overall respondents with a history of inhalant dependence was 0.3%, and 3.7% of inhalant users developed inhalant dependence. Only 2% of adult respondents in the NESARC reported lifetime inhalant use, but of this proportion nearly one in five (19%) met the criteria for a lifetime IUD. Taken together, surveys of adolescents and adults suggest that inhalant use is far more prevalent than IUDs in the general population. However, signs and symptoms of IUDs and associated criteria may be prevalent among some high-risk groups such as antisocial youth, which are commonly excluded from large surveys of noninstitutionalized populations.

Sociocultural Issues

Many solvent abusers, more than other drug users, are poor, come from broken homes, have lower self-esteem, and do poorly in school. They have difficulty with acculturation and strong peer influence that enhances their entry into inhalant use, as well as other drug use, although

findings are not wholly supportive of an acculturation stress–inhalant use relationship. The family atmosphere is often disruptive for the abusers and has been identified as less adjusted or more conflictual than for controls.

Findings in adolescents and adults suggest that inhalant users are at substantial risk for suicidal ideation and perhaps suicide itself. Studies have associated inhalant use early in life with later injection drug use. Additional findings in samples of inhalant users include significant academic problems such as high rates of dropout; suspension; and expulsion, parental alcoholism, and criminality; histories of physical or sexual abuse; deviant peers, including inhalant users; impulsive, sensation seeking, and fearless temperaments; and involvement in criminal and antisocial conduct. One trait that is often associated with "sniffers" is disruptive behavior.

Toxicology of Inhalant Abuse

High-level exposure occurs in the inhalant abuse setting at levels several thousandfold higher than the usual occupational setting. The user may appear drunk or in an intoxicated state; many symptoms resemble alcohol intoxication. An initial excitation turns to drowsiness, disinhibition, lightheadedness, and agitation. With increasing intoxication, individuals may develop ataxia, dizziness, and disorientation. In extreme intoxications, they may show signs of sleeplessness, general muscle weakness, dysarthria, nystagmus, and, occasionally, hallucinations or disruptive behavior. Several hours after, especially if they have slept, they are likely to be lethargic, or hung over with mild to severe headaches. At lower levels (just over 200 parts per million [ppm]), fatigue, headache, paresthesia, and slowed reflexes appear. Exposure at levels approaching 1,000 ppm causes confusion or delirium, and euphoric effects appear at or above that level. Physical symptoms include weight loss, muscle weakness, general disorientation, inattentiveness, and lack of coordination. Too many times, death can occur during the course of primary intoxication. When it does occur, it is usually the result of asphyxia, ventricular fibrillation, or induced cardiac arrhythmia, following high exposures to various solvents.

Neurotoxic disorders have a nonfocal presentation and may be confused with metabolic, degenerative, nutritional, or demyelinating diseases. Thus, chronic toluene abuse may clinically resemble the multifocal demyelinating disease, multiple sclerosis, on neurologic examination findings. Mild cases of intoxication may be very difficult to diagnose. The most reliable information comes from documented cases of long-term heavy exposure; details of low-level exposure and presymptomatic diagnoses are vague at best. In general, inhalant-related neurotoxic injuries rarely have specific identifying features on diagnostic tests such as computed tomography (CT), magnetic resonance imaging (MRI), or nerve conduction studies. Because many neurotoxic effects are reversible and some chronic neurotoxic injuries of the brain may not be associated with structural damage sufficiently large to be detected within the spatial resolution of MRI scanners and imaging sequences, brain imaging studies are primarily used to rule out other disorders. Chronic neurotoxic injury related to solvent abuse is slowly and incompletely reversible, and usually does not progress after cessation of exposure. In addition, acute neurotoxicities and clinical manifestations of a substance may not be attributable to the parent compound, but may be associated with a metabolite of the compound. Major neurotoxic syndromes occurring in individuals chronically exposed to select organic solvents can include peripheral neuropathy, ototoxicity, and an encephalopathy. Less commonly, a cerebellar ataxic syndrome or a myopathy may occur alone or in combination with any of these syndromes.

Clinical Neurotoxicology

Encephalopathy

There have been multiple reports on the persistent neurologic consequences of chronic toluene inhalation. Syndromes of persistent and often severe neurotoxicity include cognitive dysfunction, cerebellar ataxia, optic neuropathy, sensorineural hearing loss, and an equilibrium disorder. The encephalopathy has been characterized using CT and MRI. There are many instances of persistent neurologic deficits. However, the enduring nature of these deficits has been difficult to capture, and it is possible that brain structural changes measured with MRI or CT persist despite a return in cognitive function. Although longitudinal experiments where several brain scans are obtained over time with abstinence are lacking, most chronic solvent abusers represent the severe end of the spectrum, and the issue is further complicated by equivocal evidence concerning impairment of cognitive function in solvent abusers: reports have provided evidence both for and against recovery of cognitive impairment with prolonged abstinence.

Clinical Neuropathology

Studies using MRI demonstrate that chronic abuse of toluene-containing substances caused diffuse CNS white matter changes. MRI of individuals using a toluene-containing mixture revealed the following abnormalities: (a) diffuse cerebral, cerebellar, and brainstem atrophy; (b) loss of differentiation in the gray and white matter throughout the CNS; and (c) increased periventricular white-matter signal intensity on T2-weighted images. These findings were supported in a neuropathologic study, in which the neuropathologic and biochemical changes seen in the brains of chronic toluene abusers were identical to those seen in adrenoleukodystrophy (ALD). ALD is a rare X-linked disorder associated with accumulation of very-long-chain fatty acids in certain tissues, including brain.

In adults, toluene precipitates an organic mental syndrome characterized by personality change and intellectual decline with mild dysfunction of the peripheral nervous system. Acute toluene intoxication produces a reversible neurologic syndrome characterized by encephalopathy and cerebellar ataxia. Chronic inhalation abuse induces a more severe white matter leukoencephalopathy, characterized by a profound reduction in brain white matter regions along with cerebellar, brainstem, and pyramidal tract dysfunction. White matter changes have been reported as an increased signal in white matter areas such as corpus callosum, internal capsule, centrum semiovale, brainstem, and cerebellar peduncles in T2-weighted images along with many reports of enlarged ventricles. These changes most likely arise from a relative increase in the water content of white matter caused by demyelination.

Although an exact dose–effect relationship cannot be drawn for chronic toluene exposure, it is clear that all severely affected individuals have had heavy and prolonged exposure. The lack of correlation between the type or duration of exposure and neurologic impairment may be a result of unreliable histories or other factors, such as genetic predisposition (unlikely) or hypoxemia resulting from "huffing" or "bagging." Gradual resolution of acute toxicity and absence of withdrawal symptoms were probably due to slow elimination of "significant amounts" of toluene from the CNS.

Myelopathy (Nitrous Oxide)

N_2O abuse can be evaluated prospectively, and one cannot rely on retrospective evaluation. This is possible because N_2O is an approved anesthetic, as is sevoflurane. In human laboratory studies, the pleasurable inhalation of N_2O by humans, exposed to various concentrations of

oxygen and N_2O, has been evaluated. Effects were noted to last only a couple of minutes, and word tests demonstrated that memory retention within 5 minutes of the event was reduced. Some users liked the effect, whereas others did not. Subjects preferred different levels of exposure to obtain the preferred dose of N_2O to satisfy them.

N_2O is not an organic solvent, but has been noted to cause some unusual toxicities. In early studies, both central and peripheral nerve damage resulted following high levels of exposure, which occurred even in the presence of adequate oxygen and even after short-term use when N_2O was used as an anesthetic. This is consistent with case reports documenting numbness and weakness in the limbs, loss of dexterity, sensory loss, and loss of balance with the clinical use of N_2O. The neurologic examination indicates sensorimotor polyneuropathy. Patients with vitamin B_{12} deficiencies are especially sensitive, and a combined degeneration of the posterior and lateral columns of the cord has been observed that resembles vitamin B_{12} deficiency. Rehabilitation proceeds with abstinence from N_2O exposure and is relative to the extent of neurologic damage.

Toluene

The measure of radioactive binding in positron emission tomography (PET) studies, using radiotracers of toluene, most likely reflects both specific and nonspecific binding. However, these measures indicate high uptake and rapid clearance of [^{11}C]toluene from the brains of anesthetized baboons, consistent with clinical observations that toluene intoxication lasts approximately 5 minutes and takes 30 minutes to subside. Toluene metabolites are formed quickly and include benzoic and hippuric acids, which are excreted in urine, and benzaldehyde. There is also a clear redistribution of the labeled compound to brain regions of high white matter content, such as the corpus callosum and centrum semiovale, in agreement with molecular resonance measures of pathology observed in human abusers.

FDG PET Studies of Toluene-Induced Changes in Brain Glucose Metabolism

Toluene alters brain metabolic function in adolescent animals, and these alterations are reproducible, regionally specific, and to some extent, reversible with abstinence. Analysis of region-specific effects indicates that the thalamus and hippocampus are particularly sensitive to toluene-induced changes in FDG uptake and that the temporal cortex is particularly resistant to recovery. The highest decreases in FDG uptake in rats were in cortical regions, including the temporal and somatosensory cortices. The white matter appears more predominantly in areas such as the pons, where neural tracts are bundled together. The gray matter more predominantly occupies regions such as cortex and thalamus and consists mainly of neuronal cell bodies and unmyelinated fibers. Because white matter regions are responsible for transmission of neural signals between gray matter regions, it is feasible that the impact of toluene on white matter could be reflected by alterations in gray-matter as well as white-matter function. This is evident in the high uptake of toluene itself in lipophilic, typically white matter–rich regions, while the functional consequences of toluene exposure are largely in gray matter regions such as the cortex. Thus, solvent or toxin-induced changes in morphology and metabolism ultimately raise the question of whether changes in morphology lead to functional decline or whether functional (i.e., metabolic) deterioration produces morphological damage. Taken together with clinical findings, it is possible that initially reinforcing doses of toluene produce functional changes resulting from metabolic disturbances, which, after years of abuse, alter brain structure and contribute to the well-established leukoencephalopathy. In addition, affected areas with less lipid content, such as the frontal and temporal cortices, reflect alterations in neurochemical transmission after repeated toluene exposure.

Butane/Propane

Very little is known about the mechanism of action through which these gases affect brain function. Unlike toluene, butane and cyclopropane do not act directly through GABA-mediated mechanisms. Instead, psychoactive concentrations of these gases appear to inhibit *N*-methyl-D-aspartate (NMDA)–sensitive glutamate channels and neuronal nicotinic acetylcholine receptors, a mechanism also shared by toluene and trichloroethylene (TCE).

Clinical reports and preclinical behavioral studies support the observed differences in the mechanism of action between toluene and butane. A butane-induced "high" is known to be extremely short-lasting (of the order of minutes) and of different quality (more pronounced visual hallucinations and distorted perception of body form) from the "high" experienced after toluene inhalation, where users report that thoughts are slowed, time appears to pass more quickly, and tactile hallucinations are experienced. Toluene is much more soluble in tissues, and butane is excreted rapidly through the lungs. Furthermore, the aliphatic hydrocarbon with the shortest chain length, methane, is rarely abused because it does not induce the desired pharmacologic effects. Evidence such as this supports the notion that the pharmacokinetics and pharmacodynamics of individual inhaled solvents greatly impact their rewarding or reinforcing properties.

Acetone

Acetone is present in nail polish removers and some paint thinners. Acetone is not metabolized. It is a less potent CNS depressant than toluene or butane and is less toxic. Radiolabeled metabolic PET studies support this conclusion. Acetone diffuses more slowly into the CNS than toluene. The acetone brain/blood ratio is 0.82; the toluene brain/blood ratio is 2.7, indicating that toluene passes from the blood into the brain much faster and at much lower concentrations. It is possible that, unlike toluene, which distributes to specific regions of the brain and other lipid-rich regions of the body, acetone prefers more aqueous regions. The initial distribution of acetone in the primate brain resembles that of water, whereas toluene and butane distribute immediately from the blood into lipid-rich regions of the brain.

The abuse potential of acetone is low, since it is highly soluble in blood and solute areas and will poorly diffuse into the brain. In sum, it seems unlikely that solvent abusers would select acetone because of its slow onset and prolonged duration of action.

Chlorohydrocarbons

Trichloroethane and TCE (common in dry cleaning fluids) share a profile of acute behavioral effects similar to those of CNS depressants and reproducibly substitute for benzodiazepines in drug discrimination studies. Other similarities include the development of sensitization and tolerance, and biphasic effects on locomotor activity and operant responding.

Several neurochemical consequences of trichloroethane/TCE exposure are thought to distinguish these inhaled solvents from other volatile chemicals such as toluene or halothane. Also, trichloroethane, but not florothyl, inhibits NMDA receptor function.

Nitrous Oxide

N_2O is an abused inhalant as well as an anesthetic, used primarily in dentistry for analgesia. This inhalant differs from most small hydrocarbons; it has a well-defined site(s) of action. Results from studies support the hypothesis that both opioidergic and GABAergic neurons mediate the antinociceptive effect of N_2O at the periaqueductal gray area and A7 in the brainstem. Other work has focused on the action of N_2O through the NMDA system.

Peripheral Neuropathies and Specific Drugs

Ototoxicity

The clinical nature of ototoxicity was evaluated in 11 chronic toluene abusers by measures of brainstem auditory-evoked responses (BAERs) and MRI. Neurologic abnormalities, including cognitive, pyramidal, cerebellar, and brainstem findings, were seen in 4 of 11 individuals. MRI of the brain was abnormal in 3 of 11 individuals, and all 3 also had abnormalities on neurologic examination. BAERs were found to be abnormal in 5 of 11 individuals. All three individuals with abnormal MRI scans and neurologic examinations also had abnormal BAERs. Of the five individuals with abnormal BAERs, however, two had normal neurologic examinations and MRI scans. This study suggests that BAERs may detect early CNS injury from toluene inhalation even at a time when neurologic examination and MRI scans are normal. These results suggested that BAERs could be a screening test to monitor individuals at risk from toluene exposure for early evidence of CNS injury. Hearing deficits found in laboratory studies are produced after as little as 2 weeks of exposure to 1,200 ppm or 1,400 ppm of toluene. This is attributed to cochlear dysfunction rather than the central conduction pathology found in the human studies noted above.

n-Hexane and Methyl Butyl Ketone

These two organic solvents are classified together because both *n*-hexane and methyl butyl ketone (MBK) are metabolized to the same neurotoxin, 2,5-hexanedione (2,5-HD), and produce an identical clinical syndrome characterized by a peripheral neuropathy. MBK had limited industrial use until the 1970s when it became more widely used (e.g., as a paint thinner, for dye printing). Soon afterward, outbreaks of polyneuropathy associated with chronic exposure to MBK were reported. Originally, methyl isobutyl ketone had been used. When methyl isobutyl ketone was replaced by MBK, reports of polyneuropathy began to appear in the literature.

The clinical syndrome is characterized by the insidious onset of an initially painless sensorimotor polyneuropathy, which begins several months after continued chronic exposure. Even following cessation of exposure, the neuropathy may develop or continue to progress for up to 3 months. In severe cases, an unexplained weight loss may be an early symptom. Sensory and motor disturbance begins initially in the hands and feet, and sensory loss is primarily a small-fiber (i.e., light touch, pinprick, and temperature) with relative sparing of large-fiber sensation (i.e., position and vibration).

Peripheral neurotoxicities have been correlated with *n*-hexane, which is used as a solvent (e.g., in printing, the extraction of vegetable oils, as a diluent in cabinet finishing, for glues and adhesives). Cases of *n*-hexane polyneuropathy have been reported both after occupational exposure and after deliberate inhalation of vapors from products containing *n*-hexane, such as glues. Another major component of glues has been toluene, but polyneuropathy does not occur from inhalation of glues containing only toluene without the presence of *n*-hexane. In contrast to toluene, *n*-hexane does not usually induce significant signs of CNS dysfunction, except with high-level exposures where an acute encephalopathy may occur.

Methylene Chloride (Dichloromethane)

Methylene chloride is widely used for paint stripping, as solvent for degreasing, in rapidly drying paints, and in aerosol propellants. As with other solvents, methylene chloride is a CNS depressant at high levels of exposure and may lead rapidly to unconsciousness and death.

Methylene chloride is metabolized to carbon monoxide; consequently, both its hypoxic effect and its narcotic actions must be considered together with regard to its CNS-depressant effects. Carbon monoxide, at high levels, and other forms of cerebral hypoxia are known to cause permanent neurologic sequelae.

Methylene chloride may not be a choice inhalant if it is the only chemical present. However, inhalant abusers do inhale large quantities of methylene chloride from paint stripper solutions. In this regard, a report on the oral ingestion of this material identifies the problems that may occur after deliberate excess inhalation of methylene chloride. These include CNS depression, tachypnea, gastrointestinal injury, and high carboxyhemoglobin. In summary, the evidence suggests that methylene chloride does not produce permanent neurologic sequelae, except with massive acute exposures that are associated with hypoxic encephalopathy. No evidence exists that chronic low-level exposure causes any serious long-term CNS injury.

1,1,1-Trichloroethane

1,1,1-Trichloroethane is widely used as an industrial degreasing solvent and, compared with other solvents, is less toxic. However, several reports of severe toxicity and deaths exist in the literature. Its acute toxicity has made it unsuitable as a volatile anesthetic, and its use as a carrier in aerosols was abandoned in the United States in 1973. In those cases where postmortem examination of the brain was undertaken, the pathologic changes suggested cerebral hypoxia occurred either primary to CNS depressant effect or secondary to cardiac or respiratory arrest.

Gasoline

Gasoline is a complex mixture of organic solvents and other chemicals and metals. The inhalation of gasoline is common among various solvent abusers, especially on some remote Native American reservations. Leaded gasoline is not now readily available in the United States but still may present a problem in some areas. Although some CNS or peripheral neuropathies may occur as a result of the solvents in gasoline, there have been toxicities that resulted from tetraethyllead (or its metabolite triethyllead). In cases where high lead levels were observed, various disorders occurred, including hallucinations and disorientation, dysarthria, chorea, and convulsions. The symptoms include moderate to severe ataxia, insomnia, anorexia, slowed peripheral nerve conduction, limb tremors, dysmetria, and sometimes limb paralysis. In most cases, the electroencephalogram (EEG) is normal, but in severe states, an abnormal to severely depressed cortical EEG is observed. Because many of these symptoms in the early stages of the disease can be reversed by parenteral chelation therapy with ethylenediaminetetraacetic acid (EDTA), British anti-Lewisite (BAL) (dimercaprol), and/or penicillamine, it is important to check the serum lead levels in any chronic inhalant abuser to see whether this treatment should be prescribed.

Nonnervous System Toxicity of Inhalant Abuse

Renal Toxicity

Currently, spray paints are widely abused substances, at least in the United States. The abuse of these substances occurs not only among polydrug users but also by painters. Metallic spray paints contain large quantities of toluene; also, thinner and glue can contain high levels of toluene. The exposure to these and similar substances has resulted in the hospitalization of inhalant abusers for various kidney disorders. These subjects often have associated gastrointestinal involvement, including nausea, vomiting, and severe abdominal cramps.

Reports indicate distal renal acidosis can occur in groups of paint and/or glue sniffers. Symptoms can include hyperchloremic metabolic acidosis, hypokalemia, hypocalcemia, and other electrolyte imbalances. Solvents usually cause a unique distal-type tubular acidosis, but proximal tubules are also affected. Although the distal tubule is responsible for the known electrolyte and metabolic imbalance, the proximal type is responsible for the wasting of amino acids and other proteins. A slightly different kidney dysfunction, glomerulonephritis, has also been identified in workers using solvents, especially painters. Rhabdomyolysis is also observed after exposure to solvents. All of these reports indicate that kidney dysfunction is a common toxicity noted for solvent abusers.

There are also reports that halohydrocarbons—chloroform and others, methylene chloride, TCE, methoxyflurane, and dichloropropane—may contribute to, if not cause, renal damage. The nephrotic pathologic changes reported include tubular necrosis and calcification. Studies of humans occupationally exposed to high levels of TCE, compared with nonexposed individuals, had elevated levels of α-microglobulin excretion. This relates to an increased reported incidence of renal cell-cancer incidence in these TCE-exposed individuals.

Hepatotoxicity

Chlorohydrocarbons (e.g., TCE, chloroform, halothane) have been known for years to produce hepatotoxicities. Several reports describe solvent-related toxicities. Any individual who is chronically exposed to these compounds would expect hepatorenal insults, depending on the dose and length of exposure.

The inhalation of correction fluids for "pleasure," which did, and may still, contain TCE, and trichloroethanes or tetrachloroethanes, did lead to toxicities in inhalant abusers. Even during occupational use, exposure to chlorohydrocarbons in poorly ventilated areas is considered to lead to hepatotoxicity. Hepatocellular and other carcinomas are observed at high doses of TCE and halothane. Anesthetic chlorinated hydrocarbons (halothane, TCE, and chloroform) are also considered to be carcinogenic. Increased availability of TCE for dry-cleaning purposes could present more cases of nephrotic and hepatotoxic diseases, including cancer.

Pulmonary Toxicity

The trachea and lungs are the primary organs affected by inhalants; yet there are few cases noted where the pulmonary system is severely compromised. Although solvents irritate the pulmonary system, it is not at all clear from the limited case studies reported, to date, how extensive or what types of pulmonary damage occur that can be primarily caused by solvent exposure and not by other inspired substances that are dissolved in the solvents.

Cardiotoxicity

It is not as evident, but the results of several cases link fibrillation and other cardiac insufficiencies to the use of halocarbons and numerous others. These types of products range from anesthetics (halothane) used by hospital and other medical personnel to the more common solvents/propellants and fluorocarbons (dichloroethanes, trichloroethanes, tetrachloroethanes, and TCE) contained in cleaning fluids and other products. Most interestingly, the resuscitation of inhalant abusers following cardiopulmonary arrest does not usually occur.

Hematologic Toxicity

There are three areas of concern with regard to solvent inhalation and the hematopoietic system. First, methylene chloride exposure can increase the carboxyhemoglobin levels. The levels

of carboxyhemoglobin may become sufficiently high to cause brain damage or death. A second substance, benzene, causes aplastic anemia, acute myelocytic leukemia, and other hematopoietic cancers. Benzene is present in thinners, varnish removers, and other solvents, and in varying proportions in gasoline, sometimes at high concentrations that will produce toxic levels following episodes of inhalant abuse. A third group of substances, the organic nitrites, produce methemoglobinemia and hemolytic anemia.

The latter group, the volatile liquid isoamyl (amyl), isobutyl or butyl nitrites, propyl nitrites, cyclohexyl nitrites, and maybe other organic nitrites deserve a special discussion. These abused drugs do *not* produce the typical solvents/gases neurologic actions described above; however, they are often included in the "inhalant abuse" category. Different adult individuals (predominately homosexuals) are the primary abusers of these organic nitrites. Subjects may use them for sphincter dilation and penile engorgement. The nitrites are usually not considered acutely toxic during inhalation because of syncope (fainting).

Neonatal Syndrome

There is evidence that solvent inhalation during pregnancy produces a "fetal solvent syndrome." There are numerous cases of infants of mothers who chronically abuse solvents diagnosed with this syndrome. The mothers inhaled paint reducer, solvent mixtures from paint sprays, and drank various quantities of alcohol. Whether toluene alone (often noted as the major solvent), other solvent components, and/or these components in combination with alcohol or other environmental factors are responsible is still unsubstantiated by laboratory studies. Toluene appears to be a major contributor. The infants present with growth retardation, some dysmorphic features, including microcephaly, as well as distal renal acidosis, aminoaciduria, ataxia, tremors, and slurred speech. Toluene has been considered a human teratogen. With so little knowledge and yet with all the potential dangers associated with inhalant use, it is very important that pregnant women not be exposed to very high concentrations of solvents/gases.

Treatment

There is no accepted treatment approach for inhalant abusers. There are a variety of treatment programs for inhalant abusers used by educators, drug treatment clinics, and physicians, but there are a relatively few drug abuse treatment "professionals" who focus primarily on inhalant abusers. The available programs range from basic and limited behavioral modification to medical pharmacologic clinics (which do not usually segregate inhalant abusers from other drug abusers), but little is evidence-based treatment.

Some facilities refuse treatment of the inhalant abuser, believing that inhalant abusers are resistant to treatment. Some programs use models that range from short-term to longer periods of treatment. Longer periods of treatment are needed to be able to address the complex psychosocial, economic, and biophysical issues of the inhalant user. Many environmental stimuli are associated with these drug effects and include family problems, poverty, environment, and associations. When brain injury in a very limited number of subjects occurs, mostly in the form of cognitive dysfunction, the rate of progression in recovery is even slower.

No pharmacologic treatment is known for inhalants. Treatment becomes slower and progressively more difficult when the severity of brain injury worsens as abuse progresses from transient social use (experimenting in groups) to chronic use in isolation. Specific drug treatment may also be difficult to evaluate largely because of the weak tolerance or physiologic

dependence that occurs with inhalants. Neuroleptics and other forms of pharmacotherapy are usually not useful in the treatment of inhalant abusers. However, as alcohol is a common secondary drug of abuse among inhalant abusers, a monitored program for alcohol abuse may be useful. Other medication has been used but seldom evaluated, especially in any large population samples.

Drug screening may be useful in monitoring inhalant abusers. Routine urine screens for hippuric acid, the major metabolite of toluene, performed two to three times weekly, will detect the high level of exposure to toluene usually seen in chronic inhalant abusers. However, analysis must always take into account the average background level of hippuric acid resulting from general metabolism.

Conclusion

Inhalants represent a broad group of compounds that have abuse potential—especially for younger aged persons. Some drugs in this category are readily available and relatively inexpensive (e.g., gasoline), while others may be available in workplace settings and through occupational exposure. The consequences of use can be significant, with damage to a variety of organ systems possible. Despite the ready availability of these drugs, and the relatively common experimentation with their use (especially by children), little is known about the optimal approaches to treating the patient who is misusing these substances.

Suggested Readings

Beckman NJ, Zacny JP, Walker DJ. Within-subject comparison of the subjective and psychomotor effects of a gaseous anesthetic and two volatile anesthetics in healthy volunteers. *Drug Alcohol Depend*. 2006;81:89–95.

Filley CM, Halliday W, Kleinschmidt-DeMasters BK. The effects of toluene on the central nervous system. *J Neuropath Exper Neurol*. 2004;63:1–12.

Garland EL, Howard MO, Perron BE. Nitrous oxide inhalation among adolescents: prevalence, correlates, and co-occurrence with volatile solvent inhalation. *J Psychoactive Drugs*. 2009;41(4):337–347.

Howard MO, Balster RL, Cottler LB, et al. Inhalant use among incarcerated adolescents in the United States: prevalence, characteristics, and correlates of use. *Drug Alcohol Depend*. 2008;93:197–209.

Howard MO, Perron BE, Vaughn MG, et al. Inhalant use, inhalant use disorders, and antisocial behavior: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Studies Alcohol Drugs*. 2010;71(2):201–209.

Marsolek MR. Inhalant abuse: monitoring trends by using poison control data, 1993–2008. *Pediatrics*. 2010;125:905–913.

Maxwell JC. Deaths related to the inhalation of volatile substances in Texas: 1988–1998. *Am J Drug Alcohol Abuse*. *2001*;27(4):689–697.

Medina-Mora M, Real T. Epidemiology of inhalant use. *Cur Opin Psychitr*. 2008;3:247–251.

Perron BE, Howard MO. Adolescent inhalant use, abuse and dependence. *Addiction*. 2009;104:1185–1192.

Wu L, Howard MO. Psychiatric disorders in inhalant users: results from the National Survey on Alcohol and Related Conditions. *Drug Alcohol Depend*. 2007;88:145–155.

13 Nicotine

Nicotine causes tobacco addiction, which in turn causes serious health problems, including heart disease, lung disease, and cancer, and increased susceptibility to a variety of infectious diseases. Most of the nearly 45 million adults in the United States who smoke indicate an interest in quitting, but rates of successful cessation remain disappointingly low. The chronicity and relapsing characteristics of nicotine can be largely explained by the actions of nicotine on the brain.

Epidemiology

Prevalence

There are about 1.2 billion smokers in the world, with the prevalence varying greatly by country from less than 5% (e.g., women in China and India) to more than 55% (e.g., men in Indonesia and Russia). It is estimated that smoking causes 5 million deaths per year worldwide, and if present trends continue, 10 million smokers are projected to die per year by 2025. In the United States, data from the 2009 National Health Interview Survey conducted by Centers for Disease Control and Prevention (CDC) indicate that 20.4% of adults aged 18 years and older were current smokers. The percentage of adult smokers in the United States has not changed significantly over the past 5 years. However, these rates are substantially decreased from the late 1960s, at which time about 40% of adults reportedly were current smokers.

Prevalence rates vary greatly between men and women. Currently, in the United States the percentage of smokers is higher for men (23.3%) than for women (17.7%). Smoking rates also vary by age. For both sexes combined, the percentage of adults who report being current smokers is lower among adults aged 65 years and older (9.5%) than among adults aged 18 to 44 years (22.9%) and 45 to 64 years (22.1%). For the age groups 18 to 44 and 45 to 64 years, men were more likely than women to be current smokers. With regard to race and ethnicity, approximately 13.2% of Hispanic persons, 22.4% of non-Hispanic White persons, and 22.0% of non-Hispanic Black persons are current smokers.

Public-Health Impact

To assess the economic and public-health burden from smoking, the CDC calculates smoking-attributable mortality, years of potential life lost (YPLL), and productivity losses in the United States from smoking. Data indicate that cigarette smoking and exposure to tobacco

smoke resulted in at least 443,000 premature deaths, approximately 5.1 million YPLL, and $96.8 billion in productivity losses annually. Further, although smoking prevalence has declined dramatically since its peak in the 1960s, the number of smoking-attributable deaths has remained unchanged, primarily because of increases in population size (particularly among older age groups). Cohorts of smokers with the highest peak prevalence have now reached the ages with the highest incidence of smoking-attributable diseases.

Nicotine Dependence and Tobacco Addiction

It is primarily the pharmacologic effects of nicotine that produce dependence and tobacco addiction. Indeed, non–nicotine-containing cigarettes do not sustain addiction. Research findings have shown that, among cigarette smokers aged 12 or older, 57% met criteria for nicotine dependence. The likelihood of dependence does not correspond directly with the duration and quantity of nicotine use. Nicotine dependence can occur in smokers who report low (nondaily) levels of use. Conversely, some heavy daily cigarette smokers do not meet the criteria for nicotine dependence. Thus, factors in addition to cigarette consumption are critical in the development of nicotine dependence.

Predictors of Nicotine Dependence

Smoking onset takes place in adolescence, with most smokers trying their first cigarette before age 18. Following initial tobacco use, progression to daily smoking and development of nicotine dependence are very rapid. In one study, 25% of young tobacco users progressed to full dependence syndrome within 23 months following onset of smoking. Of note, however, is the fact that most adolescents who experiment with tobacco do not become dependent on nicotine.

Racial and gender differences in the risk of nicotine dependence have been identified. Rates of nicotine dependence are higher among whites than among minorities and among females than among males. Rates of nicotine dependence are inversely related to level of education and income. Age of onset has been identified as a risk factor. Animal studies have shown that early exposure to nicotine, including in utero exposure, predicts greater neurochemical changes, higher nicotine self-administration (SA) as adults, and more severe levels of dependence. Vulnerability to development of nicotine dependence is higher in people with psychiatric disease and/or substance abuse disorders. Some studies, but not all, have found that offspring of parents who smoke have an increased risk of becoming regular smokers or nicotine dependents. Association with peers who smoke has been shown to increase risk of dependence. Another risk factor is prenatal maternal smoking, which predicts offspring nicotine dependence. There is also evidence that sensitivity to the initial smoking experience predicts continued smoking and perhaps nicotine dependence.

Genetic Influences on Nicotine Dependence

Approximately 50% of the variance in the risk of nicotine dependence is attributable to genetic factors. Attempts to identify specific genes are complicated by the fact that nicotine dependence is complex and polygenic, involving several chromosomes that are functionally overlapping and interactive. A variety of plausible candidate genes have been examined, primarily in two main areas: genes involved in the neurotransmitter pathways for the brain reward system and genes altering nicotine metabolism.

Nicotine's addictive properties are a result of the activation of nicotinic acetylcholine receptors (nAChRs) in the brain and the impact this has on certain neurotransmitter systems

(e.g., dopamine [DA], serotonin, and γ-aminobutyric acid [GABA]). Thus, genes that encode nAChR proteins have been investigated as likely candidate genes. Several nAChR subunit genes have been identified (e.g., CHRNA3 to CHRNA6 and CHRNB2 to CHRNB4 gene clusters) and shown to be associated with smoking-related phenotypes, including linkage for nicotine dependence. Gene association studies have also identified variation in DA receptor subtypes (D1 to D5). In particular, the A1 allele of the *DRD2* gene (Taq1 A) polymorphisms has been associated with smoking initiation, cigarette consumption, and craving. One interpretation is that individuals with DRD2 A1 genotypes exhibit lower DA D2 receptor density and, therefore, may have lower levels of neuronal DA-dependent activity compared to individuals with DRD2*A2 genotypes. In an effort to compensate for deficiencies in the dopaminergic system, carriers of the DRD A1 allele use more nicotine to increase brain DA levels.

Allele frequencies have also been examined in studies of the *CYP2A6* gene. Nicotine is almost wholly metabolized by the CYP2A6 enzyme. Dependent smokers regulate the amount they smoke to maintain plasma and brain nicotine levels; thus, smoking behavior is increased when renal nicotine clearance (metabolism) is high. The hypothesis that genetically poor metabolizers (i.e., people with variant *CYP2A6* genes associated with substantially reduced enzyme activity) smoke fewer cigarettes and are less dependent on nicotine has been supported in some, but not all, studies.

Pharmacogenetic research in smoking has shown promise, with evidence that genetic variation is related to differential outcome to nicotine cessation pharmacotherapies. In studies of treatment medications, such as nicotine replacement therapy and bupropion, candidate alleles at the D2 DA receptor gene and μ-opioid receptor (MOR) gene have been shown to predict therapeutic response. Response to bupropion has also been studied, with evidence of an association with the CYP2B6 genotype and the DA DRD2 gene.

In summary, there is convincing evidence that smoking behavior and nicotine dependence are strongly influenced by genetic and environmental factors. Research has been productive in identifying genes that alter sensitivity to nicotine and potentially predict response to specific pharmacotherapies.

Determinants of Use

Nicotine Pharmacology

Nicotine is the main psychoactive ingredient in cigarettes, readily crossing the blood–brain barrier and targeting the nAChRs. The nAChR complex is diverse, consisting of five subunits. It is the α-4 and β-2 subunit receptors that account for 90% of high-affinity binding in the brain. The β-2 subunit is critical for DA release and for the behavioral effects of nicotine, while the α-4 subunit is an important determinant of nicotine sensitivity.

Activation of presynaptic nAChRs facilitates release of neurotransmitters. DA release in particular is critical to the reinforcing effects of nicotine and other drugs of abuse. Other neurotransmitters are released and mediate various behaviors in smokers, including norepinephrine (arousal, appetite suppression), acetylcholine (arousal, cognitive enhancement), serotonin (mood modulation, appetite suppression), GABA (reduction of anxiety and tension), glutamate (learning, memory enhancement), and endorphins (reduction of anxiety and tension). It is primarily through its effects on DA release that acute nicotine administration increases brain reward function.

Chronic nicotine exposure results in neuroadaptation or the development of tolerance to some of the effects of nicotine. Neuroadaptation is characterized by an increase in the

number of nAChR binding sites in the brain, which in turn leads to upregulation in response to nicotine-mediated desensitization of receptors. This process has been linked to key aspects of nicotine dependence, including nicotine withdrawal. Symptoms of nicotine withdrawal due to deficient DA responses include craving and inability to experience pleasure. These neural-plasticity changes appear to be long lasting and responsible for persistent craving and risk of relapse long after stopping smoking.

Nicotine Pharmacokinetics and Pharmacodynamics

Smoking is a highly efficient form of drug administration. Compared to absorption through mucous membranes (e.g., chewing tobacco, snuff, or nicotine gum), inhaled nicotine enters the circulation rapidly through the lungs and moves into the brain within seconds. This increased speed of absorption and entry of the drug into the brain corresponds with greater concentrations and reinforcing effects of the drug. The smoking process allows for precise dose titration. Smokers have fingertip control of the dose, on a puff-by-puff basis, so that topographic features of smoking, such as number, volume, duration, and depth of inhalation, can predict the exact level of nicotine intake.

Nicotine is metabolized to cotinine, primarily by the liver enzyme CYP2A6. Cotinine is subsequently metabolized to *trans*-3-hydroxycotinine (3HC) by CYP2A6. It is the ratio of 3HC to cotinine that has been used as a phenotypic marker for defining the rate of nicotine metabolism (i.e., CYP2A6 activity). Findings show that slower metabolizers are at lower risk to develop nicotine dependence and may have lower risk for certain cancers. In general, Asians and African Americans metabolize nicotine more slowly than do Caucasians or Hispanics. In addition, the rate of nicotine metabolism is faster in women than in men.

At low doses, nicotine acts like a stimulant, producing arousal, increased heart rate, and blood pressure. In contrast, high doses of nicotine produce ganglionic blockade, leading to bradycardia, hypotension, and depressed mental state. Tolerance to many of the acute subjective effects and physiologic effects of nicotine develops within a day for most smokers. That means that for a daily smoker, the positive rewards of smoking diminish throughout the day, and smoking becomes driven primarily by efforts to maintain a threshold level of nicotine to keep withdrawal symptoms at bay.

Environmental Factors

Cigarette smoking is maintained, in part, by conditioning. The behavior of smoking is paired, repeatedly, with specific situations (e.g., with coffee and after a meal), settings (e.g., bar), or mood states (e.g., stress and frustration). Over time, these associations cause environmental situations to become strong cues for smoking or the urge to smoke. In similar fashion, other aspects of the smoking behavior (handling the cigarette, the taste and smell of smoking) become associated with the pleasurable effects of nicotine and further strengthen the conditioning process. Functioning imaging studies have shown that just the exposure of smoking-related cues can activate cortical regions of the brain.

Conditioning develops from pairing the pharmacologic actions of nicotine with associated behaviors and environmental situations. At the same time, however, conditioning factors appear to maintain nicotine use during periods of receptor desensitization, that is, when there is a loss or decrease in the biologic response to nicotine due to prior exposure to nicotine. Thus, environmental conditioning plays a critically important role in the reinstatement or relapse to smoking in abstinent smokers. To be effective, therapies for nicotine dependence need to address the role of conditioned stimuli and conditioned reinforcers in maintaining smoking behavior.

Evaluation and Treatment

Screening and Identification

According to the *Clinical Practice Guideline on Treating Tobacco Use and Dependence* (hereafter referred to as the *Guideline*), at least 70% of smokers see a physician each year, and almost one-third see a dentist. Other smokers are likely to come in contact with physicians, nurse practitioners, pharmacists, counselors, and other clinicians. These various clinicians are in prime position to intervene with patients on their tobacco use. Many smokers report wanting to quit smoking and cite that physician's advice to quit smoking is an important motivator for attempting to stop smoking. Unfortunately, clinicians and health-care systems do not capitalize on this opportunity consistently. According to the National Committee for Quality Assurance's "State of Health Care Quality Report," improvements have been made in increasing tobacco-use interventions for patients with some form of private insurance, including Medicare; 71% to 75% of these patients received cessation advice. By contrast, however, only 25% of Medicaid patients reported any assistance with their smoking habits. In addition, only about one-third of adolescents who visited a physician or dentist reported receiving counseling regarding the dangers of using tobacco. Clearly, improvements are needed in screening and intervention with tobacco users in health-care settings.

The *Guideline* put forth compelling reasons why members of a busy clinical team should make the screening and treatment of tobacco use a priority: (1) clinicians can make a difference with even a minimal (less than 3 minutes) intervention; (2) a relation exists between the intensity of intervention and tobacco-cessation outcome (higher intensity = better outcomes); (3) even when patients are not willing to make a quit attempt, clinician-delivered brief interventions enhance motivation and increase the likelihood of future quit attempts; (4) tobacco users are being primed to consider quitting by a wide range of societal and environmental factors (e.g., public-health messages, policy changes, cessation marketing messages, and family members); (5) there is growing evidence that smokers who receive clinician advice and assistance with quitting report greater satisfaction with their health care than those who do not; (6) tobacco use interventions are highly cost effective; and (7) tobacco use has a high case fatality rate (up to 50% of long-term smokers die of a smoking-related disease).

Identifying tobacco users is, of course, the first step in this process. Formal screening instruments exist that can be used to identify smokers and their nicotine-dependence severity. The most well-known is the Fagerström Test for Nicotine Dependence (FTND). The FTND is a standardized questionnaire for assessing level of physical dependence on nicotine. FTND scores may assist in tailoring treatment; for example, higher scores suggest more intensive treatment versus lower scores, and can be used to track progress over time. Many clinicians are not accustomed to using standardized instruments, however, and therefore may be reluctant to incorporate this measure. An alternative is to simply ask the patient about tobacco use at each clinical encounter. Repeated tobacco-use screening and brief intervention is one of the top three most important and cost-effective preventive services that can be provided in medical practice.

Treatment

There are many treatment options to promote smoking cessation, both pharmacologic and behavioral. Pharmacologic therapies fall into two main categories: (1) nicotine-replacement therapies (NRTs) and (2) non-nicotine medications.

Nicotine-Replacement Therapies

The primary aim of NRT is to reduce the physiologic and psychomotor withdrawal symptoms often experienced during smoking cessation attempts, which theoretically should increase the

likelihood of abstinence. Nicotine replacement products are formulated for absorption through oral mucosa (chewing gum, lozenges, sublingual tablets, inhaler) or skin (transdermal patches). Across multiple studies, the various forms of NRT in general are associated with a 50% to 70% increase in the rate of long-term abstinence when compared to placebo treatment. Evidence that NRT helps people to stop smoking is now well accepted, and many clinical guidelines recommend NRT as the first-line treatment for people amenable to pharmacologic assistance with quitting smoking.

The choice of which form of NRT depends upon the patients' preferences, needs, tolerability, and cost considerations. The nicotine patch is distinct from the other forms of NRT in that nicotine is delivered slowly and passively throughout the day, with some brands designed for 24-hour use and some for 16-hour use; wearing the patch only during daytime has been found to be as effective as wearing it for 24 hours/day. With the patch, plasma levels tend to be similar to the trough levels seen in heavy smokers. Patches are likely to be easier to use than gum, nasal spray, or inhaler, but patches cannot be used for relief of acute cravings, nor do they replace the behavioral activities of smoking. There is evidence of benefit from combining the nicotine patch with an acute dosing NRT (e.g., gum) compared to use of a single form.

Non-nicotine Medications

Bupropion Bupropion sustained release (SR) (Zyban) is the first non-nicotine FDA-approved medication for smoking cessation. Its mechanism of action is presumed to relate to its ability to block the reuptake of DA and norepinephrine, with no clinically significant effects on serotonin. Studies comparing bupropion SR to placebo confirm the benefit of this medication, indicating that it approximately doubles long-term (>5 months) abstinence rates. Other studies also support its efficacy. While the recommended dose is 300 mg daily, at least two studies have documented no evidence of a significant difference in the odds of being quit at 12 months for 150 mg daily compared to 300 mg.

Nortriptyline Typically used as an antidepressant (tricyclic), nortriptyline does not have FDA approval for smoking cessation. It remains a second-line medication because of potential side effects and limited evidence to support its efficacy. Several studies have demonstrated benefit for nortriptyline over placebo for smoking cessation, while several have not. Comparisons of bupropion and nortriptyline have favored bupropion, but no significant differences between the two have been found.

Varenicline Varenicline (Chantix) is a highly selective partial agonist that also displays antagonist properties, that is, it prevents full stimulation of the nicotine receptor that ensues when nicotine is coadministered. Thus, varenicline has the potential to provide relief from withdrawal (agonist effect) and block the rewarding effects of nicotine (antagonist effect). It is well tolerated in most patients, although there have been reports of increased psychiatric symptoms associated with varenicline administration. In February 2008, the FDA added a warning indicating that depressed mood, agitation, changes in behavior, suicidal ideation, and suicide have been reported in patients attempting to quit smoking while using varenicline.

A randomized, double-blind clinical trial comparing varenicline (2 mg), buproprion (300 mg), and placebo showed overall continuous abstinence rates through 1-year posttreatment of 23%, 14.6%, and 10.3%. Further, varenicline nearly tripled the odds of quitting over placebo during the last 4 weeks of treatment. A recent review of nicotine receptor partial agonists for smoking cessation concluded that varenicline increased odds of quitting over bupropion SR with a minimal to moderate side effect profile. In a separate study, an additional 12 weeks of varenicline (24 total weeks) was shown to reduce the risk of relapse among smokers who were abstinent at the end of the first 12 weeks, suggesting a relapse prevention benefit as well. Smokers taking varenicline have reported significantly less craving and withdrawal symptoms.

The FDA-approved dosing of varenicline is 2 mg/day (1 mg twice daily); however, there is evidence that 1 mg daily is also effective. A meta-analysis of four studies with five study arms was

conducted to evaluate the effects of the dose, and found that compared to placebo, the 1-mg daily dose approximately doubles a smoker's likelihood of long-term abstinence from tobacco, while the 2-mg daily dose approximately tripled the likelihood of abstinence. Thus, the 1-mg dose is an acceptable alternative for smokers who experience intolerable, dose-related side effects.

Combination Smoking Treatments

Clinical-practice guidelines for tobacco treatment state that some combinations of first-line medications have been found effective for smoking cessation. Only the nicotine patch + bupropion combination has been approved by the FDA for smoking cessation; however, other combinations have been tested. A meta-analysis revealed that the nicotine patch + bupropion SR, nicotine patch + inhaler, and long-term nicotine patch + ad libitum NRT have all been shown effective relative to placebo, and are recommended for use as first-line treatments. The presumed differences in mechanisms of action may afford a broader range of biologic targets identified as important in smoking cessation.

Behavioral Therapies

The characteristics of behavioral interventions for smoking cessation vary widely. The *Guideline* examined four of these characteristics: advice to quit, intensity, treatment format, and type of clinician, as well as specific elements of various types of counseling and therapy.

Overall results revealed a strong dose–response relationship between treatment intensity (i.e., session length, total contact time, and number of sessions) and treatment effectiveness. However, evidence also indicated that physician advice to quit smoking significantly increases long-term abstinence rates, even with a modal intervention length of 3 minutes or less. Analysis of different treatment formats demonstrated that telephone and group and individual counseling all improve smoking abstinence rates compared to no intervention; further, using multiple treatment formats increases abstinence rates as compared to use of a single format. A comparison of the effectiveness of different clinician types (e.g., physician, psychologist, nurse, and dentist) revealed no significant differences in abstinence rates based on this factor. Also studied was the effectiveness of including multiple clinicians from different disciplines. Although nonsignificant statistically, findings suggest that the involvement of a variety of clinicians in treatment may be more effective than that of a single clinician.

Brief Clinician Interventions

There are five main components of a brief intervention for smoking cessation that are often referred to as "the 5 A's" and are particularly useful in a health-care setting. As mentioned earlier in this chapter, the first step is to ASK the patient at each visit if he or she uses tobacco. This can be done in either written or oral fashion with the primary goal of systematically identifying all tobacco users at every visit. Second, once a smoker has been identified, the health-care provider should ADVISE the patient to quit. The provider should present the advice clearly and strongly. The advice should also be personalized. Tobacco use should be tied to current symptoms and health concerns, and/or social and economic costs, and/or the impact of tobacco use on children or others in the household.

The next step is to ASSESS the patient's willingness to make a quit attempt. If the patient is willing to try to quit, the physician should ASSIST the patient with a plan. This plan should include first-line medications such at NRTs, bupropion or varenicline, and smoking cessation counseling. Free telephone counseling is available through various federal agencies or organizations such as the American Cancer Society. For the patient who is not interested in quitting, strategies are available to increase motivation and the likelihood of future quit attempts. Finally, the physician should ARRANGE follow-up. For patients willing to set a quit date, arrange a subsequent appointment for 1 week after that date. Multiple contacts are encouraged. For patients unwilling to make a quit attempt, be sure to repeat the 5 A's at their next clinic visit.

For patients who are unwilling to attempt to quit smoking, motivational strategies can be employed that may increase the likelihood of later quitting. These strategies have been adopted from motivational interviewing (MI), a directive yet patient-centered counseling method. There is evidence that MI is effective in increasing future quit attempts, although positive abstinence outcomes have been elusive, particularly for those already motivated to quit. As summarized in the *Guideline*, the general strategies involve exploring feelings, beliefs, ideas, and values that result in abstinence about using tobacco. The clinician selectively elicits, supports, and strengthens the patient's "change talk" (e.g., reasons, ideas, and needs for eliminating tobacco use) and commitment language (e.g, intentions to take action to change smoking behavior). Eliciting ideas about change from patients is more effective than lectures or arguments for change presented by the physician.

Based on a meta-analysis of 64 studies, more intensive counseling and behavioral interventions with demonstrated effectiveness include: (1) providing smokers with practical problem-solving skills, (2) providing support and encouragement during a smoker's direct contact with a clinician, (3) intervening to increase social support in the smoker's environment, and (4) using aversive smoking procedures (rapid smoking, rapid puffing, other smoking exposure). However, the authors of the *Guideline* in reviewing multiple studies decided not to recommend extra-treatment social support as well as aversive smoking based on questionable effectiveness and side effects from the latter.

Special Considerations

Nicotine and Psychiatric Comorbidities

Tobacco smoking is highly prevalent and more intense in psychiatric patients. Comorbidity rates are particularly high for schizophrenia and depression, where smoking rates of 70% to 90% have been reported compared to <25% in the general population. Those who have a psychiatric diagnosis and are nicotine dependent (7%) consume 34% of all cigarettes. Early onset of tobacco use has been associated with greater risk of later psychiatric problems.

It is commonly assumed that psychiatric patients use tobacco for self-medication. For example, the actions of nicotine on nAChRs improve attention in schizophrenia by normalizing several deficits in sensory processing. Moreover, a genetic link between the α-7 nAChR subunit and schizophrenia has been found. Nicotine improves attention in ADHD (attention-deficit hyperactivity disorder) patients likely through its effects on DA release (similar to stimulant ADHD medications).

Increased smoking and nicotine dependence in schizophrenics may represent an attempt to overcome the potentially dysphoric and unwanted side effects of traditional neuroleptic medications caused by DA blockade. A related hypothesis is that neuroleptic medications may block the aversive properties of nicotine, thereby increasing sensitivity to the dependence producing rewarding properties of nicotine. Some clinical evidence suggests that smoking may be associated with reduced symptoms of parkinsonism but increased tardive dyskinesia. Studies of patients with schizophrenia who are treated with atypical (e.g., clozapine, olanzapine) rather than conventional antipsychotics have reported lower frequency of smoking and higher cessation rates.

Smokers with depression are less likely to quit and more likely to experience severe withdrawal symptoms, including depressed mood. Depressed smokers themselves often perceive smoking as a self-medicating strategy, reporting an increased likelihood of smoking during negative emotional situations than nondepressed smokers. In terms of antidepressant effects, nicotine has been shown to improve psychomotor retardation, sleep, and overall depressive symptomatology. The release of serotonin and norepinephrine in the brain by nicotine is similar to the neurochemical effects of certain antidepressant medications. Additionally, cigarette smoking inhibits monoamine oxidase A (MAOA) and monoamine oxidase B (MAOB), similar to the antidepressant effect of monoamine oxidase inhibitors (MAOIs).

Tobacco smoke activates the cytochrome P450 1A2 (CYP1A2) enzyme that is responsible for the metabolism of many commonly used psychiatric drugs. This increased CYP1A2 activity by tobacco smoke can result in substantially lower serum concentrations of psychiatric drugs in smokers compared with nonsmokers. Cigarette smoking has been shown to be associated with increased clearance of fluphenazine, haloperidol, olanzapine, and tiotixene, as well as some benzodiazepines. Faster metabolism of these drugs can result in need for higher dosages, which can increase side effects, cost, adherence, and efficacy. It is important that plasma levels of psychiatric drugs be carefully monitored in patients who are attempting to stop smoking.

In summary, understanding how psychiatric comorbidities contribute to smoking and vice versa is increasingly important, especially as this represents a growing subpopulation of difficult-to-treat smokers. The literature to date highlights key mechanisms explaining this comorbidity.

Nicotine and Other Drug Dependence

The prevalence of tobacco use among individuals who use alcohol and/or other illicit drugs is high (approximately 75%). Compared with non–substance-abusing populations, substance abusers tend to smoke more heavily, report more symptoms of nicotine dependence, experience more severe withdrawal symptoms, and have greater difficulty quitting smoking. Substance abusers who smoke are at higher risk of health consequences due to the synergistic effects of smoking and alcohol/drugs on the development of cardiovascular disease and cancers.

The comorbidity of nicotine with other substance use disorders (SUDs) may be due to a common genetic vulnerability. Support for this idea comes from classic genetic studies showing that polygenic genetic variants influence risk of addiction to substances in general, rather than to specific substances. One approach has been to identify genetic variants associated with personality-related phenotypes. Impulsivity, for example, defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli, without regard to the negative consequences of these reactions to themselves or others, is highly associated with addictive disorders. Not surprisingly, candidate genes with variants for impulsivity have been associated with alcoholism and other addictions. Other studies have identified genetic variants associated with risk-taking traits and addiction. Genetic linkage studies have also identified genetic variants of stress responsivity, that is, hypothalamic–pituitary–adrenal (HPA) axis function, with addiction risk. Thus, multiple genetic variants that influence vulnerability to addiction in general might explain the high rates of nicotine dependence in people with other drug-dependence disorders.

Pharmacologic mechanisms may explain the strong comorbidity. Combined drug effects may be additive, that is, producing enhanced rewarding effects, or modulatory. Both nicotine and alcohol, for example, have anxiolytic and antidepressant effects, which appear to be additive when the drugs are used together. At the same time, alcoholic individuals may use nicotine to offset or delay the sedative and cognition-impairing effects of alcohol. Nicotine effects have been shown to modulate alcohol withdrawal symptoms and mitigate some of alcohol's neurotoxic effects. Finally, the direct actions of nicotine on cholinergic systems, that is, nAChRs, appear to be involved in the development and maintenance of psychostimulant-rewarded behaviors. From this, it has been proposed that exposure to nicotine may facilitate dependence on cocaine and other stimulants.

From a behavioral perspective, environmental cues present during combined drug use acquire strong motivating and controlling properties. Models of young adult peer influence also offer possible explanations for the concurrent use of cigarettes and other drugs. The "gateway" theory of substance use predicts that use of a less dangerous drug (e.g., nicotine) increases the risk of starting to consume other more harmful drugs, in a so-called "staircase" fashion. In general, research on patterns of onset of substance use among adolescents show typical progression through initiation of tobacco, alcohol, and marijuana before use of other illicit drugs. Substance-use progression appears to be influenced not only by causal biologic mechanisms, but also by variables such as drug availability and attitudes.

In summary, co-occurring use of nicotine and other substances is highly prevalent and associated with harmful consequences. Most patients seek treatment for a single-drug problem, despite their codependence. A better understanding of the genetic, neurochemical, and behavioral factors that underlie comorbid addictions will improve prevention and treatment efforts.

Conclusion

Research has shown that nicotine dependence produces numerous changes to behavioral and neural functioning, and these changes can be modulated by environmental and genetic factors. Certain individuals appear to be more vulnerable to nicotine dependence, with new evidence that genetic factors contribute significantly to this vulnerability. As researchers continue to identify specific genes involved in nicotine dependence, the findings are likely to have important implications for improving existing smoking cessation treatments.

The first step in treatment is identifying tobacco users and characterizing the degree to which the patient is physically dependent on nicotine, either formally using the FTND or informally during a clinical interview. All smokers should be provided with a recommendation to quit and offered behavioral and/or pharmacologic treatment. Various NRT products, bupropion SR, varenicline, and combination therapy are all effective first-line tobacco treatments. Brief clinician interventions for smoking should also be implemented by all health-care providers to every patient at every visit. More intensive behavioral treatments are also available if warranted.

Federal regulation of nicotine products offers the promise of a nicotine-reducing strategy to make cigarettes less addictive. Studies on the feasibility of nicotine reduction will need to address the concern that smokers will smoke more cigarettes to compensate for lower nicotine levels. Current knowledge about the clinical pharmacology of nicotine will be critical in future decisions about harm reduction and federal regulatory strategies.

Suggested Readings

Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;49:57–71.

Buka SL, Shenassa ED, Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *Am J Psychiatry*. 2003;160(11):1978–1984.

Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2007;(1):CD006103.

Carter B, Long T, Cinciripini P. A meta-analytic review of the CYP2A6 genotype and smoking behavior. *Nicotine Tob Res*. 2004;6(2):221–227.

Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. *2007*;(1):CD000031

Li MD, Cheng R, Ma JZ, et al. A meta-analysis of estimated genetic and environmental effects on smoking behavior in male and female adult twins. *Addiction*. 2003;98(1):23–31.

Portugal GS, Gould TJ. Genetic variability in nicotinic acetylcholine receptors and nicotine addiction: converging evidence from human and animal research. *Behav Brain Res*. 2008;193(1):1–16.

Rose JS, Dierker LC, Donny E. Nicotine dependence symptoms among recent onset adolescent smokers. *Drug Alcohol Depend*. 2010;106(2–3):126–132.

Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2008;(1):CD000146.

Ziedonis D, Hitsman B, Beckham JC, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob Res*. 2008;10(12):1691–1715.

14 Caffeine

Caffeine (1,3,7-trimethylxanthine) is the most widely used mood-altering drug in the world. Caffeine is found in more than 60 species of plants and is the best-known member of the methylxanthine class of alkaloids. The dimethylxanthines, which include theophylline and theobromine, are structurally related compounds that are also found in various plants.

Caffeine occurs naturally in a variety of plant-based products, including coffee, tea, cocoa, kola nut, guarana, and maté. In addition to beverages made from these plants, significant amounts of caffeine are found in foods such as coffee ice cream, coffee yogurt, and dark chocolate. Caffeine is added to cola and noncola soft drinks as well as to other food items such as energy drinks, water, candy bars, mints, and gum. Caffeine is also added to prescription and over-the-counter (OTC) medications, including stimulants, analgesics, weight-loss supplements, and nutritional supplements.

In the United States, coffee and soft drinks are the major dietary sources of caffeine. The FDA limits the amount of caffeine that can be added to soft drinks to 0.2 mg/ml or 71.5 mg for a 12-oz serving. It is noteworthy that energy drinks often contain significantly higher levels of caffeine than those permitted in soft drinks with levels ranging from 50 to over 500 mg per can or bottle.

Epidemiology

Based on the Continuing Survey of Food Intakes by Individuals in 1994 to 1996 and in 1998, it is estimated that 87% of the population in the United States aged 2 years and older regularly consume caffeine, with an average daily consumption of about 193 mg. Caffeine use tends to increase with age, with the highest consumption observed among adults aged 35 to 64 years. Caffeine consumption among adult consumers in the United States is estimated to be about 280 mg, and higher daily intakes have been estimated for some European countries. Coffee is the major source of caffeine for adults, followed by soft drinks and tea, whereas soft drinks are the major source of caffeine among children and adolescents.

Genetics

There is evidence that genetic factors account for some of the variability in the use and effects of caffeine. Large-scale twin studies have shown that relative to dizygotic twins, monozygotic twins have higher concordance rates for total caffeine consumption, heavy caffeine

consumption, coffee and tea intake, caffeine tolerance, caffeine withdrawal, caffeine intoxication, and caffeine-related sleep disturbances, with heritabilities ranging between 34% and 77%. Findings from twin studies have also suggested that there may be common genetic factors that underlie the use of caffeine, cigarette smoking, and alcohol.

Association studies have also been conducted to evaluate how specific gene variations are related to individual differences in the use and effects of caffeine. Because caffeine's primary mechanism of action is adenosine receptor antagonism, one particular gene that has been the focus of attention is the A_{2A} receptor gene (*ADORA2A*). Another gene of interest is the CYP1A2 gene, which is linked to enzymes responsible for caffeine metabolism.

Pharmacokinetics

After oral consumption, caffeine is rapidly and completely absorbed. Caffeine rapidly passes through the blood–brain barrier, which accounts for the quick onset of mood-altering effects. Peak caffeine blood concentration (C_{max}) is generally reached in 30 to 45 minutes. Caffeine is highly lipid soluble and is rapidly and widely distributed throughout all body tissues and fluids, including breast milk and semen. There is no placental barrier to caffeine, and levels of caffeine in the fetus approach maternal levels. Saliva caffeine concentrations are highly correlated with plasma caffeine concentrations and are used as a noninvasive alternative to measuring serum levels.

Caffeine metabolism is complex, and more than 25 caffeine metabolites have been identified in humans. The primary metabolic pathways involve the cytochrome P-450 liver enzyme system (primarily the CYP1A2 isoenzyme), which carries out the demethylation of caffeine to three pharmacologically active dimethylxanthines: paraxanthine, theophylline, and theobromine. These active metabolites need to be considered in understanding the pharmacologic actions of caffeine, especially the primary metabolite paraxanthine. The half-life of caffeine is typically 4 to 6 hours; however, the rate of caffeine metabolism is quite variable across healthy adults and can range from 2 to 12 hours. Due to impaired enzyme functioning, caffeine metabolism is significantly slowed among individuals with liver disease as well as women in the second and third trimesters of pregnancy, who show about a threefold increase in the half-life of caffeine. Fetuses and newborns lack the liver enzymes needed to metabolize caffeine. Thus, caffeine metabolism in infants prior to 6 months of age is very slow, with a half-life of 80 to 100 hours. Tobacco smoking increases the rate of metabolism of caffeine due to stimulation of the CYP1A2 enzyme, with smokers metabolizing caffeine about twice as fast as nonsmokers.

An implication of the role of cytochrome P-450 liver enzymes in metabolizing caffeine is that other therapeutic drugs may pharmacokinetically interact with caffeine, and caffeine can impair the metabolism of other drugs, thus interfering with their safety and therapeutic effectiveness. Numerous compounds have been shown to significantly inhibit the metabolism of caffeine, and caffeine has been shown to interfere with the metabolism of medications.

Neuropharmacology

Adenosine

The primary mechanism of action of caffeine is nonselective antagonism at adenosine receptors. Adenosine is an endogenous nucleoside that plays a role in a number of central and peripheral nervous system functions. Although four adenosine receptor subtypes have been identified,

A_1 and A_{2A} receptors are the major targets of caffeine. A_1 and A_{2A} receptors are both G protein–coupled receptors that produce a variety of downstream cellular effects via multiple mechanisms, including inhibition and activation of adenylyl cyclase, respectively, and inhibition and activation of various ion channels (e.g., Ca^{2+}).

Adenosine inhibits the release of excitatory neurotransmitters, reduces the spontaneous rate of neuron firing, and has anticonvulsant effects. There is evidence that the accumulation of adenosine, triggered by energy depletion, functions as a sleep-promoting factor. Adenosine in the periphery causes cerebral vasodilation, constricts bronchial smooth muscle, produces negative inotropic/chronotropic effects on the heart, and inhibits gastric secretions, lipolysis, and renin release. Caffeine, which is structurally similar to adenosine, binds with adenosine receptors and produces effects that are consistent with reversal of the inhibiting effects of adenosine. For example, in the CNS, caffeine increases spontaneous neuronal firing, increases the turnover or levels of various neurotransmitters (e.g., acetylcholine, norepinephrine, dopamine [DA], serotonin, glutamate, and γ-aminobutyric acid [GABA]), has convulsant activity, increases motor activity, and inhibits sleep. Some of the peripheral nervous system effects of caffeine include cerebral vasoconstriction, relaxation of bronchial smooth muscle, and increased gastric secretions.

Dopamine

There is evidence that some of the motor and reinforcing effects of caffeine are mediated by dopaminergic mechanisms. Caffeine antagonizes adenosine at receptors that are colocalized and that functionally interact with DA receptors (i.e., adenosine–dopamine heteromers). Functionally, caffeine produces its motor and reinforcing effects in part by releasing the pre- and postsynaptic brakes imposed by antagonistic adenosine–dopamine interactions. DA release in the shell of the nucleus accumbens (NAcc) appears to be a neuropharmacologic mechanism underlying the abuse potential of many drugs. In vivo microdialysis studies demonstrate that caffeine increases DA release in the dorsal shell of the NAcc.

Other Mechanisms

Caffeine can also inhibit phosphodiesterase activity and mobilizes intracellular calcium release. However, these effects are generally observed at levels much higher than typical dietary doses. Nevertheless, it is possible that these mechanisms may mediate some of the effects produced by high doses of caffeine, such as those associated with caffeine intoxication.

Physiologic Effects

At moderate dietary doses, caffeine increases blood pressure and tends to have no effect or to reduce heart rate. It constricts cerebral blood vessels and reduces cerebral blood flow. It dilates bronchial pathways, although not as effectively as theophylline, and increases the rate of respiration. It stimulates gastric acid secretion and colonic activity. Caffeine produces dose-related thermogenic effects and lipolysis and has been shown to be ergogenic during exercise. It increases plasma epinephrine, norepinephrine, rennin, and free fatty acids. It increases diuresis and the urinary excretion of calcium, magnesium, potassium, sodium, and chlorides. Caffeine also increases adrenocorticotropic hormone (ACTH) and cortisol levels. It increases insulin levels and reduces insulin sensitivity in healthy individuals, and increases postprandial glucose and insulin responses among patients with type 2 diabetes who are habitual coffee drinkers.

Therapeutic Uses

Caffeine is commonly used to increase energy and alertness and ward off fatigue. Studies demonstrate that caffeine can enhance cognitive and motor performance, especially under conditions of fatigue, sleep deprivation, or caffeine withdrawal. Caffeine is also used to enhance athletic performance due to its ergogenic effects, and has been restricted by some major athletic governing bodies. Caffeine can enhance the analgesic effects of certain medications, and it is currently added to a variety of OTC and prescription analgesics used to treat various types of pain, including headache. As a respiratory stimulant, caffeine is one of the standard treatments for apnea of prematurity in neonates.

Caffeine and Health

There is no evidence for nonreversible pathologic consequences of caffeine use (e.g., cancer, congenital malformations). However, there are some groups of individuals who are considered to be at higher risk for caffeine-related problems, including pregnant women, children, adolescents, and the elderly. Furthermore, individuals with medical problems such as hypertension, diabetes, cardiac problems, urinary incontinence, insomnia, and anxiety may be more vulnerable to the adverse effects of caffeine. Epidemiologic research also suggests that caffeine and/or coffee consumption may offer some protective effects against specific diseases.

Negative Health Effects

Research has shown that caffeine can increase blood pressure by 5 to 15 mm Hg systolic and 5 to 10 mm Hg diastolic for several hours in healthy adults. It has been argued that, even after taking the effects of tolerance into account, the hypertensive effects of caffeine represent an important cardiovascular risk factor. Caffeine can influence heart-rate variability and increase arterial stiffness, with peak effects about 60 minutes after ingestion, but the clinical significance of these findings is not clear. Both caffeinated and decaffeinated coffees contain lipids that significantly raise serum total and low-density lipoprotein (LDL) cholesterol. The highest levels of lipids are delivered from espresso, French press, Turkish, and boiled coffee. Epidemiologic studies examining the relationship between coffee consumption and risk of myocardial infarction (MI) on the whole have been equivocal; however, an analysis suggests that coffee-associated risk of MI is much greater among coffee drinkers who have the CYP1A2 genotype associated with slow caffeine metabolism.

Caffeine also increases detrusor instability (i.e., unstable bladder) in patients with complaints of urinary urgency and detrusor instability. Chronic caffeine consumption has been shown to contribute to urinary incontinence in psychogeriatric patients, and caffeine reduction can improve urinary incontinence symptoms. Caffeine increases the urinary excretion of calcium; however, the amount of increased calcium loss due to caffeine is likely not clinically significant in individuals with adequate calcium intake. Associations between high caffeine consumption and bone fractures have been observed in some epidemiologic studies, particularly among women with low calcium intake; however, a direct effect of caffeine on the increased likelihood of fractures has not been observed. Caffeine has also been shown to impair glucose metabolism and insulin sensitivity among individuals with type 2 diabetes and among pregnant women with gestational diabetes.

Caffeine readily crosses the placental barrier and is distributed to all fetal tissues, including the CNS. Fetuses lack the necessary enzyme systems to metabolize caffeine. Research suggests that maternal caffeine use increases the likelihood of spontaneous abortion in a roughly dose-dependent fashion. Associations between high caffeine use and decreased fecundity and

reduced fetal growth have also been observed. Comprehensive scientific reviews of research on caffeine and pregnancy have concluded that reproductive-aged women should consume no more than 300 mg of caffeine per day.

There is no evidence that caffeine has negative effects on cancer risk, fibrocystic breast disease, peptic or duodenal ulcers, or risk of stroke.

Positive Health Effects

Case control and epidemiologic studies have suggested a relationship between caffeine consumption and reduced risk of Parkinson disease. Epidemiologic studies have also reported an association between coffee drinking and reduced incidence of chronic liver disease, although the potential mechanisms are unclear. Additionally, epidemiologic studies have reported a protective effect of coffee drinking for risk of developing type 2 diabetes, with the effects attributed to coffee constituents other than caffeine.

Subjective Effects

Acute doses of caffeine in the typical dietary dose range (i.e., 20 to 200 mg) produce a number of positive subjective effects, including increased well-being, happiness, energy, alertness, and sociability. In habitual caffeine consumers, positive subjective effects are most reliably demonstrated when caffeine is administered after a period of caffeine abstinence and thus may in part represent a reversal of withdrawal. Negative subjective effects typically emerge at higher caffeine doses. Acute doses of caffeine greater than 200 mg are more likely to produce increased reports of anxiety, jitteriness, tense negative mood, upset stomach, insomnia, and "bad effects." Individual differences in caffeine sensitivity and tolerance seem to play an important role in the likelihood and severity of negative subjective effects (e.g., individuals with panic disorder or generalized anxiety disorder tend to be particularly sensitive to the anxiogenic effects of caffeine). The negative subjective effects of caffeine tend to be relatively mild and short-lived.

Performance

Many studies have examined the effects of caffeine on human performance. Caffeine improves sustained attention (or vigilance), reaction time, and tapping speed relative to placebo, although results are variable across studies and the effects are often small. The effect of caffeine on memory has also been investigated, but there is little evidence for an association. A number of studies using military personnel have demonstrated that caffeine can improve performance relative to placebo on military-type cognitive (e.g., vigilance) and physical tasks (e.g., running times) after periods of prolonged wakefulness.

In general, controlled studies show that relative to placebo, caffeine can enhance performance during endurance exercise (e.g., 30 to 120 minutes), can reduce ratings of perceived exhaustion or effort, and can improve speed and/or power output in simulated race conditions. Some studies have also demonstrated a beneficial effect of caffeine during short-term high-intensity exercise and anaerobic resistance training.

Caffeine and Sleep

It is well documented that caffeine increases wakefulness and inhibits sleep onset. Caffeine ingested throughout the day or before bedtime has been shown to interfere with sleep onset, total time slept, sleep quality, and sleep stages. Caffeine's effects on sleep appear to be dose dependent, with greater amounts of caffeine causing greater sleep difficulties. The closer caffeine is taken to bedtime, the more likely it is to produce disruptive effects. However, 200 mg of

caffeine taken early in the morning has been shown to produce small but significant effects on the following night's total sleep time, sleep efficiency, and EEG power spectra. Caffeine-induced sleep disturbance is greatest among nonconsumers of caffeine. Although there is evidence for tolerance to the sleep-disrupting effects of caffeine, tolerance appears to be incomplete, and thus regular caffeine consumers may still be vulnerable to caffeine-related sleep problems.

In addition to caffeine's ability to disrupt sleep, there have been case reports of caffeine causing hypersomnia. Furthermore, acute abstinence after chronic caffeine consumption has been shown to increase daytime sleepiness as well as to increase nighttime sleep duration and quality.

The DSM-5 includes a diagnosis of substance- or medication-induced sleep disorder for caffeine, which is characterized by a prominent and severe sleep disturbance that is etiologically related to caffeine use. Caffeine is most often associated with insomnia.

Reinforcement

Across studies, the overall incidence of caffeine reinforcement in normal caffeine users is approximately 40%, with a higher incidence (i.e., 80% to 100%) of reinforcement under conditions of repeated caffeine exposure. In choice studies, subjects who choose caffeine tend to report positive subjective effects, whereas those who choose placebo are more likely to report negative subjective effects (e.g., jitteriness) at low to moderate caffeine doses. Caffeine reinforcement has also been observed in animals using self-administration (SA), conditioned place preference, and conditioned taste-aversion procedures. In contrast to classic abused stimulants such as amphetamine and cocaine, caffeine SA is observed in animals under a relatively narrow range of conditions.

Tolerance

High doses of caffeine (400 to 1,200 mg/day) administered throughout the day have been shown to produce "complete" tolerance to some, but not all of the effects of caffeine. However, typical dietary doses of caffeine do not usually produce complete tolerance to caffeine's effects. Complete tolerance (i.e., no difference between placebo and caffeine after prolonged caffeine administration) to subjective effects (e.g., energetic) has been demonstrated after 300 mg t.i.d. for 18 days and 200 mg b.i.d for 14 days, but not after lower doses or shorter exposure periods. Substantial but incomplete tolerance has been shown to the sleep-disruptive effects of high doses of caffeine (e.g., 400 mg t.i.d. for 7 days).

Physical Dependence and Withdrawal

The caffeine withdrawal syndrome has been well characterized. Headache is a hallmark feature of caffeine withdrawal with approximately 50% of regular caffeine users reporting headache by the end of the first day of abstinence. Such headaches have been described as diffuse, throbbing, gradual in development, and sensitive to movement. Caffeine constricts cerebral blood vessels via antagonism of adenosine. Caffeine abstinence produces rebound cerebral vasodilatation and increased cerebral blood flow, and such vascular changes are a likely mechanism underlying caffeine withdrawal headache. Other commonly observed caffeine withdrawal symptoms include fatigue, decreased energy/activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability, and foggy/not clearheaded. In addition,

flu-like symptoms, nausea/vomiting, and muscle pain/stiffness can be present. Withdrawal symptoms typically emerge 12 to 24 hours after the last dose of caffeine and peak within the first 2 days. Symptoms usually persist anywhere from 2 to 9 days, although there are reports of caffeine withdrawal headache lasting for up to 3 weeks. The severity of caffeine withdrawal can range from mild to incapacitating. There is variability in withdrawal severity both within and across individuals.

Although there is wide variability across individuals, in general the likelihood and severity of caffeine withdrawal increases as daily caffeine dose increases. Significant withdrawal symptoms can be observed in individuals consuming as little as 100 mg caffeine per day—the amount in a small cup of brewed coffee. Caffeine withdrawal can occur after relatively short-term exposure to daily caffeine (e.g., after just three consecutive days of 300 mg/day caffeine). Withdrawal symptoms are usually alleviated quickly after caffeine reexposure (i.e., 60 minutes or less). Caffeine withdrawal can be suppressed by caffeine doses well below the usual daily dose (e.g., 25 mg caffeine suppressed withdrawal after daily doses of 300 mg).

Although most withdrawal research has been with adults, there is evidence that children can also experience caffeine withdrawal symptoms upon abstinence. It is possible that children may be even more susceptible to experiencing withdrawal episodes as they likely have less control over the regular availability of caffeine-containing products. Caffeine withdrawal has also been documented in neonates born to mothers who have had recent caffeine exposure.

The observations that caffeine withdrawal can cause clinically significant distress or functional impairment have resulted in the inclusion of caffeine withdrawal as an ICD-10 and DSM-5 diagnosis; the latter includes five potential symptoms (three of which must be present for the diagnosis). Caffeine withdrawal should be considered when patients present with headaches, fatigue, mood disturbances, impaired concentration, and flu-like symptoms. Patients are often asked to stop food and fluids before certain blood tests, surgery, or medical procedures (e.g., colonoscopies, fasting blood sugar tests) and may experience adverse effects that could go unrecognized as caffeine withdrawal. Caffeine withdrawal has been identified as a significant cause of postoperative headaches.

Caffeine Intoxication

Caffeine intoxication is currently defined in DSM-5 by a number of symptoms and clinical features that emerge in response to excessive consumption of caffeine. The most common features of caffeine intoxication include nervousness, restlessness, insomnia, gastrointestinal upset, muscle twitching, tachycardia, and psychomotor agitation. Fever, irritability, tremors, sensory disturbances, tachypnea, and headaches have also been reported in response to excess caffeine use. DSM-5 requires that the diagnosis be dependent on recent consumption of a high dose of caffeine (>250 mg). High-dose intoxicating effects of caffeine are very unpleasant and are not usually sought out by users. Individual differences in sensitivity to caffeine and tolerance likely play a role in vulnerability to caffeine intoxication. Although caffeine intoxication can occur in the context of habitual chronic consumption of high doses of caffeine, it most often occurs after consumption of large doses in infrequent caffeine users, or in regular users who have substantially increased their intake. There are generally no long-lasting consequences of caffeine intoxication, although caffeine can be lethal at very high doses (e.g., 5 to 10 g).

It appears that reports of caffeine intoxication may be increasing with the growing popularity of highly caffeinated energy drinks. It has been postulated that the potential for caffeine intoxication to occur from consumption of energy drinks may be greater than other dietary sources of caffeine because of the absence of caffeine-content labeling and appropriate health

warnings, and their appeal and marketing to young and perhaps nontolerant individuals. Consumption of about eight cans of energy drinks (or 640 mg caffeine) was implicated in the cardiac arrest suffered by a 28-year-old male motocross racer.

Caffeine and Anxiety

The anxiogenic effects of caffeine are well established. Acute doses of caffeine, generally greater than 200 mg, have been shown to increase anxiety ratings in nonclinical populations, with higher doses sometimes inducing panic attacks. Individuals with anxiety disorders tend to be particularly sensitive to the effects of caffeine. Experimental studies have demonstrated that caffeine exacerbates anxiety symptoms in individuals with panic disorder and generalized anxiety disorder to a greater extent than in healthy control subjects. It has been suggested that individuals with anxiety disorders may find the stimulus effects of caffeine aversive and therefore may naturally limit their caffeine intake. Some correlational studies have found that individuals with anxiety disorders, such as panic disorder, report consuming less caffeine than healthy controls. However, other studies have shown a positive relationship between anxiety disorders or greater anxiety levels and caffeine use, or no relationship. It seems reasonable to conclude that some but not all highly anxious individuals will limit caffeine, and it is possible that some may fail to recognize the role that caffeine plays in their anxiety.

Abstention from caffeine has been shown to produce improvements in anxiety symptoms among individuals seeking treatment for an anxiety disorder. Interestingly, individuals with high caffeine consumption have been shown to have greater rates of minor tranquilizer use (e.g., benzodiazepines) relative to those with low to moderate caffeine consumption.

The DSM-5 includes a diagnosis of caffeine-induced anxiety disorder. Caffeine-induced anxiety disorder is characterized by prominent anxiety, panic attacks, obsessions, or compulsions etiologically related to caffeine use. The prevalence and incidence of caffeine-induced anxiety disorder is not known.

Caffeine Dependence and Caffeine Use Disorder

Substance use disorder (SUD) in DSM-5 (or substance dependence in DSM-IV) is defined by a cluster of cognitive, behavioral, and physiological symptoms indicating that an individual continues to use a substance despite experiencing significant substance-related problems. The DSM-5 (and DSM-IV) does not include caffeine in its diagnostic schema for SUD or substance dependence. In contrast, the WHO's ICD-10 includes a diagnosis of substance dependence on caffeine, using very similar diagnostic criteria as the DSM-IV. Caffeine Use Disorder is included in DSM-5 as a condition for further study.

A number of published studies have described adults and adolescents who report problematic caffeine consumption and fulfill DSM-IV-TR substance dependence criteria on caffeine. For example, one investigation found that 16 of 99 individuals who self-identified as having psychological or physical dependence on caffeine met DSM-IV criteria for substance dependence on caffeine, when only a restrictive set of four of the seven DSM-IV criteria that seemed most appropriate to problematic caffeine use were assessed (use despite harm, desire, or unsuccessful efforts to stop, withdrawal, and tolerance). Using the same four criteria, another study identified adolescents who fulfilled diagnostic criteria for caffeine dependence. A study of pregnant women found that 57% of caffeine users fulfilled DSM-IV criteria for lifetime substance dependence on caffeine by endorsing three or more of the seven criteria.

The one population-based survey to date suggests that when individuals in the general population are surveyed about their caffeine use, a surprisingly large proportion endorse substance-dependence criteria. In a random digit dialing telephone survey in which all seven DSM-IV criteria for substance dependence were assessed, 30% of caffeine users fulfilled diagnostic criteria by endorsing three or more dependence criteria. When the more restrictive set of four criteria were used, as in the studies described above, 9% met criteria for substance dependence.

Available research and case reports suggest that a clinically meaningful caffeine-dependence syndrome (or caffeine use disorder) does exist. Additional research is needed to determine the prevalence of the disorder, the utility and clinical significance of the diagnosis, its relationship with other drug dependencies, and effective treatment strategies. Therapeutic assistance should be made available for those who feel that their caffeine use is problematic and have been unable to quit on their own. The Composite International Diagnostic Interview–Substance Abuse Module (CIDI–SAM), a well-regarded structured interview focused on SUDs, contains a section for caffeine dependence according to DSM-IV-TR and ICD-10 criteria.

Caffeine and Other Drugs of Dependence

Alcohol

Heavy use and clinical dependence on caffeine is associated with heavy use and clinical dependence on alcohol. In one study, almost 60% of individuals fulfilling DSM-IV diagnostic criteria for substance dependence on caffeine had a history of alcohol abuse or dependence. Despite common lore that caffeine reverses the impairing effects of alcohol, controlled research suggests that such effects are generally of small magnitude and highly inconsistent across different types of behavioral and subjective measures. There is suggestive evidence that individuals consuming caffeine with alcohol tend to underestimate their levels of intoxication and impairment and may be more prone to injury. The popular practice of combining caffeinated energy drinks and alcohol, presumably to counteract the sedative effects of alcohol, suggests there is a need for research in this area.

Benzodiazepines

Benzodiazepines and benzodiazepine-like drugs (e.g., zolpidem) are widely used in the treatment of anxiety disorders and insomnia. Animal and human studies suggest a mutually antagonistic relationship between caffeine and benzodiazepines. An important clinical implication is that caffeine use should be evaluated when treating anxiety or insomnia with benzodiazepines. One study reported that a greater percentage of heavy caffeine consumers also use benzodiazepine minor tranquilizers; however, in general, rates of caffeine intake are similar among benzodiazepine users and nonusers.

Nicotine and Cigarette Smoking

Epidemiologic studies have shown that cigarette smokers consume more caffeine than nonsmokers, a finding that is consistent with the observation that cigarette smoking increases caffeine metabolism. Several studies have shown that cigarette smoking abstinence results in significant increases in caffeine blood levels among heavy caffeine consumers, presumably due to a reversal of smoking-induced increased caffeine metabolism. Although it has been posited that this effect could make smoking cessation attempts more difficult, the clinical significance has not been

demonstrated. Some human and animal studies have demonstrated that caffeine can increase the reinforcing and discriminative stimulus effects of intravenous nicotine. Some studies have failed to show that caffeine administration reliably increases cigarette smoking or nicotine SA.

Cocaine

There is little epidemiologic data on the co-occurrence of caffeine and cocaine use. One study reported that the prevalence of caffeine use among cocaine abusers is lower than the general population. Interestingly, in that same study, cocaine users who consumed caffeine reported using less cocaine than those who do not regularly consume caffeine. The subjective effects of intravenous caffeine have been reported as cocaine-like in one study, but not another. Intravenous caffeine administration has been shown to produce a significant increase in craving for cocaine in cocaine abusers; however, oral administration of caffeine has not produced this effect. Although the documented interactions between caffeine and cocaine are interesting, the clinical importance has not been established.

Clinical Implications

Given the wide range of symptoms produced by excessive caffeine use and withdrawal, as described throughout this chapter, caffeine use should be routinely assessed during medical and psychiatric evaluations. Caffeine use or intoxication should be assessed in individuals with complaints of anxiety, insomnia, headaches, palpitations, tachycardia, or gastrointestinal disturbance. Caffeine intoxication should be considered in the differential diagnosis of amphetamine or cocaine intoxication, mania, medication-induced side effects, hyperthyroidism, and pheochromocytoma. Likewise, caffeine withdrawal should be considered when patients present with headaches, fatigue, mood disturbances, or difficulty concentrating. Caffeine withdrawal should be considered in the differential diagnosis of migraine or other headache disorders, viral illnesses, and other drug withdrawal states.

Caffeine interacts with a number of medications. Caffeine and benzodiazepine-like drugs (e.g., diazepam, alprazolam, triazolam) are mutually antagonistic, and thus, caffeine use may interfere with the efficacy of benzodiazepines. Caffeine may also interfere with the metabolism of the antipsychotic clozapine as well as the bronchodilator theophylline to an extent that may be clinically significant. Case studies have suggested that caffeine withdrawal may be associated with increased serum lithium concentrations and lithium toxicity. Numerous compounds have been shown to decrease the rate of elimination of caffeine, including oral contraceptive steroids, cimetidine, and fluvoxamine.

Treatment

Reduction or elimination of caffeine is advised for individuals who have caffeine-related psychopathology or when it is believed that caffeine is causing or exacerbating medical or psychiatric problems, or interfering with medication efficacy. A surprisingly large percentage of caffeine users in the general population (56%) report a desire or unsuccessful efforts to stop or reduce caffeine use. Fourteen percent of adults with a lifetime history of caffeine use report stopping caffeine completely, usually due to health concerns or unpleasant side effects.

There are no published reports of treatment interventions designed to assist individuals who would like to completely eliminate caffeine. Several reports suggest the efficacy of a

structured caffeine reduction regimen (i.e., caffeine fading) for achieving substantial reductions of caffeine intake. A study of patients recruited from a urinary continence clinic found that a 4-week reduction program was effective at reducing caffeine intake as well as urinary frequency and urgency outcomes.

Given the limited number of treatment strategies that have been evaluated for reducing or eliminating caffeine consumption, a reasonable approach is to adapt validated behavioral techniques used to treat dependence on other drugs (e.g., tobacco dependence). Effective behavior-modification strategies include coping response training, self-monitoring, social support, and reinforcement for abstinence. Substance-abuse treatment strategies, including motivational interviewing and relapse prevention, could also be readily applied to the treatment of caffeine dependence. Providing a list of caffeine-containing products may help to increase awareness of sources of caffeine and should facilitate self-monitoring efforts. Some individuals may not readily accept the idea that caffeine is contributing to their problems (e.g., insomnia, anxiety). Such individuals should be encouraged to engage in a caffeine-free trial. There is some evidence that withdrawal symptoms may thwart quit attempts. Gradually reducing caffeine consumption may help attenuate withdrawal symptoms. In general, reduction schedules over the course of 3 to 4 weeks have been shown to be effective. No data about the probability of relapse is currently available, although relapse after caffeine reduction has been reported.

Suggested Readings

Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clin Pharmacokinet*. 2000;39:127–153.

Cornelis MC, El-Sohemy A, Campos H. Genetic polymorphism of the adenosine A2A receptor is associated with habitual caffeine consumption. *Am J Clin Nutr.* 2007;86:240–244.

Frary CD, Johnson RK, Wang MQ. Food sources and intakes of caffeine in the diets of persons in the United States. *J Am Diet Assoc*. 2005;105:110–113.

Garrett BE, Griffiths RR. Intravenous nicotine and caffeine: subjective and physiological effects in cocaine abusers. *J Pharmacol Exp Ther*. 2001;296:486–494.

Higdon JV, Frei B. Coffee and health: a review of recent human research. *Crit Rev Food Sci Nutr*. 2006;46:101–123.

Juliano LM, Griffiths RR. A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology (Berl)*. 2004;176:1–29.

Killgore WD, Rupp TL, Grugle NL, et al. Effects of dextroamphetamine, caffeine and modafinil on psychomotor vigilance test performance after 44 h of continuous wakefulness. *J Sleep Res*. 2008;17:309–321.

Reissig CJ, Strain EC, Griffiths RR. Caffeinated energy drinks—a growing problem. *Drug Alcohol Depend*. 2009;99:1–10.

Ross GW, Abbott RD, Petrovitch H, et al. Association of coffee and caffeine intake with the risk of Parkinson disease. *JAMA*. 2000;283:2674–2679.

The Care Study Group. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective observational study. *BMJ*. 2008;337:a2332.

15 Anabolic–Androgenic Steroids

All of the anabolic–androgenic steroids (AAS) are analogs of testosterone, and all promote muscle growth (anabolic) and masculinizing (androgenic) effects to greater or lesser degrees. As opposed to the corticosteroids and female gonadotrophic steroids like estrogen and progesterone, athletes and others may use the AAS illicitly in the supraphysiologic doses necessary for increasing lean body mass, shortening muscle recovery time, and increasing strength. There remains little doubt that the AAS do enhance muscle growth, strength, and in some cases, athletic performance, although the side-effect profile of the drugs limits their nonclinical use to those willing to risk significant harm, in addition to legal jeopardy and disqualification from legitimate sports competitions. The excess levels of testosterone which all of the AAS elicit in the nonhypogonadic user stimulate muscle growth as long as the user exercises those muscles, but also provoke ligament rupture, cardiac lipoprotein abnormalities, virilizing effects in women, feminizing effects in men, and psychiatric abnormalities.

History of the AAS

Testosterone was first synthesized in 1935; despite hints and suppositions, no conclusive evidence exists for performance-enhancing use of steroids by competitive athletes until the 1950s. Although records are understandably sparse, AAS use by the Soviet National Weightlifting teams of the mid-1950s has been deemed quite likely. The obvious masculinized appearance of female track-and-field athletes from the Eastern European countries in the late 1950s and early 1960s raised suspicions, which were ultimately confirmed, that the women were taking testosterone and/or AAS.

The former German Democratic Republic (GDR) sports establishment, assisted by physicians and other scientists, encouraged the use of AAS by several generations of athletes. The GDR athletic/medical establishment kept careful records of the substances athletes took, as well as the improvement in athletic performances attributable to the drugs. Using an "On-Off Protocol," the scientists were able to prove that a particular athlete's 2-m improvement in her shot-put score was attributable to the Oral-Turbinol she took, and not to other variables like additional training, nutrition, or coaching. In order to avoid detection, the athletes' testosterone:epitestosterone (T:E) levels were closely monitored, and they were given the biologically inert epitestosterone for the purpose of passing drug tests. The GDR scientists also dutifully recorded the AAS sequelae both acutely and over the years: hirsutism, acne, amenorrhea, ovarian cyst formation, voice changes, libido disturbance, hepatomegaly, and bile duct damage.

In response to the increasing use of performance-enhancing drugs, the International Olympic Committee banned the use of the AAS in 1967, began general drug testing in 1968, and started specifically testing for AAS in 1976. The Olympics were eventually followed by the U.S. National Collegiate Athletic Association (NCAA) and professional sports organizations in banning and testing for the AAS and other performance-enhancing drugs.

The Anabolic Steroids Control Act of 1990 added the AAS to schedule III of the Schedule of Federal Controlled Substances. The rescheduling listed common AAS used by athletes, provided jail time for any advisor who induced another person to take AAS, and included human growth hormone (HGH) in the same category of substances. In contrast to the Anabolic Steroids Control Act of 1990, the Dietary Supplement Health and Education Act of 1994 (DSHEA) weakened the prevention and enforcement efforts directed at the AAS. In essence, DSHEA eliminated the FDA's ability to regulate the myriad products considered herbs, nutritional supplements, or dietary supplements. The broad definition of these "nondrug" substances was intended to include substances like "ginseng, garlic, fish oils, psyllium, glandulars, and mixtures of these . . . ." In the DSHEA legislation, the manufacturers were forbidden from making any claims of medical effectiveness and admonished to adhere to good manufacturing practices, but were allowed to provide third-party educational materials, as long as the materials presented a (undefined) balanced view of the science underlying whatever claims were made about the supplement. Substances like dehydroepiandrosterone (DHEA) and melatonin were specifically protected by DSHEA from FDA oversight. The result of DSHEA's deregulation of the supplement industry was a concomitant looseness in the production, packaging, and labeling of nonpharmaceutical supplements.

Epidemiology of AAS Use

The epidemiology of AAS use in the United States is complicated by several definitional, scientific, and practical variables. The fluidity of boundaries between testosterone, the synthetic AAS, and nutritional supplements makes survey work problematic, and often the survey takers are reluctant to disclose their illicit behavior. Individuals coming from various perspectives—users, drug testers, sports officials, and legislators—have vested interests in promoting high or low estimates of those who are actually taking AAS.

In an attempt to quantify AAS use and attitudes among professional athletes, all members of the National Football League's retired Player's Association were sent a survey about their AAS use. Of those admittedly self-selected former players, 9.1% admitted using AAS during their careers. Predictably, those who had played positions requiring the most size and strength reported the highest use of AAS, with offensive and defensive linemen admitting rates of 16.3% and 14.8%, respectively. Also predictably, among those players who were active in the 1980s, a total of 20.3% admitted that they had used AAS during their careers.

Data supplied by government agencies and universities provide more accurate assessments of drug use. For the last 33 years, the Survey Research Center in the University of Michigan's Institute for Social Research has published a yearly assessment of the drug-related behaviors, attitudes, and values of U.S. high school and college students. Since 1991, the surveyors have asked about the AAS, and have therefore been able to track usage and attitudes for a generation of young American people. They found that there was a sharp increase in the use of AAS by high school students in the late 1990s, and then a decrease in use up until the present. In recent years, there has been an increase in those 12th graders who say that they see "great risk" in using steroids, which likely caused the concomitant decrease in use.

Indications for AAS Use

Although the AAS have now become synonymous with cheating in athletic competition, they were initially prescribed for legitimate medical conditions, and continue to have well-defined indications for the treatment of various chronic diseases and medical conditions. Treatment of both hypogonadism and growth hormone deficiency (GHD) in males can include the use of testosterone or the AAS.

Regardless of whether they are used for medically managed and legitimate purposes, or ad hoc and illegitimately, the anabolic effects of the AAS do not necessarily confer functional strength. Even with necessary weight-bearing exercise as a concomitant, muscle growth derived from the AAS improves the size of the muscle more than the function: the earliest widespread use of AAS by nonelite athletes was in the bodybuilding community, where the desired end result was muscle size and definition, rather than actual strength. Of course, some AAS use obviously does promote functional strength. Although in many sports an overabundance of muscle can degrade necessary agility and range of motion, many athletes have learned to titrate their dosages to promote more modest muscle growth while enhancing muscular injury healing.

AAS Metabolism

Males produce about 95% of their testosterone, the endogenous analog for all the AAS, in testicular Leydig cells, with the rest produced in the adrenal glands. Females produce relatively small amounts of testosterone in the ovaries. Most circulating testosterone is bound to sex hormone-binding protein (SHBP); only the free testosterone is biologically active. The hormone's androgenic effects are mediated by the metabolism of testosterone to the more-potent 5α-dihydrotestosterone (DHT) by the 5α-reductase, which resides in specifically male target tissue like the prostate gland, seminal vesicles, and external genitalia. These androgenic, or virilizing, effects occur in the male fetus, adolescent, and adult, to varying degrees according to the level of circulating testosterone. In some other tissues, like adipose and brain, aromatase converts circulating testosterone to estradiol, a fact of great importance to those who ingest exogenous testosterone or AAS.

The anabolic effects of testosterone and its AAS mimickers are promotion of bone and muscle growth, as the hormone promotes protein synthesis, decreases protein catabolism, and increases erythropoiesis. Although AAS with pure anabolic effects in the absence of any androgenic side effects would be ideal for athletes, no such compound has yet been developed. However, testosterone and the various AAS vary widely in the ratio of anabolic to androgenic effects. Testosterone and methyltestosterone (Android and others) have about a 1:1 ratio of androgenic to anabolic effects, fluoxymesterone (Halotestin and others) has a 1:3 ratio, and oxandrolone (Oxandrin) can have a 1:13 ratio.

All endogenous testosterone derives from (noncirculating) cholesterol, the basic steroid molecule that is metabolized to androstenedione and pregenenolone, and then to testosterone. Testosterone is eventually broken down into 5α-DHT and estradiol in peripheral tissue. Modification of the basic four-ringed steroid structure confers varying degrees of oral availability, serum half-life, and side-effect profile.

For instance, substitution of a methyl or ethyl group for the hydrogen at the 17th position of the cyclopentane ring confers oral availability on the resultant AAS by reducing hepatic first-pass metabolism. Paradoxically, these orally available compounds—like stanozolol (Winstrol)—have turned out to confer more adverse effects than do the injectable compounds, because of their hepatotoxicity. Esterification at the 17-β position allows for

longer serum half-life of the molecule because of increased lipophilicity and a resultant slower release from the oily injection vehicle into the blood stream. Testosterone cypionate (Depo-testosterone) and nandrolone decanoate (Deca-Durobolin) both have longer half-lives than their nonesterified building-block molecules, with that half-life directly related to the length of the ester chain.

There are four basic ways in which structural and pharmacokinetic properties can be expressed from the basic testosterone structure. First, the standard testosterone molecule can be utilized parenterally, as a skin patch, skin cream, or alternatively in a micronized oral preparation. Second, esterification at the 17-β site promotes lipophilicity on the testosterone cypionate, propionate, enanthate, and undecanoate preparations. Third, manipulation at the 17-α site produces methyltestosterone, danazol, and oxandrolone, which resist hepatic first-pass metabolism and become orally available, but therefore have increased liver toxicity. Finally, various modifications at the A, B, or C rings (as with mesterolone, nortestosterone, and nandrolone) provide (variously) slowed metabolism, enhanced androgen receptor affinity, resistance to aromatization to estradiol, and decreased metabolite binding to androgen receptors.

AAS-related "dietary supplements" are simply prohormones that have the same or similar biologic effects as the AAS themselves, but remained available long after the AAS were placed on the Federal Schedule. For instance, the prohormone supplements DHEA and androstenedione were legal and available over the counter (OTC) several years ago. Although these supplements usually are less potent than the AAS, they are converted to testosterone and cause measurable androgenic and anabolic effects.

Designer AAS

A variety of AAS—the "designer steroids"—have been designed specifically to evade drug testing and provide a high anabolic–androgenic profile. Although epitestosterone was used by the GDR to evade drug tests and is still prescribed by some physicians despite its biologic inertness and ineffectuality for any purpose other than evading drug testing, other more sophisticated strategies have been developed for evading those tests. For instance, norbolethone, which was initially packaged as "The Clear," was developed in the 1960s and never marketed because of concerns about potential toxicity, but came to light as a present-day illicit AAS when a U.S. cyclist was found to have an elevated T:E ratio at the 2000 World Cycling Championships in Belgium (and eventually found to have been using norbolethone). After the exposure of norbolethone as "The Clear," it was changed to tetrahydrogestrinone (THG), a previously unknown molecule structurally related to two AAS already banned by the World Anti-Doping Agency (WADA): gestrinone and trenbolone.

AAS users obtain information about these substances from a large variety of sources: friends, suppliers, easily obtainable manuals, and—probably most importantly—sophisticated Internet sites, blogs, and chat rooms. The information that users get, both on optimum regimens and managing the inevitable side effects of AAS use, ranges from scientifically accurate to frankly criminal. But since all of the advice constitutes the practice of medicine without a license, there is little chance for second opinions and considered trials, which are, ideally at least, the province of legitimate medical practice.

The underground AAS pharmacologists have come up with several protocols of AAS use, the first of which is "stacking" in which the user takes several different agents from different classes of AAS in order to reap the particular benefits of each. Pyramiding is the not-unreasonable pattern of tapering up the ingested AAS and then tapering down at the end of a cycle, to avoid withdrawal.

Complications of AAS Use

Use of the AAS has been associated with numerous medical problems, some more serious than others. Most serious is the occasional cardiac death attributed to the AAS. Two bodybuilders (aged 29 and 30) collapsed and died without any obvious reasons, and were found to have been using stanozolol, nandrolone, and testosterone, but no drugs of abuse or ethanol. Cardiac pathology revealed normal gross cardiac pathology, so simple cardiomegaly was not the cause of death. The T:E ratio in one case was 28.7, and in the second was 42, far above 6 commonly considered the upper limit of normal. Despite the absence of gross cardiomegaly, the pathology report did show focal myocardial fibrosis and contraction band necrosis; the cardiac vessels and conduction systems appeared free of pathology.

A small study of 6 AAS-using bodybuilders compared to 9 non–AAS-using bodybuilders and 16 age-matched sedentary controls showed by Doppler echocardiography of the left ventricular (LV) myocardium that there was no increase in LV wall thickness in the AAS users. However, the AAS users exhibited a smaller passive component to LV filling, which was thought to be potentially related to their AAS use.

In a less serious, though arguably more common, way, AAS users consistently suffer from serum lipoprotein abnormalities caused by AAS use. AAS users consistently experience falling levels of high-density lipoprotein (HDL) after a few days of AAS use, probably related to stimulation of hepatic triglyceride lipase, which is responsible for modulating HDL-2 and apoliprotein-A1. Interestingly, the 17-alkylated AAS reduce HDL by about half, while nandrolone and testosterone esters have little effect, probably because testosterone does not induce triglyceride lipase. Total cholesterol often remains stable in AAS users, because low-density lipoprotein (LDL) is increased by AAS use.

Despite the clear evidence that AAS use causes perturbations in serum lipid profiles, and the connection between lowered HDL levels and heart disease, there is as yet little evidence that AAS users suffer clinically significant lipid profile abnormalities. One study of the reversibility of AAS-related side effects found that HDL decreased, in fact resolved, after the 12 to 43 months in which the subjects had not been taking AAS, after their long-term use.

Musculoskeletal injuries related to AAS use by adults are usually related to tendon and ligament damage caused by AAS-mediated muscle growth, without concomitant connective tissue growth. In addition, the AAS combined with exercise may interact with tendon collagen fibrils, decreasing the tensile strength of the tendon, just when it is needed to handle the newly enlarged musculature.

Although hepatic pathology is often cited as one of the most worrisome potential side effects of AAS use, the literature reveals several relatively inconsequential hepatic conditions associated with AAS, and only a few serious maladies. Pelioisis hepatitis—blood-filled cysts in the liver—has been associated with tuberculosis, the use of oral contraceptives by women, and AAS use by men. Despite the understandable concern about having any sort of liver pathology, peliosis hepatitis is itself usually considered a benign finding, and is usually discovered only incidentally. Similarly, liver function tests (LFTs) are often elevated in those who are presently using AAS or have recently stopped, but the LFTs usually normalize after a relatively short period of time, with systemic damage to the liver unclear.

The most worrisome hepatic side effect linked with the AAS is hepatocellular carcinoma. This tumor occurs mostly in those over 65 years of age, has about a 3:1 male to female prevalence ratio, a poor prognosis, and few distinct risk factors: previous hepatitis C infection, heavy alcohol consumption, and diabetes/obesity. However, between 15% and 50% of new cases have none of these risk factors, leading to a search for other associations or etiologies. Since the disease is more prevalent in men—who have higher endogenous testosterone levels than women—AAS use should be one possible line of inquiry. But the reports on hepatocellular

carcinoma in AAS users are case reports that suggest but do not prove a connection between the use of AAS by the subjects and their subsequent cancer diagnoses.

The most common sex-specific side effects of the AAS in men, testicular atrophy and gynecomastia, are caused by down-regulation of testicular production of testosterone and aromatization to estrogen, respectively. Although the AAS certainly cause testicular atrophy and subsequent impotence, loss of libido, and decreased sperm count, it is less clear that the AAS actually cause permanent infertility. In men, the AAS apparently directly damage sperm via altered meiotic segregation, but this effect usually resolves after cessation of AAS use.

Deca-Durabolin (nandrolone decanoate) is quite popular among AAS users because it has little liver toxicity and a high anabolic:androgenic effect ratio. However, the molecule is a progestin and can incite gynecomastia, suppression of the hypothalamic–pituitary–testicular axis, and complete cessation of endogenous testosterone production. The subsequent impotence can be addressed by the use of testosterone production stimulants like human chorionic gonadotropin (HCG) both during and after the Deca-Duroblin cycle, but there is no guarantee of any salutary effect. Many Deca-Duroblin users complain of impotence long after they have stopped using the drug, and even after attempts at stimulation of testosterone production.

Women who ingest AAS experience the effects of an abnormally high testosterone level, and therefore show easily predictable effects: increase in muscle size, deepening of the voice, increased facial hair, clitoral enlargement, and menstrual problems.

The damaging physical effects of the AAS on children and adolescents are even more marked and well described than on adults. A long list of risks specific to children and adolescents who use AAS includes potential abnormalities in sexual development modulated by testosterone. Other worrisome potential consequences include psychiatric effects and musculoskeletal problems. Although adolescents, like adults, face the danger of tendon rupture from accelerated muscle growth, adolescents have the unique added problem of premature epiphyseal plate closure (with the potential that premature closure of the plate results in short stature).

Psychiatric Complications of AAS Use

The AAS also cause behavioral and psychiatric phenomena, the most distinctive of which is known popularly as “roid rage.” The peer-reviewed literature contains multiple case series and literature reviews documenting AAS-related hostility, aggression, hallucinations, and delusions.

AAS-related mood perturbations may be even more prominent in children. In one report, researchers surveyed 86,000 6th, 8th, and 11th graders about their use of drugs and alcohol and their attitudes toward school, family, and community. Not surprisingly, the percentage of AAS users increased as the students aged (for both boys and girls). Aggressive behavior toward others was admitted by 64.1% of the boys who had ever used AAS, as compared to 22.6% who had never used AAS. Of those who used AAS, both boys and girls had higher rates of having experienced suicidal ideation, compared to non–AAS-using boys and girls. Although these data show association, not causation, the connection between AAS and emotional abnormalities in high school students deserves closer scrutiny.

For adults, AAS-related affective symptoms are much more common than psychosis, and the affective symptoms are generally experienced by unsophisticated AAS users who are taking dosages at the high end of the spectrum, far beyond the dosages for performance enhancement. Mood symptoms can include depression, hypomania, and frank mania. One manifestation of withdrawal from AAS can be a profound depression, which has been implicated in the completed suicide of some users.

Although the very existence of true physiologic dependence and withdrawal from AAS has been questioned, careful analysis shows that both phenomena occur, especially in the heavy AAS user. Typical of withdrawal are symptoms such as dysphoria, fatigue, psychomotor retardation, impaired concentration, and suicidal ideation. This symptom picture often resolves after several days.

When compared to cocaine and heroin, the AAS are decidedly less likely to cause addiction problems like tolerance, withdrawal, and continued use despite the user's awareness of adverse consequences. However, researchers have put the "addictiveness" of the AAS on the spectrum closer to mild reinforcers like caffeine, nicotine, and benzodiazepines.

Substances Used Concomitantly with the AAS

A variety of other substances are often used along with the AAS, some to augment the effects of AAS and some to counteract AAS side effects. One of the most commonly used adjuncts to the AAS is HGH (or recombinant human growth hormone [rHGH]). Native HGH is produced by the anterior pituitary, and the most common form of the hormone contains 191 amino acids. It is only available in injectable form, has a short circulating half-life (about 20 minutes) as well as a biologic half-life of 9 to 17 hours. HGH has been available commercially for 40 years, and has well-defined pediatric indications (e.g., for idiopathic short stature, Turner syndrome, Prader–Willi syndrome).

Athletes taking HGH hope for the anabolic and lipolytic effects seen in patients with GHD and others with genuine HGH deficiencies, although the data supporting any sustained good effects in normals who take nothing but HGH are not particularly convincing. Reported side effects of HGH include insulin resistance, increases in very low density lipoproteins (VLDLs), arthralgia, myalgia, hypertension, cardiac failure, and an increased rate of malignancies. Although the illicit use of HGH is banned by all sports organizations, no widely available test procedure to detect HGH has been found.

In addition to the AAS, stimulants are often used by athletes trying to gain a competitive advantage. Doping athletes can use commonly prescribed attention-deficit hyperactivity disorder (ADHD) remedies like amphetamine (Adderall and others), methylphenidate (Ritalin and others), OTC drugs such as caffeine or pseudoephedrine, or banned but previously available supplements such as ephedra. On occasion, athletes will even try highly toxic drugs of abuse like cocaine for performance enhancement, although this strategy usually quickly leads to disaster. One commonly abused stimulant is clenbuterol, a β_2-adrenergic agonist, prescribed as a decongestant but used by athletes as a partitioning agent.

In attempts to "flush their system" and obtain a false-negative urine toxicology results, athletes sometimes use diuretics such as loop diuretics, various herbal preparations, and simple overingestion of water. Consequently, loop diuretics are banned by most sports organizations unless the athlete has a documented therapeutic use exemption (TUE). Since diuretics are perceived as relatively benign, athletes often significantly underestimate the potential risks they face of dehydration, heat stroke, kidney failure, hyponatremia, and hypokalemia with their use.

HCG can be used by AAS users to counteract the AAS-stimulated down-regulation of androgen production by the interstitial cells of the testes. HCG stimulates the testes to again produce testosterone, even in the ex-AAS user who may have stopped using AAS but whose testicular function did not return. In addition, HCG is reputed to raise testosterone levels without affecting the T:E ratio, another reason athletes might use the substance.

Ethics of AAS Use

Any consideration of the ethics of performance enhancing substance (PES) use in sports necessitates an understanding of the meaning of sport, and some definition of what actually constitutes a PES. The main focus of most sports—intense competition—lends itself to whatever sort of enhancement an athlete can muster, substances included. A swimmer choosing to wear a speed-enhancing suit, a bicyclist training at high altitude, or a skier using expensive waxes are all normative events in sport, but all are also regulated by authorities within the sport. What if an athlete wants to avoid traveling to the mountains and simply uses a hypoxic chamber? Or takes a substance like erythropoietin (EPO), which also raises hemoglobin levels?

The use of substances to improve performance seems to many a separate case, but the same sorts of ambiguities exist in this category. Some substances, like protein powders, are allowed by all major sports, while others, like the AAS, are banned by sports organizations. Some legitimate medications, like the β-agonists used to treat asthma, are banned by some sports organizations and not others, while other medications like the β-blockers used to treat hypertension are banned in some sports but not others. Just to confuse the picture, all major sports organizations must allow for the possibility that some banned substances—most notably stimulants and diuretics—may be medically necessary for a particular athlete and therefore undeniable for those who meet clinical criteria for taking that medication. Separating out those athletes who merely want the medication as opposed to those who both want and need the medications is the difficult task faced in the granting of sports TUEs, as described below.

Antidoping programs and the necessary testing often appear to be unnecessarily paternalistic. This certainly seems to be an incongruity in athletics: if society allows adults to smash into opposing linebackers and drive race cars at 180 miles/h for the sake of sport, how can society forbid those same individuals from taking another acknowledged risk involving the PES? There is, however, an important difference between the risks inherent in a sport and those that the athlete chooses to take on, and the athletes' choices are hardly unconstrained. If unregulated, the enormous pressures put on athletes—even those who are not professional—result in potentially self-destructive behaviors with the PES that could lead to dangerous drug use, and which could spread to other athletes. Each sport has the right and obligation to regulate the boundaries of competition.

Therapeutic Use Exemptions

All major sports organizations, both professional and amateur, have policies in place that contemplate the use of banned substances by athletes who take the medications for legitimate medical reasons: the TUE. While the idea is simple, the line between the two often becomes blurred, changeable, and entirely indefinable. The WADA publishes criteria for TUEs. Most TUEs in sports are for stimulants used to treat ADHD, β-adrenergic agonists to treat chronic obstructive pulmonary disease (COPD), and β-blockers to treat asthma.

Legal Issues in the Use of AAS

Despite the widespread nature of antiaging clinics that advertise and prescribe HGH with the veneer of legitimacy, and the clandestine pharmacies that provide the substance to athletes, those prescriptions are, contrary to most off-label prescriptions, specifically banned by the

FDA. The FDA has noted that HGH is not a dietary supplement, and specifically has banned its use for antiaging, bodybuilding, or athletic enhancement.

The AAS are on the Federal Schedule III list, putting them in the same category as the following (quite dissimilar) substances: codeine, ketamine, and buprenorphine, all of which have well-accepted medical uses. The AAS were placed on the Schedule III list as an acknowledgment that they have some therapeutic uses and may have to be prescribed to certain individuals. But practically speaking, most AAS are provided illegally, and have high degrees of criminal activity associated with them.

Testing for AAS

In the most common test for AAS, exogenous use of testosterone or AAS can be detected by checking the urinary T:E ratio using high-resolution gas chromatography/mass spectroscopy (GC/MS). Since epitestosterone is unaffected by exogenous testosterone, the usual 1:1 ratio will shift upward if the user ingests testosterone. Because some individuals have naturally elevated T:E ratios, sports organizations define an upper limit of normal for this ratio, usually 4:1 or 6:1. If an athlete claims to have a naturally elevated T:E ratio, sequential testing over several months can prove or disprove the claim because T:E ratios are stable unless manipulated by exogenous administration of testosterone. Epitestosterone has no physiologic effect, so the only reason to ingest epitestosterone would be to deceive a drug test.

Although laboratory protocols are vital in obtaining an accurate result, so are the forensic quality of the collection, packaging, transport, and laboratory handling of the samples. The WADA, for instance, published a 22-page protocol for urine collection alone, which assigns a "Doping Control Officer" who arranges a chaperone to accompany the athlete from the moment the athlete is notified of the required drug test until he or she arrives at a "Doping Control Station." The document describes the right of the athlete being tested to have a representative accompany him or her, provisions for (very minimal) privacy and confidentiality, and defines target testing for specific athletes or categories of athletes, weighted selections, and random selections. In addition, a valid "Chain of Custody" between the donating athlete, the collector, and the laboratory must be in place. Usually, collecting agencies immediately split the donated urine sample into an "A" and "B" sample for later separate testing if one sample is found to contain a banned substance. Immediate testing at the collection site for pH, temperature, and specific gravity can increase the likelihood that a sample is valid. These sorts of carefully planned routines and procedures are absolutely necessary, both in order to provide accurate results, and to address the inevitable legal challenges that arise when a positive result causes loss of income and/or public announcement of a player's name.

Treatment of AAS Users

Treatment of AAS use must begin with a comprehensive evaluation focused on the actual effects of the substances used, any withdrawal if the substance is stopped or decreased, and concomitant substance use or mental illness. Many AAS users who have used small amounts of AAS or used AAS for a short period of time stop without any untoward effects. Often, they must stop their use to avoid sanctions or detection, or because of parental disapproval. However, some AAS users find it difficult to stop their use, some experience withdrawal, and an even smaller percentage show classic signs of addiction: continued use despite knowledge of adverse consequences, compulsive use, and sustained withdrawal.

For those AAS users who require treatment, the evaluating clinician should be knowledgeable about AAS, addiction in general, and the particular ethos of the culture within which the user resides. As with all addiction, the clinician should advise that the user avoid—in Alcoholics Anonymous parlance—the people, places, and things associated with the AAS use. For the athlete using AAS, this often means eschewing the gyms and practice fields where he or she had obtained the substance and isolating himself or herself from teammates, both difficult but necessary tasks in avoiding further use. The necessary paradigm shift, away from intense competition and toward a healthy lifestyle, can be managed with the help of a therapist or counselor knowledgeable about competitive athletics, and in the best situation, knowledgeable about the athlete's particular sport.

The affective syndromes like depression and anxiety that can arise from stopping AAS may have catastrophic consequences, including self-harm and completed suicide. The clinician assisting a person stopping AAS should therefore monitor the user carefully for incipient affective symptoms and aggressively treat any symptoms that do arise. Antidepressant medications such as fluoxetine and venlafaxine may be used in treating persistent dysphoria, but since their response time is 2 to 6 weeks, the depressed AAS users should remain under closely monitored psychotherapy during (at least) that time.

Similarly, AAS withdrawal can be treated symptomatically with hormonal treatment under the care of an endocrinologist experienced in working with AAS users. Endocrinologists may recommend gradually tapering dosages of testosterone, the AAS that the individual was using, and even attempt stimulation of the hypothalamic–pituitary–testis axis via hormonal manipulation. The treating endocrinologist and psychiatrist should collaborate closely to render optimum care while keeping the patient as free as possible of AAS withdrawal symptomatology, both physical and psychiatric.

Conclusion

The science around the use of AAS for performance enhancement is relatively meager for easily understandable reasons; most use is illicit and therefore hidden from scientific inquiry, and the large doses of AAS used by many users could not be ethically prescribed to study subjects because of potential danger associated with such use. This justifiably sparse body of scientific knowledge about AAS effects and side effects, however, engenders discourse on the subject which is long on opinion and philosophy, but short on fact.

Some argue that the AAS present reasonable risks that should be assessed not by legal authorities or sports organizations, but by the users themselves. They argue that reasonable adults should make their own choices and point out that allowing legitimate use of the AAS would eliminate the criminal manufacturing and distribution practices now in place, as well as allow legitimate physicians to give advice to athletes using the AAS. Despite the lack of ultimate clarity on the side-effect profiles of the AAS, it is clear that they cause physical as well as psychiatric morbidity far in excess of any benefit. But in fact, legitimate avenues are already available for those patients with a legitimate need for the AAS (for example, physicians who treat HIV and other wasting disease may prescribe the AAS without concern about censure).

The use of AAS for legitimate medical purposes deserves more inquiry into present uses, and investigations of potential beyond the relatively small group of wasting diseases for which those medications are now indicated. The use of AAS for performance enhancement, anathema though it is to most of the medical world, deserves further research if only to further clarify the dangers of illicit use and develop better strategies for prevention, testing, and treatment.

Suggested Readings

Gorayski P, Thompson CH, Subhash HS, et al. Hepatocellular carcinoma associated with recreational anabolic steroid use. *Br J Sports Med*. 2008;42:74–75.
Green G. Performance-enhancing drug use. *Orthopedics*. 2009; 32;647–649.
Horn S, Gregory P, Guskiewicz K. Self-reported anabolic androgenic steroids use and musculoskeletal injuries: findings from the center for the study of retired athlete's health survey of retired NFL players. *Am J Phys Med Rehab*. 2009;88(3):192–200.
Kicman AT. Pharmacology of anabolic steroids. *Br J Pharmacol*. 2008;154:502–521.
Murray T. Doping in sport: challenges for medicine, science, and ethics. *J Int Med*. 2008;264:95–98.
Olshansky SJ, Perls TT. New developments in the illegal provision of growth hormone for "anti-aging" and bodybuilding. *JAMA*. 2008;299(23):2792–2794.
Pope HG, Katz DL. Affective and psychotic symptoms associated with anabolic steroid use. *Am J Psychiatry*. 1988;145(4):487–490.
Trenton AJ, Currier GW. Behavioral manifestations of anabolic steroid use. *CNS Drugs*. 2006;19(7):571–595.
Vieira RP, Franca RF, Dasmagceno-Rodriguez NR, et al. Dose-dependent hepatic response to sub chronic administration of nandrolone decanoate. *Med Sci*. 2009;40(5):842–847.
Yesalis CE, ed. *Anabolic Steroids in Sport and Exercise*. 2nd ed. Champaign, IL: Human Kinetics 2000:51–72.

Section 3

Compulsive and Addictive Behaviors

16 Eating Disorders

Eating disorders (EDs) and substance use disorders (SUDs) share several common elements. Both groups of illnesses are characterized by high rates of morbidity and mortality. Both pose substantial clinical challenges to the highly experienced clinician. Both have high rates of relapse and recidivism. Additionally, both sets of illnesses commonly co-occur with each other and with a number of other Axis I and Axis II diagnoses, further complicating assessment and treatment. Because of the frequent co-occurrence of SUDs and EDs, investigators have long searched for common etiologic factors in the development and perpetuation of these illnesses. To date, no single link or factor has emerged, yet the high rate of co-occurrence itself holds important implications for appropriate diagnostic assessment and treatment, and will likely guide future directions of investigation.

Brief Descriptions of Major Eating Disorder Syndromes

DSM-5 includes a section on Feeding and Eating Disorders, which includes conditions such as pica and rumination disorder. For purposes of the present review, the focus here will be on anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED). Other Specified Feeding or Eating Disorder is an additional category that can be used for categorizing patients who do not clearly fulfill the criteria for the other major EDs (e.g., atypical anorexia nervosa, purging disorder).

Anorexia Nervosa

DSM-5 has three criteria for AN: a restriction of energy intake that leads to significantly low body weight, a fear of gaining weight (or behavior that interferes with weight gain), and a disturbance in the perception of body weight or shape. There are two subtypes of AN—a restricting type and a binge-eating/purging type.

Bulimia Nervosa

A diagnosis of BN in DSM-5 requires the patient to have five features. The two key features are binge episodes of eating and compensatory behaviors to prevent weight gain after a binge (e.g., purging, excessive exercise). BN does not occur exclusively during episodes of AN.

Binge-Eating Disorder

DSM-IV had included research criteria for BED (as a condition that required further study), but BED was included in DSM-5. This condition has features similar to those of BN (i.e., recurrent episodes of binge eating), but there is no compensatory behavior found in BN (i.e., the patient does not purge, misuse laxatives or diuretics).

General Epidemiology of Eating Disorder Syndromes

Estimates suggest that 0.5% to 2.0% of girls and women are affected by AN across their lifetime. While a 1:10 male-to-female ratio in diagnosis has been frequently cited, recent epidemiologic work reflects a less severe but still highly significant gender difference. A review of incidence studies further suggests that the number of new cases per 100,000 population has increased over the 20th century, although the size of the increase was modest.

The prevalence estimates of BN have varied widely since its inclusion as a diagnostic category in the DSM in 1979. This variation may relate to changes in definitions, populations examined, and, possibly, prevalence over time. A review of epidemiologic studies suggests that approximately 2% to 3% of young women meet DSM-IV-TR criteria for BN, with a lifetime prevalence of 1.5% for females and 0.5% for males. For both AN and BN, studies of incidence and prevalence have struggled to explain whether variances in prevalence are due to actual change, recall bias, growing awareness of the syndromes, or changes in media attention to the illnesses over time.

A number of studies indicate that BED is more common than either AN or BN in the general population. Data from one national study found lifetime prevalence estimates for BED to be 3.5% in women and 2.0% in men. This was nearly double the rates reported for AN and BN combined in that survey. The prevalence of BED is noted to be even higher among the obese and in those seeking bariatric surgery or other weight loss interventions.

Demographics of Eating Disorder Syndromes

While most commonly developing during the adolescence and young adulthood, EDs can occur at any point in the life cycle. The peak in age of onset for AN occurs between ages 13 and 17, although some patients develop anorexia earlier in childhood and some in later adulthood. The peak in age of onset for BN ranges from late adolescence through young adulthood. Although less is known about the onset and natural course of BED, it appears that a majority of individuals develop this illness in young-to-middle adulthood. Unlike AN and BN, severe dieting behaviors and profound concern about weight are not necessarily present prior to the onset of binge-eating behavior. Although AN and BN and, to a lesser extent, BED are all more common in females, it is important not to neglect these EDs in men. Few gender differences in the specific features, symptoms, morbidity, and mortality of the disorders have been found by researchers.

Comorbidity of Eating Disorders and Substance Abuse

SUDs and EDs commonly co-occur in both clinical populations and research samples. The overall prevalence of drug and alcohol abuse in ED patients is approximately 50%, compared with a prevalence of approximately 9% in the general population. Conversely, over 35% of individuals

with SUDs report having EDs compared with a rate of 1% to 3% in the general population. Lifetime prevalence studies have reported the rates of SUD to be up to 27% in populations with AN, with significantly higher rates in the binge–purge subtype; up to 55% in those with BN; and 23% of those with BED. A meta-analysis of 16 studies confirmed higher prevalence rates of drug use in individuals with EDs than in controls. In particular, the analysis showed elevated levels of opiate abuse, cannabis abuse, and general illicit drug use. Risk was shown to be higher in individuals with BN, somewhat less in those with BED, and negligible in those with restrictive AN.

Conceptual Issues and Confounding Factors in Assessing Comorbidity

In addition to many of the usual confounding factors in studies (recruitment methods, population selection, standardized interviews vs. self-reports, etc.), there are numerous complexities in evaluating the relationship between SUDs and EDs. This perhaps reflects the underlying heterogeneity in the definition of comorbidity. Various studies of comorbidity have used alternate definitions including co-occurrence of disorders that are random and independent, co-occurrence of disorders that share common etiologic underpinnings, or different disorders that may have a shared causal relationship. Overlapping diagnostic criteria may lead to falsely elevated rates of comorbidity. For example, the impulsivity criterion of borderline personality disorder can be met by binge behavior in AN, BN, and BED, or the substance use in SUD. Carefully designed trials have suggested that some of the apparent co-occurrence between EDs and SUDs may be, at least in part, related to other psychiatric comorbidities.

A number of investigators have pointed out the critical importance of selecting appropriate control groups to allow for correct interpretation of patterns of comorbidity. These control groups might include psychiatric populations without the ED and/or SUD. Several studies with relevant control groups have shown that, although EDs and SUDs co-occur, the co-occurrence is less striking in the relevant comparison group as opposed to the frequently used "normal" control group. Some studies have elucidated that patients with restrictive or nonpurging AN may be less likely to develop SUDs. This factor needs to be considered when interpreting earlier work that did not take into consideration the importance of the subtyping of AN patients. A further limitation in some studies is the lack of inclusion of rates of individuals with subthreshold EDs. Clinically, the finding of an association between subclinical ED and SUD suggests the importance of a thorough assessment to facilitate early treatment.

Relationship of Substance Use to Binge Eating

It is of clinical and theoretic importance that among individuals with some form of ED, nicotine, alcohol, or illicit drug use is much more common in those individuals who binge eat, regardless of whether they have AN, binge–purge-type AN, BN, or BED. This was replicated in a 10-year prospective study. The risk of onset of an SUD in persons hospitalized for AN was six times greater among those who reported binge eating while underweight compared with those with no history of binge eating as reported during the index hospitalization. Some epidemiologic studies have reported that alcohol use disorders were much more prevalent among women with AN with binge eating compared with those with AN without binge eating, although this pattern has not been consistently noted. A sample of ED probands from the Price Foundation Genetic Study revealed that the prevalence of SUD differed across the AN subtypes, with increased prevalence in the group with binge eating. Similarly, individuals who purged were more likely to report substance abuse than those who did not purge.

Patterns of Substance Abuse in Eating Disorders

It is important to note that because of their drive for thinness, ED patients may be motivated to utilize appetite-suppressing substances (e.g., cocaine, amphetamines, and thyroid hormone). However, it has also been noted that the use of substances that promote appetitive behavior (e.g., cannabis and opiates) is not uncommon among patients with EDs. In some cases, patients may be unaware that these agents may trigger binge behavior. Further, patients with EDs frequently misuse or abuse drugs not usually considered as drugs of abuse, including laxatives, diuretics, thyroid hormone, and insulin.

Hypotheses to Explain the ED–SUD Comorbidity

Several hypotheses have been proposed to account for the comorbid occurrence of EDs and SUDs. These have generally been separated into those postulating a "shared etiology" versus a "causal etiology." The "shared" etiology hypotheses suggest that both disorders stem from a common underlying predisposition and broadly include personality (i.e., both sets of illnesses result from a so-called addictive personality), family history (i.e., both sets of illnesses share family risk factors), developmental factors (i.e., both sets of illnesses result from susceptibility to external pressure such as cultural pressures to be thin in EDs and peer pressure to experiment with drugs in adolescence in SUDs), and biogenesis (i.e., both sets of disorders share a common biologic vulnerability toward addiction to substances, or to starvation or bingeing and purging). The "causal" etiology hypotheses focus on the influence one disorder may have on the development of another. These hypotheses include self-medication (i.e., individuals with EDs use drugs to diminish hunger, modify affects, increase energy, etc.) and food deprivation (i.e., individuals with restrictive food intake are prone to excessive substance use as a compensatory behavior).

Possible Shared Causation of EDs and SUDs

Various animal models of eating behavior have been utilized in attempts to understand etiologic factors in the development of EDs. Some animals exhibit binge-like behavior when exposed to certain environmental factors (e.g., food restriction, stress, intermittent exposure to highly palatable food) thought to play a role in the development of human EDs. Notably, not only do these animals overeat palatable food, but they have also been shown to be more prone to develop addictive behavior when exposed to alcohol and cocaine. These studies suggest that under certain conditions, palatable food may produce oversensitivity of reward circuits as has been postulated to occur in SUDs. Some studies have focused on the endogenous opiate peptides (EOP) as likely candidates for dysregulation in both ED and SUD. The activity of the EOP has been shown, in animal models, to have an impact on patterns of food and alcohol consumption. Naltrexone, an opiate antagonist, has been used as a treatment in BN and in alcohol and drug addiction. Other neurochemical systems that have received research attention include the γ-aminobutyric acid (GABA), serotonin, cholecystokinin, peptide YY, and dopamine (DA) systems, all of which can have an important impact on food and alcohol consumption.

Environmental and Social Factors

A number of studies have suggested that family conflict and parental modeling behavior are also major risk factors for both ED and SUDs. Just as some children may learn about dieting

or an emphasis on weight from parents, they may also learn from parents to use substances as a way of coping with stress. Broader sociocultural influences may also contribute to the development of both sets of illnesses. The media, social environment, and peer social interaction all may play a significant role in the initial experimentation with dieting, bulimic behavior, and similarly, the initiation of drug use. Culture may also provide potent reinforcement as a perpetuating factor in both ED and SUDs.

Individual Factors, Personality, and Impulsivity

Some researchers have proposed that an addictive personality might predispose certain individuals to become addicted to one or multiple substances and/or behaviors, such as those involved in EDs. Proponents of this theory, from both biobehavioral and dynamic perspectives, view food and substances as addictive substrates. While theoretically appealing, empirical evidence for this connection in personality is not conclusive. Efforts to isolate psychological characteristics common to ED and substance abuse patients have not been successful. However, it has been commonly hypothesized that an association between SUDs and EDs reflects the influence of the underlying personality traits such as impulsivity. Borderline personality disorder and other cluster B personality syndromes are commonly present in individuals with EDs and substance abuse disorders, but are most frequently seen in women with co-occurring ED and SUD.

The role of childhood trauma in the etiology of EDs and SUDs has been the subject of numerous studies. Childhood sexual abuse predicts the onset of a myriad of psychiatric disorders, including, but not exclusively, EDs and SUDs. One study examining the differential rates of sexual abuse among the subtypes of EDs revealed that women with comorbid BN and substance dependence had the highest frequency and the most severe history of sexual abuse. However, some investigations suggest that sexual abuse is only one component of a larger and more complex etiologic picture.

Finally, the risk of co-occurring mood disorders is high in populations with EDs and SUDs. Depression has commonly been cited as a possible link between EDs and SUDs. A "self-medication" hypothesis suggests that those with mood alterations and/or body dissatisfaction, coupled with impulsivity, might be predisposed to use substances in an attempt to alleviate these symptoms.

An Allostatic Model of Eating Disorders

Koob and LeMoal proposed a model of dysregulation of the brain reward system for understanding drug addiction. This model has salient features applicable to conceptualizing the development of EDs. The model was based on the homeostasis and allostasis hypotheses. Homeostasis, a self-regulating process for multisystem coordination of an organism's response to an acute challenge, fails in alcoholism, drug addiction, and AN and BN, leading eventually to death or chronic impairment. The allostatic state is a state of chronic deviation of the regulatory system from its normal homeostatic operating level. In other words, an allostatic state is a dysregulation of reward circuits with compensatory activation of brain and hormonal stress responses. The allostatic load is defined as the cost the body has to pay for adapting to adverse psychological and physical situations. It represents the presence of excessive demand on regulatory systems or the failure of these systems to relax when the demand is over. The latter may explain frequent relapses in both AN and BN. A vulnerable phenotype such as AN or BN may respond to various stresses by an allostatic maladaptation. The state of allostasis reflects both genetic and environmental factors and thus involves multiple brain mechanisms, including dysfunction of neurotransmitters and aberrations of neuropeptides.

Examples of Neurobiologic Dysregulation in ED and SUD

Corticotropin-Releasing Factor (CRF) and Endogenous Opioid Peptides (EOPs)

Individuals with SUDs have a compulsion to take drugs, and AN patients have a compulsion to exercise. SUD patients have a loss of control in limiting drug intake, and bulimics have a loss of control in limiting food intake. Individuals with both sets of diagnoses are characterized by engagement in repetitive dysfunctional behaviors without sufficient concern for the negative consequences and are unable to change their behaviors. There are both positive psychological and physiologic reinforcements for restricting food for AN patients. Losing weight by restricting food makes those with EDs feel that they are in absolute control of themselves, and later these time-consuming weight-losing obsessions and compulsive behaviors provide a secondary reinforcement for avoiding perceived aversive or threatened environmental events. The physiologic reinforcement may reflect an increased secretion of CRF, which has an anorectic effect and a direct effect on the CNS mediating autonomic and behavioral responses to stresses. BN patients have a relief from dysphoria or anxiety with binge eating. Their purging behavior may produce a "high" related to EOPs and may actually become an addictive state.

Dopamine, Serotonin, and Neurobiologic Reward Systems

Dopaminergic neuronal function modulates feeding behavior, motor activity, reward-motivated behavior, and drug-seeking behavior. AN patients have restricted feeding, hyperactive stereotypic motor activity, anhedonic behavior, negative affect, and reduced novelty seeking. BN patients engage in binge/purge behavior and have a high comorbidity with alcoholism and drug addiction.

There is evidence of altered dopaminergic function in AN. Increased binding of D2/D3 receptors in the anteroventral striatum, a region that involves optimal responses to reward stimuli, was found in patients who had recovered from AN. Another study showed a significant association between the frequency of functional polymorphisms of dopamine D2 receptor genes and AN, suggesting that the D2 receptor gene is a susceptibility factor in the development of this disorder. Women who were recovered from the restricting type of AN showed greater hemodynamic activation in the caudate compared to healthy women.

Serotonergic neuronal systems are also involved in the modulation of appetite, motor activity, mood and obsessional behaviors, and impulse control. Features of anxiety, perfectionism, and obsessionality are present in both AN and BN; however, as noted, impulsivity is associated only with binge behavior. There is evidence for disturbances in the serotonergic neurotransmitter system in EDs. Recovered AN and BN individuals have reduced postsynaptic 5-HT_{2A} receptor activity relative to controls in the subgenual cingulate, mesial temporal, and parietal cortical regions. Recovered bulimic-type AN patients have increased 5-HT_{1A} postsynaptic activity in the subgenual cingulate and mesial temporal regions as well as frontal cortical regions and increased presynaptic 5-HT_{1A} autoreceptor activity in the dorsal raphi nucleus. Increased 5-HT_{1A} postsynaptic activity has been reported in BN patients. 5-HT_{1A} and 5-HT_{2A} receptors coexist and interact in the frontal cortex, amygdala, and hypothalamic regions and contribute to the modulation of DA neuronal activity. An aberration of serotonin neuronal modulation may be a vulnerability for developing either AN or BN during adolescence in response to stressful events.

The repetitive compulsive behaviors in EDs may involve the same neural circuits of the corticostriatal–thalamic loops that maintain the allostatic state of compulsive drug taking. These most likely involve DA, serotonin, opioid peptides, GABA, and glutamate.

Genetic Vulnerability for Allostasis in Eating Disorders

Genetic factors can act as mechanisms in an organism to produce differential sensitivity in the brain reward and stress systems that interact with environmental factors to produce a state of allostasis when activated. Individuals may be vulnerable to developing EDs because of intrinsic specific brain neurocircuitry that interacts with environmental life events and stresses. AN is highly familial, with a relative risk of 11.3 in family members of probands with AN.

Special Considerations in ED–SUD Comorbidity

Assessment of Patients

Patients with ED–SUD comorbidity require careful and thorough assessment to identify and characterize the nature, extent, and temporal relationship of the symptomatic elements of both disorders. With respect to substance use, patients should be directly asked about the age of first use, age of first regular use, age of first problems, age of first treatment, efforts to reduce use, longest periods of abstinence, patterns and quantity of use, and triggers for relapse. The interviewer should obtain details regarding the impact of each substance use on work, school, home, as well as familial and nonfamilial relationships. Special attention should be paid to the use of substances while driving or in other physically hazardous situations. Similar inquiries should be directed toward the use of commonly misused over-the-counter (OTC) substances such as laxatives, diet pills, appetite suppressants, diuretics, and stimulants. Syrup of Ipecac, an emetic designed for use in accidental poisoning, is commonly misused by bulimic patients. The agent is toxic to smooth and striated muscle and can lead to toxic, potentially fatal, cardiomyopathy. Another important area of assessment should focus on the misuse of prescribed medication by the ED patient. Some patients may take higher- or lower-than-prescribed dosages of medications that they believe may impact weight or appetite. Some examples of prescribed medications misused by ED patients include various anticonvulsants (e.g., topiramate and memantine) and hormones (e.g., thyroid). Topiramate, in particular, should be used with caution in patients with a history of AN or weight loss, in light of its tendency to induce weight loss in some patients. Diabetic patients may avoid taking prescribed amounts of insulin and/or oral hypoglycemic agents as a means of avoiding incorporation of sugars or to induce polyuria and diuresis.

Assessment of the patient with comorbid SUD and ED illnesses should include a family history focusing on mood and anxiety disorders in addition to the primary illnesses in light of the strong heritability of both disorders. Family history should seek to obtain information about parental attitudes and behaviors in relation to weight, shape, physical appearance, and dieting. Similarly, a history of substance use (e.g., type and severity) in the family should be determined. In addition to developmental and childhood history, direct questions regarding emotional, physical, or sexual abuse should not be overlooked in light of data suggesting that childhood abuse is an extremely common antecedent of these disorders.

Treatment Delivery for Comorbid Patients

Despite the high rates of ED and SUD comorbidity discussed earlier in this chapter, there has been surprisingly little attention in the literature to the complex treatment planning and decision-making essential to effective treatment of this population. Patients must be motivated and ready to make radical changes in behavior. Patients with substance abuse must be motivated

to abstain from alcohol and drugs, and patients with EDs must be motivated to abstain from bingeing and/or purging, or committed to normalizing restrictive eating behavior. The comorbid patient has the difficult task of attempting to do both. Unfortunately, there has been little consensus and no clear guidelines regarding how to best manage co-occurring ED and SUD. Treatment delivery for patients with substance abuse and other psychiatric disorders is often described as sequential or integrated. Sequential treatment involves treating either the SUD or the ED first, without specific focus on and attention to treatment of the other disorder. Patients are then transferred to a different setting for treatment of the other disorder. While patients will often describe that they feel overwhelmed by simultaneous treatment of both disorders, sequential treatment can lead to a pattern of symptom replacement or substitution. Some patients describe a worsening of ED symptoms as they attempt to abstain from drugs and/or alcohol, and conversely, some patients describe exacerbation or relapse into substances as they attempt to normalize eating behavior. A second treatment delivery option would be parallel treatment in which a patient might receive treatment for both disorders concurrently, but by different providers or in different treatment settings. A third treatment delivery paradigm provides integrated, concurrent treatment of both disorders. While offering a number of potential advantages over sequential or parallel treatment, perhaps because of the resource-intensive nature of such settings, few integrated ED and SUD programs currently exist.

Elements of Treatment Integration

The integrated treatment of EDs and SUDs presents new challenges as well as new therapeutic opportunities. Assessment should include a full inventory of symptoms of both illnesses for all patients. Often, patients may conceal or minimize the elements of either the ED or the SUD. In nonintegrated programs, the treatment team may focus primarily or exclusively on their more comfortable area of primary experience. In this regard, the patient and therapeutic staff may consciously or unconsciously collude to avoid focus on the substance use problem. Often, patients with co-occurring ED and SUD do not receive structured assessment or treatment for EDs in addiction treatment programs, and similarly, substance abuse assessment and treatment may be lacking in many ED programs. A thorough medical evaluation should not assume that weight loss or various physiologic derangements result from either the ED or the SUD. Evaluation should address the interactive effects of ED pathology and substance use on cardiovascular, gastrointestinal, hematologic, and endocrine/metabolic systems. Laboratory evaluation can be of use in identifying surreptitious ED and SUD. Decisions regarding whether detoxification can occur on the integrated unit should be individualized and based on the degree of medical instability.

Treatment Approaches for Co-Occurring Substance Use and Eating Disorders

Patients who are in simultaneous, integrated treatment for SUDs and EDs require multidimensional therapies. The abrupt cessation of ED behaviors coupled with abstinence from alcohol and/or substances may be terrifying, with the creation of profound psychic stress and anxiety. This creates a therapeutic crisis for many patients. A number of therapeutic interventions, both pharmacologic and psychotherapeutic, may be utilized on the integrated treatment unit to provide support, reduce resistance, and facilitate sustainable change.

Pharmacologic Treatment

Medications may be useful adjuncts in the integrated treatment of EDs and SUDs. Cyproheptadine in high doses (up to 24 mg/day) can facilitate weight gain in anorectic restrictors and also

provide a mild antidepressant effect. Although chlorpromazine was the first drug to treat AN, no double-blind controlled studies are available to show the efficacy of this drug for inducing weight gain and reducing anxiety in anorectic patients. In open-trial observations, chlorpromazine may be helpful in the severely obsessive–compulsive or agitated anorectic patient. It may be necessary to start at a low dose of 10 mg two or three times per day and to gradually increase the dosage while monitoring blood pressure. Newer antipsychotics such as olanzapine have also been shown to be useful for severely obsessive–compulsive or agitated anorectic patients. Tricyclic antidepressants and serotonin reuptake inhibitors (SSRIs) are not particularly effective and have undesirable side effects for severely emaciated anorectic patients.

For patients with BN and out-of-control bingeing and purging, fluoxetine has been approved by the FDA. The only other SSRI studied in a randomized, controlled trial and shown to be effective is sertraline. In patients who do not respond to an SSRI, topiramate may be helpful. Since weight loss is a side effect of this medication, it should be used only in patients in the high normal or overweight range. It is necessary to begin this drug in very low doses of 25 mg/day, gradually increasing the dose to avoid adverse side effects such as paresthesias and cognitive word-finding difficulties. As mentioned previously, this drug has some abuse potential in individuals who are convinced that higher doses at more regular intervals might lead to greater degrees of weight loss.

There has been limited research on compounds that might simultaneously reduce or alleviate eating disturbance and substance abuse. Ondansetron, a 5-HT_3 antagonist, has been shown to be of potential benefit in the treatment of alcohol dependence and in BN, but this agent has not gained widespread use in the treatment of either illness, nor has it been systematically evaluated in patients with comorbid ED and SUD, perhaps because of prominent side effects including abdominal pain. Naltrexone, an opioid antagonist approved for the treatment of alcohol and opioid dependence, has also been utilized in patients with BN despite the lack of systematic investigation. Extreme care should be undertaken in the pharmacologic treatment of patients with concurrent SUDs and EDs. The combined physiologic derangements of both illnesses render these patients even more vulnerable to cardiovascular, hepatic, gastrointestinal, and cognitive/neurologic effects than either disorder in isolation.

Psychological Treatments

Various psychotherapeutic interventions targeting motivation (e.g., motivational enhancement techniques), mood regulation and coping skills (e.g., dialectal behavior therapy and cognitive–behavioral therapy [CBT]), and relationship maintenance (e.g., interpersonal psychotherapy) benefit the patient with co-occurring ED and SUD. CBT is a well-researched and proven method for the treatment of BN. Although research on the effectiveness of CBT for the treatment of AN is much more limited, clinical evidence and data in support of its utility are emerging. Essentially, the cognitive-behavioral model for the treatment of EDs emphasizes the important role of both the cognitive (e.g., attitudes regarding the importance of weight, shape, and their control) and the behavioral (e.g., dietary restriction and binge eating) factors that maintain the ED and associated pathology. The treatment is presented in additive stages with an initial emphasis on stabilization of symptoms and behavioral change. As treatment progresses, the behavioral coping strategies are supplemented with cognitive restructuring techniques, including work on interpersonal issues, body image, and affect regulation. The final stage of CBT concentrates on relapse prevention and maintenance planning. Many of the treatment elements provided in CBT specifically target behaviors that may underlie concurrent substance abuse disorder and ED symptoms.

It is recommended that patients with co-occurring illness receive intensive CBT in the milieu, in groups, and during individual psychotherapy. Therapists with highly specific training provide a variety of CBT-based group therapies including the following: standard CBT for EDs, body image, skills training, self-esteem, motivation to change, and coping skills training. These groups are based on salient elements of the standard CBT treatment protocols. Each of these important elements of treatment is expanded (and modified for adolescents vs. adults), creating separate and independent

group therapies. The overall effect is that patients receive all elements of CBT, but in a more intensive dose during integrated treatment of the SUD and ED. Additionally, other more specialized groups, such as CBT-based Trauma Recovery Group, can be offered as appropriate.

Another therapy showing promise in the integrated treatment of this population is dialectical behavior therapy (DBT). With its focus on mindfulness, awareness of problems and choices of responses to those problems, coping skills training, and mood regulation techniques, this form of treatment concurrently benefits ED and SUD, as well as commonly occurring personality elements. Finally, in light of the powerful ambivalence notable in both illnesses independently, and the co-occurring patient, the motivational enhancement techniques have been of great therapeutic value in integrated treatment strategies. Further research into treatment strategies to address these disorders is greatly needed in light of their potential for relapse, morbidity, and mortality.

Conclusion

The ED and SUD frequently co-occur, suggesting the possibility of shared etiologic and perpetuating factors, although this remains speculative. Regardless, the shared illnesses require diligent identification efforts through comprehensive medical and psychiatric assessment. Effective treatment should concurrently address the core vulnerabilities of each disorder. While more research is needed to identify the most efficacious treatment, integrated approaches using interventions such as CBT, DBT, and motivational enhancement strategies are currently recommended.

Suggested Readings

Blinder BJ, Cumella EJ, Sanathara VA. Psychiatric comorbidities of female inpatients with eating disorders. *Psychosom Med*. 2006;68:454–462.

Calero-Elvira A, Krug I, Davis K, et al. Meta-analysis on drugs in people with eating disorders. *Eur Eat Disord Rev*. 2009;17:243–259.

Frank G, Bailer U, Henry S, Drebets W, et al. Increased dopamine D_2, D_3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [11C] raclopride. *Biol Psychiatry*. 2005;58:908–912.

Franko DL, Dorer DJ, Keel PK, et al. Interactions between eating disorders and drug abuse. *J Nerv Ment Dis*. 2008;196(7):556–561.

Hudson J, Hiripi E, Pope HG Jr, et al. The prevalence and correlates of eating disorders in the National Comorbidity Survey replication. *Biol Psychiatry*. 2007;61:348–358.

Keski-Rahkonen A, Hoek H, Susser ES, et al. Epidemiology and course of anorexia nervosa in the community. *Am J Psychiatry*. 2007;164:1259–1265.

Koob GF, LeMoal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. *Nat Neurosci*. 2005;8(11):1442–1444.

Krug I, Treasure J, Anderluh M, et al. Present and lifetime comorbidity of tobacco, alcohol and drug use in eating disorders: a European multicenter study. *Drug Alcohol Depend*. 2008;97:169–179.

Strober M, Freeman R, Lampert C, et al. Controlled family study of anorexia nervosa and bulimia nervosa: evidence of shared liability and transmission of partial syndrome. *Am J Psychiatry*. 2000;157(3):393–401

Wagner A, Aizenstein H, Venkatraman V, et al. Altered reward processing in women recovered from anorexia nervosa. *Am J Psychiatry*. 2007;164:1842–1849.

17 Pathologic Gambling

Common perceptions of gambling typically involve high risk or fairly rapid outcomes, or both, such that a long-term real estate or stock investment may be risky but may not be considered as gambling by the general public. Gambling disorder (GD) is a clinical diagnosis in DSM-5 defined by the presence of four or more inclusionary criteria related to gambling and the acknowledgment that the GD is not better accounted for by manic symptomatology. Unlike DSM-IV, in which Pathologic Gambling (PG) was included in the section on Impulse Control Disorders (and required five criteria), GD in DSM-5 is included in the section on Substance-Related and Addictive Disorders. However, virtually all research has used criteria for PG, rather than GD, and most of this chapter focuses upon PG.

The term "probable pathological gambling" is sometimes used when achieving threshold scores using screening instruments (e.g., South Oaks Gambling Screen [SOGS]), rather than relying on meeting DSM criteria (e.g., through a clinical interview). Given that estimated rates of PG are often higher when a screening instrument was used compared with a full DSM-IV clinical diagnosis, some cases of "probable pathological gambling" may not meet the DSM-IV criteria for "PG." "Problem gambling" is typically used as a broader term for a pattern of gambling that still is related to difficulties in one's life but may or may not meet the full criteria for PG. That is, "problem gambling" has been used at times inclusive of PG and at others exclusive of PG. In the gambling literature, problem gambling is often operationally defined as meeting three to four or, in other cases, one or more of the inclusionary diagnostic criteria for PG. "Disordered gambling" is a general term including both problem gambling and PG. "Recreational gambling" describes gambling behavior that would not fall under disordered gambling, where the behavior is carried out in moderation without loss of control or marked negative consequences. However, a precise threshold for a difference between recreational and problem gambling has not been uniformly agreed upon.

Diagnosis of Pathologic Gambling

A diagnosis of GD is made according to the DSM-5 based on the presence of at least four out of nine indications of "persistent and recurrent problematic gambling behavior," which are not better accounted for by manic behavior. As gambling behavior is considered to lie along a continuum, alternative conceptualizations of (and thresholds for) GD and PG have been discussed. Some of the DSM-IV and DSM-5 inclusionary criteria for PG/GD were modeled after those for substance use disorders (SUDs), and the DSM-5 criteria for GD distinguish between grades of severity (mild, moderate, severe), unlike DSM-IV.

Epidemiology of Gambling: Prevalence

The vast majority of adults report having gambled at some point in their lives. Estimates of disordered gambling based on screening instruments suggest 2.5% of the U.S. population display problem gambling, while lifetime prevalence of PG is estimated to be between 0.4% and 3.4% of the U.S. adult population, with several large surveys using diagnostic assessments indicating past-year prevalence estimates in the United States in the range of 0.1% to 0.3%. A study of probable PG in North America revealed that prevalence estimates for the general adult population (1.60%) were significantly lower than those for adolescent populations (3.88%). The general adult, adolescent, and college student (4.67%) rates have been found to be significantly lower than the estimated prevalence for adults who were either receiving psychiatric treatment (including treatment for SUDs) or were in prison (14.23%).

Demographic variables such as sex, age, and race appear to influence gambling participation. Men are approximately two times more likely than women to develop PG, yet women may suffer from more physical and mental health complications than men at the same severity of disordered gambling. Boys make up a larger proportion of problematic or pathologic gamblers (estimated ratios range from 3:1 to 5:1), gamble more frequently and wager larger amounts, begin at an earlier age, and more often prefer skill-based games. African Americans are disproportionately represented in populations of disordered gamblers. Controlling for socioeconomic status, a U.S.-based telephone survey found that black youths displayed higher rates of frequent gambling than did white youths.

There is some evidence for demographic differences based on individuals' gambling motivations. Recreational gamblers who report gambling for excitement tend to be younger, with more symptoms of impaired impulse control (e.g., SUDs, incarceration, larger wins and losses), and reported engaging in more forms of gambling and experiencing more gambling problems. Men are more likely to cite excitement seeking as their motivation for gambling, while women are more likely to report gambling as a form of escape or relief from dysphoria or boredom.

Various forms of gambling exist and differ in significant ways, such as the level of skill required (e.g., electronic gambling machines versus poker), timing of the gambling sequence (e.g., fast-paced electronic gambling machines versus slower lotteries), and size of the wager. There have been debates regarding whether features of electronic gambling machines make them more "addictive" than other forms of gambling.

Social and Environmental Factors

The acceptability and accessibility of gambling in the United States and around the world have typically increased recently, and although gambling was previously illegal in all but a few regions of the United States, it is now legal in nearly every state. Gambling-related problems may increase with this greater availability of legal gambling outlets. Greater proximity and accessibility to gambling venues have been associated with increased gambling behavior, albeit not consistently, so increases in legal gambling venues should be carefully considered within a public health perspective.

The percentage of the general adult population reporting having gambled increased from 68% in 1975 to 86% in 1998. Data from a meta-analysis of North American studies between 1974 and 1997 were consistent with an increase in rates of problem and PG across time within the general adult population, but not within the adolescent, college, or psychiatric treatment and prison-dwelling adult populations. One hypothesis is that increasing social acceptability with more legalized gambling venues relates to increasing gambling rates. Prevalence studies in the

United States suggest that estimates of problem and PG in 12- to 17-year-olds have increased from 1989 (median 10%, range 9% to 20%) to 1999 (median 14%, range 10% to 26%), while overall gambling rates rose from 45% to 66% in the juvenile population in the same time frame. Given the association between an earlier onset of gambling and more severe gambling problems in adulthood, increased rates of juvenile gambling have raised concerns that rates in adult populations may increase further with time. However, tempering these views are data (from recent prevalence estimate surveys) showing that rates of problem and PG in the United States and Canada are similar to or lower than those reported in earlier prevalence estimate studies, despite increases in gambling availability. These findings suggest that increased availability of gambling does not alone predict rates of problematic or PG. Together, these findings indicate that at the population level, factors influencing engagement in gambling at multiple levels remain relatively poorly understood.

Co-Occurring Psychiatric Disorders

Gambling problems have been associated with increased odds of having Axis I psychiatric disorders (in particular depression, bipolar disorder, anxiety, and SUDs), and this association appears stronger in women than in men. Multiple Axis II disorders have also been associated with problem and PG. High frequencies of attempted suicide (17% to 24%) have been reported in individuals either receiving professional treatment for PG or regularly attending Gamblers Anonymous (GA). Higher rates of disordered gambling are associated with psychotic disorders in community and clinical samples. Although high rates of co-occurrence have been found for multiple disorders across genders, women with PG appear more likely than men with PG to suffer from a comorbid mood disorder or to experience gambling-related anxiety, while men appear more likely to suffer from comorbid SUDs (including alcohol dependence). Juveniles with problem or PG appear more likely than their non-problem gambling peers to report dissociative experiences while gambling. A U.S.-based telephone survey of community-dwelling subjects found a high co-occurrence of gambling problems and alcohol problems in youths (age 14 to 21).

The co-occurrence of psychiatric disorders appears to be related to the number of PG criteria met, rather than an association being restricted to individuals who qualify for the clinical definition of PG (i.e., ≥5 DSM-IV criteria). However, associations with advantageous health measures appear more mixed at lesser severities of gambling pathology. For example, recreational gambling is associated with increased odds of a SUD in most cases except in samples of older adults where recreational gambling has been associated with better ratings of subjective general health.

The etiologies of co-occurring psychiatric disorders with PG are not well understood, but the disorders may arise from common factors, such as impulsivity or risk-taking, and may include shared genetic and environmental contributions. Individuals with PG and co-occurring SUDs have higher estimates of other psychiatric comorbidities at each gambling severity level, and first-degree relatives of individuals with PG display increased rates of mood disorder and alcohol dependence, findings that suggest common vulnerability factors between the disorders.

Another non-mutually exclusive explanation is that development of PG or other psychiatric disorders could contribute to the development of the other. For instance, debts and strained interpersonal relationships related to PG could increase the risk of developing depression, anxiety, or substance abuse, or alternatively, depressed individuals may turn to gambling as a means of escape. One study has found that phobias, antisocial personality disorders, and most SUDs tend to temporally precede PG, suggesting that these disorders may represent risk factors or share vulnerability factors with PG, while depression and stimulant dependence tend to develop after PG, suggesting these disorders may represent a reaction to some aspect of PG.

As compared with recreational gamblers who do not abuse substances, those who do abuse substances are more likely to be younger, unmarried males who began gambling prior to the age of 18 and gamble for excitement or to win money. Comorbid alcohol use problems in problem gamblers are associated with reports of more forms of gambling performed, suicide attempts, gambling-related arrests, tobacco and drug use, and family histories of alcohol and drug use, further suggesting the potential contribution of poor impulse control across a broad range of behaviors.

Social and Public Health Costs of Gambling

Estimates of the amount of money spent on gambling in the United States (including payouts) rose from approximately $17.4 billion in 1974 to $860 billion in 2001, and costs attributed to problem and PG in the United States have been estimated in the 1990s to be approximately $5 billion annually.

Gambling may have multiple personal and societal impacts. Individuals with PG typically gamble beyond their means, and may incur substantial debts and experience bankruptcies. PG may involve financial "bailouts" and the willingness to risk close relationships in order to pursue gambling. In more severe cases of PG, illegal behaviors (e.g., theft) may be committed in order to support the gambling behavior. Damaging behaviors such as domestic violence, child abuse, and child neglect may contribute to high rates of divorce and poor mental and physical health of family members of individuals with gambling problems.

Health problems such as hypertension, insomnia, gastrointestinal complaints, and cardiac arrests have been associated with disordered gambling. The presence of indicators of sustained stress in individuals with PG and indicators of acute stress during the act of gambling, such as increased salivary cortisol, hypertension, immune system changes, elevated heart rate, and higher levels of epinephrine and norepinephrine or their metabolites, suggest that stress may be a moderating factor in some of the health issues that commonly co-occur with PG.

PG as Addiction or Impulsive–Compulsive Spectrum Disorder

Models of PG primarily conceptualized it as a behavioral addiction, or as part of a spectrum of disorders lying along an impulsive–compulsive spectrum with such disorders as obsessive–compulsive disorder (OCD). Interestingly, DSM-5 shifted this conceptualization to GD as an addictive disorder, along with the other SUDs. Evidence exists in support of both conceptualizations of PG, which are not mutually exclusive. Proposed core components of addiction, including appetitive urges or cravings prior to the behavior, diminished self-control, compulsive or continued engagement in the behavior despite adverse consequences, have been observed in both PG and SUDs, as have other aspects of addiction, including tolerance and withdrawal.

The phenomenology and clinical definition (according to the DSM) of PG/GD share similarities with both SUDs and OCD. Individuals with OCD, SUDs, or PG may experience motivations to perform behaviors (e.g., compulsive behavior, drug taking, gambling), may be preoccupied with thoughts of the behavior, and may demonstrate a diminished ability to resist drives to engage in excessive performance of the behavior. In contrast with the individuals with OCD, individuals with PG/GD or SUDs tend to experience the persistent thoughts about the behavior, anticipation of the behavior, and actual performance of the behavior as pleasurable or egosyntonic, particularly in early stages of the disorders. In contrast, individuals with OCD tend to

experience these motivations as ego-dystonic (i.e., inconsistent with the patient's self-image and distressing) and engagement in the subsequent behavior as a relief or release. Since individuals with PGs or SUDs experience these behaviors as ego-syntonic, they may not believe they have a problem, or may deny or minimize problems, typically unlike individuals with OCD. Excessive risk aversion and overestimation of risk, characteristics associated with compulsive disorders, including OCD, are not regularly observed in PG; rather, individuals with PG are more likely to display excessive risk-taking and underestimation of risks associated with other ICDs and SUDs. PG/GD also resembles SUDs in that the severity of behavioral engagement runs along a continuum (abstinence to PG), and it is possible for problematic behavior to resolve without formal treatment. Women display a similar "telescoping" effect with PG that has been observed with alcoholism and drug dependence, meaning that women tend to begin the behavior later in life but tend to progress to problematic stages at a faster rate than do men. Whether the phenomenon of "telescoping" in part reflects a gender difference in the willingness to seek treatment earlier in the course of illness is not entirely clear. While some ICDs such as trichotillomania are associated with elevated odds of OCD, PG is not; however, PG carries elevated odds of SUDs.

Candidate Mediators of Pathologic Gambling

A number of candidate factors have been proposed to contribute to the progression to and persistence of PG, including aspects of cognition, specific neurotransmitter systems and regional brain functioning, and genetic factors. These domains are not independent nor are their contributions mutually incompatible.

When viewing PG as a nonsubstance or "behavioral" addiction, it may represent an important model of addiction without the potentially complicating toxic effects of exogenous substances, ones that may or may not be linked to the core processes of addiction. One complicating factor of much addiction research is determining which factors in individuals with current SUDs represent preexisting vulnerabilities and which result from repeated substance use or reflect changes arising during the course of addiction. Since gambling does not involve the introduction of exogenous substances, abnormalities in groups of individuals with PG are sometimes interpreted as preexisting vulnerability factors, although longitudinal studies are needed to directly parse potential influences related to the progression of addiction. Neuroadaptation, the alteration of neural circuitry, can occur in response to repeated exposure to exogenous substances (e.g., drugs of abuse), but may also occur following high frequency exposure to nonsubstance rewards. Tolerance and withdrawal, phenomena observed in PG as well as SUDs, are often conceived of as indications of neuroadaptation. As such, repeated engagement in gambling behavior may lead to the development of neuroadaptation or aberrant learning mechanisms that may themselves contribute to PG. A combination of premorbid vulnerabilities alongside changes resulting from repeated engagement in gambling behavior may account for the development of PG.

Impaired Cognition, Impulsivity, and Cognitive Distortions

Individuals with PG have been shown to be impaired on laboratory tasks of cognition, including measures of cognitive control (e.g., Stroop), planning, attention, and timing. Individuals with PG have repeatedly been shown to report higher levels of self-rated impulsivity and to display impulsivity on laboratory measures, including impaired ability to withhold a prepotent response (impaired response inhibition reflective of response impulsivity) and steeper rates of temporal discounting of rewards (rapid delay discounting reflective of choice impulsivity). Individuals with PG demonstrate less optimal decision-making on laboratory measures, for example, by

showing greater preference for risky choices relative to their non-PG peers. Self-rated impulsivity has been associated with gambling severity in adults and juveniles, and adolescent impulsivity ratings are associated with later development of disordered gambling. Poor impulse control on laboratory measures has been predictive of relapse in PG patients receiving treatment.

Impulsivity is a characteristic of multiple disorders associated with PG, including personality disorders, affective disorders, schizophrenia, SUDs, and neurologic diseases. Similarly, high rates of PG in adolescence have been proposed to be related to impulsivity, a feature of that developmental life phase.

Gambling-related cognitive biases or distortions have been shown in pathologic gamblers in interviews as well as during the "thinking aloud" method, where gamblers are asked to voice their thoughts aloud as they gamble. Some of these cognitive biases are based on a failure to appreciate the independence of trials or the randomness of outcomes. Many of these cognitive biases have been found in recreational as well as pathologic gamblers, raising questions regarding their centrality to PG. The "illusion of control" refers to the belief by the gambler that certain behaviors or rituals can increase their probability of success above that of the objective probability of the situation, or that one can control the outcome of a gamble. The "availability bias" occurs when individuals selectively recall large wins, which leads them to overestimate the likelihood or size of future "payouts." The "gambler's fallacy" refers to the belief that if an unlikely event has occurred that soon the reverse outcome will occur to even out the probabilities (e.g., after consecutive "heads" coin tosses, a "tails" outcome is more likely). In reality, each event (e.g., roll of dice, spin of roulette wheel) is independent, and the probability of an outcome is not influenced by prior trials. The gambler's fallacy could lead an individual to bet on a certain outcome that has not occurred in some time, believing it is "due." On the other hand, a belief that a certain outcome has repeatedly occurred may be interpreted as meaning it could happen again (certain dice being "hot" and having repeatedly good outcomes). "Loss-chasing," where an individual follows a gambling loss with continued gambling and an often riskier bet with the aim of winning back the amount lost, is observed in individuals who meet criteria for PG/GD as well as those who do not. Interventions aimed at teaching independent odds have demonstrated that while individuals typically learn the mathematical concepts underlying gambling, impact on problem gambling behaviors have yet to be convincingly demonstrated.

Neurotransmitter Systems

Disruptions to several neurotransmitter systems, including those relating to norepinephrine, serotonin, dopamine (DA), opioids, and γ-aminobutyric acid (GABA), have been proposed to contribute to PG. Physiologic arousal and excitement accompany the act of gambling, and subjective reports indicate that pathologic gamblers experience more intense gambling-related excitement than do recreational gamblers. Norepinephrine contributes to the regulation of arousal, attention, and aspects of impulsivity. Proximal measures of central norepinephrine levels (e.g., metabolites) are increased in men with PG as compared to those without. Pharmacologic challenge study results suggesting reduced sensitivity to postsynaptic α-2 adrenergic receptors in PG may be consistent with abnormally high norepinephrine secretion in PG. Levels of norepinephrine correlate with the gambling outcome and the urge to begin or continue gambling in problem gamblers, consistent with a role of norepinephrine in moderating gambling behavior. Norepinephrine and DA levels increase during the act of gambling to a greater extent in pathologic gamblers relative to recreational gamblers.

Lower levels of DA and higher levels of DA metabolites in the cerebrospinal fluid (CSF) of pathologic gamblers may indicate abnormal regulation of the DA system. PG has been observed in patients with Parkinson disease, a neurologic disease primarily characterized by loss of nigrostriatal DA neurons. Multiple factors have been reported as being associated with PG and other ICDs in Parkinson disease. These factors include ones related to clinical

features of Parkinson disease (e.g., age at Parkinson disease onset), ones seemingly unrelated to Parkinson disease (e.g., personal history of an ICD prior to Parkinson disease onset), and ones related to the treatment of the disorder (e.g., DA agonists and other treatments for Parkinson disease, as well as the relative amount of DA replacement). Both drugs with prodopaminergic (amphetamine) and DA receptor antagonistic (haloperidol) properties have been found to promote gambling-related motivations and responses, suggesting that a role for DA in PG warrants additional investigation.

Serotonin has long been implicated in impulse control. Pathologic gamblers have decreased levels of serotonin metabolites and abnormal responses to serotonergic agonists like metachlorophenylpiperazine, in which they report a subjective "high" and demonstrate exaggerated prolactin increases, mirroring findings observed in alcoholic patients.

Casino gambling is associated with increased plasma concentrations of cortisol indicating activation of the hypothalamic-pituitary-adrenal (HPA) axis. During gambling, greater increases in heart rate and higher peripheral epinephrine and DA levels in problem gamblers may indicate exaggerated anticipatory autonomic arousal or increased sympathetic activity. Peripheral cortisol reactivity to stress has been demonstrated in problem gamblers, consistent with moderate levels of stress during gambling. Studies of β-endorphin levels in problem gamblers have shown mixed results, leading to the suggestion that a role for endorphins may differ across forms of gambling.

Genetics

Consistent with the studies of either central or peripheral neurotransmitter markers described above, genetic studies have preliminarily implicated genes involved in monoamine function. These genes include ones coding for dopamine D1, D2, and D4 receptors (*DRD1, DRD2, DRD4*), a tryptophan enzyme (tryptophan 2, 3-dioxygenase) involved in serotonin metabolism, and monoamine oxidase A, a protein relevant to norepinephrine, serotonin, and DA systems. One analysis indicated that genes important for norepinephrine, serotonin, and DA systems may contribute relatively equally to an additive risk for PG. An earlier study implicated the TaqA1 allele of *DRD2* in PG, but PG no longer showed an association with the TaqA1 allele after accounting for race and other DSM diagnoses. Additionally, more recent studies with sibling pair designs have not replicated an association with the TaqA1 allele, and the TaqA1 allele has also been shown to be in linkage disequilibrium with other genes (e.g., *ANKK1*) that might explain an association with addictive disorders.

Polymorphisms in the promotor region of *DRD1* have also been associated with SUDs and attention-deficit hyperactivity disorder as well as with PG, in preliminary studies, and D1 receptors have been implicated in reward processing and addiction, suggesting that *DRD1* may be important for the neurobiology of ICDs in general. Since many of the genes implicated in PG are also associated with other disorders consisting of impulsive–compulsive and addictive behaviors, this may support the concept that an individual with a combination of these risk factors has a raised vulnerability to develop impulse control or addictive disorders, but the specific form of impulsive or addictive behavior may also be influenced by environmental factors. Consistently, studies of male twins have found significant overlaps in the genetic and environmental contributions to PG and alcohol dependence as well as to PG and other externalizing behaviors. Future studies using state-of-the-art approaches (e.g., genome-wide association studies) are needed in order to better understand genetic contributions to PG.

Neuroanatomy

Few functional brain imaging studies have been conducted in individuals with disordered gambling. The findings show abnormal activation in frontal–striatal regions, brain regions implicated in impulse control and decision-making, and draw similarities with and differences from SUDs and OCD.

Decreased activation of the right ventrolateral prefrontal cortex (PFC) during monetary wins and losses in problem gamblers was associated with poor performance (i.e., perseveration) on a task of probabilistic reversal learning, measuring components of reward learning, and cognitive flexibility. The same individuals with problem gambling demonstrated intact performance and normal dorsal frontostriatal brain activity during an executive function task measuring planning. These findings could be consistent with PG resembling OCD or SUD, since hyporesponsiveness of the ventrolateral PFC was found in individuals with OCD on the same task of reversal learning and hyporesponsiveness of the PFC to monetary reward has been observed in cocaine-dependent individuals.

Initial viewing (prior to self-reported onset of gambling urges) of gambling-related cues was associated with lower regional activity in the frontal cortex (e.g., inferior frontal cortex, superior frontal gyrus), basal ganglia (e.g., caudate), and thalamus in individuals with PG relative to control comparison subjects without the disorder; these regions previously have been found to show increased regional activity in OCD subjects during symptom provocation. After the self-reported onset of gambling urges, while viewing arguably more provocative gambling-related cues, the PG group relative to a control comparison group demonstrated hypoactivation in the ventral anterior cingulated portion of the ventromedial prefrontal cortex (vmPFC), a region associated with hyperactivation in cocaine-dependent individuals while viewing cocaine-related cues. A direct comparison in a male sample of the neural correlates of craving in cocaine dependence and gambling urges in PG found shared activation differences in the affected groups (as compared to control groups) during viewing of the diagnostic group–specific material (gambling tapes for pathologic subjects, cocaine tapes for cocaine-dependent subjects) with respect to relatively diminished activations in specific brain regions including the ventral striatum and ventral PFC. Together, these findings suggest similarities between PG and SUDs as well as OCD. During a simulated gambling task, pathologic gamblers demonstrate diminished activity in the ventral striatum and vmPFC relative to healthy controls, and these regional functional magnetic resonance imaging (fMRI) BOLD signals correlated negatively with gambling severity ratings within the group with PG. Relative to healthy controls, pathologic gamblers displayed less brain activity in the vmPFC during performance of the Stroop task, a measure of cognitive control, selective attention and response inhibition, and individuals with SUDs with or without PG showed less activation of the vmPFC when performing a decision-making test (the Iowa Gambling Task). Pathologic gamblers watching a gambling scenario activated the dorsolateral PFC more than did control subjects, and this regional increase in activation was associated with higher baseline and greater cue-induced increases in self-reported gambling urges.

Studies have investigated common gambling phenomena in healthy (nondisordered gambling) adults with fMRI. Loss-chasing was associated with increased activity in brain in regions including the vmPFC, while resisting the opportunity to loss-chase and quitting the gambling session was associated with activity in the ventral striatum, dorsal anterior cingulate cortex, anterior insula, and middle frontal gyrus. "Near-misses" occur when an unsuccessful outcome gives the appearance of coming close to winning, for example, when two out of three signals line up on a fruit machine and the third symbol is off by one, and have been proposed to promote gambling. Healthy individuals who felt they had more control over the situation reported near-misses as unpleasant but as increasing their desire to continue playing. Regional changes in brain activity during "near-misses" were similar to that following a monetary win (i.e., striatum, insula). Activation of the rostral anterior cingulate during near-misses was associated with healthy individuals' degree of perceived control over the situation, while insula activity was related to their motivation to continue gambling after a near-miss. The authors concluded that the ability for near-misses to recruit reward circuitry may underlie their ability to promote ongoing gambling. However, as these studies did not involve individuals with PG, their relevance to PG requires further, direct examination.

Taken together, a relatively consistent finding across studies involves diminished activation of the vmPFC and ventral striatum in individuals with PG. The majority of the imaging studies

in PG only included men and excluded individuals with comorbid psychiatric disorders. Given the difference in the clinical profile and demographics of individuals with comorbid psychiatric disorders, it will be important to directly assess brain function in women and youth with PG before generalizing the findings in adult males to all individuals with PG.

Treatment

There are no FDA-approved drugs with an indication for PG. Selective serotonin reuptake inhibitors (SSRIs), mood stabilizers, and opioid antagonists have demonstrated efficacy in treating PG in double-blind placebo-controlled trials, with the strongest evidence in support of opioid antagonists (naltrexone, nalmefene). Other medications across a range of pharmacologic classes (e.g., lithium carbonate, *N*-acetyl cysteine) have also shown efficacy in PG treatment. It has been suggested that clinicians should consider comorbid diagnoses when choosing a pharmacotherapy for PG. For instance, individuals with co-occurring anxiety disorders may respond well to SSRIs like escitalopram, whereas those with co-occurring bipolar disorders may respond well to mood stabilizers like lithium. Other clinical measures may be used to guide the selection of pharmacotherapies. For example, positive responses to opiate antagonist treatment have been associated with positive family histories of alcoholism and strong gambling urges.

Evidence for the efficacy of psychotherapies such as cognitive behavioral therapy, motivational enhancement therapy, and imaginal desensitization in the treatment of PG has been observed in controlled clinical trials, and other forms of nonpharmacologic treatments such as aversion therapy, cognitive restructuring (of erroneous gambling-related beliefs), and personalized feedback have had encouraging results in preliminary studies. However, the psychological mechanism by which these treatments reduce gambling behavior remains unclear.

In addition, the majority of states in the United States with legalized gambling operate problem gambling telephone helplines. The 12-step program, GA, has meetings throughout the world. Such self-help treatment options are widely used and often encouraged by clinicians as an adjunct to professional treatment. Many individuals report success with GA, and GA attendance in a gambling treatment program has been associated with better clinical outcome. However, data suggest there is frequent discontinuation after attending one or two GA meetings and low rates of long-term abstinence (7.5% at 1 year), suggesting GA may not be efficacious as a stand-alone treatment for most individuals.

While historically PG may have been thought to follow a chronic, persistent course, studies suggest high rates of natural recovery from PG. These findings suggest that many individuals can shift from exhibiting PG to demonstrating controlled gambling or abstinence without the aid of formal treatment.

Only a small proportion of individuals with disordered gambling seek treatment, many of whom are identified by screening when being treated for other disorders (e.g., SUDs). One contributing factor to low rates of treatment seeking may be that only a small proportion of individuals with gambling problems perceive themselves as having one. Furthermore, treatments for PG have traditionally focused solely on abstinence-based goals, which some individuals may be unwilling to pursue. However, some studies suggest a goal of controlled gambling may provide similar levels of success as abstinence-based goals.

Despite the wealth of treatment options for PG, the field of PG treatment lags behind treatment of SUDs in availability of empirically validated treatments with clearly demonstrated treatment efficacy. There have been relatively few controlled treatment trials or direct evaluations of the clinical efficacy of interventions like GA. Meta-analyses of PG treatment studies have shown substantial estimated effect sizes for both pharmacologic (0.78) and nonpharmacologic (2.01 posttreatment, 1.59 at longer term follow-up) treatments, yet one meta-analysis found the quality of study design to relate inversely to the effect size within cognitive and

behavioral treatment studies for PG, such that the most poorly designed studies indicated the most robust treatment effects.

Many of the treatment trials should be interpreted with caution as they have only compared active treatments without a "no treatment" control arm, have been open-label, lacked pretreatment data, or used small samples. Of the controlled trials, many exclude patients with comorbid SUD, including alcohol abuse, or Axis 1 psychiatric disorders, including depression and anxiety, all of which have high rates of comorbidity with PG. Many studies include solely or predominantly adult male subjects, raising questions of the generalizability of these results to women, juveniles, and patients with co-occurring disorders. Many of the longer duration clinical trials report a significant effect of time on treatment outcome, independent of treatment group, perhaps reflecting the tendency for gambling patterns to fluctuate over time and a possible influence of nonspecific factors or natural recovery in the clinical improvement.

Conclusion

The increased availability and social acceptance of legalized gambling throughout the world in the past few decades appear to have contributed to increased public and clinical awareness of PG. A growing body of research has furthered the understanding of neurobiologic, cognitive, and genetic factors that may contribute to the development or persistence of PG and contributed to the development of evidence-based treatments to address this potentially devastating disorder.

Suggested Readings

Brewer JA, Grant JE, Potenza MN. The treatment of pathological gambling. *Addict Disord Treat*. 2008;7(1):1–13.

Dell'Osso B, Altamura AC, Allen A, et al. Epidemiologic and clinical updates on impulse control disorders: a critical review. *Eur Arch Psychiatry Clin Neurosci*. 2006;256(8):464–475.

Gooding P, Tarrier N. A systematic review and meta-analysis of cognitive-behavioural interventions to reduce problem gambling: hedging our bets? *Behav Res Ther*. 2009;47(7):592–607.

Kessler RC, Hwang I, LaBrie R, et al. DSM-IV pathological gambling in the National Comorbidity Survey Replication. *Psychol Med*. 2008;38(9):1351–1360.

Liu T, Maciejewski PK, Potenza MN. The relationship between recreational gambling and substance abuse/dependence: data from a nationally representative sample. *Drug Alcohol Depend*. 2009;100(1–2):164–168.

Potenza MN. Review. The neurobiology of pathological gambling and drug addiction: an overview and new findings. *Philos Trans R Soc Lond B Biol Sci*. 2008;363(1507):3181–3189.

Potenza MN, Fiellin DA, Heninger GR, et al. Gambling: an addictive behavior with health and primary care implications. *J Gen Intern Med*. 2002;17(9):721–732.

Potenza MN, Leung HC, Blumberg HP, et al. An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. *Am J Psychiatry*. 2003;160(11):1990–1994.

Reuter J, Raedler T, Rose M, et al. Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nat Neurosci*. 2005;8(2):147–148.

Slutske WS. Natural recovery and treatment-seeking in pathological gambling: results of two U.S. national surveys. *Am J Psychiatry*. 2006;163(2):297–302.

18 Sexual Addiction

The concept of sex addiction has developed to refer to persons whose behavior is hypersexual, who compulsively seek out sexual experiences, and whose behavior becomes impaired if they are unable to gratify their sexual impulses. This concept derived from the model of addiction to such drugs or addiction to behavioral patterns such as gambling. The phenomenon of a person whose entire life revolves around sex-seeking behavior and activities, who spends an excessive amount of time in such behavior, and who often tries to stop such behavior but is unable to do so in spite of adverse consequences is well known to clinicians. Compulsive sexual behavior is coupled with extreme sexual preoccupation, and patients often incorporate diverse normal and abnormal practices in their sexual activities.

Other commonly used terms for this problem are hypersexuality, sexual compulsivity, and sexual impulsivity. Hypersexuality is descriptive of the behavior but not the pathology of this condition. There are compulsive elements in addictive behavior, but differentiations can be made in the relatively ego-dystonic nature of compulsions and the ego-syntonic nature of sex addiction. More importantly, compulsive behavior does not, in and of itself, provide pleasure in the activity, while sex addiction usually does. The term "sex addiction" discerns the difference between compulsively accessing the pleasure centers of the brain and the nonpleasure behavior that is more typical of obsessive–compulsive acts. Similarly, features of impulse control disorder are present in sex addiction. Impulsive behavior often is used to relieve the tension of an arousal drive about which the person may feel ambivalence, whereas addictions serve as a palliative or escape from a painful affect such as anxiety, depression, or narcissistic injury.

Diagnosis

Sex addiction is a behavior involving significant and destructive loss of control of the sexual impulse. Sex addicts are motivated to gratify their sexual impulses regardless of interference with relationships, work, or danger to reputation, status, and even physical well-being. Eventually, the need for sexual activity increases and the person's behavior is driven solely by the persistent desire to experience the sex act. Although there may be feelings of guilt and remorse after the act, they are not sufficient to prevent its recurrence, and usually sex addicts cannot refrain from their behavior, even when they attempt to do so. Most acts culminate in a sexual orgasm, although a sense of excitement usually accompanies the sex-seeking behavior even in the absence of an orgasm. The patient invests a great deal of time in the behavior, including fantasy, preoccupation, and preparation as well as engaging in sexual activity.

Etiology

The incidence of sex addiction is unknown, but has been estimated to afflict 3% to 6% of Americans. It is more frequently seen in men in a ratio of men to women that has been reported variously as 3 to 1 and 4 to 1. However, in cybersex the ratio is more equal, with more than 40% of participants being female. Sex addiction usually begins in adolescence when the hormonal changes of puberty and the psychological challenge of consolidating a sexual identity are normal developmental events in the course of a person's growth. The mastery of these adolescent challenges goes awry in the sex addict's development. The problem intensifies during the addict's 20s to 40s, when the disorder becomes fully manifested and affects the person's life in adverse ways. In general, the course of untreated sex addiction involves hypersexual behavior, interrupted by periods of abstention when the addict tries to control the addiction, followed by relapses, and further episodes of sexual activity.

Studies have shown that sex addicts frequently come from families with multiple addictions. Some workers hypothesize that increased orgasmic excitability or impaired orgasmic control may be a biologic contributant to sex addiction. Hypersexual activity of the type seen in sex addiction can sometimes be a symptom of organic pathology. Specifically, it can be the manifestation of a lesion in the medial basal–frontal, diencephalic, or septal region. Such behavior can also occur in the context of a seizure disorder, most often in association with temporal lobe epilepsy. Additionally, it can occur when cerebral functioning is impaired and normal inhibitory controls no longer function, as in the dementias.

Studies have found many families of sex addicts to be rigid or disengaged. Hypocrisy is another characteristic of these patients' families. That is, the families will proclaim a highly moral, even rigid set of values publicly, which they privately violate. The dynamics in the families from which these patients come and the patients' resulting behavior prevent the learning and experiencing of intimacy. From a psychodynamic perspective, sex addiction can be viewed as an intimacy disorder.

Sex addicts report a disproportionately high incidence of childhood trauma and abuse; 72% report a history of physical abuse, 81% report a history of sexual abuse, and 97% report emotional abuse. Some clinicians report that patients repeat significant emotional scenarios and actual behaviors from their abuse experiences in their sex addiction behaviors. Other sex addicts deal with their past traumas by indulging in high-risk behaviors. These may be looked at as a conditioned response linking sex or excitement with fear, or a counterphobic attempt to master engendered feelings of helplessness and danger.

Types of Behavioral Patterns

The paraphilias constitute the behavioral patterns most often found in the sex addict. As defined in DSM-5, the essential features of a paraphilia are recurrent and intense sexual arousals that are culturally unacceptable, including exhibitionism, fetishism, frotteurism, sexual sadism, voyeurism, transvestism, and pedophilia.

Paraphilias are associated with clinically significant distress or impairment and almost invariably interfere with interpersonal relationships, and they often lead to legal complications. In addition to the paraphilias, however, sex addiction can also include behavior that is considered normal, such as coitus and masturbation, except that it is promiscuous and uncontrolled.

In nonparaphilic sex addiction, the aim is constant physical gratification that many therapists interpret as an excessive need for an "orgasmic high" to alleviate unrecognized emotional

pain. Women sex addicts frequently use sexual behavior to engage addictively in romantic relationships in order to fill unmet needs for love, attachment, dependency, and admiration.

Many sexual behavior patterns express anger, sometimes called eroticized anger, which is a major component of most sex addictions. However, the patient notices only the sex component of the behavior, not the anger. For example, intrusive sex behaviors involve patients who are frotteurs (people who press their genitalia against others, usually in crowded situations such as subways), Peeping Toms, obscene phone callers, and professionals such as doctors, dentists, therapists, or clergy who touch patients or congregants under the guise of performing professional tasks. The intrusion is sexual, but anonymous or masked, and leaves the sex addict unaccountable to the victim. In these cases, the sex addict is putting something over on, or stealing sex from, the victim. In seductive role sex, the excitement lies in the seduction and conquest, not in the sex act itself. This behavior pattern has also been called Don Juanism.

Comorbidity

Many sex addicts have an associated psychiatric disorder, including an anxiety disorder, depressive disorder, bipolar disorder, schizophrenia, antisocial personality disorder, or borderline personality disorder. Dual diagnosis implies that the psychiatric illness and the addiction are separate disorders; one does not cause the other. The diagnosis of comorbidity is often difficult to make because addictive behavior (of all types) can produce extreme anxiety and severe disturbances in mood and affect, especially when addictive behavior is treated. If, after a period of abstinence, symptoms of a psychiatric disorder remain, the comorbid condition is more easily recognized and diagnosed than during the addictive period. Finally, there is a high correlation between sex addiction and substance use disorders, up to 80% in some studies.

The term "fusion" is often used when two addictions are almost always indulged at the same time. For instance, cocaine use is almost always connected with sexual activity or intent, with both habits containing a compulsive element. Other instances of fusion can involve use of alcohol to enable the person to indulge in high-risk sex, or gambling to increase general excitement levels before having sex. An ironic comorbid diagnosis that is appropriate for a number of sex addicts is sexual aversion disorder. In these cases, the patients are averse to and compulsively avoid sex with spouses or long-term partners, while addictively pursuing high-risk sex outside a relationship. Comorbidity not only complicates the task of diagnosis but also complicates treatment.

Cybersex Addiction

Cybersex addiction has been called the crack cocaine of sexual addiction. The escalation of behavior that is inherent to the problem of sex addiction is exponentially increased when the Internet is used for compulsive sexual activity. Nonsex addicts may visit pornography sites on the Internet on an occasional basis, but they do not become sex addicts. However, persons already addicted to sexual behavior and persons who are vulnerable to the addictive process are quickly hooked by the Internet. Studies have shown that sex-related sites have become a highly profitable economic sector of the Internet. Cybersex has become a problem in the workplace: 70% of Internet pornography surfing occurs during daytime work hours; and one in six workers is estimated to have a problem with sexual behavior online.

Relationships are profoundly affected by Internet addiction. Patients report that they withdraw from close interactions with spouses, other family members, and friends. Their marital sex life decreases. The sex addicts invest their time as well as their emotional energy in online

relationships. Patients report becoming rapidly obsessed with behaviors that they never tried or never even knew about before their Internet experiences. The effect of these affairs on partners and family is as destructive as that of an actual affair. One study reported a divorce rate of 28% following the discovery of an online affair, and consideration of divorce in over 60% of the couples where the sex addict's behavior had been discovered.

It is estimated that 1% of the population in the United States suffers from Internet sex addiction. Studies of cybersex addicts report the majority to be male, heterosexual and married. Women are a larger proportion of addicts on the Internet than they are in the overall category of sex addicts. In addition to serving as a catalyst for persons who might never have become sex addicts without the Internet, cybersex can intensify existing addictive behavior and can precipitate new compulsive off-line behavior.

Treatment

Sex addiction is a chronic disease. It usually has a relapsing, remitting course. The aim, as with all chronic disease, is to keep it in remission. In sex addiction, this means enabling patients to control the destructive behavior, to help them evolve a healthier sexuality, and to mitigate the psychological distress associated with the disorder as much as possible. Numerous treatment approaches, such as inpatient therapy, 12-step groups for sex addiction, other therapeutic groups, medication, psychodynamic psychotherapy, couple therapy, and sex therapy, are used in treating sex addiction. Frequently, a combination of many of these modalities is necessary for treatment to be effective.

The initial factor that is necessary for therapeutic engagement is the patient's recognition that there is a serious problem, whether this recognition is a result of the patient's insight or imposed upon the patient by an intervention. The intervention can be initiated by spouse, family, colleagues, employers, or the legal system. The greater the acceptance by the patient of the presence of the pathology, the greater the chance of successful treatment.

Inpatient Therapy

Hospitalization as the first step in a treatment process is most appropriate for patients who are suicidal or dangerous to others. Paraphilias that involve victims such as pedophilia, frotteurism, or exhibitionism may require that the patient be hospitalized. Some nonparaphilic patients who cannot refrain from excessive sexual activity even though they are participants in outpatient programs are also good candidates for hospitalization.

Treatment in these settings involves multiple approaches. In addition to the removal of the patient from the pervasive sexual stimuli of the general culture, he or she participates in a 12-step program, similar to the program developed for Alcoholics Anonymous. Education regarding the disorder is provided didactically and in therapy. Family meetings also educate family members about the problem and provide opportunities for the families and patient to reconnect in a moderated setting. Medication may be prescribed for the patient and individual therapy is a part of most programs.

Group Therapy

There are several forms of 12-step programs available: Sex Addicts Anonymous (SAA), Sex and Love Addicts Anonymous (SLAA), Sexaholics Anonymous (SA), and Sexual Compulsives Anonymous (SCA). The first step in all these groups requires personal acceptance of the problem by the addict, which is emphasized by the public profession of one addiction to the group.

The patient receives immediate support for recognizing his or her problem. The next two steps address the addict's conflicts over dependency and control as the addicts admit their powerlessness to regulate their behavior and accept the necessity of help from a "higher power." The remaining steps emphasize spirituality, require the patients to further confront the problem by making an inventory of behavior that has harmed others and, where possible, make amends for that behavior. The final step advocates helping others who have the same problem. All the 12-step programs follow this format; their differences lie in their definitions of sobriety.

Twelve-step programs have been extremely effective in counteracting sexual addiction and preventing relapse. Many workers believe that they are essential to recovery, even though empirical evidence reveals that many recovering addicts do not complete all the steps of such a program. The nature of these fellowships varies from group to group, reflecting the characteristics of the individuals who attend them. There is a danger that some sex addicts will use a group setting to connect with another group member in order to act out their addiction. However, the benefits of these groups appear to far outweigh the risks, and constructive rehabilitation occurs significantly more than destructive behavior.

Other Therapy Groups

Participation in a therapy group of any type is beneficial to those who are addicted to sex. Support, confrontation, breakthrough of isolation, and the counteracting of denial and rationalization all aid the recovery process. Also, group acceptance is a significant factor in reducing the shame, conscious or unconscious, which contributes to perpetuation of the sex addiction cycle. The group provides a safe forum in which the addict learns to make meaningful connections with others. Groups can be educational and informational, cognitive-behavioral, or supportive or psychodynamic in orientation. Studies have shown that groups with structure are the most effective for persons with sex addiction disorder. In a structured group, the leader or the structure itself makes the greatest contribution to the group, which helps bolster the psychological frailties of the recovering patient. Additionally, groups function as a benign superego, providing nonshaming, nonpunitive controls for the addict who has insufficiently developed internal controls.

Pharmacotherapy

Pharmacotherapy is an important modality for reducing patient symptomology. The most commonly used medications are the antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs). Agents that have been found to be effective include fluoxetine, sertraline, paroxetine, and fluvoxamine. The effectiveness of these medications derives from their side effect of reducing libido that has been reported in nonsex addict populations, from their use in treatment of obsessive–compulsive disorders (OCD), and also from their antidepressive effects. Studies report an effective response rate to these medications of 50% to 90%. Other antidepressants that have proved effective in treating sex addiction include imipramine, nefazadone, despramine, and clomipramine. However, clomipramine also has the paradoxical effect in some persons of producing spontaneous orgasms. Lithium is effective in the treatment of bipolar patients who evince hypersexuality in a manic episode. As is true in psychiatric disorders in general, pharmacotherapy is most effective when it is combined with other treatment modalities, particularly group or individual therapy.

Cognitive-Behavioral Therapy (CBT)

Cognitive-behavioral approaches to sex addiction usually emphasize altering the maladaptive core beliefs that are thought to underlie the patient's addictive behavior. Cognitive-behavioral techniques for sex addiction are typically utilized in the context of therapy groups, although individual approaches are used as well.

The goal in CBT is to have the patient recognize and stop the addictive behavior. CBT requires a profession of commitment to the treatment process. In the group setting, members benefit from peer support and from confrontation by peers who are uniquely sensitive to manipulations by a patient who seems to be less than honest with himself or herself about addictive activities. An educational component is sometimes interwoven in the therapy with the therapist providing didactic material. Members of the sex addict's family may become involved in therapy. The concept of sex addiction as a disorder rather than a lack of will helps diminish the shame felt by the addict. CBT facilitates more adaptive social functioning through exercises in problem-solving and through assertiveness training. The compilation of factors that are significant in "triggering" a relapse is part of relapse prevention techniques. Patients are advised on how to deal with the triggers and how to deal with an episode of addictive sexual behavior should a lapse occur. Patients rehearse relapse prevention actions such as avoidance of triggering situations. In the group setting, contacting a group member for support when urges to act out occur is a crucial component of treatment. Rewards to prevent the addict from feeling excessively deprived are also an important part of the therapeutic process.

Psychodynamic Psychotherapy

Psychodynamic or insight-oriented psychotherapy to treat the sex addict is usually necessary to treat the dysfunctions of character or personality that are often comorbid with sex addiction. Psychodynamic psychotherapy involves treatment in a dyadic setting with a therapist who is skilled in the use of transference and familiar with the use of psychodynamic constructs. Therapy has an open-ended time frame and the focus is on the patient's verbal associations, dreams, and fantasies, and the transferential relationship to the therapist. The therapist is more interactive and directive than a traditional analytic psychotherapist.

Adding psychodynamic conceptualizations to behavioral techniques helps patients recognize affects of which they are unaware, helps them develop healthy defenses in place of the unhealthy defenses of denial, repression, dissociation, or somatization, and frees them from the destructive behavior caused by unrecognized, unresolved inner conflicts, needs, and fears. Finally, it helps them correct distorted perceptions of themselves and others.

An important concept in understanding the psychological development of a person's sexuality is the relationship between the child and his or her parents, particularly the mother. The first experience of intimacy occurs with the mothering person. That intimacy becomes the basis for subsequent experiences, including sexual experiences. Under positive circumstances, mothering experiences that gratify need appropriately and set boundaries on behavior are the basis on which future comfortable intimacy is established. Abusive, ambivalent, or neglectful mothering, in infancy, childhood, and later development, sets the stage for fear of hurt or loss and for reactive, retaliatory rage with subsequent, potentially intimate experiences. During their first year of recovery, many patients report painful memories from childhood that had been repressed and clarity about early wounds emerge. When past experiences and their associated affects become conscious, memories are expressed in words. Physiologic patterns, such as the development of psychosomatic disease, and behavioral patterns, such as addiction that the patient used to cope with early hurts, then become amenable to modification.

The replay of old reaction patterns, affects, and fantasies in a current time frame, and in a personalized context, is the patient's expression of his or her transference. The transference resuscitates, in a moderated and safe setting, the patients unsatisfied claims for love, feelings of shame or humiliation, and prohibited aggressive feelings. This phenomenon offers an excellent opportunity for modification of distorted emotional responses and unhealthy behavior. Many sex addicts experience unrecognized, painful affects such as anxiety or unacceptable anger as the urge to act out sexually. Those affects are unconsciously translated into urges that often precipitate hypersexual behavior. Addicts, because of neglectful or abusive caretaking in early childhood, never developed the skills to cope with uncomfortable affects and react

to them as overwhelming threats that may cause psychological disintegration. The addictive behavior provides the patient not just with a hedonic escape, but is unconsciously experienced by the patient as a necessary defense for his or her emotional survival.

In the context of the therapeutic relationship, patients' shame about their behavior diminishes. They learn from the therapist that sex addiction is a disorder, not an inherent weakness or character flaw. At the same time, they are confronted with the responsibility for dealing with it. The patients' capacity for coping with stress and for controlling hypersexual behavior develops as they internalize the therapist's caretaking functions and nonjudgmental attitude. They identify with and accept cultural standards for appropriate behavior. Self-care functions can develop through internalization of the message that the patient is valued as a person and worth taking care of.

In the course of therapy, patients recognize the stresses, both external and internal, that trigger addictive behavior. They learn to communicate with others more effectively as they become less ashamed and fearful, and they see themselves and the external world through a less distorted lens. Their expectations of themselves and others become more realistic, and they make greater use of such defenses as anticipation and suppression that help prevent relapse. Ideally, these gains are used not just to deal with the sex addiction, but are applied both to the addict's personal relationships and to his or her work life.

Abstinence

Many sex addicts episodically refrain for all sexual behavior as a way of controlling their addiction. During these periods sexual impulses are dealt with by repression, which is ultimately ineffective. Without treatment, the addictive pattern breaks through. However, abstention is usually prescribed in the initial phase of recovery. At the beginning of treatment, it is easier for the patient to abstain than to transition from addictive sexuality to healthy sexual behavior. Many patients report relief at not having to deal with sex at all; they feel freed from an activity that has controlled them.

The majority of patients report that a celibacy period is a helpful component of treatment. Eventually, the addicts leave the shelter of abstinence and work on gratifying their sexual impulses in the context of healthy, intimate, and nonexploitative relationships. Couple therapy and sex therapy can be useful in this regard.

Couple Therapy

During the course of a patient's addiction, his or her relationship with a partner is hurt by secrecy and lies that clearly interfere with intimacy. When the patient is recovering, he or she must deal with shame or guilt and vulnerability while the spouse or partner must deal with feelings of betrayal, rejection, anger, and loss. Couple therapy provides a controlled forum to confront and process these feelings. The emphasis is on restructuring the couple's interaction and sometimes exploring the dynamics of each partner. Also, this type of therapy can engage the spouse and the energy in the relationship as agents of therapeutic change. Major goals of couple therapy include improving the communication skills, the conflict resolution skills, and the problem-solving skills of the couple, usually with behavioral techniques. The addition of an insight-oriented approach can lead to improvement in the fulfillment of individual needs for attachment and intimacy, and to increase trust and equitability in the relationship.

Sex Therapy

Sex therapy may be necessary to help the patient's transition to a healthy mode of expressing sexual impulses or to augment couple therapy. Frequently, sex addicts suffer from a particular

sexual dysfunction. This is not as ironic as it seems because the same developmental factors that are prevalent in the creation of a sex addict may lead to a sexual dysfunction.

The following factors have been found to be causative in erectile disorders: fear of punishment; castration anxiety, fear of injury as a result of opening up to others; fear of harming women through intercourse; and fear of retaliation from other men at successful sexual relations. Biologic factors may contribute to these dysfunctions and to premature ejaculation, but psychological or mixed factors are causative in 50% of cases. Psychological issues are causative in a higher percentage of cases in young and middle adulthood, particularly if there are no physical health issues.

Among women, dynamic factors that have been noted in sexual dysfunction include fear of direct injury to the vagina from the penis, inability to trust a sexual partner, reluctance to make oneself vulnerable related to previous experiences of loss, separation, or abuse, and fear of loss of control if sexual feelings are let loose.

Regardless of etiology, the final common pathway of sexual dysfunction is performance anxiety. A behavioral approach is utilized to minimize anxiety. Specific exercises, both in communication and for sex play are prescribed for the couple. The exercises are performed in the couple's own home and discussed weekly or twice-weekly in psychotherapy sessions. The aim of therapy is to establish or reestablish communication within the marital unit. Sex is emphasized as a natural function that flourishes in the appropriate domestic climate and improved communication is encouraged toward that end. To minimize performance anxiety, the couple are prohibited from any sex play other than that prescribed by the therapist. Beginning exercises usually focus on heightening sensory awareness to touch, sight, sound, and smell. Initially, intercourse is interdicted and the couple practice giving and receiving bodily pleasure without the pressure of having to achieve penetration or orgasm.

The individuals alternately invite each other for exercise sessions and alternate in caressing one another. This structure inherently confronts inhibitions about sexual approach in an intimate relationship and reinforces the idea that a person has to "give to get." Exercises involving genital stimulation and quiet penetration (no thrusting) are added before the couple is advised to attempt intercourse. Psychotherapy sessions follow each new exercise period, and problems and satisfactions, both sexual and in other areas of the couple's lives, are discussed. The introduction of new exercises is geared toward the couple's progress.

One of the most effective treatment modalities is the use of sex therapy integrated with psychodynamic and psychoanalytically oriented psychotherapy. The material and dynamics that emerge in patients in analytically oriented sex therapy are the same as those in psychoanalytic psychotherapy, such as dreams, fear of punishment, aggressive feelings, difficulty trusting a partner, fear of intimacy, oedipal feelings, and the fear of genital mutilation. The sex therapy is conducted over an extended period that allows for the learning of sexual satisfaction in the context of the patients' day-to-day lives.

Paraphilias

Paraphilic sex is an integral part of the behavior of a significant number of sex addicts. There are nonparaphilic sex addicts and people with a paraphilia who are not sex addicts. However, it is not surprising for one person to suffer from both disorders, since they share similar epidemiologies and etiologies. As is true for sex addiction, paraphilias are seen much more frequently in males, in a reported ratio of 4 to 1. More than 50% of paraphilias have their onset before age 18, and patients with paraphilias frequently have 3 to 5 paraphilias, either concurrently of at different times in their lives. The occurrence of paraphilic behavior peaks between the ages of 15 and 25 and gradually declines. Few acts of criminal paraphilia (such as exhibitionism) are seen in men aged 50 years old. Many acts of paraphilia that occur are practiced in isolation or with a cooperative partner.

Psychoanalytic theory holds that persons with a paraphilia have failed to complete the normal developmental process toward sexual adjustment. The paraphilia is the method used to cope with the anxiety caused by threat of castration by the father and separation from the mother. However bizarre its manifestation, the resulting behavior provides an outlet for the sexual and aggressive drives that otherwise would have been channeled into normal sexual behavior.

Learning theory proposes that children learn paraphilias through early experiences that condition them to perform the perverse act. The first shared sexual experience can be important in that regard. Experiencing molestation as a child can predispose a person to accept continued abuse as an adult, or conversely, to become an abuser of others. Also, early experiences of abuse that are not specifically sexual, such as spankings, enemas, or verbal humiliation, can be sexualized by a child and form the basis for a paraphilia. Learning theory indicates that because the fantasizing of paraphilic interests begins at an early age and because personal fantasies and thoughts are not shared with others (who could block or discourage them), the use and misuse of paraphilic fantasies and urges continues uninhibited through adolescence and early adulthood. Eventually, when the person realizes that his or her sexual urges and behavior deviate from societal norms, the repetitive use of paraphilic fantasies already has become ingrained as have the sexual thoughts and behaviors associated with these fantasies.

Some studies have identified abnormal biologic findings in persons with paraphilias, such as abnormal hormonal levels, hard and soft neurologic signs, and chromosomal abnormalities. However, these studies investigated only known paraphiliacs who were referred to medical centers; they did not use control groups or random samples.

Different modalities are used to treat persons with paraphilias. These include external control, chemical reduction of sexual drives, treatment of comorbid conditions such as anxiety or depression, CBT, group therapy, aversive behavioral conditioning, and dynamic psychotherapy.

The use of antiandrogenic agents is usually limited to the treatment of criminal paraphiliacs (e.g., pedophiles or exhibitionists). Antiandrogens such as cyproterone acetate and medroxyprogesterone acetate may decrease paraphilic behavior by decreasing serum testosterone levels to subnormal concentrations. These agents decrease the sex drive but do not alter the paraphilic fantasy that propels deviant sexual behavior.

CBT is used to disrupt learned paraphilic patterns and modify sexual behavior. The technique seems most effective when used in the context of group therapy, although it can also be utilized in individual therapy. The interventions include social skills training, sex education, cognitive restructuring (confronting and destroying the rationalizations used to support the victimization of others or to support the acceptability of the paraphilia), and development of victim empathy. Imaginal desensitization, relaxation techniques, and learning what triggers the paraphilic impulse so that such stimuli can be avoided are also taught. Aversive techniques include imagining or seeing pictures of paraphilic behavior and concurrently being exposed to or imagining noxious stimuli such as foul odors or vomiting.

Insight-oriented psychotherapy is particularly helpful to patients with comorbid anxiety disorders, mood disorders, or personality disorders. With this approach, patients have the opportunity to understand their dynamics and the events that caused the paraphilia to develop. In particular, they become aware of the daily events that cause them to act on their impulses (e.g., fantasized or real rejection). Treatment helps them deal with life stresses better and enhances their capacity to relate to a life partner. Psychotherapy also allows patients to regain self-esteem, which in turn allows them to approach a partner in a more normal sexual manner. Sex therapy is an appropriate adjunct to treatment of patients who suffer from specific sexual dysfunctions when they attempt nondeviant sexual activities.

A poor prognosis for paraphilias is associated with an early age of onset, a high frequency of acts, no guilt or shame about the act, and substance abuse. The prognosis is somewhat better when patients have a history of coitus in addition to the paraphilia and when they are self-referred rather than referred by the legal system.

The Recovery Process

The recovery of a sex addict is a complicated, long-term process. It has been described by clinicians and researchers in terms of phases of recovery and in terms of behavioral and characterological changes seen through the spectrum of time. The phases that are defined include recognition of the addictive problem, intervention with the aim of behavior modification, and a period of stabilization that involves abstaining from addictive behavior and dealing with the affects that result from withdrawal from the addiction as well as the affects that are no longer masked or avoided by compulsive sexuality. Later phases of recovery involve focusing on underlying developmental issues including abuse, family-of-origin issues, and dealing with shame and unresolved grief. Recovery also requires addressing work, marriage, and family issues that may have arisen as a result of the addict's behavior. Relapse prevention is a necessary component throughout the recovery process.

Treatment methods can overlap and they can be utilized synchronously. As a rule, directive, educative, chemical, and behavioral approaches such as didactic material about sex addiction, pharmacotherapy, and behavior therapies are utilized in the early phases of therapy. Psychodynamic psychotherapy that focuses on the healing of early wounds and trauma and includes goals of character change, the development of new values, and increased self-esteem is utilized in later phases of recovery, although CBT can be used for these purposes as well. Twelve-step programs are part of the therapeutic regimen throughout recovery, first for support and guidance in stopping addictive behavior and later as a method of continued support and relapse prevention.

A poor prognosis in sex addiction is associated with early age of onset, the presence of multiple addictions, a high frequency of hypersexual behavior, and an absence of anxiety or guilt about the behavior. A more favorable prognosis exists when the patient has a stable work life, good intelligence, the absence of nonsexual antisocial personality traits, and the presence of a successful adult attachment. As in therapy in general, the capacity for insight and a strong motivation to change augur a successful outcome. In spite of continued hypersensitivity to emotional stress, and vulnerability to relapse, the recovered addict can lead a productive life that includes an intimate sexual relationship and rewarding connections to others.

Suggested Readings

Anderson N, Coleman E. Childhood abuse and family sexual attitudes in sexually compulsive males: a comparison of three clinical groups. *Am J Prev Psychiatry Neurol*. 1990;3:8–15.

Black DW. The epidemiology and phenomenology of compulsive sexual behavior. *CNS Spectr*. 2000;5:26–35.

Cooper A, Delmonico DL, Burg R. Cybersex users, abusers, and compulsives: new findings and implications. *Sex Addict Compuls J Treat Prevent*. 2009;7:5.

Kafka MP. Successful antidepressant treatment of nonparaphilic sexual addictions and paraphilias in men. *J Clin Psychiatry*. 1991;52:60.

Perera B, Reece M, Monahan P, et al. Relations between substance use and personal dispositions towards out-of-control sexual behaviors among young adults. *Intern J Sexual Health*. 2009;21:87–95.

Quadland MC. Compulsive sexual behavior: definition of a problem and an approach to treatment. *J Sex Marital Ther*. 1985;11:121.

Raymond NC, Coleman E, Miner NH. Psychiatric comorbidity and compulsive/impulsive traits in compulsive sexual behavior. *Compr Psychiatry*. 2003;44:370.

Reid RC, Bruce NC. Exploring relationships of psychopathology in hypersexual patients. *J Sex Martial Ther*. 2009;35:294.

Schwartz MF, Brasted WS. Sexual addiction. *Med Aspects Hum Sex*. 1985;19:103.

19 Internet Addiction

Despite the enormous positive changes to society resulting from the Internet and other forms of electronic communication in the last 20 years, a small proportion but large number of users have experienced excessive and/or problematic involvement with these media, often associated with significant psychopathology. Although much needs to be learned about these phenomena and considerable debate exists among experts as to whether inappropriate applications of electronic media should be considered disorders in their own right, what is indisputable is that there are millions of individuals worldwide whose problematic use of these media is associated with significant psychopathology, clinical distress, and functional impairment. Mental health professionals, schools, and national governments have been inundated with the challenges of having to deal with the problems presented by such individuals, and the costs to society in lost productivity, increased morbidity, and rarely, cases of mortality resulting from the complications of Internet addiction, the most widely used term to describe these pathologic symptoms and behaviors, have been staggering.

DSM-5 does not include Internet addiction as a disorder, but it does include proposed criteria for an Internet gaming disorder (IGD) in its section on Conditions for Further Study. IGD is distinct from Internet gambling (which should be included in the diagnosis of a Gambling Disorder in DSM-5). There are nine criteria for IGD, and a diagnosis of this disorder requires the person to fulfill at least five of the nine criteria. The criteria are generally consistent with those used for other substance use disorders (SUDs) in DSM-5 (e.g., continued use despite psychosocial problems, tolerance, unsuccessful efforts to cut down or quit the behavior).

The term "Internet addiction" will be used throughout this chapter to describe problematic use of all types of new electronic media developed for the general public in the last 20 to 30 years. It should be noted, however, that an increasing number of experts have argued for either broadening its definition to one that does not presume any specific etiology or changing its name to one that better describes the full range of activities implied by the use of the label "Internet addiction." One definition of Internet addiction that does not imply any specific etiology and is consistent with the growing consensus of how to describe these phenomena is "the inability of individuals to control their Internet use, resulting in marked distress and/or functional impairment in daily life." A more accurate term proposed in an effort to reduce stigma and be more inclusive in describing the problems exhibited by individuals using the full range of electronic media is "pathological use of electronic media" (PUEM).

Epidemiology

General Population

According to Internet World Stats, a Web site that measures Internet usage with data supplied from the Nielsen Company and U.S. Census Bureau, 74% of the population of North America (in excess of 250 million people) were Internet users in the spring of 2009. These data suggest that even if prevalence rates for Internet addiction were small, the number of affected individuals would be quite large. The true prevalence of Internet addiction is difficult to ascertain, since such great variability exists in diagnostic definitions, sampling methods, and other aspects of epidemiologic study designs. While more than a dozen studies have been published that address the prevalence of Internet addiction, most study samples have been restricted to a narrow demographic and/or geographical area and generally focus on students or other young people. Other studies with big sample sizes that have not oversampled young people have been criticized for gathering data exclusively online. Examples of these types of studies include one of the personal computer users between the ages of 16 and 24 years (so-called Net-geners) from Hong Kong, reporting that almost a third of the sample met criteria for Internet addiction. In China, estimates suggest that from 5 to more than 10 million of the country's 300 million Internet users have "Internet addictions" and that adolescents are especially vulnerable. Two studies from Iran yielded markedly different findings, with one study of high school students indicating a 3.7% prevalence rate of Internet addiction, while another, based on a sample of Northern Iranian Internet users, reported a 22.7% rate. An online UK study involving more than 300 university students reported an 18% prevalence rate of Internet addiction.

Data regarding gender differences in Internet addiction are also mixed, with most studies finding a higher prevalence of affected males. In the Hong Kong-based "Net-geners" study mentioned above, however, more females than males were found to be addicted.

Methodologically, two studies stand out as being community based and reasonably representative, offering epidemiologic data regarding Internet addiction in the general populations of the United States and Western Europe. The first is a 2006 telephone survey of 2,513 randomly selected representative U.S. adults. The authors employed four different symptom criteria sets for their analyses. In this sample, Internet addiction ranged from 0.3% to 0.7%, depending on which criteria were used. Of note, persons under the age of 18 were excluded from participating in the study. The authors did not report gender data.

The second, a 2009 study, reported data obtained from a random and representative sample of the adult population of Norway. The sample contained almost 3,400 people between the ages of 16 and 74, of whom 87% indicated they were Internet users. In this sample, 1% of the subjects met the criteria of Internet addiction. Male gender and young age were found to put respondents at highest risk of Internet addiction; 4.1% of men aged 16 to 29 were addicted to the Internet compared to only 1.7% of women in the same age group. The percentage of men meeting criteria for at-risk Internet use jumped to almost 20% for young men aged 16 to 29.

A cautious interpretation of these studies suggests that the general population prevalence of Internet addiction may be approximately 1%, that it affects more males than females, and that it tends to be found predominantly in younger people.

Children and Adolescents

Numerous cross-sectional studies have been published regarding the problematic use of electronic media in children and adolescents. Given the recent advent of these technologies, there

has been little opportunity for longitudinal research examining how their widespread uses affect normal childhood development and the risk for Internet addiction, other psychopathology, and long-term functional impairment not only in the general pediatric population but also in vulnerable youth already suffering from or at elevated risk for psychiatric illness.

Video game use has become a major focus of study, given the increasing amount of time devoted to it by youth in recent years and concerns about the potential adverse impact of violent video games as well as the risk for "addiction" to playing these games. The first published study of the prevalence of video game addiction based on a large, national sample of youth representative of the general population employed an online survey methodology and criteria for problematic video game use based on DSM-IV criteria for pathologic gambling. The sample included 1,178 youth between the ages of 8 to 18. Approximately 88% of the sample played video games at least some of the time. Approximately 8.5% met the criteria for pathologic use of video games, and those receiving this diagnosis achieved significantly worse grades in school and had significantly higher rates of attention problems. In recent years, text messaging on cellular phones has also exploded in popularity among teenagers, raising concerns about its impact on youth. According to the Nielson Corporation, in the fourth quarter of 2008, teenagers sent an average of 2,272 text messages per month, close to 80 per day, a doubling of the average from just 1 year earlier.

Phenomenology

In recent years researchers worldwide have variably described the symptoms of Internet addiction, resulting in multiple definitions, each with its own specific diagnostic criteria. Most include some combination of excessive and/or inappropriate use of the Internet or other electronic media associated with clinical distress and functional impairment. A major challenge in defining the syndrome has been the problem of conceptualizing exactly what types of disorders Internet addiction may represent.

Much of the debate concerns disagreement surrounding whether to label Internet addiction as a disorder in its own right as opposed to considering it to be just one manifestation of another, more inclusive disorder. Some propose that it is best viewed as akin to disorders of substance dependence, whereas others argue that it more closely resembles an impulse-control disorder. In fact, as described below, some of the diagnostic criteria for Internet addiction have been based on those for pathologic gambling, a DSM-IV impulse-control disorder that is often also referred to as a prototype of a "behavioral addiction," accompanied by psychological withdrawal symptoms such as irritability and agitation, suggesting that the clinical features of impulse-control disorders and substance dependence may overlap to at least some degree. Notably, some of the most heated opposition to labeling Internet addiction as a type of "addiction" resembling that seen with substance dependence comes from substance dependence experts. On the basis of the limited research to date, they argue that insufficient evidence of physiologic markers of intoxication and withdrawal in individuals with Internet addiction renders problematic characterizations of Internet addiction as a true addiction.

These distinctions are important because they focus on the fact that Internet and computer use per se is generally not the end purpose of excessive users. Most Internet addicts demonstrate high specificity in the activities in which they become overinvolved, ranging from social involvements, problem solving, novelty seeking, information gathering, shopping, day trading, video gaming, and sexual stimulation and gratification. Lumping together all those who spend excessive hours online, such as Internet gamblers; Internet shoppers; Internet pornography addicts; lonely hearts seekers on dating services; Wikipedia contributors; Second-Life participants; social networkers; bloggers; texters; users of gaming consoles, Wii, bridge, or chess

players; and those finding a myriad of other Internet-mediated activities to become preoccupying, may cause researchers to miss the trees for the forest. The Internet may simply serve as a common pathway and conduit through which all these individuals can more easily access their routes to a variety of behaviors that are engaged to excess.

Nevertheless, taking into account the variable definitions of Internet addiction, as described in more detail later in this chapter, reports of impairment as a result of excessive Internet use indicate that these syndromes exact a high cost on individuals and society. There is considerable data showing that Internet addiction is associated with substantial functional impairment in affected individuals worldwide and in all age groups.

Evolution and Development of Diagnostic Criteria for Internet Addiction

The first formal attempt to establish identifying symptoms for addiction to the Internet was proposed by Young who in 1998 modified the pathologic gambling criteria from the DSM-IV to develop an eight-item questionnaire that has been widely used to screen for Internet addiction. After gathering data from clinicians who had treated the condition, Young and colleagues further delineated and proposed several subcategories of Internet addiction:

1. Cybersexual addiction: Compulsive Internet use to access pornographic material.
2. Cyber-relationship addiction: Maintaining online relationships to excess.
3. Net compulsions: Compulsive online gambling, shopping, or online trading.
4. Information overload: Excessive Web site surfing or search engine use.
5. Computer addiction: Using the computer to play games compulsively.

Young's criteria have been criticized for being weighted too heavily on self-report and could also be applied to other behaviors that would appear to be more consistent with an impulse-control disorder rather than a true addiction. Others have also argued that Young's diagnostic criteria lack items that account for functional impairment secondary to the addictive behavior. Accordingly, Beard and Wolf expanded Young's criteria by adding three additional criteria. These additional criteria tap functional impairment due to Internet use, deceptive behavior regarding use of the Internet, and going online as a means of escape from problems or mood disturbance.

Shapira and colleagues conceptualized the phenomena as "problematic Internet use," and considered Internet addiction to be more closely aligned with impulse-control disorders than with an addiction per se. They proposed a third set of criteria that identified problematic Internet use modeled on impulse-control disorders found in the DSM-IV-TR.

Determinants of Internet Use

Several features distinguish Internet use from that of other activities and from substance use that can evolve into an addiction: (a) Internet use offers a mechanism for accessing information and for various types of interactive activities, both constructive and maladaptive, and (b) Internet use constitutes an essential part of normal existence in the modern world. For those reasons, it is difficult to disentangle the extent to which spending large periods of time on the Internet represents evidence of a disorder specific to this medium, evidence of other

mental illnesses, or simply variants of normal behavior. That is, how much "wheel spinning" or how many nonproductive activities manifesting distraction from primary tasks occurs when the individual is presumably engaged in an Internet-mediated functional activity is important to measure in determining whether use of such media is abnormal. Fortunately, recognizing this potential confound and the fact that, for many youth and adults, academic and occupational success is contingent on spending enormous amounts of time on the Internet, some researchers have controlled for this variable and still found that problematic Internet use is independently associated with functional impairment regardless of the amount of time engaged in a particular activity. Nevertheless, in contrast to syndromes of substance dependence where objective, physiologic evidence of tolerance and withdrawal can be noted with specific levels and duration of consumption, such signs and symptoms are neither as clear-cut nor have they been systematically studied in Internet-related addictions.

Etiology and Predisposing Factors

Since intense debate exists about whether Internet addiction should even be considered a disorder, it is not surprising that no single cause has been identified (apart from the contributing factor of access to the Internet). However, as with most psychiatric disorders, etiologic factors are thought to be multifactorial.

Psychological Theories

Cognitive-Behavioral Theory

Several investigators have suggested that compulsive use of the Internet provides ultimately dysfunctional and ineffective methods for regulating negative emotions related to cognitions associated with low self-esteem and self-critical thoughts. Despite the short-term emotional alleviation and distraction, longer-term negative consequences include worsening relationships and poor school or work performance. This pattern then fuels a vicious cycle in which worsening self-esteem and poorer self-appraisal lead to further maladaptive use of the Internet, culminating in social withdrawal and greater exacerbation of the psychopathology that led to excessive Internet use in the first place.

Social Skills Deficit Theory

Some have postulated that individuals with poor social competence who may also be anxious about social interactions are drawn to the anonymity of the Internet and the opportunities it affords for developing relationships in less threatening circumstances than those occurring face-to-face. Additionally, individuals have greater control regarding their self-presentations and their ability to construct more favorable images for those they may be trying to impress. While this feature of Internet-mediated communication may help depressed or socially anxious individuals overcome social inhibitions, it may also potentially contribute to an avoidance of true intimacy.

Family History

Little research exists in this area. In one small study, all but one of 20 individuals with problematic Internet use had a positive family psychiatric history. In this sample, depression was present in at least 65% of first- or second-degree relatives, 50% of relatives had bipolar disorder, and 60% had substance dependence. Unfortunately, no inquiry was made as to whether any relatives suffered from problematic Internet use.

Neurobiology

Although research in this area is in its infancy, initial reports have revealed neurobiologic differences between individuals with Internet addiction and nonaffected controls. Many of the reported findings resemble those found in individuals suffering from substance dependence. For example, one preliminary study using position emission tomography showed evidence for release of striatal dopamine (DA) release resulting from video game playing. In addition, the dopamine D2 receptor gene allele polymorphism, DRD2 Taq1A1 was found more frequently among 79 adolescents who played video games excessively compared to 75 normal controls, a potentially significant finding in that this allele has been hypothesized to increase vulnerability to addictive behaviors.

Preliminary research has also linked excessive Internet use in adolescent males with the homozygous short allelic variant of the serotonin transporter gene (*SS-5HTTLPR*), a genetic polymorphism previously associated with vulnerability to depression. In addition, compared to controls these adolescents scored higher on the Beck Depression Inventory, suggesting that they may have genetic characteristics and clinical features similar to those suffering from depression.

Environmental Factors

Several investigators have found associations between family dysfunction and adolescent Internet addiction. In one South Korean cohort, for example, exposure to "violence" between parents or being a victim of "violence" perpetrated by the parent was associated with adolescent Internet addiction. Similarly, a Chinese study of middle school students found strong associations between a history of physical abuse and meeting criteria for Internet addiction. In a study of almost 9,000 Taiwanese adolescents, low family monitoring, low feeling of connection to school, high family conflict, having friends who were habitual alcohol drinkers, and living in a rural community were each associated with an increased likelihood of meeting criteria for Internet addiction. Among Chinese University students, being from a single-parent family and homesickness were associated with Internet addiction. Of course, access to the Internet is a significant environmental factor: in a cohort of almost 900 Greek adolescents, having access to the Internet at home and accessing the Internet to play games were predictors of Internet addiction, especially among males.

Preexisting and Concurrent Psychiatric Comorbidities

In a 2-year prospective study of 2,293 Taiwanese adolescents (1,179 boys and 1,114 girls), hostility and attention-deficit hyperactivity disorder (ADHD) were found to be the leading risk factors for the occurrence of Internet addiction among males and female adolescents, and depression and social phobia predicted Internet addiction among female, but not male, adolescents. Several cross-sectional studies have shown that comorbidity is the rule rather than exception in individuals with Internet addiction. Those most commonly noted psychiatric conditions that appear to occur with Internet addiction include mood disorders, anxiety disorders, impulse-control disorders, substance dependence, and ADHD. In China, which is experiencing an epidemic of Internet addiction, one report indicated that 30% of those diagnosed with Internet addiction have concurrent significant anxiety or depression, and 30% have ADHD.

Additional Complications

Abundant evidence suggests that individuals identified as suffering from Internet addiction and related disorders frequently suffer from significant psychiatric and medical complications. In 2006, the Korean government estimated that among the estimated 210,000 South Korean children and adolescents between the ages of 6 and 17 suffering from Internet addiction, about 80% required psychotropic medication and one-fifth to one-quarter required hospitalization. In fact, a major impetus in South Korea for identifying Internet addiction as a major public health problem was the report of 10 deaths resulting from cardiopulmonary causes, such as thromboembolism, occurring in Internet cafés among young healthy men who had played for more than 16 consecutive hours, and, in one case, a total of 80 hours. The increasing occurrence of this variant of thromboembolism has led to its being labeled "e-thrombosis."

Sleep deprivation is another adverse consequence of excessive use of electronic devices. Among 100 adolescents 12 to 18 years of age, increased time using different forms of electronic devices after 9 pm significantly correlated with decreased sleep, increased consumption of caffeinated products, and greater risk for daytime sleepiness, including sleepiness in the classroom. Teens getting 8 to 10 hours of sleep on school nights, considered optimal for teenagers, spent significantly less time using electronic devices whereas those sleeping less used these devices 1.5 to 2 times longer. These patterns of reduced sleep in teenagers have been associated with a variety of psychological and physical problems as well as decreased quality of life. For additional perspective, in a Chinese study of more than 3,000 cases of Internet addiction, 80% of whom were adolescent males, the average amount of time spent on the Internet was 9 hours per day.

Numerous social, psychological, academic, and occupational complications of Internet addiction have been identified. In young people, poor academic performance sometimes leading to school failure, disrupted family relationships, and social isolation are among the more common. Other serious functional impairments resulting from problematic Internet use include legal difficulties and job loss.

Concerns have been voiced that playing violent video games may be associated with increases in violent behavior. This issue became a focus of national concern after the Columbine High School shootings in Littleton, Colorado, when it was learned that the teenage assailants were fascinated by violent video games including one licensed by the U.S. Military, used for training soldiers to "effectively kill." One representative study examining the psychological and behavioral effects of increasingly graphic violent video games on users found aggressive behavior and delinquency to be positively associated with playing violent video games. This association was stronger in previously aggressive individuals and in males, reflecting that psychologically vulnerable individuals and males may be at greater risk to act out violently in real life after engaging in such fantasy activities.

Decreased work productivity has been a major cause of functional impairment in adults with problematic Internet use. One review of this topic reported that one in four employees engage in problematic Internet use and estimated the annual costs to American corporations in lost productivity to range from 1 to 54 billion dollars. Because these problems are so widespread, employers at most large public and private institutions have instituted employee Internet use policies to address them.

Most concerning, certain dysfunctional behaviors occurring with electronic devices are associated with increased risks of harm to self or others. The use of cell phones and texting messages while driving result in decreased reaction time and increased distractibility leading to increased risks of motor vehicle accidents. These public health hazards have resulted in the passage by many localities of laws prohibiting handheld cell phone use while driving. Nevertheless, despite using a methodology thought to underestimate cell phone usage and

examining cell phone use only during daytime hours, the National Highway Traffic Safety Administration's 2007 annual survey of cell phone use while driving found significant increases in the use of cell phones and other handheld devices while driving compared to the previous year. At any given time, approximately 6% of drivers were using handheld devices and 11% were using either handheld or hand-free devices, representing a total of more than 1 million vehicles at any given moment in which a driver was using a cell phone. The highest frequency of use, 8.8%, occurred in 16- to 24-year-olds, an already high-risk group for automobile accidents. More disturbingly, a study of driver cell phone use at night found the highest rate of 12% to be among females 16 to 29 years old, much higher than the daytime rate among young people, especially concerning since young drivers are at most risk for having accidents at night.

The consequence of these worsening trends has been a public health crisis: a 2003 Harvard study estimated that there are more than 2,500 traffic fatalities annually secondary to distractions caused by cell phone use. The U.S. Department of Transportation reported that driver distraction, mostly caused by cell phones, resulted in more than a doubling of this number of fatalities in 2008 (almost 6,000), accounting for about one-sixth of all fatal crashes; additionally, half a million people were injured in car crashes in 2008 as a result of driver distraction primarily caused by mobile phones. And research has shown that using a cell phone while driving is as dangerous as driving legally intoxicated with a blood alcohol level of 0.08%.

Finally, the potential for exploitation and abuse by others, particularly among young people, is heightened by the increased social networking activities occurring via these media. Examples of situations that can result in unintended tragic ends include unsuspecting victims befriending sexual predators on the Internet and the perpetration of public humiliation, which has led to suicide, in the wake of the phenomenon called "sexting" in which typically teenagers send sexually explicit messages to friends on cell phones, sometimes including nude photos of themselves, which may then be maliciously more widely disseminated to others. Notably, up to 20% of teens in surveys report sending or posting nude photographs of themselves. Furthermore, even teens who send and receive explicitly sexual messages about themselves and their friends have been charged and on occasion convicted of disseminating and/or possessing child pornography.

Evaluation and Treatment

Various psychosocial treatment programs have been proposed, and numerous Internet addiction treatment counselors and centers have emerged throughout the world. Most of the treatment literature concerning Internet addiction consists of case reports, case series, and occasional open-label medication trials. In China, treatments employed at the General Hospital of Beijing's Military Region's Addiction Medicine Center (AMC), a major treatment and research center for Internet addiction, have included behavioral training, medication treatment for patients with psychiatric symptoms, dancing and sports, reading, karaoke, and elements of the "12-Step" programs of Alcoholics Anonymous. Family therapy has also been included as an important treatment component.

Escitalopram has shown some promise in treating Internet addiction. After a case report described successful treatment of a condition characterized as severe Internet addiction with 10 mg/day of escitalopram, an open-label study was organized involving a sample of 19 adult subjects with "Internet usage disorder," defined as use of the Internet that was time-consuming, uncontrollable, distressing, and causing social, financial, or occupational dysfunction. A 10-week trial of escitalopram, 20 mg today, resulted in significant improvement on the two primary outcomes measures, the Clinical Global Impressions-Improvement scale (CGI-I) and total time

spent per week in nonessential Internet activities. At the end of treatment, 64% of subjects were considered CGI-I responders, and weekly time on the Internet was reduced from 37 to 16.5 hours. In a subsequent double-blind discontinuation phase, no differences were found between the two groups; both the escitalopram and placebo groups maintained their improvements.

Does Treating Comorbid Conditions Impact Internet Use?

Preliminary studies suggest that problematic Internet use can be reduced through successful treatment of comorbid conditions commonly associated with Internet addiction.

Attention-Deficit Hyperactivity Disorder (ADHD)

An open-label study evaluated the efficacy of stimulant treatment on ADHD symptoms and Internet usage in Korean children, aged 8 to 12, who had ADHD and were video game players. One of the study's aims was to assess whether improvement in ADHD symptoms correlated with a reduction of Internet addiction symptoms, since previous research has shown a high rate of comorbidity between the two syndromes and video game playing has been associated with release of DA, one mechanism through which stimulant medications operate. Based on the Korean version of the Young Internet Addiction Scale, YIAS-K, about 50% of the sample met criteria for Internet addiction. At the end of treatment, significant reductions were found for both ADHD and Internet addiction symptoms, and improvements in ADHD symptoms and decreased Internet use (i.e., time spent playing video games) were correlated. Of note, since playing video games has been associated with improvements both in attention and visual spatial functioning, the authors speculate that video game playing in untreated ADHD individuals may represent attempts at "self-medication."

Recommendations for Evaluation and Treatment of Individuals with Internet Addiction

For all the reasons regarding the lack of consensus about the nature of these somewhat heterogeneous conditions noted above, highly specific recommendations regarding how to treat this large group of patients are difficult to formulate. With this caveat in mind, it is prudent to use a flexible, biopsychosocial approach. Of key importance for all general psychiatric and mental health evaluations is that clinicians should routinely inquire about every patient's use of the Internet, both to assess whether Internet use (and the use of other electronic media and devices) per se poses a major source of distress and impairment and to ascertain if problems associated with Internet use represent manifestations of some other psychiatric disorder requiring treatment. Unlike in Asian countries like China, Korea, and Taiwan where routine screening for Internet addiction is now commonplace, contemporary American psychiatrists appear to not routinely inquire about Internet use, and, as a result, many Americans with Internet addiction go undetected. In addition, the diagnosis of comorbid conditions associated with Internet addiction is delayed when questions about Internet use are omitted, since the primary manifestation of the comorbid syndrome, for example addiction to pornography, may be mediated only by activity on the Internet.

A good quality assessment includes asking the patient to describe and quantify how much he or she uses the Internet and other electronic media and whether the patient or family members feel that the patient's use is a problem that interferes with relationships, school, and/or work. The inquiry should also investigate the various types of electronic activity in which the individual engages and the patient's perception of what attracts him or her to using the Internet and other electronic media and the needs that such use seems to satisfy, in order to assess whether the patient uses the Internet and e-media as a vehicle for expressing clinically

concerning preoccupations and urges, for example, cravings for violence manifested by playing violent video games, which may in turn lower inhibitions against behaving violently in the real world. For depressed individuals, "surfing the Net" or playing video games may be a manifestation of social withdrawal related to difficulties coping with painful life circumstances. For shy and socially anxious individuals, such use may offer routes for engaging in social interaction in less anxiety-provoking circumstances than face-to-face encounters, but, as mentioned above, may deleteriously perpetuate avoidance of more mature intimacy. Also, since Internet addiction has been described as having many features of both addictions and impulse-control disorders, patients should be asked if they experience cravings regarding using the Internet, difficulties resisting impulses to use the Internet, and the extent to which they become extremely irritable, anxious, and/or depressed when forced to stop using it.

The evaluation should also routinely include standard assessments for the major psychiatric disorders, in particular ADHD, mood disorders, anxiety disorders, substance dependence, and impulse-control disorders, all so commonly comorbid with Internet addiction and which frequently lead to it. In addition, assessment for personality characteristics, such as shyness, which place individuals at higher risk for problematic Internet use, should be performed.

A thorough clinical interview and/or the routine use of a screening questionnaire developed for detecting Internet addiction are all reasonable methods for conducting an assessment. Administration of an Internet addiction rating scale can help determine the severity of impairment and provide a baseline against which to measure response to treatment. Obtaining collateral information from family, school, personnel, and friends is necessary to complete an accurate clinical picture and assessment of severity of distress and impairment.

Treatment Approaches

An individualized approach is essential. To start, concrete behavioral interventions, including setting explicit goals for abstinence or for significant reductions of time spent in the dysfunctional activities may help alleviate the difficulties and offer opportunities for reversing the impairments they inflict. Treating common comorbid conditions such as mood and anxiety disorders and ADHD may frequently ameliorate Internet addiction. Interventions that have been efficacious for substance dependence and impulse-control disorders should be considered as well.

Gaining an understanding of the functions that problematic Internet use serve may help lead to successful interventions. For example, depressed individuals may reduce their reliance on the Internet when their mood improves and they have less need to withdraw from others. Particularly with children and adolescents, but with adults as well, addressing family problems that may be fueling the Internet addiction may help alleviate the disorder and may help support treatments to limit the patient's use of the Internet. Concerned family members may also be willing to confront the patient's problematic Internet use and encourage the patient to adhere to treatment.

Finally, outpatient and residential inpatient facilities devoted to treating this syndrome have appeared and in some locations proliferated. Clinicians dealing with patients presenting with these disorders will wish to learn about their treatment philosophies and other practical aspects of their programs and requirements.

Conclusion

Excessive and/or problematic use of the Internet and related electronic media has become a worldwide mental health problem of epidemic proportions in industrialized nations, and American pediatricians have raised concerns that Internet addiction might become a "new common chronic disease of childhood" and "major public health problem for the United States

in the 21st century." Although further research is needed to better define its boundaries and diagnostic criteria and to assess whether it merits inclusion in the DSM as a distinct disorder, abundant evidence exists that Internet addiction is associated with significant clinical distress, functional impairment, and high rates of comorbidity. In the 21st century, psychiatrists and other mental health professionals must consider this syndrome in the differential diagnosis of their patients' presenting problems and be able to utilize a flexible, biopsychosocial approach in understanding and treating this condition. Well-designed treatment studies of psychosocial interventions and medications are necessary to inform evidence-based practices that can reduce the considerable psychological and economic costs to society imposed by this new but rapidly proliferating syndrome.

Suggested Readings

Ha JH, Yoo HJ, Cho IH, et al. Psychiatric comorbidity assessed in Korean children and adolescents who screen positive for Internet addiction. *J Clin Psychiatry.* 2006;67:821–826.

Han DH, Young SL, Churl N, et al. The effect of methylphenidate on Internet video game play in children with attention-deficit/hyperactivity disorder. *Compr Psychiatry*. 2009;50:251–256.

Meerkerk GJ, Van Den Eijnden RJJM, Vermulust AA, et al. The Compulsive Internet Use Scale (CIUS): some psychometric properties. *CyberPsychol Behav*. 2009;12:1–6.

Murali V, George S. Lost online: an overview of internet addiction. *Adv Psychiatr Treat.* 2007;13:24–30.

Niemz K, Griffiths M, Banyard P. Prevalence of pathological Internet use among university students and correlations with self-esteem, the General Health Questionnaire (GHQ), and disinhibition. *CyberPsychol. Behav.* 2005;8:562–570.

Park SK, Kim JY, Cho CB. Prevalence of Internet addiction and correlations with family factors among South Korean adolescents. *Adolescence.* 2008;43:895–909.

Shapira NA, Goldsmith TD, Keck PE Jr, et al. Psychiatric features of individuals with problematic internet use. *J Affect Disord*. 2000;57:267–272.

Shaw M, Black DW. Internet addiction. *CNS Drugs*. 2008;22:353–365.

Widyanto L, Griffiths M. Internet addiction: a critical review. *Int J Ment Health Addict.* 2006;4:31–51.

Widyanto L, McMurran M. The psychometric properties of the Internet addiction test. *CyberPsychol Behav.* 2004;7:443–450.

Section 4

Treatment Modalities

20 Methadone Maintenance Treatment

Methadone maintenance, available in the United States since the 1970s, is one of the primary treatment modalities for the treatment of opioid dependence. It has undergone considerable expansion in the United States. In 1988, 650 programs treated about 100,000 patients. As of 2009, over 1,200 programs existed. In 2007, 265,217 patients were treated in opioid treatment programs (OTPs), the vast majority with methadone. Methadone treatment for opioid dependence has spread worldwide, and methadone was included in the 2005 WHO List of Essential Medications.

Efficacy of Methadone Treatment for Opioid Dependence

A meta-analysis found that patients receiving methadone maintenance were three times as likely as control subjects to remain in treatment and one-third as likely to have used heroin. Methadone maintenance treatment also has been shown to have a positive effect on rates of crime and to reduce HIV risk behavior (e.g., reductions in needle use, sexual risks). Opioid-dependent individuals exhibit mortality rates 6 to 20 times that of the age-matched population, but methadone treatment may partially reverse this risk. Controlled trials of methadone treatment show reduced mortality for persons in methadone treatment. A cost-effectiveness analysis found that the cost of methadone treatment per life-year gained falls well within the range of other commonly used medical treatments such as coronary artery bypass surgery or renal dialysis.

Methadone Pharmacology

Marketed methadone contains a racemic mixture of two stereoisomers, levo (L)-methadone and dextro (D)-methadone. L-methadone has the majority of pharmacologic activity, although D-methadone has some antitussive action and may contribute to some side effects. Oral methadone is supplied as a tablet, a rapidly dissolving wafer, and a premixed liquid.

Methadone is readily absorbed after oral ingestion, with an average bioavailability of about 80%, but interindividual variation can range from 41% to 95%. Initial effects can occur within 30 minutes, but peak effects and peak plasma levels occur on average about 4 hours following ingestion. Methadone has an average terminal half-life of 22 hours (range, 5 to 130 hours). The majority of methadone leaves the circulation and enters tissue stores in

liver, kidneys, lungs, and brain. Tissue stores can be released back into the circulation typically when serum levels fall but also potentially at unanticipated times and at unexpectedly rapid rates. The methadone remaining in the blood is 60% to 90% bound to plasma proteins, mainly to α_1-acid glycoproteins.

As might be anticipated from the wide variability in half-life, the metabolism of methadone is complicated. An array of evidence suggests that the metabolism is catalyzed primarily by the liver enzyme CYP450 3A4 with possible additional contributions by other enzymes, including 2B6, 2D6, and possibly, but to a smaller extent, 1A2, 2C9, and 2C19. All of these enzymes exhibit wide interindividual variation in activity based largely on genetics and to a lesser extent on environmental factors. Methadone can also induce its own metabolism so that serum levels and effects may decline over time. Methadone is metabolized primarily to the inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). Most parent drug and EDDP elimination occurs through the kidneys, with some eliminated in the feces.

The primary pharmacodynamic target for methadone is the μ-opioid receptor, but methadone, unlike most other opioids, also antagonizes the *N*-methyl-d-aspartate (NMDA) receptor and blocks the serotonin and norepinephrine transporters. In addition, methadone inhibits the cardiac potassium channel hERG (human ether-a-go-go), which can cause a prolonged QT interval on the ECG. Given acutely prior to the development of tolerance, methadone has typical μ-opioid agonist effects, including miosis, analgesia, sedation, possible euphoria, decrease in gut motility, release of histamine, and respiratory depression.

Clinical Use of Methadone

Methadone Induction

The induction period encompasses the time from the first administered dose until the point when a stable methadone dose is reached, typically a span of 2 to 4 weeks. Prior to inducing a patient onto methadone, a medical history, physical examination, and laboratory tests (including urine toxicology) should be completed. The patient should sign a consent document that also lays out the expectations for methadone treatment.

Prior to administering the initial dose, the responsible clinician should ascertain that the patient is not exhibiting any clinical evidence of sedation or intoxication. The initial dose of methadone can range from 5 to 30 mg, with 30 mg being the maximum allowed first dose. An additional 10 mg can be added after a period of observation if 30 mg does not adequately suppress withdrawal. The maximum allowed total dose for the first day is 40 mg unless the program physician clearly documents in the record that 40 mg did not suppress opioid withdrawal. If any question exists as to the appropriate initial dose, it is wisest to err on the side of a lower dose to avoid any potential risks of intoxication or overdose.

The clinician should evaluate the patient 2 to 4 hours following the initial dose. If the patient shows no signs of withdrawal or intoxication and reports feeling comfortable, the appropriate first-day dose has been achieved. If there are signs or symptoms of withdrawal, the clinician can administer additional doses of methadone to a maximum of 40 mg total for day 1. In the rare instance when a patient appears sedated or intoxicated 2 to 4 hours after the initial dose, the patient should be kept in the clinic for observation until the effects have resolved.

The patient will return to the clinic on subsequent days for evaluation and observed medication administration. It will typically require 4 to 5 days on a given dose to ascertain the ultimate effect of a dose. The most judicious approach is to increase the dosage in 5- to 10-mg increments every 4 to 5 days.

Determining the Stable Dose of Methadone

The overall goals for the induction period and beyond are to attain a methadone dose that suppresses opioid withdrawal symptoms throughout the 24-hour dosing interval, eliminates craving or desire for other opioids, creates sufficient tolerance to prevent euphoria caused by self-administration (SA) of illicit opioids, eliminates the use of illicit opioids as evidenced by self-report and urine toxicology testing, and minimizes side effects so that the patient is not experiencing intoxication and can function normally. Frequently, all these goals cannot be met by doses that are safely reached during the induction period. In that circumstance, ongoing methadone dose increases in increments of 5 to 10 mg every 5 to 7 days should be continued until these goals are achieved. Once the daily dose exceeds 40 mg, 10-mg increments generally are safe and appropriate. For most patients, the stable dose will reside in the range of 80 to 120 mg/day, though some patients do well on lower doses and some require higher doses.

Patients may also miss methadone doses because of failure to attend the clinic. If more than 1 consecutive day is missed, the patient should receive a medical evaluation, and the methadone dose may need to be temporarily reduced if a loss of tolerance is suspected. A common practice after 2 or 3 days is to restart the patient at 50% of his or her established maintenance dose. After missing 4 or more days of methadone, the most cautious course of action is to restart methadone at 30 mg or less and then retitrate the dose upward in a fashion analogous to induction to return ultimately to the stable dose.

Methadone Serum Levels

For a few select patients, obtaining serum methadone levels may be helpful. Suggested minimally therapeutic trough levels range from 100 to 400 ng/mL. Peak serum levels also vary widely among stable methadone patients. The best available evidence indicates that the rate of decline from peak to trough, rather than absolute levels, optimally predicts the presence of withdrawal symptoms and instability, but determining the rate of decline requires multiple samples over a 24-hour period, a sampling regimen generally not possible. The ratio of peak to trough may serve as a surrogate for the rate of decline. A peak-to-trough ratio of greater than 2:1 may be an indicator of inadequate coverage, and such patients may respond best to a split-dosing regimen rather than to an increase in daily dose.

Methadone Drug Interactions

Drug–drug interactions that are clinically significant induce the enzymes catalyzing the metabolism of methadone, resulting in a decrease in the methadone serum level and emerging opioid withdrawal. Drugs known to cause this effect include the anticonvulsants phenytoin and carbamazepine; the antibiotic rifampin; and antiretroviral medications lopinavir, efavirenz, and nevirapine. These medications are best avoided in methadone-treated patients, but if their use is essential, often fairly substantial increases in the methadone dose are required to eliminate withdrawal symptoms. Other antiretroviral medications may alter methadone pharmacokinetics but do not appear to result in clinically observed withdrawal.

Finally, methadone can prolong the QT interval on the ECG. Numerous other drugs also have a similar effect. Although the issue has not been well studied, it seems probable that the combination of methadone with other drugs that prolong the QT interval could have additive effects increasing the risk for QT prolongation.

Managing Methadone Side Effects

Many side effects of methadone can be managed by incremental dose reductions. If dose reductions are not reasonable because the patient has continued illicit opioid use or still has

withdrawal symptoms, other interventions can be applied to manage some of the commonly occurring side effects.

Constipation is one of the most frequent and bothersome side effects in patients on methadone, and can be managed by encouraging patients to drink more water, eat a diet high in fiber, and engage in exercise. If these measures are ineffective, laxatives can be used.

Edema can also be an unpleasant side effect of methadone. How methadone causes edema remains unknown. Edema seldom responds to sodium restriction. It sometimes responds to a decrease in methadone dosage. If severe edema does not respond to these measures, diuretics often prove helpful.

Methadone can cause hormonal alterations related to sexual functioning. In men, reports of methadone side effects include orgasmic and erectile dysfunction, and decreased sexual desire. Sexual dysfunction may respond to a methadone dosage reduction. If that is not possible or does not help, erectile function often improves with use of phosphodiesterase type 5 inhibitors. Testosterone replacement can ameliorate sexual dysfunction among methadone-treated men with low serum testosterone levels.

For women on methadone, depressed libido and oligomenorrhea or amenorrhea have been reported; however, some improvements are also noted after stabilizing in treatment. Irregular menses may lead some women to believe incorrectly that they cannot become pregnant or are pregnant when they are not. For symptomatic female patients, a medical workup is indicated that includes a discussion of the possibility of becoming pregnant without regular menses and about the use of birth control. Referral to an endocrinologist or gynecologist can identify or rule out other medical conditions that can cause amenorrhea or oligomenorrhea.

Hyperhidrosis or excessive sweating is a common complaint among methadone patients. One potentially effective intervention is to lower the methadone dose. In patients treated with drugs that induce hyperhidrosis such as cholinesterase inhibitors, selective serotonin reuptake inhibitors, or tricyclic antidepressants, using an alternative to one of these medications can decrease the severity of sweating. Antihistamines may alleviate sweating in methadone patients. The newer nonsedating antihistamines do not incur a risk of increase in the QT interval.

Methadone has a black box warning for QT interval prolongation. Some evidence suggests that a corrected QT interval longer than 500 msec increases the risk for torsades. It is reasonable to consider obtaining ECGs on methadone patients who have known structural heart disease or who have a history of syncope or a family history of sudden cardiac death, since there can be genetic predisposition to a prolonged QT interval. If patients on methadone have a QTc interval above 500 msec, consideration should be given to discontinuing other medications that also prolong the QTc interval, to stopping illicit cocaine use, correcting electrolyte imbalances, and reducing the methadone dose if clinically feasible.

Methadone Medically Supervised Withdrawal and Tapering

Medically supervised withdrawal or tapering from methadone may be performed for several reasons. In the majority of cases, it should be avoided because relapse rates to dependence on illicit opioids tend to be high. If medically supervised withdrawal must be done, slower tapers lead to superior outcomes. One reasonable approach is to use a 180-day schedule to perform induction and stabilization, similar to what would be done for a maintenance patient and continue a stable dose to the 120-day mark. At that point, the dose can be tapered over 60 days with the understanding that the rate of taper should slow in the latter part of this interval. Shorter tapers can be conducted in analogous fashion.

For patients receiving an administrative discharge from a methadone program, the usual custom is to perform a taper over 21 days. Although this time frame almost universally militates against success, it does balance the patient having an opportunity to make alternative plans against the need to have the patient leave the program relatively quickly.

For patients requesting a voluntary taper, a number of signs of stability should be in place before considering a taper. It is not unusual for such tapers to last months or even years. A good option is to allow the patient to halt the taper or regain the previous higher dose upon request if the patient experiences any instability. The taper should definitely be stopped if any obvious signs of instability occur. As the daily dosage drops below the 40 to 60 mg/day range, the rate of taper usually has to be decreased. Patients who successfully complete the taper should be encouraged to continue counseling and may want to begin opioid antagonist therapy with naltrexone once they no longer have physiologic dependence.

Nonopioid Substance Use

Alcohol

Among patients seeking treatment for opioid dependence, rates of alcohol dependence range from 24% for a current to 50% for a lifetime diagnosis. Alcohol can act additively with methadone and other opioids to suppress CNS activity and respiratory drive, increasing the risk of overdose. Alcohol can also induce the activity of cytochrome P450 enzymes, thereby enhancing the metabolism of methadone and destabilizing the patient. Patients who have indicators of alcohol problems tend to have poorer methadone treatment retention and more illicit drug use than patients without alcohol problems.

Active alcohol abuse or dependence when recognized in methadone maintenance should be treated aggressively. The mainstay of treatment involves behavioral interventions, including contingency management, motivational interviewing, relapse prevention, and 12-step facilitation with referral to Alcoholics Anonymous. Using the latter intervention would require some alterations for methadone patients who could experience stigmatization at 12-step meetings because of their methadone prescription. Pharmacologic interventions for alcohol dependence should also be considered, although naltrexone, as a μ-opioid antagonist, is contraindicated in methadone patients (as an acute dose of it will precipitate withdrawal in an opioid-dependent person). However, monitored disulfiram is used frequently.

Benzodiazepines

The prevalence of current benzodiazepine abuse in methadone patients has been estimated to be between 25% and 50%. The respiratory depressant effects of methadone and benzodiazepines are synergistic. Use of benzodiazepines may require methadone dose reductions in the event of oversedation. If the benzodiazepines are prescribed for anxiety or insomnia, ideally the care can be coordinated and an alternative agent may be used. In the case of benzodiazepine dependence, abrupt cessation can cause a medically significant withdrawal syndrome. Options for treating benzodiazepine dependence include a slow outpatient taper, or admission to an inpatient unit for medically supervised withdrawal of benzodiazepines. Outpatient tapers often prove difficult.

Cocaine and Amphetamines

Studies show that there are high rates of lifetime and current cocaine dependence in methadone-treated patients. Behavioral treatments, particularly contingency management and cognitive–behavioral therapy, effectively reduce cocaine use among methadone patients. Several specific pharmacotherapy interventions for cocaine dependence among methadone patients have been

tested with generally disappointing results with the exception of disulfiram, which shows promise even among patients who do not have alcohol dependence.

Because methamphetamine and other stimulant use among methadone patients seem to be infrequent, a paucity of data exists on this topic. Behavioral interventions would be similar to those used for cocaine.

Cannabis

Cannabis use among methadone patients is reported to range from 54% to 79%. Cannabis use itself does not have a measurable negative effect on typical methadone treatment outcomes such as treatment retention, illicit opioid use, or employment. Undoubtedly, some methadone patients with cannabis dependence could benefit from cannabis abstinence. However, there is a growing body of experimental literature suggesting that stopping regular cannabis use may be difficult because of withdrawal symptoms, including anxiety, depression, irritability, craving, decreased quantity and quality of sleep, and decreased appetite. As with other forms of substance dependence, patients with cannabis dependence usually respond to cognitive–behavioral therapy and contingency management.

Tobacco

The rate of tobacco smoking among methadone patients is about 80%, and many evince interest in quitting. Since methadone patients have a high prevalence of diseases caused or exacerbated by tobacco smoking, smoking cessation could have a substantial impact on health outcomes in this population. Also, heavy smoking strongly predicts cocaine and illicit opioid use among methadone patients. Long-term quit rates fall in the range of 5% when transdermal nicotine and intensive behavioral interventions are used. Other forms of smoking cessation pharmacotherapy such as bupropion, varenicline, or combination of transdermal nicotine with immediate release forms of nicotine replacement like gum or lozenge have not been investigated in methadone patients.

Co-Occurring Psychiatric Disorders

Opioid-dependent patients on methadone maintenance exhibit high rates of co-occurring, non–substance-related, psychiatric disorders, including major depression, bipolar disorder, anxiety disorders, and personality disorders. There are also high rates of posttraumatic stress disorder, and eating disorders and attention-deficit hyperactivity disorder have also been reported to occur not infrequently in methadone patients. In general, the treatment for these disorders should be identical to that provided to any psychiatric patient, including pharmacotherapy and psychotherapy.

Assessment for co-occurring psychiatric disorders requires a thorough psychiatric interview. High rates of substance-induced psychiatric disorders also occur among methadone patients. Observing a patient through a several-week period of abstinence to see if symptoms remit may demonstrate that the disorder is not a primary psychiatric disorder and obviate the need for specific treatment. Particularly with depressive symptoms, many patients show improvement during their first weeks of methadone treatment.

When psychiatric severity is assessed dimensionally rather than categorically, patients with low psychiatric severity derive no added benefit when psychotherapy is added to basic counseling, whereas patients with moderate or high psychiatric severity show significant improvements in outcome with the addition of psychotherapy to counseling.

Co-Occurring Medical Disorders

Medical disorders are prevalent among opioid-addicted populations in part due to the route of drug administration. Injection drug users are at risk for infectious diseases such as pneumonia, tuberculosis, endocarditis, sexually transmitted diseases, soft tissue infections, bone and joint infections, CNS infections, HIV, and viral hepatitis. Drug smoking also leads to medical complications, particularly pulmonary concerns. Cocaine and methamphetamine, taken by any route, can also cause myocardial ischemia and/or infarction as well as cardiac arrhythmias, cerebrovascular accidents, seizures, gastroduodenal ulceration, and acute renal failure. Excessive alcohol use has the potential to damage nearly every organ system.

Both acute and chronic pain are not infrequent consequences of these co-occurring medical disorders or traumatic injury. A key principle in managing pain in methadone patients is that the daily methadone dose, which is intended to prevent withdrawal symptoms and opioid cravings, will not provide relief from either form of pain. When pain occurs, conservative measures such as nonsteroidal anti-inflammatory medications can be tried, but opioid analgesics should not be denied to patients on methadone if they have a painful condition for which a clinician would normally prescribe opioids. Higher doses of opioid analgesics may be required to control pain than would be used in an average, nonopioid-dependent individual with the same condition. Acute pain requiring opioids can be treated with a short-acting opioid. Chronic pain often responds well to additional amounts of methadone in pill form prescribed for pain and given in divided doses throughout the day, although other opioids can also be prescribed.

Psychosocial and Ancillary Services

Studies of various intensities of psychosocial services in OTPs indicate that patients who receive minimal psychosocial services do not fare as well as those who receive moderate or high levels of services. However, the lower cost-effectiveness of more intensive services may nullify any slight advantage they hold over moderate services.

The accumulated general knowledge on modalities of psychotherapy indicates that individual therapist's skill at creating a therapeutic alliance has a stronger effect on outcomes in psychosocial interventions for substance dependence than the specific modality applied. Nevertheless, a variety of specific modalities have been applied to patients with opioid dependence, such as individual drug counseling, cognitive–behavioral therapy, supportive–expressive psychotherapy, relapse prevention, contingency management, and medical management. A meta-analysis of psychosocial interventions for substance use disorders, that included interventions for opioid dependence, found that both cognitive–behavioral therapy and contingency management had positive moderate effects with contingency management holding a slight advantage.

Contingency management shapes behavior (e.g., illicit drug use) in a preferred direction (e.g., toward abstinence) by offering desired rewards contingent on behavior change, and numerous studies demonstrate its benefit in methadone maintenance. An approach that is already frequently applied in methadone programs, provision of methadone take-home doses contingent upon negative urine specimens, clearly increases abstinence rates. Another approach that shows tremendous promise grants vouchers that can be redeemed for goods or services contingent upon negative urine specimens, but this approach has not yet gained a strong foothold in clinical settings.

Urine Testing

Drug testing identifies ongoing or sporadic drug use and potential safety issues. The results should be used as part of the treatment plan; a negative test should be used to discuss successful strategies, and a positive test to explore obstacles to abstinence and to identify additional recovery resources. To avoid confusion between licit and illicit drugs, programs generally require the patient to report or bring in all prescriptions for controlled substances and to coordinate care with the prescriber. The frequency of urine testing can be increased after a positive test result in order to clarify a lapse from a more extensive relapse.

Fear of sanction such as loss of take-home doses may lead a patient to avoid testing positive for drugs of abuse by tampering with the urine sample. To discourage tampering, programs are required to test on a random schedule. Reliance on urine observation to minimize falsification is not required, although at times it may be necessary. Temperature testing is less intrusive and can also identify altered specimens. A laboratory can check the validity of a urine sample by performing a urine creatinine analysis.

Take-Home Status

Regulations allow take-home doses of methadone for stable patients and can ultimately be advanced to a maximum of a 1-month supply of take-home doses for patients in continuous treatment for 2 years or longer. Since patients highly value take-home doses, take-home privileges can be effectively used in a contingency management plan. Patients who comply with program rules and responsibilities, including abstinence from illicit drug use, qualify for additional take-home doses. Patients who do not comply and/or supply positive urine specimens lose the privilege of take-home doses. Such procedures actually reduce illicit drug use.

OTP physicians must consider the patient's ability to store, take, and transport take-home doses safely. In the United States, there are federal criteria for take-home privileges. Many programs are closed for dispensing on Sundays and holidays. Typically, it does not pose an undue risk to provide a take-home dose once per week on days the clinic is closed for patients who do not strictly meet all of the federal criteria. Occasionally, an individual patient may be so unstable that arrangements must be made to provide observed methadone dosing 7 days per week.

Diversion Risk Reduction Plan

Although diversion of take-home doses of methadone to individuals for whom it is not prescribed certainly occurs, few data exist to indicate the frequency of such events. From the data that are available, methadone diversion is not an exceedingly common event, but some diversion of methadone will inevitably occur, so programs must develop and apply diversion reduction plans. Careful application of criteria for take-home eligibility and removal of take-home privileges quickly with evidence of instability constitute the foundations of diversion reduction. Instituting a random callback system is also feasible and creates an additional safeguard. All take-home privileges can be revoked from patients who fail a callback.

Managing Problematic Behavior

Prevention of problematic behavior represents a necessary first step. Establishing a clear program structure and conveying to all patients a set of expectations and rules both orally and in writing at the outset and throughout treatment and then enforcing the expectations consistently and fairly will encourage patients to keep their behavior within appropriate boundaries. When problematic behaviors do occur, the program has essentially two sanctions available as a consequence: (1) removal of take-home privileges or denial of take-homes for some specified time into the future and (2) program discharge. Oftentimes, a dynamic tension exists between the direct interests of the patient and maintaining the integrity and safe milieu of the program necessitating difficult clinical and administrative decisions.

Occasionally, patients return to the clinic to report theft, loss, or misuse of their take-home doses. Generally, unless the patient can provide a police report documenting the theft, missing take-homes should not be replaced. If the patient has admitted loss of take-home doses, there is clear evidence that the patient is not sufficiently responsible to manage take-home doses, and the patient should be placed on daily observed ingestion. If a patient reports running out of take-home doses because of taking a larger dose than prescribed, take-home privileges should be suspended, and the patient should be evaluated for a methadone dose increase.

Loitering can usually be handled through repeated warnings and removal of take-home privileges. Rarely would loitering require program discharge. In contrast, drug possession or dealing on the premises, methadone diversion, and theft all involve criminal activity. In most cases when such criminal activity is detected, program discharge is the most reasonable response. Falsification of urine specimens falls somewhere in between. A patient who attempts to falsify presumably is motivated by a desire to obtain or maintain take-home doses that would be lost because of a drug-containing specimen. In that case, removal of take-home privileges for a specified time such as several months may be an adequate response to deter such behavior in the future. Repeated attempts at falsification may render discharge necessary.

A patient appearing intoxicated in the clinic poses both safety and liability concerns and requires immediate actions. The patient should be evaluated by medical staff to determine if the methadone dose should be withheld or if it is safe to provide a partial dose. If the intoxication appears serious, the patient should be transferred to an emergency room. If the intoxication appears to be mild, the patient should be observed in the clinic until it resolves. If alcohol is involved, a breathalyzer reading should be obtained, and the patient not released until below the legal limit. If the patient drove a vehicle to the clinic, the keys should be taken from the patient and not returned until the intoxication has resolved. Should the patient be noncompliant and attempt to drive while still intoxicated, the police should be called to protect public safety.

A repeated pattern of appearing intoxicated in the clinic raises the issue of whether the patient can be safely treated with methadone in an outpatient setting. If inpatient treatment is available, it should be strongly considered. If inpatient treatment is not available or is tried and fails to eliminate the episodes of intoxication, after ample warnings in writing with the patient as a signatory, discharge from methadone treatment may be the only option.

Verbal abuse, threats, or actual violence create a direct safety risk to other patients and staff, and, if permitted, make attending treatment or working at the program untenable. In these instances, discharge is almost always the only reasonable course to pursue. Patients who incur an administrative discharge for any of these reasons would usually be given a 21-day methadone taper. In rare cases because of safety concerns, an immediate termination of methadone may be needed. Clinics need to have an appeal or advocacy process. Oftentimes, depending on the nature of the problematic behavior, transfer to another clinic can be facilitated or readmission at a later date can be planned contingent on resolution of the problematic behaviors.

Methadone in Pregnancy

Methadone maintenance is the preferred treatment for opioid addiction during pregnancy. Because of its long duration of action, methadone provides reasonably constant opioid effects, thereby preventing the fetus from undergoing repeated cycles of excessive effect punctuated by periods of withdrawal that would occur in a pregnant woman using short-acting opioids. Compared to no treatment, to treatment without medication, or to medically supervised withdrawal, methadone maintenance along with prenatal care reduces the risk of maternal and fetal complications. The basic approach to methadone treatment is similar for pregnant women as for other patients, but the physiology of pregnancy demands careful attention to methadone dose adjustment. During the latter stages of pregnancy, particularly the third trimester, increasing blood volumes in pregnant women almost always necessitate an increased methadone dose. At times, a single daily methadone dose does not fully prevent emergence of opioid withdrawal, and the pregnant patient should receive a split dose of methadone if logistically possible.

Methadone should be continued during and after delivery. For most women, the dose needs to be reduced postpartum, guided by clinical monitoring, generally either to a dose similar to the dose prior to pregnancy or, for women who began methadone maintenance during pregnancy, to approximately half the doses they received in the third trimester.

Although methadone is excreted in breast milk, most mothers maintained on methadone should be encouraged to breast-feed because the health advantages of breast-feeding outweigh the risks of infant exposure to methadone. Exceptions occur for women who are HIV positive and/or who have ongoing use of illicit drugs or alcohol. Hepatitis C infection does not pose a contraindication to breast-feeding.

Methadone use during pregnancy predisposes the newborn to the neonatal abstinence syndrome (NAS). High variability occurs among infants in both incidence and severity of NAS, neither of which appears to be directly related to the maternal dose or duration of methadone exposure. Caretakers sometimes can treat infants with NAS solely with nonpharmacologic treatment (e.g., reduction in external stimulation and physical soothing). Most, however, require pharmacologic treatment, which typically involves some form of opioid medication.

Medical Maintenance and Interim Maintenance

Medical Maintenance is a model of care in which patients who have stabilized in an OTP transfer their methadone care to a physician practicing in an office-based setting. Typically, patients come in to pick up their methadone once per week to once per month, see the physician, provide a urine specimen, and receive take-home doses until the next appointment. Trials indicate that the majority of already stabilized patients succeed in medical-maintenance treatment and that patients randomly assigned to medical maintenance have equivalent outcomes to clinic-based patients. While such medical-maintenance treatment of stabilized methadone patients is legally permissible in the United States via an exception to the methadone treatment regulations, the process to obtain such an exception is sufficiently cumbersome that very few medical-maintenance practices have been established.

In some areas of the United States, methadone treatment is not readily available to all individuals seeking such treatment. Interim methadone maintenance is designed as a service that provides medication-only treatment as an alternative to having individuals who desire methadone treatment wait with no treatment until a slot in comprehensive treatment becomes available. As per federal regulations, interim methadone provides methadone induction and then a daily, stable observed dose of methadone with no take-home doses and no other services except

emergency counseling. Interim methadone compared to a wait-list control in randomized-controlled trials has demonstrated reduced illicit drug use and higher rates of subsequent entry into comprehensive methadone treatment.

Conclusion

Methadone maintenance is effective in the treatment of opioid dependence. Methadone has several pharmacologic characteristics, which make it ideal for treating opioid dependence but which also demand knowledge and care for it to be prescribed safely. Opioid-dependent patients treated with methadone often have complex presentations, with use of multiple substances in addition to opioids, and with a high prevalence of co-occurring disorders. Specific treatments directed toward these disorders, along with ongoing counseling, can improve outcomes. Careful clinical monitoring includes urine testing, a diversion risk reduction plan, and interventions to prevent problematic behaviors by patients. Increasing evidence shows that less restrictive forms of methadone maintenance, such as medical maintenance, and less intensive forms, such as interim maintenance, are safe and effective to treat the individual and address the public health and safety aspects of opioid addiction.

Suggested Readings

Brooner RK, King VL, Kidorf M, et al. Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Arch Gen Psychiatry*. 1997;54:71–80.

Calsyn DA, Malcy JA, Saxon AJ. Slow tapering from methadone maintenance in a program encouraging indefinite maintenance. *J Subst Abuse Treat*. 2006;30:159–163.

Dutra L, Stathopoulou G, Basden SL, et al. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry*. 2008;165:179–187.

Ferrari A, Coccia CP, Bertolini A, et al. Methadone—metabolism, pharmacokinetics and interactions. *Pharmacol Res*. 2004;50:551–559.

Mattick RP, Breen C, Kimber J, et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2003:CD002209.

McLellan AT, Arndt IO, Metzger DS, et al. The effects of psychosocial services in substance abuse treatment. *JAMA*. 1993;269:1953–1959.

Nunes EV, Quitkin FM, Donovan SJ, et al. Imipramine treatment of opiate-dependent patients with depressive disorders. A placebo-controlled trial. *Arch Gen Psychiatry*. 1998;55:153–160.

Peirce JM, Petry NM, Stitzer ML, et al. Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment: a national drug abuse treatment clinical trials network study. *Arch Gen Psychiatry*. 2006;63:201–208.

Schwartz RP, Highfield DA, Jaffe JH, et al. A randomized controlled trial of interim methadone maintenance. *Arch Gen Psychiatry*. 2006;63:102–109.

Strain EC, Bigelow GE, Liebson IA, et al. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. *JAMA*. 1999;281:1000–1005.

21 Buprenorphine Treatment

Opioid abuse and dependence remain substantial public health problems throughout much of the world. Up until 1996, methadone, levomethadyl acetate (LAAM), and naltrexone were the only pharmacologic agents approved to treat opioid dependence in the United States and for much of the world. In that year, France was the first country to approve the use of buprenorphine for this treatment. Since the late 1990s, buprenorphine has gained widespread use in the world.

History

The chemical compound known as buprenorphine, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6, 14-ethenomorphinan-7-methanol, hydrochloride [5-α, 7-α (S)], was first synthesized in 1966 (Reckitt and Colman, Hull, United Kingdom) and quickly found use as a potent analgesic agent. Jasinski and colleagues learned about the unique partial agonist qualities of buprenorphine and hypothesized that this agent might also be used in the treatment of opioid dependence. In experiments they conducted at the Addiction Research Center, adult males with prior opioid dependence were maintained on 8 mg/day of subcutaneous (SC) buprenorphine; when these individuals were given acute doses of morphine, they experienced an attenuated euphoric response. When three of these same individuals were given acute doses of 4 mg SC naloxone, they had on average fewer withdrawal signs and symptoms than seven individuals maintained on morphine 30 mg SC four times daily, prompting the researchers to conclude buprenorphine showed promise as a pharmacologic agent in the treatment of opioid dependence. These early results were substantiated when buprenorphine was shown to decrease heroin self-administration (SA) in heroin-dependent individuals. Buprenorphine was also shown to have a ceiling for euphoric effects, and it could almost completely block acute opioid effects for 24 hours, with residual blockade of acute effects lasting for 98 hours after drug administration.

After these promising results, a sublingual (SL) version was developed for human clinical trials. Studies examining the efficacy of 8 mg SL buprenorphine as compared to methadone for maintenance therapy were conducted. Several early clinical trials showed equivalence of buprenorphine with methadone in terms of retention and rates of opioid-positive urine samples. Most of these initial trials only tested a fixed 8 mg daily SL buprenorphine dose. Further trials showed superiority of 12- and 16-mg doses of buprenorphine over low-dose methadone. In a major clinical trial, 220 opioid-dependent persons were randomized to low-dose methadone (20 mg), high-dose methadone (60 to 100 mg), buprenorphine (16 to 32 mg), or LAAM (75 to 115 mg). Study retention rates were much greater and opioid use was much

less in the high-dose methadone, LAAM, and buprenorphine treatment arms as compared to the low-dose methadone group. High-dose methadone had the highest retention rate (73%), followed by buprenorphine (58%) and LAAM (53%), although these results were not statistically different. LAAM had the lowest rate of opioid-positive urinalysis per week (53%), followed by buprenorphine (62%) and methadone (62%). Given the preponderance of evidence, the FDA gave approval for the use of buprenorphine (Subutex) and buprenorphine/naloxone (Suboxone) in the treatment of opioid dependence in the United States in October 2002, 6 years after approval in France.

As a partial agonist with a longer time to peak effect relative to morphine, buprenorphine has many useful features as a pharmaceutical treatment for opioid dependence. However, it is an opioid and has potential for abuse. Case reports of buprenorphine diversion and illicit use from New Zealand were published as early as 1983, where buprenorphine was marketed for analgesia as Temgesic. More reports came from other countries throughout the 1980s and early 1990s. Given a growing concern of diversion, a combination product with buprenorphine and naloxone was developed to decrease the risk of illicit use by injection. Efficacy studies showed that naloxone was not well absorbed when given in an SL formulation and that the combination product produced similar reductions in illicit opioid use as buprenorphine alone.

Pharmacokinetics

Buprenorphine has low oral bioavailability due to substantial first-pass metabolism in the small intestine and liver, so the medication has been administered intravenously (IV), intramuscularly (IM), sublingually, and transdermally (TD). Original efficacy studies in the treatment of opioid withdrawal and dependence used an SL buprenorphine solution dissolved in 30% ethanol, whereas buprenorphine is currently marketed as an SL tablet with and without the addition of naloxone, and a soluble film (SF) that includes naloxone (there is not an SF that is only buprenorphine). The most widely used buprenorphine formulations in the United States for opioid dependence are SL buprenorphine hydrochloride or buprenorphine hydrochloride combined with naloxone hydrochloride in a 4:1 ratio (tablet or SF). Generic formulations of buprenorphine and buprenorphine/naloxone tablets are available; the buprenorphine/naloxone SF (Suboxone) is not available as a generic.

Pharmacokinetic studies of the SL tablet (8 mg) compared to the SL buprenorphine solution (8 mg/mL) revealed a relative bioavailability of 49% (based on area under the curve [AUC]) in an acute dosing model of nondependent volunteers, but this could range between 60% and 70% (AUC) after 7 to 14 days of daily buprenorphine dosing. There is a large intersubject variability in the SL absorption of buprenorphine, but there seems to be less intrasubject variability, especially when examining the SL tablet formulation. SL absorption usually is dependent on saliva pH and length of time held under the tongue, but one study failed to find a clinically significant difference in buprenorphine absorption at differing saliva pHs and at times greater than 2.5 to 3 minutes held under the tongue. In clinical practice, patients are told to hold the tablet under their tongue until it dissolves, which occurs on average after 5 minutes. In some people, tablet particles can still remain after 10 minutes, but this does not affect bioavailability of buprenorphine. The SF is also held in the mouth (under the tongue), and dissolves quite rapidly.

Buprenorphine is highly lipophilic and therefore has a large volume of distribution. In plasma, it is usually protein bound but readily crosses the blood–brain barrier. Buprenorphine is metabolized by enzymatic transformation, mainly through the cytochrome P450 3A4 isozyme, to the active metabolite norbuprenorphine. After glucuronidation, buprenorphine and its metabolites are excreted primarily through the fecal route (70%) as unconjugated buprenorphine or the metabolite norbuprenorphine. Around 30% is excreted in urine in the conjugated

form, and dose adjustments usually do not need to be made in persons with severe renal impairment or who are on dialysis. Buprenorphine and its major metabolite are inhibitors of cytochrome P450 3A4 and 2D6 and could show significant drug–drug interactions if concomitant drugs that affect these enzymes are taken.

The addition of naloxone does not interfere with buprenorphine's pharmacokinetics but is mainly used as a deterrent against diversion and parenteral misuse of buprenorphine. There is very little absorption (≤10%) of SL-administered naloxone. Naloxone is metabolized using similar enzymatic transformation and glucuronidation as buprenorphine, although its elimination half-life is much shorter (1 to 2 hours) when compared to buprenorphine. Naloxone can cause withdrawal effects if the tablet is crushed and injected in persons dependent on opioids. Likewise, as a partial agonist, buprenorphine itself can precipitate withdrawal if given to individuals maintained on other full μ-opioid receptor (MOR) agonists, as buprenorphine has higher affinity to the receptor. This is a rare occurrence, but has been seen, especially when transitioning high-dose methadone-maintained individuals to buprenorphine.

Pharmacodynamics

Buprenorphine is a synthetic derivative of the morphine alkaloid thebaine and has approximately 25 to 40 times the analgesic potency of morphine when administered IV and is 15 times more potent than intramuscular morphine when administered SL. Unlike morphine, buprenorphine displays both typical MOR agonist and antagonist properties, making it an ideal candidate for the treatment of opioid dependence. The agonist effects—miosis (clinically insignificant), respiratory depression, decreased gastrointestinal motility, euphoria, and sedation—occur at lower doses of the drug, while antagonist effects occur only with increasing doses of buprenorphine given to persons maintained on another primary MOR agonist. These properties allow for a "ceiling effect" on respiratory depression, making for a better safety profile than pure MOR agonist.

The onset of buprenorphine's drug effect is slower than morphine, with mean peak effect seen between 40 and 60 minutes (producing a lower peak euphoric rush compared to other opioids), but the duration of action is longer, with a terminal half-life of 32 to 37 hours. Most likely this is a route of administration effect, as IV-administered buprenorphine produces similar drug-liking responses as IV morphine in persons with an opioid abuse history. The long terminal half-life allows for once daily or even less frequent dosing patterns. Buprenorphine's receptor binding properties help explain its partial agonist profile; it binds to MORs with greater affinity and can displace other agonists from these sites. Higher doses of an antagonist (3 and 10 mg/70kg IM naloxone or 3 mg/70 kg PO naltrexone) are required to displace buprenorphine from MORs as compared to methadone. Buprenorphine is also a weak κ-opioid receptor antagonist, δ-opioid receptor antagonist, and opioid receptor-like 1 (ORL-1) partial agonist, but the full understanding of these actions is not yet known. It is currently hypothesized that its ORL-1 effects could be involved in or mediate buprenorphine's bell-shaped dose–response curve.

Efficacy in the Treatment of Opioid Dependence

This section examines the peer-reviewed papers reporting on results regarding the efficacy of buprenorphine and buprenorphine/naloxone in the treatment of opioid dependence (both maintenance and detoxification treatment). While the utility of detoxification as a treatment intervention has been called into question, detoxification followed by significant psychosocial

rehabilitation does have proven benefit. It is with that overall treatment goal that opioid detoxification with buprenorphine is discussed.

Buprenorphine/naloxone and buprenorphine have been shown to provide greater suppression of opioid withdrawal symptoms in both inpatient and outpatient detoxification settings as compared to clonidine, dihydrocodeine, and lofexidine, and show similar results as methadone. Retention rates in these clinical trials have usually been higher in the inpatient as compared to outpatient setting, but one multisite trial conducted by the National Institute on Drug Abuse Clinical Trials Network did not find a significant difference between setting types. Drug abstinence at the end of outpatient detoxification is achieved at relatively low rates (17% to 29%). Higher treatment success following opioid detoxification (as defined by study completion and drug-free urinalysis on the last day of study) is associated with better control of withdrawal symptoms during treatment, fewer comorbid substance use disorders (SUDs) including nicotine dependence, and higher baseline anxiety levels. Long-term abstinence following detoxification, however, is rarely achieved or sustained unless ongoing rehabilitation and treatment are continued.

Consensus treatment guidelines advocate long-term maintenance therapy as a first-line strategy in adult opioid-dependent participants. In one of the first randomized controlled clinical trials of buprenorphine maintenance, daily SL buprenorphine (8 mg) was shown to be as effective as 60 mg methadone in terms of retention and opioid-negative urines, and superior to 20 mg methadone. Further double-blind clinical trials replicated these early results using a clinically relevant flexible dose schedule, although a Swiss multisite trial showed higher dose methadone (60 to 120 mg) had better retention rates than moderate dose buprenorphine (12 to 16 mg). These early trials defined maintenance treatment as lasting between 8 and 16 weeks. Studies of longer duration (6 to 12 months) initially showed results favoring high-dose methadone compared to buprenorphine in terms of retention, opioid-free urine toxicology screens, and withdrawal symptoms. A meta-analysis by the Cochrane Review examined 24 randomized and controlled clinical trials and concluded that buprenorphine is less effective at retaining patients in treatment than methadone delivered at adequate doses. However, results for opioid-free urines showed no inferiority of buprenorphine and the authors concluded that buprenorphine is an effective intervention for the maintenance treatment of opioid dependence. Buprenorphine/naloxone combinations have also shown to be as effective as buprenorphine alone. Longer-term effectiveness trials in primary care clinics have shown buprenorphine to be a safe and successful treatment not only in the United States but also in over a dozen countries on six continents. These studies have shown that there is a large dropout rate in the first 3 months of treatment, but that this can be reduced somewhat by a quick induction phase to eliminate withdrawal symptoms. Given this large dropout rate, more research is needed into optimally choosing candidates for buprenorphine treatment. Patient variables such as gender, age, lifetime opioid use, and the particular opioid abused (heroin, methadone, or other prescription opioids) could be predictors of treatment outcomes as a few studies have shown.

Optimal Use of Buprenorphine

The use of buprenorphine (most commonly buprenorphine/naloxone in the United States) in an outpatient medical practice for opioid dependence consists of three main phases: induction, stabilization/maintenance, and (if necessary) withdrawal. Induction onto buprenorphine, defined here as the first 24 to 72 hours of starting on buprenorphine, requires first a comprehensive medical evaluation to establish a diagnosis of opioid dependence, drug use history and any complicating medical, psychiatric disorders or SUD, concomitant medications, and drug allergies. There are no absolute contraindications to buprenorphine, except for documented

previous allergic reactions to the medication or naloxone. The medication is not approved for children (<16 years of age) or pregnant women.

There are two separate induction strategies for persons previously on short-acting opioids (e.g., heroin) versus long-acting opioids (e.g., methadone). This discussion will first focus on buprenorphine induction for dependence on short-acting opioids. Patients should be told to come to the office in mild opioid withdrawal, usually 4 to 12 hours after their last dose of opioid. A clinician should verify the withdrawal syndrome with a standard rating scale such as the Clinical Opiate Withdrawal Scale (COWS). Depending on the level of prior opioid use, the patient should be given 2/0.5 or 4/1 mg of SL buprenorphine/naloxone and monitored in the office for any side effects, including worsening opioid withdrawal or opioid toxicity. The patient should be instructed to place the tablet(s) or SFs under the tongue and keep them there for a sufficient time to dissolve, without talking or swallowing. If the mouth is dry, the patient should be instructed to drink water first. If side effects occur, they should be treated with the appropriate medications. If withdrawal is not relieved by the initial buprenorphine dose, the patient can be redosed up to a recommended maximum total dose of 8/2 mg buprenorphine/naloxone on the first day. Previous research has shown that rapid induction of buprenorphine and buprenorphine/naloxone is safe and leads to better retention, so a patient should usually reach their maintenance dose (12 to 16 mg) on the second day. If the patient requires >16/4 mg per day, further titration can occur to a maximum dose of 32/8 mg.

There were some initial fears that giving persons already in mild opioid withdrawal SL naloxone in the form of buprenorphine/naloxone would worsen withdrawal, so the U.S. guidelines published in 2004 recommended using buprenorphine (without naloxone) during the initial induction and then switching to buprenorphine/naloxone. However, clinical experience and research has shown that SL naloxone does not induce further withdrawal, and most practitioners start induction with buprenorphine/naloxone without sequelae. Buprenorphine/naloxone should be used for all phases of maintenance unless the subject has a documented allergy to naloxone; buprenorphine alone should be rarely used.

When the patient is dependent on long-acting opioids, the induction phase ideally requires an initial taper of the long-acting opioid. In the case of methadone, a person should be tapered to 30 to 40 mg daily dose if possible before buprenorphine induction. The patient should be instructed to present to the office 24 to 36 hours after the last methadone dose in order to show some mild opioid withdrawal. They should be told there is a small risk for worsening withdrawal symptoms after starting buprenorphine/naloxone. The rest of the induction phase is the same as with short-acting opioids. The patient should take no more methadone after the first dose of buprenorphine/naloxone. In case there are fears that a protracted methadone taper may trigger relapse before starting buprenorphine/naloxone, there is a study that has shown that there can be safe transition to buprenorphine/naloxone in some persons maintained on 100 mg of methadone. Results from that study suggest that small repeated doses of buprenorphine/naloxone (2/0.5 mg) spaced approximately 2 hours apart will decrease the risk of buprenorphine-precipitated withdrawal.

Although opioid dependence is typically required for buprenorphine maintenance, one exception requires more discussion. A physician may decide to prescribe buprenorphine to a person who is not currently opioid dependent but at high risk for relapse or developing opioid dependence, for example, a recently released prisoner with opioid dependence prior to incarceration or a person using opioids after a recent detoxification attempt. This induction should start with a smaller buprenorphine/naloxone dose (2/0.5 mg) and should be titrated up to clinical effect more slowly (e.g., dose increases every 3 to 7 days).

Stabilization is the phase where the patient is maintained on the same dose of buprenorphine/naloxone and is referred to/engaged in concurrent psychosocial counseling/rehabilitation. At this point, the patient may choose to take buprenorphine on alternate days, but this is not the general recommendation and is done rarely in clinical practice. Twice-daily dosing may also be required, especially in patients with comorbid pain.

Withdrawal from buprenorphine can be accomplished rapidly in an inpatient setting (≤3 days) or during a protracted outpatient taper. In the past, 0.3 mg IM buprenorphine was given two to three times daily for a rapid 3-day withdrawal. However, this treatment is no longer recommended and IM buprenorphine is not approved for opioid-dependent treatment. Instead, inpatient settings may use a SL buprenorphine taper. The superiority of moderate or long-term taper of buprenorphine has not yet been fully determined, although most studies show a substantial increase in opioid positive urines after any buprenorphine taper. Whether or not to stop buprenorphine treatment should be decided on a case-by-case basis by the physician and patient, weighing the risks of continued treatment against the risks of relapse following withdrawal.

Legal Issues

Office-based treatment of opioid dependence with buprenorphine did not come easily in the United States. Pharmacologic treatment of opioid dependence had been hindered by the Harrison Narcotic Act of 1914, which was interpreted by courts after 1917 to forbid physicians from prescribing opioids specifically for the treatment of opioid dependence. Prosecution of physicians violating this act and subsequent legislation continued until the American Medical Association and American Bar Association issued a joint report questioning these policies in 1958. Methadone subsequently became available for the treatment of opioid dependence and has proven to be a reliable and beneficial treatment. However, administrative fears of diversion, overdose, and physician prescribing practices led to very stringent and convoluted policies that governed its use, including an ability to dispense methadone only at approved clinics and hospital pharmacies. These policies, codified in the Narcotic Addict Treatment Act (NATA) of 1974, as well as a cadre of various state and local regulations, governed the medical treatment of opioid dependence up until 2001.

As stated earlier, buprenorphine showed early promise as a treatment for opioid dependence. However, it required an act of Congress in the United States to approve its use by individual physicians in an office-based setting. That bill was the 2000 Drug Addiction Treatment Act (DATA), which had taken 5 years of political maneuvering to become law. DATA allowed physicians to prescribe narcotics in an office-based setting and pharmacists to dispense certain narcotics (currently only buprenorphine) for the treatment of opioid dependence. The wording leaves open the possibility of "any approved narcotic drugs in schedule III, IV, or V . . . for maintenance or detoxification treatment," so other medications may also be used in the future in office-based settings under DATA. DATA did specify requirements before physicians could legally prescribe buprenorphine for opioid dependence. If a physician meets those requirements, he or she must apply for and receive a Department of Health and Human Services (DHHS) waiver (http://www.buprenorphine.samhsa.gov) and be given a specific Drug Enforcement Agency (DEA) number before writing the first prescription.

Given concerns over diversion, DATA limited the number of buprenorphine-approved patients (initially 30 per physician group/institution) and prescribed a 3-year monitoring phase after buprenorphine was approved by the FDA for treatment of opioid dependence. In 2005, the effects of DATA on opioid dependence received a good review; thus, DHHS expanded the number of potential buprenorphine patients per individual prescriber to the current levels (100 per year after the first year of approval) and removed the group practice restriction. Nevertheless, DHHS and DEA still have the authority to repeal the law without Congressional approval if those organizations are concerned about buprenorphine's effects on public health, making it easy to end office-based treatment of opioid dependence in the future.

In the United States, the rate of physicians applying for and receiving a DHHS waiver to prescribe buprenorphine has not been as quick as first predicted. As well, about half of all

the physicians qualified to prescribe buprenorphine are addiction specialists. This indicates that primary care doctors are not expanding access to buprenorphine by becoming prescribers in the numbers that were originally projected. Reasons for this hesitation include lack of qualified counseling services, staff training, visit time required for induction phase, lack of buprenorphine availability in local pharmacies, and pain medicine concerns. Future campaigns should address these needs in order to increase access to buprenorphine maintenance treatment.

Outside of the United States, countries have various legal restrictions on the prescribing and dispensing of buprenorphine and buprenorphine/naloxone. The following is not meant to be an exhaustive description of policies regulating buprenorphine in every country, but does illustrate the parameters of buprenorphine's use in non-U.S. countries. In France, the initial country to approve the use of buprenorphine for the treatment of opioid dependence, a national policy places physicians in primary care or specialized drug treatment facilities as the "gatekeepers" of patients' access to buprenorphine and allows community pharmacies to dispense it. Physicians can prescribe buprenorphine with up to a 28-day supply, but patients can only get up to 7 days of medication from the pharmacy unless the physician allows for longer periods. This system has led to buprenorphine being the primary medication used in opioid replacement therapy (ORT) throughout the country. Unlike France, Australia has both national and state laws that govern the use of buprenorphine for ORT. In this country, community pharmacists are the "gatekeepers" of patients' access to buprenorphine. Both physicians who prescribe buprenorphine and at least one pharmacist in the pharmacy that dispenses it must receive specialized buprenorphine training. States set up differing laws regarding take-home availability, but in general, all buprenorphine must be taken by the patient and witnessed by a staff member in a community pharmacy. National law does offer every other day or thrice-weekly dosing to stable patients who do not want to come daily for treatment. Finally, the "gatekeepers" in Italy (physicians) can only be found in specialized ORT facilities, and these prescribers must have received specialized training for buprenorphine. The medication is then dispensed daily in these facilities and must be witnessed, similar to methadone. In conclusion, eligibility criteria for buprenorphine, its prescribing and dispensing authority, or even the ability to offer ORT are governed by statutes that are essentially unique to each country where this medication is available.

Safety Concerns

The most common side effects from buprenorphine result from its opioid agonist properties and are seen when given to a nondependent person. These can include nausea, vomiting, sedation, and dizziness. Respiratory depression from buprenorphine, a serious and often fatal complication of other opioids, has been examined extensively in humans and animals. Studies concluded that there was a ceiling effect for respiratory depression unlike pure MOR agonist, and that this depression was not clinically significant. If severe respiratory depression does occur in the community, it is usually due to concurrent use of benzodiazepines and/or alcohol. This rare respiratory depression is difficult to treat with standard opioid antagonists; the best recommendation is to provide a continuous naloxone infusion until the buprenorphine has been cleared from the patient. However, case reports have also shown benefit from high-dose single injection of naloxone (4 to 6 mg IV bolus given within a correct dose window) and doxapram, which stimulates respiratory drive via peripheral and central means.

There has also been particular interest on the cognitive and psychomotor effects of buprenorphine, especially as ORT is meant to help facilitate a person's return to employment, family involvement, and other important societal functions. However, many of the published

studies examining acute and chronic dosing effects on cognition have methodologic problems that make conclusions difficult, for example, not matching groups on characteristics known to influence cognitive performance like premorbid IQ and allowing persons with active substance use to participate in studies. Nevertheless, some conclusions may be drawn that appear consistently throughout the literature. First, with a decrease in use of heroin or other illicit opioids while on buprenorphine maintenance, a person's executive function, selective attention, and concentration usually improve. Second, there appears to be relatively slower acute reaction time when comparing persons maintained on methadone to persons on buprenorphine. Third, buprenorphine seems to have less of an effect on decision-making skills than methadone. Finally, researchers have demonstrated that driving is not significantly impaired during buprenorphine maintenance, and the addition of small amounts of alcohol (0.05% blood alcohol concentration) to chronic buprenorphine dosing does not show any worse performance than in non–drug abusing controls. Thus, the majority of the peer-reviewed studies indicate that buprenorphine may have less cognitive side effects than methadone, but like methadone, buprenorphine may help increase functioning to baseline by decreasing illicit substance use. However, better designed, prospective research is needed in this area to validate these conclusions.

In light of the growing concern over cardiac arrhythmias from QTc prolongation in methadone maintenance, studies have examined the risk for electrocardiogram abnormalities with buprenorphine and buprenorphine/naloxone. Researchers have concluded that buprenorphine does not significantly prolong the QTc at clinically indicated dosing ranges and may be safer than methadone in this respect. However, if patients are taking known inhibitors of cytochrome P450 3A4, such as certain medications to treat HIV, there is a slightly increased but not clinically significant risk of QTc prolongation.

Deaths associated with buprenorphine have received public scrutiny, especially as methadone-related overdoses have increased. The number of calls to U.S. Poison Control Centers after buprenorphine exposure has gone from 13 in 2000 to almost 6,200 in 2008, and a similar increase has been reported in France. In some countries, the number of reported deaths related to buprenorphine increased after its introduction, especially if combined with benzodiazepines. Whether this trend improves as physicians and patients become more knowledgeable about the medication remains to be seen. The experience in France, which approved buprenorphine in 1996, has shown that the death rate related to buprenorphine is lower than methadone, and there is evidence for this same finding in Australia.

Diversion of buprenorphine was one of the original feared effects of office-based treatment. As the use of buprenorphine for opioid dependence has risen, diversion of supplies onto the black market has increased. In some locations outside of the United States where the heroin supply has been curtailed, this diversion is more frequent per capita than methadone. In the United States, a survey of 1,000 patients seeking drug-abuse treatment at standard drug-abuse clinics showed that 35% of individuals self-reported misuse of buprenorphine to get high during the initial 2 years of treatment, and this number fell to below 20% by the end of the survey period. In that same study, less than 3% of all persons presenting for ORT in 2007 gave buprenorphine as their drug of choice to get high. Vigilance should be maintained in the United States to prevent more diversion while not restricting this valuable pharmacotherapy from reaching patients in need.

Following diversion, illicit injection of buprenorphine (8 to 16 mg daily) has been associated with several cases of hepatitis, all in persons with underlying liver disease (i.e., hepatitis C and alcoholic hepatitis). There is also evidence that hepatitis can occur in persons taking SL buprenorphine as prescribed, but these individuals also had underlying risk factors. Physicians should check liver function tests before induction and after maintenance has been achieved in those persons with known or at risk for liver dysfunction. Other side effects associated with the injection of SL buprenorphine are similar to most other illicit IV drugs, and include infectious

endocarditis, myositis, acute limb ischemia sometimes requiring amputation, and embolic stroke. Even with these risks of buprenorphine, studies have shown an overall decreased mortality in persons exposed to and compliant with ORT—including buprenorphine.

Special Populations

Although the FDA and most international governments have approved buprenorphine only for adults, research has shown promising results for buprenorphine's use in adolescents, pregnant women, and incarcerated populations. First, there is no FDA-approved treatment for opioid dependence in adolescents (<16 years old). However, a clinical trial showed promise for this medication's longer-term use in this population. Researchers randomized 152 persons aged 14 to 21 years with DSM-IV opioid dependence to either a 14-day buprenorphine detoxification and subsequent counseling or 12 weeks of buprenorphine maintenance along with counseling. Primary outcomes examined were opioid positive urine toxicology and treatment retention. At week 12, only 20.5% of adolescents randomized to detoxification remained in the study versus 70% in buprenorphine maintenance. There was no statistical difference in opioid positive urines between the groups at week 12, but there were significantly lower positive urines in the maintenance group at weeks 4 and 8. Maintenance participants had lower self-reported cocaine, marijuana, and injection drug use, and attended more counseling sessions than the detoxification group. During 12-month follow-up, the detoxification group was over twice as likely to have an opioid positive urine as the maintenance group. Overall, this trial pointed to the potential value of longer-term buprenorphine treatment for adolescents with opioid dependence. More research is needed on buprenorphine for this population, but it is likely that there is value in including opioid agonist treatment for adolescents.

Buprenorphine (and buprenorphine/naloxone) is an FDA pregnancy category C medication, indicating not enough studies have been done to advise the use of this medication during pregnancy. The standard of care for opioid-dependent pregnant women has been methadone in a specialized treatment facility. There have been multiple peer-reviewed articles published on buprenorphine treatment of opioid dependence in pregnancy. In reviewing outcomes of these studies, authors examined birth weight, prematurity, neonatal abstinence syndrome (NAS), perinatal complications, and some long-term follow-up data on women and their offspring. In two studies comparing women without substitution therapy to buprenorphine and methadone, buprenorphine had less incidence of NAS compared to methadone, although not all studies have found this outcome. When NAS was present, it had a later onset than methadone but seemed to be shorter in length. Studies have shown no difference in neonatal weight, length of hospitalization, or frequency of birth defects/neonatal demise in buprenorphine as compared to methadone-treated women. If women are to be prescribed buprenorphine during pregnancy, they should be informed that research is still ongoing into the neonatal and maternal outcomes. As well, induction onto buprenorphine may be complicated by precipitated withdrawal if the woman has been using long-acting opioids, but the maintenance phase with buprenorphine typically requires few dose adjustments. Finally, breast-feeding can usually continue if the mother remains on buprenorphine as there is low oral bioavailability of the medication. However, this recommendation is not yet backed by definitive studies.

The use of opioid agonist treatment in the prison system has been advocated by the Centers for Disease Control and Prevention (CDC) and the WHO due to the high incidence of substance use in the year prior to incarceration, and the benefits to individual and public health. However, many facilities in the United States offer no agonist treatment, some offer only methadone, and methadone is usually only for chronic pain and in pregnant women with opioid dependence. A low percentage of facilities offer buprenorphine treatment. Internationally, 29 countries or

territories offered ORT to prisoners in 2008, which was an increase over previous years. Most facilities prefer a drug-free detoxification environment to opioid agonist treatment. These facilities also do not always refer inmates to postrelease methadone or buprenorphine providers, doing so in less than half of all cases. Research is ongoing into the cost savings, decreased recidivism, decreased HIV transmission, and effects on substance relapse postrelease associated with buprenorphine (and methadone) treatment for this population. This research is needed to help sway prisons and jails to treat opioid dependence like other medical illnesses during incarceration.

Conclusion

Buprenorphine provides patients and health-care providers an alternative to methadone for the treatment of opioid dependence. It is often preferred over methadone by patients for its ease of use, availability, and safety/side effect profile. This chapter has shown the intense work done by researchers, lawmakers, physicians, advocates, and patients themselves to bring this treatment to the market. Buprenorphine has unique risks and benefits, which should be weighed for every potential patient; it also appears to be roughly equivalent in many outcomes compared to methadone. Long-term data are still being collected, but the French experience shows that benefits can occur with buprenorphine's ready availability. Hopefully, these results will be reproduced in other parts of the world, for the benefit of persons who suffer from opioid dependence.

Suggested Readings

Bell JR, Butler B, Lawrance A, et al. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug Alcohol Depend*. 2009;104:73–77.

Cicero TJ, Surratt HL, Inciardi J. Use and misuse of buprenorphine in the management of opioid addiction. *J Opioid Manag*. 2007;3:302–308.

Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003;349:949–958.

Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2009;(3):CD002025.

Johnson RE, Chutuape MA, Strain EC, et al. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med*. 2000;343:1290–1297.

Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med.* 2010;363:2320–2331.

Mattick RP, Kimber J, Breen C, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008;(2):CD002207.

Soyka M, Hock B, Kagerer S, et al. Less impairment on one portion of a driving-relevant psychomotor battery in buprenorphine-maintained than in methadone-maintained patients: results of a randomized clinical trial. *J Clin Psychopharmacol*. 2005;25:490–493.

Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine–naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA*. 2008;300:2003–2011.

Ziedonis DM, Amass L, Steinberg M, et al. Predictors of outcome for short-term medically supervised opioid withdrawal during a randomized, multicenter trial of buprenorphine–naloxone and clonidine in the NIDA clinical trials network. *Drug Alcohol Depend*. 2009;99:28–36.

22 Naltrexone and Other Pharmacotherapies for Opioid Dependence

Naltrexone

Pharmacology

Naltrexone hydrochloride was first synthesized in the 1960s for use in the treatment of heroin dependence. Naltrexone has several routes of administration, including oral administration, implants, and suspended release injection. It is marketed under the trade names Revia and Depade; and the extended release under the trade name Vivitrol. Naltrexone has a half-life of about 4 hours, and the active metabolite 6-β-naltrexol has a half-life of about 12 hours. Two related drugs include naloxone and methylnaltrexone bromide. Naloxone is shorter acting than naltrexone and not absorbed orally; it is the treatment of choice for opioid overdose and is part of the combination treatment of buprenorphine and naloxone for opioid maintenance therapy. Methylnaltrexone bromide (Relistor) is marketed as a treatment for opioid-induced constipation.

Naltrexone and its active metabolite, 6-β-naltrexol, are competitive antagonists at μ, κ, and δ receptors. This competitive antagonism means naltrexone binds to the opioid receptor, competing with opioid drugs (e.g., heroin and morphine). Naltrexone acts by reversibly blocking the physiological and subjective effects of opioids, thereby attenuating the euphoric effect of opioid drugs, rendering them less rewarding and less reinforcing. Naltrexone can also be used in opioid detoxification; however, it can precipitate opioid withdrawal and should be used with care in opioid-dependent populations. Although its mechanism of action suggests it would be an ideal medication for opioid dependence, its clinical utility is not supported by clinical studies.

Naltrexone is also used in the treatment of alcohol dependence. Alcohol produces a wide variety of pharmacological effects on a number of different neurotransmitter systems, including the dopamine (DA), opioid, glutamate, serotonin, and GABA (γ-aminobutyric acid) systems. Like all drugs of abuse, alcohol stimulates DA release in the mesolimbic pathway and dopaminergic release contributes to its reinforcing effects. However, DA release is not critical in promoting continued alcohol consumption. The rewarding effect of alcohol is also related to its ability to stimulate the opioid system. After preclinical evidence showed that naltrexone reduces alcohol euphoria and consumption in laboratory animals, naltrexone was examined as

a possible treatment for alcohol use disorders in humans. Given the complexity of the reward circuitry and of alcohol's complex effects on multiple neurotransmitter systems, questions remain about the exact mechanism of action of naltrexone's effect on alcohol reward.

Efficacy of Naltrexone

Naltrexone for Maintenance Therapy

After abstinence is achieved, naltrexone can be used for maintenance therapy in order to prevent relapse. Due to the risk of precipitating withdrawal, abstinence from opioids is a prerequisite for the use of naltrexone as a maintenance pharmacotherapy. For patients who have not undergone documented detoxification, it is recommended that patients successfully complete a naloxone or naltrexone challenge to confirm abstinence prior to dosing. Naltrexone prevents relapse by blocking the effects of opioids, serving as a deterrent to further use.

Oral naltrexone was approved for use in opioid dependence in the United States by the FDA in 1984. Although in theory naltrexone should be an ideal candidate for the treatment of opioid dependence, clinical data supporting naltrexone's efficacy in opioid dependence are not robust. Some reviews have suggested that naltrexone is not superior to placebo for retention or relapse rates. However, the studies are plagued by poor retention rates, which have been as low as 4%. Nevertheless, some evidence does suggest that naltrexone use is associated with lower heroin use and decreased criminal activity. When examining treatment studies with high retention rates, naltrexone decreased opioid use, craving, and even psychiatric symptoms compared to controls. Naltrexone seems to be particularly beneficial for patient populations who are highly motivated to remain opioid-free, such as health-care professionals and legally mandated opioid-dependent individuals.

Doses and Routes of Administration

The standard prescribing dose of oral naltrexone is 50 mg/day, which is a dose that is sufficient to block the pharmacological effects of 25 mg of intravenous (IV) heroin for 24 hours. The frequency of naltrexone oral administration can vary from 50 mg/day to 100 mg/every other day to 150 mg/every third day: for every 50 mg dose, the duration of action extends by 24 hours. Since higher doses can be taken less frequently, medication may be administered by others, and this has the potential to improve compliance. Compliance is a major issue, as patients who want to resume opioid use can skip doses to resume drug use. Naltrexone use is not associated with tolerance or withdrawal.

Naltrexone is also available in a 4-week extended-release injection that is marketed in the United States as Vivitrol. (There is not a generic form for this formulation.) Patients receive an intramuscular gluteal injection that contains microspheres of encapsulated naltrexone (380 mg/injection). The microspheres degrade over time and naltrexone is continuously released. An advantage of this route of administration is that some side effects that some patients report with the rapid uptake of naltrexone when administered orally are minimized.

Opioid-Dependent Patients for Whom Naltrexone Is Optimal

As mentioned above, naltrexone is best for highly motivated patients who are interested in opioid abstinence. The addition of effective psychosocial treatments which address compliance can increase the effectiveness of naltrexone pharmacotherapy. For example, the inclusion of psychosocial treatments targeting compliance, involvement of the family, and family therapy all increase compliance. External motivation, such as risk of loss of license for health-care professionals or those who are under legal mandate to remain abstinent, also increases compliance and therefore effectiveness of naltrexone.

Naltrexone in Combination with Other Medications/Therapies

In most randomized clinical trials, naltrexone has been combined with some form of psychotherapy. Naltrexone has been evaluated with cognitive behavioral therapy, 12-step facilitation, supportive therapy, and medical management. It is recommended by the FDA that naltrexone be prescribed in conjunction with an adequate psychosocial intervention.

Safety of Naltrexone

Side-Effect Profile

Naltrexone is generally well tolerated. The most common side effects with 50 mg/day oral administration are nausea, headache, dizziness, fatigue, vomiting, anxiety, and sleeplessness; less common side effects include anxiety and sleepiness. Use of extended-release injections can reduce symptoms, such as nausea, that are associated with oral dosing. Some side effects specific to injections include pain, tenderness, induration, swelling, erythema, bruising, and pruritus at the injection site.

Naltrexone is metabolized by the liver and can be associated with hepatotoxicity, although usually if given in much higher doses than the 50 mg currently recommended. Nevertheless, liver function tests should be evaluated before the use of naltrexone and periodically during treatment, and it is generally recommended that individuals whose liver function tests are three to five times normal should not be prescribed naltrexone.

Questions have been raised about whether long-term therapy with naltrexone may be associated with dysphoria. Theoretically, dysphoria could occur because naltrexone, as an opioid receptor antagonist, competes with endogenous opioid peptides. A review, however, indicated that most studies have not found evidence of dysphoria with long-term naltrexone therapy.

Contraindications

It should be remembered that naltrexone is an opiate antagonist and as such is contraindicated in those patients with chronic pain who are being treated with opiates as it will precipitate withdrawal. In addition, worsening of pain has been reported with naltrexone. Before starting naltrexone, patients should discontinue opioids for a minimum of 7 to 10 days. Patients taking naltrexone should be provided with a wallet card explaining that they are currently prescribed naltrexone. This safety measure will reduce complications for treatment in cases of emergency when opioid administration could be advisable. Naltrexone is contraindicated in pregnant and lactating women. As mentioned above, naltrexone should not be used in individuals who have seriously compromised liver function.

Use of Naltrexone in Other Populations

Naltrexone has been evaluated for a number of other addictive and impulsive spectrum disorders, including cocaine dependence, tobacco dependence, problem gambling, kleptomania, and eating disorders. It has also been evaluated as an adjunctive medication in other psychiatric disorders and to treat opiate-induced adverse events.

Naltrexone has been evaluated for cocaine dependence, and given the high comorbidity with alcohol dependence, particular emphasis has been on treating those with both alcohol and cocaine dependence (given naltrexone's efficacy for alcohol dependence as well—see the chapter on alcohol treatments for further information in this regard). In an early study, naltrexone was found to be less effective than disulfiram for cocaine- and alcohol-dependent individuals. For individuals with alcohol dependence who also use cocaine, doses higher than the standard 50 mg/day could be more effective.

Some randomized clinical trials have examined the effect of naltrexone on smoking cessation rates. In addition to examining naltrexone alone, the drug has also been used as an adjunct pharmacotherapy to other established treatments, such as nicotine replacement therapy. In general, findings have been inconsistent. The primary benefits of naltrexone for smoking cessation include that it might limit weight gain and that it is useful in treating polydrug abuse.

Impulse Control Disorders: Problem Gambling and Kleptomania

There is evidence that suggests that naltrexone administration may reduce gambling urges and behaviors. A family history of alcoholism has been identified as a clinical predictor of naltrexone response for problem gambling. However, naltrexone in the concurrent treatment of problem gambling and alcohol use disorder is not supported. Naltrexone has also been used in the treatment of kleptomania. Doses have typically been higher than those used in the treatment of substance use disorders (SUDs) (e.g., mean dose of 116 mg/day in one study and 135 mg/day in another study).

Eating Disorders: Bulimia, Anorexia Nervosa, Binge Eating Disorder

Studies examining the efficacy of naltrexone in treating eating disorders have had mixed results. These studies used chronic naltrexone administration. While there have been some indications that naltrexone improves clinical outcomes in the treatment of bulimia, other studies have had negative results. Limited evidence also suggests that naltrexone might be beneficial in the treatment of binge eating disorder, and there is some evidence that naltrexone can improve clinical outcome for anorexia nervosa in some patients.

Other Pharmacotherapies for Opioid Dependence

Nonopioid Treatment Alternatives: Clonidine and Lofexidine

The acute opioid-withdrawal syndrome is a time-limited phenomenon, generally of brief duration. Following the abrupt termination of short-acting opioids such as heroin, morphine, or hydromorphone, withdrawal signs and symptoms usually subside by the second or third opioid-free day. Although the opioid-withdrawal syndrome can be extremely uncomfortable for the opioid-dependent individual, in contrast to the syndrome associated with the withdrawal of certain other drugs such as benzodiazepines and alcohol, it does not ordinarily pose a medical risk to the individual. The exception may be, however, in patients already severely compromised where dehydration secondary to vomiting, diarrhea, and sweating could be a significant factor in precipitating a medical crisis. Thus, there is a particular appeal for treating this syndrome symptomatically, especially with medications that do not themselves produce physical dependence. It must be recognized, however, that medically supervised withdrawal from opioids is only one of the initial steps in the treatment process of rehabilitating opioid-dependent individuals if complete and permanent abstinence is the treatment goal.

Clonidine is an α_2-adrenergic agonist that has been used for the treatment of various disorders including hypertension, autism, attention-deficit hyperactivity disorder, and various types of pain. Clonidine has been shown to be useful in the medically supervised withdrawal of patients from methadone, heroin, and other opioids, as well as preparing individuals for stabilization onto the opioid antagonist naltrexone.

The capacity of clonidine to ameliorate withdrawal-associated effects (e.g., lacrimation and rhinorrhea) is linked to its modulation of noradrenergic hyperactivity in the locus ceruleus. Additionally, clonidine may affect central serotonergic, cholinergic, and purinergic systems. It

seems to be most effective in suppressing certain opioid-withdrawal signs and symptoms, such as restlessness and diaphoresis. However, clonidine is not well accepted by the addicted patient because it does not produce morphine-like subjective effects or relieve certain types of withdrawal distress, such as anxiety. Sedation and hypotension also limit its utility. No fixed-dosing guidelines are currently available, and dosages are generally individualized to each patient based on therapeutic response and side-effect limitations.

Interestingly, clonidine abuse by users of illicit opioids and other drugs has been reported since the early 1980s. This abuse may be secondary to a desire to obtain various drug-related effects, such as sedation, euphoria, or hallucinations. Clonidine may also be used to prolong and enhance the effects of heroin or other opioids. One report described the intentional ingestion of clonidine patches by individuals on a chemical dependency unit who may have done so to obtain psychoactive effects or to alleviate opioid-withdrawal symptoms.

Secondary to an effort to identify an agent with less sedating and hypotensive effects than clonidine, a number of other α_2-adrenergic agonists (lofexidine, guanabenz, guanfacine) have been evaluated for their ability to moderate the opioid-withdrawal syndrome. Of these, lofexidine, a clonidine analogue licensed in the United Kingdom for opioid medical withdrawal treatment, has been the subject of much clinical evaluation. Lofexidine enjoys widespread usage in the United Kingdom as the only α_2-adrenergic agonist approved there to relieve symptoms in patients undergoing withdrawal from opioids. Lofexidine is suggested to be used typically for a period of 7 to 10 days at maximal single doses of 0.8 mg, usually taken three times per day, in dosages ranging up to 2.4 mg/day.

Studies conducted in the early 1980s provided initial data indicating that lofexidine could be effective in suppressing some of the signs and symptoms of opioid withdrawal. More recent trials have provided further evidence for the efficacy of lofexidine. These trials included both open-label and double-blind evaluations, using both inpatient and outpatient populations.

When lofexidine was compared to clonidine, both treatments were generally found to produce similar therapeutic effects, but lofexidine typically was better tolerated. When lofexidine was compared to clonidine in an outpatient, double-blind trial, both medications produced positive treatment outcomes, but clonidine was associated with more hypotensive effects and required more home visits by medical staff. In a double-blind, inpatient study, lofexidine and clonidine were reported to be equally effective in treating the withdrawal syndrome. Clonidine, however, was associated with more hypotension and better treatment retention than was noted for lofexidine. In another double-blind, inpatient study using methadone-stabilized opioid-dependent individuals, both lofexidine and clonidine produced a similar suppression of withdrawal symptoms, but lofexidine was associated with less hypotension and fewer adverse events.

In an inpatient human laboratory study, oral pretreatment with placebo, lofexidine (0.4, 0.8, and 1.6 mg), and clonidine (0.1 and 0.2 mg) were compared in individuals maintained on 30 mg of methadone who received intramuscular naloxone doses of 0, 0.1, or 0.3 mg (a total of 18 separate experimental sessions). Both lofexidine and clonidine produced dose-related decreases in blood pressure and heart rate, but neither medication mitigated the subject-reported discomfort of precipitated opioid-withdrawal or autonomic signs of withdrawal.

Additional studies using diverse paradigms have also supported the therapeutic effectiveness of lofexidine. For example, a naltrexone–lofexidine combination was associated with a more rapid resolution of the opioid-withdrawal syndrome than was a 7-day lofexidine-only treatment schedule, without substantial increases in withdrawal symptoms or hypotensive side effects. When used in a 3-day opioid medical withdrawal procedure with adjunct medications (oxazepam, baclofen, ketoprofen, naloxone, and naltrexone), lofexidine-treated individuals showed significantly lower levels of withdrawal symptoms and fewer mood problems, as well as less sedation and hypotension.

When lofexidine was compared to buprenorphine in an open-label study, patients receiving buprenorphine reportedly had less-severe withdrawal symptoms and were more likely to

complete medical withdrawal treatment. In another open-label evaluation, a noninferiority approach was utilized to compare buprenorphine to lofexidine in 210 randomized individuals undergoing medically supervised withdrawal from heroin. Sixty-five percent of those on buprenorphine and 46% of those on lofexidine completed medical withdrawal, with 46% in the buprenorphine and 36% in the lofexidine group reporting abstinence at 1 month. Interestingly, results from 271 individuals who declined randomization and chose their treatment instead were similar to those obtained from the randomized groups of individuals.

Twelve randomized controlled trials comparing buprenorphine to clonidine or lofexidine for modifying the signs and symptoms of opioid dependence in individuals who were primarily opioid dependent were reviewed. Findings indicated that buprenorphine was more effective than either clonidine or lofexidine in treating opioid withdrawal as evidenced by reduction in symptoms of opioid withdrawal, and by patients remaining in and completing medical withdrawal treatment.

LAAM: An Opioid Agonist Alternative to Methadone

Levomethadyl acetate (LAAM) is a derivative of methadone and, similar to methadone, is a synthetic μ-opioid agonist. LAAM was initially developed in the late 1940s by chemists in Germany seeking an analgesic substitute for morphine. The opioid effects produced by LAAM and its active metabolites, along with the potential for administering the parent drug on alternate days or on a three-times-weekly schedule (thus eliminating the need for "take-home" doses), fostered interest in its potential use as an alternative to methadone. For example, a single take-home dose of methadone can eliminate only one clinic visit per week, as methadone must be administered daily. However, a single take-home dose of LAAM could obviate the need for five clinic visits per week, as patients could receive in-clinic doses on Mondays and Wednesdays and a single take-home dose on Fridays.

While it was noted early in the development of LAAM that it could alleviate the signs and symptoms of opioid withdrawal following the termination of morphine administration, it was also observed that giving LAAM on a daily basis could lead to signs indicative of opioid toxicity, such as severe nausea and vomiting and respiratory depression. LAAM had also been shown to produce effects that were qualitatively similar to morphine and methadone. LAAM is converted to two pharmacologically active compounds by *N*-demethylation (*nor*-LAAM and *dinor*-LAAM) in addition to inactive compounds. The long half-lives of the *nor*-LAAM and *dinor*-LAAM metabolites, 48 and 96 hours, respectively, contribute to the extended duration of activity of LAAM.

Numerous studies provided evidence for the effectiveness of LAAM as an opioid-dependence treatment agent, and LAAM was approved in the United States in 1993 for the management of opioid dependence. A number of factors limited the widespread use of LAAM, including regulatory issues, clinic-staff resistance, and the reluctance by practitioners to consider LAAM as a viable alternative to methadone. Most importantly, however, LAAM has been associated with serious cardiac adverse events, including *torsade de pointes*. Roxane Laboratories, which marketed LAAM, indicated in 2003 that it would no longer make LAAM available for clinical use. Although LAAM is still approved for use by the FDA, it is no longer approved for use in Europe.

Other Opioid Agonists: Morphine, Codeine, and Dihydrocodeine

In addition to LAAM discussed above, other opioid agonists including codeine, dihydrocodeine, and morphine have been evaluated for the maintenance treatment of opioid dependence and medically supervised opioid withdrawal. Compared to methadone and buprenorphine, these medications have shorter durations of actions (although sustained-release formulations have been assessed and are used clinically), and may thus be less suitable as maintenance medications. Factors that need to be considered when assessing the viability of these potential treatment agents are cost; medical safety; abusability, abuse liability, and potential for diversion; ease

of use; and patient acceptability, among others. None of these medications are approved for the treatment of opioid dependence in the United States. However, it has been reported that dihydrocodeine is the second most commonly prescribed opioid-dependence treatment medication (following methadone) by general practitioners in the United Kingdom.

In a retrospective investigation from Germany, medical withdrawal treatment outcome differences were assessed in codeine-substituted patients, methadone-substituted patients, and patients injecting heroin illicitly. The treatment regimen utilized methadone in a tapering dosage, and was independent of the opioid substance that patients were using. Methadone-substituted (50.4%) and codeine-substituted (45.5%) patients finished medical withdrawal treatment significantly more often than heroin-dependent patients (35.9%).

An open-label study of dihydrocodeine conducted in the United Kingdom assessed dihydrocodeine for the medical withdrawal of methadone-maintained patients. All patients initially had their methadone dosages reduced to 10 to 30 mg/day. Dihydrocodeine was then substituted for methadone, initially from 240 mg/day in four divided doses upwards to 600 mg/day over 7 days and then down to 60 mg/day over the next 7 days. Thirteen individuals successfully completed the program, with three of those beginning treatment with naltrexone. One individual relapsed to heroin use, and six dropped out of the program between days 3 and 11 during the dihydrocodeine treatment phase.

In a 3-year follow-up study in Germany, 199 individuals from a random sample of 297 individuals receiving codeine or dihydrocodeine maintenance treatment for opioid dependence were followed up with regard to measures such as health, employment, criminal activity, and other outcome assessments. Out of the original sample of 297, 65% were still in treatment after 3 years. Over the 3-year period, 4% of the sample (12 patients) had died; 5 of the 12 were drug-related and 5 were AIDS-related. Generally, it was observed that there was improvement in their general physical condition, as well as medical and mental health. There was also a decreasing trend in criminal activity based on measures of conflicts with police, convictions, and imprisonment.

Dihydrocodeine has been compared to buprenorphine and methadone with regards to addiction treatment efficacy. In a randomized controlled trial, 235 patients were recruited for study participation, with 218 ultimately attending the initial treatment. In this open-label design, 110 patients were randomized to receive methadone and 108 to receive dihydrocodeine. There was no statistically significant difference between the groups for retention in treatment at follow-up, the primary outcome measure, when assessed at 6, 12, or 18 months. At 18 months, 88% of the dihydrocodeine patients remained in treatment compared to 77% on methadone. It was recommended, although not required, that patients remain with their assigned treatment for the duration of the study, or for as long as methadone or dihydrocodeine prescribing continued. Eighteen of the patients who had been randomized to receive dihydrocodeine changed to methadone; three changed from methadone to dihydrocodeine. There was improvement over time compared to baseline on the various secondary outcome measures (including illicit opioid use, reported crime, and physical health), with no significant differences in these outcomes between groups.

A randomized controlled trial compared buprenorphine and dihydrocodeine for opioid medical withdrawal, using an open-label design. The study recruited 60 individuals who were using illicit opioids. Dose-reduction schedules for sublingual buprenorphine and oral dihydrocodeine were at the discretion of the treating physician but could not exceed 15 days. The primary outcome measure was abstinence from illicit opioids (as assessed by a urine sample) at the final study medication prescription. While a significantly higher proportion of individuals randomized to buprenorphine (21%) compared to dihydrocodeine (3%) provided an opioid-negative urine sample, only 23% of individuals overall completed the course of withdrawal medication and provided the required final urine sample.

Various studies have shown positive and encouraging results with regard to the use of slow-release oral morphine for the treatment of opioid dependence, and this medication has been used as an addiction pharmacotherapy in various countries. Formulations for once-daily administration have been developed, which could make the medication suitable for maintenance

or medical withdrawal treatment. This formulation has been evaluated in both comparative and noncomparative studies. In one of the former, 103 of 110 patients completed a 3-week study in Austria designed to assess treatment satisfaction. Patients reported significant reductions in somatic complaints, cravings for heroin and cocaine, and withdrawal symptoms compared to baseline. Cocaine consumption as assessed from urine drug screens was also significantly reduced; benzodiazepine consumption remained almost unchanged over the study period.

Slow-release oral morphine has also been compared to methadone. In an open-label crossover study, 18 methadone-maintenance patients were recruited to receive slow-release oral morphine once daily for approximately 6 weeks; methadone maintenance was resumed following this evaluation period. Patient outcomes were assessed during the transition between medications and also after at least 4 weeks on a stable dose of each medication. Three individuals dropped out of the study, two choosing to return to methadone maintenance. The mean initial methadone maintenance dosage was 78 mg (range 25 to 120 mg), while the mean final slow-release oral morphine dosage was 347 mg (range 120 to 570 mg). The transfer from methadone to slow-release oral morphine was not found to be associated with significant changes in the severity of opioid withdrawal across the first 5 days of treatment. The majority of the study patients preferred slow-release oral morphine to methadone.

The opioid agonist medications discussed above have the potential for being useful pharmacotherapies for addiction. However, the medication development pathway would depend on a number of steps. These would include securing regulatory approval, getting the medication onto hospital and third-party payer formularies, developing reimbursement policies, and having clinicians use the medication.

Heroin

Following the first studies of heroin maintenance that were conducted in the United Kingdom in the 1970s and the first trial of heroin-assisted treatment in Switzerland in 1994, a number of studies conducted in North America and Europe have assessed the utility of using heroin to treat opioid-dependent individuals who typically were refractory to standard treatment such as methadone.

Most studies have involved the use of injected heroin, although utility of oral heroin (both immediate- and sustained-release) and inhaled heroin was also sometimes evaluated. Participants in the studies were typically individuals who did not respond adequately to methadone or other treatments; in some but not all cases, patients also received methadone. Main outcome measures often involved retention in treatment and assessments of illicit opioid and other drug use. Overall, the therapeutic outcomes of the various studies have been generally positive, although evidence of long-term benefit is generally lacking.

Results from randomized controlled trials have generally indicated that treatment with heroin, when compared to methadone treatment, is associated with comparable retention, improved health and functioning, and less self-reported illicit heroin use.

One study evaluated injectable heroin ($n = 115$) compared to oral methadone ($n = 111$) in patients who had not benefited from at least two previous attempts at opioid dependence treatment, including methadone maintenance treatment at a dosage of 60 mg or more per day. This study was part of the North American Opiate Medication Initiative and was an open-label, randomized trial conducted in Canada (the cities of Montreal and Vancouver). Heroin was self-administered under supervision in the treatment clinics up to three times daily at a maximum dosage of 1000 mg/day; methadone was dispensed on a daily basis (no maximum dose indicated). The primary outcome measures were retention in addiction treatment at 12 months (or abstinence from opioids) and reduction in illicit drug use or other illegal activities. The results indicated that individuals assigned to heroin treatment were more likely to stay in treatment and reduce use of illegal drugs and engagement in illegal activities than those assigned to methadone. Sixteen of the 115 individuals in the heroin group had a life-threatening overdose or

seizure during the study. One death occurred during the study, a methadone group individual who reportedly died from an opioid overdose.

Heroin treatment for opioid dependence is a pharmacotherapeutic option in only a few countries, including the United Kingdom, the Netherlands, and Switzerland, and there are a limited number of individuals receiving such treatment. For example, it has been reported that in the United Kingdom in 2000, only 46 physicians had prescribed heroin and less than 450 patients were receiving it.

Conclusion

Opioid dependence is a chronic, relapsing medical disorder, often described as a brain disease with behavioral components. It requires comprehensive, multimodal, long-term treatment, as many patients also abuse or are dependent upon other substances. Many also have other medical and psychiatric comorbidity. Various types of pharmacotherapies with different modes of action have been used and continue to be evaluated as treatments for opioid dependence. Because no single medication will be appropriate for every individual, it is important that clinicians have a variety of therapeutic agents available to them. Additionally, pharmacotherapy is not a treatment end in itself; other adjuncts to successful treatment may include psychotherapy, social rehabilitation, vocational training, and others. Intraindividual treatment may also change over time as patients cycle through periods of abstinence and drug use. Rational medication therapy begins with an understanding of not only the addiction generally but also the specific dynamics of the addiction process that affect the overall success of treatment. While the mainstays of methadone and buprenorphine provide effective treatment to many persons with opioid dependence, other medications such as naltrexone (oral and injectable extended release) have a role in the treatment of this patient population. Other medications also may be used for withdrawal (e.g., clonidine, lofexidine) or may have promise as treatment agents (e.g., dihydrocodeine, heroin, LAAM).

Suggested Readings

Anglin MD, Conner BT, Annon J, et al. Levo-alpha-acetylmethadol (LAAM) versus methadone maintenance: 1-year treatment retention, outcomes and status. *Addiction*. 2007;102:1432–1442.

Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence. *Arch Gen Psychiatry.* 2006;63:210–218.

Mitchell TB, White JM, Somogyi A, et al. Slow-release oral morphine versus methadone: a crossover comparison of patient outcomes and acceptability as maintenance pharmacotherapies for opioid dependence. *Addiction*. 2004;99:940–945.

Oviedo-Joekes E, Brissette S, Marsh DC, et al. Diacetylmorphine versus methadone for the treatment of opioid addiction. *New Engl J Med*. 2009;361:777–786.

Raistrick D, West D, Finnegan O, et al. A comparison of buprenorphine and lofexidine for community opiate detoxification: results from a randomized controlled trial. *Addiction*. 2005;100:1860–1867.

Robertson JR, Raab GM, Bruce M, et al. Addressing the efficacy of dihydrocodeine versus methadone as an alternative maintenance treatment for opiate dependence: a randomized controlled trial. *Addiction*. 2006;101:1752–1759.

Strang J, Bearn J, Gossop M. Lofexidine for opiate detoxification: review of recent randomised and open controlled trials. *Am J Addict*. 1999;8:337–348.

Tucker TK, Ritter AJ. Naltrexone in the treatment of heroin dependence: a literature review. *Drug Alcohol Rev.* 2000;19:73–82.

Walsh SL, Strain EC, Bigelow GE. Evaluation of the effects of lofexidine and clonidine on naloxone-precipitated withdrawal in opioid-dependent humans. *Addiction*. 2003;98:427–439.

Wedam EF, Bigelow GE, Johnson RE, et al. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Arch Intern Med*. 2007;167:2469–2475.

23 Alcohol Abstinence Pharmacotherapy Treatment

In general, medications for maintaining abstinence from alcohol use achieve their effect through either of two proposed mechanisms—stabilizing systems that have adapted to chronic alcohol exposure and which have become dysregulated with a reduction in alcohol intake, or interfering with the reinforcing effects of alcohol consumption.

Medications Approved for Use in the United States

Disulfiram

Disulfiram was a medication originally explored for use as an antiparasitic, and discovered to have aversive qualities in the context of alcohol drinking. In the United States, it was approved by the FDA for the treatment of alcohol dependence in 1951.

Pharmacology of the Medication/Treatment

Disulfiram's mechanism of action is to block the oxidation of alcohol to acetate through the irreversible inhibition of the enzyme acetaldehyde dehydrogenase, which can increase the plasma level of acetaldehyde 5 to 10 times greater than under normal circumstances of drinking. The buildup of acetaldehyde, which is the oxidation product of ingested alcohol via alcohol dehydrogenase, produces highly unpleasant symptoms in the patients, such as nausea, vomiting, throbbing headache, tachycardia, dysphoria, flushing, hypotension, vertigo, diaphoresis, and dyspnea. As such, the actual mechanism of disulfiram in the reduction of alcohol intake lies in its aversive qualities, and thus its ability to increase motivation for sobriety through potential, or more rarely, actual punishment.

Efficacy of the Medication/Treatment

Although disulfiram has been in use for over 60 years, there have not been a substantial number of well-controlled efficacy studies, and those that have been performed used various outcome measures with differing results. Some studies show an improvement in days drinking and reduction in quantities of alcohol consumed. In the largest clinical trial (a multicenter cooperative study by the U.S. Department of Veterans Affairs), there were no significant differences in the intention-to-treat analysis of abstinence rates among the three treatment groups receiving a daily dose of disulfiram 250 mg, disulfiram 1 mg (an inactive dose), or a vitamin. However, those in the disulfiram 250 mg group had significantly fewer drinking days than subjects in

the other two groups. Nonadherence was a confounding factor in this study, in that 80% of subjects did not take the study medication regularly. Interestingly, the small subset of patients across groups who were adherents of the protocol demonstrated reductions in their alcohol consumption.

Safety of the Medication/Treatment

Disulfiram is associated with rare but serious side effects such as hepatotoxicity, cholestatic and fulminant hepatitis, optic neuritis, peripheral neuritis, polyneuritis, and, in high doses, psychotic symptoms. Contraindications to the use of disulfiram include ischemic heart disease and pregnancy. Disulfiram inhibits the induction of hepatic enzymes and, thus may interfere with the metabolism of concomitantly administered medications. As such, disulfiram enhances the effects of the coumarin anticoagulants and the phenytoin anticonvulsants. In general, disulfiram is used safely in patients who clearly understand the need to avoid consumption or skin contact with all alcohol-containing materials, as even a small dose of alcohol can lead to a buildup of acetaldehyde. This means, in addition to abstaining from consumption of beverage alcohol, the patient must avoid contact or ingestion of alcohol found in foods, over-the-counter cold and other medications, mouthwashes, colognes, and lotions in order not to have an aversive reaction. Clearly, clinical judgment is a factor in choosing an optimal candidate for this medication.

How the Medication/Treatment Is Optimally Used

Disulfiram is available in 250-mg tablets, and patients should start with an initial oral dose of 250 mg daily, and may be built up to 500 mg daily. Disulfiram should not be taken unless the blood alcohol concentration is zero or until the patient has not consumed any alcohol for at least 12 hours. In addition, as disulfiram is an irreversible aldehyde dehydrogenase inhibitor, the potential for a disulfiram reaction continues until new enzyme is synthesized, which may be up to 2 weeks after discontinuation of treatment. Typically, disulfiram is used for treating patients with prior failure of one or more courses of psychosocial treatment and who are motivated to achieve complete abstinence. In patients newly diagnosed with alcohol dependence, disulfiram has not been recommended as a first-line medication, as there are other FDA-approved medications for the treatment of alcohol dependence with more benign side-effect profiles and ease of use. However, there are instances where it is imperative to demonstrate sobriety, such as in legal agreements and consent decrees, where the supervised use of disulfiram can increase the likelihood that a particular patient will abstain from alcohol.

Special Considerations

A well-researched and effective behavioral strategy that optimizes the adherence to disulfiram is Behavioral Couples Therapy (BCT), which provides contingency for sobriety and increased social support for the patient's efforts to change. In BCT, a couple signs a contract stipulating that the partner will watch the patient take a daily dose of disulfiram and record it on a calendar, then the patient and partner thank each other for their efforts, and will not argue or even discuss the patient's drinking behavior. A meta-analysis of randomized studies of BCT showed superior impact on frequency of alcohol use, consequences of use, and relationship satisfaction over individual interventions for alcohol and drug abuse.

Oral Naltrexone

Naltrexone is a μ-opioid antagonist that was approved in 1994 by the FDA for the prevention of relapse to heavy drinking in alcohol-dependent individuals. As an opioid antagonist, it was originally approved and marketed as a treatment for opioid dependence.

Pharmacology of the Medication/Treatment

Endorphins and enkephalins, which are naturally occurring opiates, are released as a result of alcohol consumption. Dopamine (DA) is released from the nucleus accumbens (NAcc) when these opiates bind to brain receptor sites, resulting in some of the pleasurable effects of alcohol. In research with humans, as compared to non–alcohol-dependent persons and their family members, a family history of alcoholism is associated with decreased baseline β-endorphin levels and an exaggerated increase in β-endorphin as a response to alcohol. This suggests that at least one component of the vulnerability to the development of alcohol dependence is based upon an increased sensitivity to alcohol-induced endorphin release and subsequent reinforcement. Naltrexone blocks the opioid-mediated release of DA in the NAcc that is typically induced after alcohol consumption, thus diminishing alcohol's positive reinforcing effects. In addition, alcohol craving is reduced by naltrexone in both social drinkers and alcohol-dependent patients, which may be another mechanism of its action.

Efficacy of the Medication/Treatment

Two early trials demonstrated that naltrexone was efficacious in treating alcohol dependence by reducing relapse to heavy drinking. Although most randomized controlled trials (RCTs) of naltrexone demonstrate significant reductions in drinking behavior, a few have not. In a meta-analytic approach examining 14 RCTs of naltrexone and placebo, it was found that the administration of naltrexone over the short term (<12 weeks) significantly decreased the rate of relapse to heavy drinking, but did not have a significant effect on the rate of abstinence. A Cochrane collaborative study performed a meta-analysis of 24 RCTs of naltrexone and placebo, and found that in short-term studies, the rate of relapse to heavy drinking was reduced by 36% with naltrexone. A smaller effect size was demonstrated for maintenance of abstinence.

Evidence suggests that the main clinical effect of naltrexone is a reduction in relapse to heavy drinking. This finding has implications based upon severity of symptoms, patient capacity, and patient goals, as to how naltrexone should be included in treatment planning. There is a lesser effect on maintenance of complete abstinence.

Safety of the Medication/Treatment

Typical dosage for naltrexone is 50 mg once daily as an adjunct to psychosocial treatment of alcohol dependence. Naltrexone has a $t_{½}$ of only several hours in the plasma, but a major metabolite, 6-hydroxy-β-naltrexol, accumulates with regular dosing and demonstrates mild μ-opioid antagonism. Since naltrexone is an opiate antagonist, patients receiving naltrexone should be screened for opiate use so that administration does not precipitate acute opioid withdrawal symptoms. Naltrexone-associated side effects are more frequent in the first days of therapy. The most common side effects are CNS symptoms (headache, dizziness, and fatigue) and gastrointestinal-related (nausea) symptoms. Naltrexone has few interactions with other medications as it is metabolized by a hepatic nonmicrosomal oxidase system. As μ-opioid receptors (MORs) are blocked by naltrexone, naltrexone-treated patients will generally find opioids ineffective for analgesia. A "black-box" warning regarding liver function exists for naltrexone (when used in high doses), but at the recommended doses there is no evidence for hepatotoxicity. Reported hepatotoxicity in alcohol-dependent patients was attributable to elevations of liver enzymes that were reversible.

How the Medication/Treatment Is Optimally Used

The role of genetic markers in the clinical response to naltrexone for alcoholism has been examined. A particular single-nucleotide polymorphism (SNP) has been identified in exon 1 of the gene encoding for the MOR (*OPRM1*), which is a missense A-to-G (A118G) substitution coding for the amino acid aspartate instead of asparagine (Asn40Asp). This SNP is associated with altered μ-receptor response to endogenous opioids and to MOR antagonists, such that

individuals carrying at least one copy of the Asp40 allele demonstrate increased alcohol-induced reward and a greater decrease in the rewarding effects of alcohol in the context of naltrexone. Therefore, in certain cohorts of patients, naltrexone may be more efficacious, suggesting that better characterization of these higher responders is an appropriate venue for exploration. Several studies have examined in alcohol-dependent subjects the effect of the Asn40Asp SNP on the clinical response to naltrexone and have found that, compared to subjects homozygous for the Asn40 allele, carriers of the Asp40 allele in fact demonstrate superior response to naltrexone.

Ethnic and Racial Differences in Naltrexone Response

One factor in the varying results for the association of Asn40Asp SNP and clinical responsivity to naltrexone may be the ethnic differences in the tested subjects with regard to the frequency of the Asp40 SNP. The frequency of the Asn40Asp SNP is estimated to be less than 5% in individuals of African descent, whereas it is about four times greater in those of European descent and up to 58% in Asians. If the OPRM1 Asp40 polymorphism renders increased response to μ-receptor antagonism, then those of African ancestry may be less likely to benefit from naltrexone.

Injectable Naltrexone

Naltrexone was approved by the U.S. FDA in April 2006 in an injectable, extended-release formulation for the treatment of alcohol dependence.

Pharmacology of the Medication/Treatment

For the purposes of injection, 380 mg of naltrexone is encapsulated in biodegradable microspheres that slowly release naltrexone over a 30-day period after injection. The naltrexone released has the same μ-opioid antagonist properties as orally administered naltrexone. The microspheres are composed of a polylactide-co-glycolide polymer that is used extensively in other extended-release drugs, such as in absorbable sutures as well as in long-acting risperidone. A pharmacokinetic analysis after injection of naltrexone 380 mg demonstrated sustained therapeutic plasma levels for 30 days, without significant drug accumulation. Plasma levels of naltrexone show peak concentrations 2 to 3 days after an intramuscular (IM) injection and demonstrate a slow decline for the next 30 days. Since oral naltrexone is dosed at 50 mg/day, over 30 days the monthly cumulative dose is 1,500 mg, whereas an IM injection of naltrexone given every 30 days results in a lower monthly dose of 380 mg. In addition, injectable long-acting naltrexone does not demonstrate the typical daily fluctuations in plasma concentrations associated with daily oral dosing of naltrexone.

Efficacy of the Medication/Treatment

A 6-month, multisite, double-blind RCT evaluated the efficacy and safety of long-acting injectable naltrexone 190 or 380 mg (Vivitrol) in alcohol-dependent subjects over 24 weeks. Alcohol abstinence was not required of subjects at study entry, and there was no lead-in with oral naltrexone prior to naltrexone injection. The primary outcome, targeted at the expected main effect of naltrexone in alcohol dependence, was the event rate (number of drinking days/total number of days at risk) of heavy drinking (≥5 standard drinks/day for men and ≥4 standard drinks/day for women). IM naltrexone reduced the rate of heavy drinking by 25% in the 380 mg group and by 17% in the 190 mg group, compared to placebo. Heavy-drinking days were reduced by 48% by long-acting injectable naltrexone, including those actively drinking and patients who were abstinent at treatment entry. For subjects abstinent before injection, injectable naltrexone treatment effects were greater—compared to those actively drinking at injection who had a 21% decrease in the event rate of heavy drinking, those who had a period of 7-days abstinence prior to first injection had an 80% reduction. Secondary outcomes included

the event rates of risky drinking (>2 drinks/day for men and >1 drink/day for women) and of any drinking days. Injectable naltrexone was not associated with a significant reduction in risky drinking or rate of any drinking days (complete abstinence) compared to placebo.

There appears to be a dose–response effect for IM naltrexone, with outcomes for 190 mg generally intermediate between that of the approved 380 mg IM dose and placebo.

Overall, the clinical outcomes for long-acting injectable naltrexone in alcohol-dependent patients are consistent with the meta-analyses of RCTs of oral naltrexone in demonstrating reduction in relapse to heavy drinking. IM naltrexone has advantages over oral naltrexone in that it has less potential for hepatotoxicity, once-monthly administration is sufficient to sustain therapeutic plasma levels for a month, and the route of administration likely improves adherence in clinical populations.

Safety of the Medication/Treatment

Compared to the oral formulation of naltrexone, an advantageous pharmacokinetic property of IM naltrexone is its reduced first-pass elimination, which exposes the liver to less of the drug cumulatively and thus reduces the potential for hepatotoxicity. Pharmacokinetic studies comparing plasma concentrations after a single IM dose of naltrexone found similar levels of naltrexone and its primary metabolite 6β-naltrexol and similar cumulative exposure over 63 days in subjects with mild (Child-Pugh grade A) and moderate (Child-Pugh grade B) hepatic impairment and in matched control subjects. Thus, this route of administration may be advantageous in using naltrexone with patients who have chemical or infectious hepatitis, or other liver impairment. Given the risk of hepatotoxicity with continued drinking, subjects treated with 380 mg IM naltrexone experience greater improvement in γ-glutamyl transpeptidase levels compared to controls ($P = 0.03$).

Adverse events (AEs) associated with long-acting injectable naltrexone have been reported to be nausea, headache, fatigue, decreased appetite, dizziness, and injection site pain.

How the Medication/Treatment Is Optimally Used

The greatest advantages of the long-acting IM formulation of naltrexone are the low dosing frequency, the more or less continuous exposure of MORs to naltrexone, and the high intrinsic medication adherence. The low dosing frequency can be helpful in supporting patients to return for the next dose. The nature of the formulation ensures that the patient will be exposed to the effects of the medicine for at least 30 days, until they return for the next dose administration. The fact that the medication can more easily be framed as a background for recovery can allow clinicians to focus upon delivering or providing for convergent (e.g., cognitive–behavioral therapy [CBT] to reduce acting on craving as the drug reduces craving) or complimentary (self-help groups to support abstinence) psychosocial interventions that work synergistically with naltrexone's main effects on drinking behavior.

Acamprosate

Acamprosate was approved for use by the U.S. FDA in July 2004 for the treatment of alcohol dependence in conjunction with psychosocial support. Its indication is for the maintenance of abstinence from alcohol in alcohol-dependent patients who are abstinent at treatment initiation.

Pharmacology of the Medication/Treatment

Acamprosate is a taurine analogue that, similar to taurine, activates glycine receptors (GlyRs) in the NAcc and also acts as a weak partial *N*-methyl-D-aspartate (NMDA) receptor antagonist. In animal models, strychnine-sensitive (competitive antagonist) GlyRs in the NAcc and nicotinic acetylcholine receptors (nAChRs) in the ventral tegmental area are involved in regulating DA release and mediating alcohol-induced DA elevation in the mesolimbic DA system. In animal models of direct and systemic administration, acamprosate appears to decrease

alcohol intake through primary interactions with GlyRs in the NAcc and secondarily with the ventral tegmental nAChRs, both of which increase extracellular DA in the NAcc. In addition, acamprosate is believed to modulate glutamatergic hyperactivity associated with changes in the balance of excitatory and inhibitory neuroregulation in the context of chronic alcohol exposure. It has been proposed that acamprosate may modulate both ionotropic and metabotropic central NMDA receptors at regulatory sites, such as m-glu-R5 receptors, to normalize NMDA glutamatergic hyperexcitability and reestablish homeostasis in the absence of alcohol.

Efficacy of the Medication/Treatment

Two meta-analyses support that acamprosate is efficacious in helping patients with alcohol dependence to maintain abstinence from alcohol. Pooled data from 17 placebo-controlled trials determined for acamprosate a significantly higher proportion of subjects maintaining complete abstinence and a relative benefit of 1.47 over placebo of attaining 6 months of complete abstinence, a moderate to strong effect. Similarly, in a different meta-analysis of 12 RCTs, acamprosate treatment was associated with a significant increase in the abstinence rate and the cumulative abstinence duration (CAD). Further, data from these systematic evaluations suggest that acamprosate has moderate benefits on overall treatment adherence and a small positive impact upon treatment retention.

Taken together, there is a good evidence base to conclude that acamprosate compared to placebo increases abstinence and decreases drinking days in patients with alcohol dependence. However, two large U.S. studies did not find similar results for the efficacy of acamprosate, and have dampened clinical enthusiasm for the medication. There may be differences in study methods and the characteristics of the populations being studied that may account for some of these striking and consistent differences in outcome. Nonetheless, there are strong data supporting acamprosate efficacy in long-term studies and its strongest effects have been demonstrated in subjects who have been recently detoxified.

Safety of the Medication/Treatment

Acamprosate, which does not undergo hepatic metabolism, is excreted entirely in the urine as unchanged drug, and does not interact significantly with other medications. When acamprosate is used with other medications such as disulfiram, diazepam, or even alcohol, there are no pharmacokinetic interactions. Acamprosate has a favorable safety and tolerability profile supported by the extant clinical trial data. Acamprosate was demonstrated to be safe, well tolerated, and compared to placebo, without significant discontinuation due to AEs in a meta-analysis of 10 RCTs. For acamprosate compared to placebo, the highest frequency AEs have been diarrhea and flatulence, which occurred relatively infrequently. Transient diarrhea typically occurs in the first 4 weeks of treatment, with decreasing incidence over time, and is of mild to moderate severity.

How the Medication/Treatment Is Optimally Used

Acamprosate is formulated in a tablet containing 333 mg, which is recommended to be taken as two tablets three times a day. Given the strength of evidence for optimal response in already-abstinent patients, initiation of acamprosate treatment should begin as soon as possible after abstinence is achieved and the period of acute withdrawal has passed. Treatment should be continued even if a patient relapses.

Special Considerations

Patients with Impaired Renal Function A linear correlation between decreases in the clearance of creatinine and that of acamprosate has been demonstrated, suggesting that patients with impaired renal function could accumulate acamprosate with prolonged dosing. Therefore, it is recommended that in patients with moderate renal impairment (creatinine clearance of 30 to 50 mL/min) the standard dose be halved to one 333 mg tablet three times a day. In patients with severe renal impairment (creatinine clearance $<$30 mL/min), acamprosate is not recommended.

Combination Treatment (Naltrexone and Acamprosate) Since the major effects of naltrexone and acamprosate appear to be different and appear to work by different mechanisms, namely reduction in relapse to heavy drinking in the case of naltrexone, and maintenance of abstinence in the case of acamprosate, it is a reasonable strategy to test the efficacy in alcohol dependence by combining the two medications. A few clinical trials have examined this approach, but demonstrating such synergistic effects has been less than straightforward, and the use of the combination is not currently supported by a robust database of evidence.

Medications Not Approved for the Treatment of Alcohol Dependence

Topiramate

As antiseizure medications tend to increase GABAergic activity or reduce glutamatergic activity, initial RCTs of several medications have been conducted in the treatment of alcohol dependence, including divalproex, and carbamazepine, with modest positive effects. However, topiramate has the most extensive evidence to date for efficacy in randomized, controlled trials.

Pharmacology of the Medication/Treatment

Topiramate's utility in the treatment of alcohol dependence is hypothesized to act to reduce alcohol's reinforcing effects in the central nervous system through binding to a nonbenzodiazepine site on $GABA_A$ receptors so as to increase GABAergic activity and also by inhibiting glutamatergic activity through binding and inhibiting activity of corticomesolimbic AMPA (amino-3-hydroxy-5-methyl-4-isoxazole)/kainate glutamate receptors that have been upregulated due to chronic alcohol exposure.

Efficacy of the Medication/Treatment

A double-blind 12-week RCT comparing topiramate (titrated up to 300 mg/day as tolerated) and placebo in alcohol-dependent subjects receiving outpatient psychosocial support found that, compared to those receiving placebo, the topiramate group had a 27.6% lower percentage of heavy-drinking days, and 26.2% more abstinent days. Similarly, a multisite 14-week double-blind trial of topiramate (titrated up to 300 mg/day or maximum tolerated) and placebo in subjects with alcohol dependence who received a weekly treatment adherence enhancement therapy also found topiramate demonstrated a 16.2% mean reduction in the percentage of self-reported heavy-drinking days compared to placebo, and an 8.44% mean reduction in the rate of self-reported heavy-drinking days over the study interval. Interestingly, a 12-week double-blind RCT compared topiramate (titrated to 300 mg/day), naltrexone (50 mg/day), and placebo in alcohol-dependent outpatients who were 1- week postdetoxification at study entry. Although there were no significant differences between naltrexone and topiramate in time to first relapse, CAD and heavy-drinking weeks, topiramate was superior to placebo, and demonstrated trends toward superiority over naltrexone.

Safety of the Medication/Treatment

Over the approved therapeutic dose range of 200 to 800 mg/day, topiramate follows linear pharmacokinetics. The relative bioavailability is 80% and is not affected by food, with nearly complete oral absorption within 2 hours of administration. The drug is not widely metabolized in vivo and is mostly eliminated (70%) unchanged in the urine. Side effects reported in clinical trials have included dizziness, paresthesias, psychomotor slowing, memory/concentration impairment, and weight loss.

How the Medication/Treatment Is Optimally Used

Topiramate should be titrated slowly starting at 25 mg/day and increasing at 25 mg/week until the patient reaches the 300 mg/day dose demonstrated effective in clinical trials. The slow titration decreases the frequency of neurocognitive side effects and discontinuation rates as compared to patients taking 50 mg/day and titrated at 50 mg/week, but takes 12 weeks to reach the target dose. It is unclear as to whether topiramate in doses less than 300 mg/day is effective in alcohol dependence. Given reports of seizures upon abrupt withdrawal of topiramate in patients without a prior seizure history, it is suggested that topiramate be tapered at the rate of 25% every 4 days for a period of 16 days.

Special Considerations

Patients with Impaired Renal Function The product packaging states that patients with moderately impaired kidney function (creatinine clearance 30 to 69 mL/min/1.73 m^2) had a 42% decrease in the clearance of topiramate. Since topiramate is mostly excreted unchanged in the urine, it is suggested that for patients with a creatinine clearance below 70 mL/min/1.73 m^2 and a resulting reduction in clearance of topiramate, 50% of the recommended dose should be given.

In postmarketing studies of topiramate, a normal anion gap hyperchloremic metabolic acidosis was a rare dose-related serious AE. Because topiramate is a weak carbonic anhydrase inhibitor, the kidneys may leach bicarbonate levels such as can be seen with acetazolimide. Therefore, during topiramate treatment, serum bicarbonate levels should be monitored at baseline and over the course of treatment. If a metabolic acidosis develops, of which paresthesias are a common sign, topiramate dose should probably be reduced or discontinued.

Baclofen

Baclofen is a potent and stereoselective $GABA_B$ agonist that has been used in clinical practice for the treatment of spasticity and is widely used as a muscle relaxant.

Pharmacology of the Medication/Treatment

In animal models, baclofen reduces the alcohol self-administration (SA), suppresses acquisition and maintenance of alcohol drinking, relapse-like drinking, and the reinforcing, rewarding, stimulating, and motivational properties of alcohol in rodents.

Efficacy of the Medication/Treatment

In humans, 30 mg/day decreases alcohol withdrawal symptoms in alcohol-dependent patients in equivalence to that of diazepam. However, it is as yet unclear that baclofen when used in uncomplicated withdrawal has the same efficacy as benzodiazepines in reducing the incidence of seizures or delirium. There is some evidence that baclofen can reduce drinks per drinking day and heavy-drinking days in alcohol-dependent subjects, and improve rates of abstinence. However, the overall evidence base for this medication's use in alcoholism treatment is limited.

Safety of the Medication/Treatment

The common AEs associated with baclofen treatment are sleepiness, vertigo, nausea, and abdominal pain, all of which resolve in the first week of treatment. There have been no serious AEs, and baclofen does not appear to have abuse liability. So far, treatment with baclofen appears relatively safe; however, its abuse potential has not been well assessed, and abrupt withdrawal has been linked to withdrawal-related delirium that appears not to be dose-related. The short-term efficacy of baclofen in the treatment of alcohol dependence is promising, but further controlled studies with larger numbers of subjects will be needed to make a compelling argument for its safety and appropriateness for general use.

Serotonergic Medications

Serotonin reuptake inhibitors (SRIs) have been demonstrated in animal studies to decrease the consumption of alcohol and enhance serotonergic function in the CNS, and they are used as antidepressants and anxiolytics in clinical treatment. Findings from RCTs of SRIs for the treatment of alcohol dependence are inconsistent, and meta-analytic procedures on the data suggest that the best use of SRIs may be in treating major depression in patients with co-occurring alcohol dependence. One of the major issues with the efficacy of SRIs in the treatment of alcohol dependence appears to hinge on the discovery of a differential therapeutics based upon typology. Studies suggest that alcohol use subtype (using dimensions such as age of onset and degree of psychopathology) may be associated with a differential response to SRIs, although the pattern of differential response has not been consistent across studies (i.e., whether beneficial effects interact in a positive or negative way between subtype and active medication).

The efficacy of ondansetron (an antinausea medication that acts as a 5-HT_3 receptor antagonist) was compared to placebo in an 11-week, double-blind, RCT trial of subjects with either early- or late-onset alcohol dependence who also received adjunctive CBT. Although there was no significant effect in the overall subject cohort, subjects in the early-onset alcoholism group who received ondansetron showed significant reductions compared to placebo in self-reported drinking. Significant reductions in drinking compared with placebo were reported only in the early-onset alcoholism subset, findings that were corroborated by significant reductions in plasma carbohydrate-deficient transferrin. There were no significant differences in outcome with ondansetron or placebo in subjects with late-onset alcoholism.

Taken together, these studies suggest that subtyping of patients with alcohol dependence may help resolve conflicting research findings on serotonergic treatment of alcohol dependence, and if validated, may support the use of SRIs and other serotonin-active agents in specially selected subpopulations of patients with alcohol dependence.

Dopamine (DA) Active Medications

Data from preclinical research have illuminated the role of DA in the positively reinforcing and stimulant-like effects of alcohol, so a reasonable hypothesis is that by blocking DA, one may affect alcohol drinking in humans. In rats, alcohol consumption induces release of DA from the NAcc, the common reward system circuit implicated in the rewarding effects of all drugs of abuse. Mesostriatal DA activity is decreased in rodents by chronic alcohol administration. In persons with alcohol-dependence, DA and metabolites are decreased with chronic alcohol consumption.

When alcohol-dependent patients in human laboratory studies were pretreated with the antipsychotic medication haloperidol (a DA antagonist), it reduced craving and consumption of alcohol. Haloperidol also decreased the euphorigenic and stimulating effects of alcohol in social drinkers. Compared with heavy social drinkers given placebo before an alcohol challenge, those pretreated with 5 mg of the olanzapine (a DA antagonist) had a decreased urge to drink.

Whereas DA antagonists have held promise based upon reasonable, neurobiologically based hypotheses, preclinical research, and data from human laboratory studies, in randomized clinical trials for alcohol dependence the results have mostly been negative. RCTs of both traditional and atypical antipsychotics have generally not demonstrated positive effects on craving or relapse in patients with alcohol dependence.

Conclusion

The use of medications to treat alcohol dependence has received increased scrutiny due to its potential impact in improving drinking outcomes as well as enhancing the effectiveness of

current behavioral treatment approaches. As our understanding of the underlying neurochemistry and neurobiology of alcohol has progressed, medications have been developed that target specific neurotransmitter systems involved in the development and maintenance of alcohol dependence. Although there has been increasing progress in the differentiation of efficacious medicines for alcohol dependence, there are still many areas that need further development. Alcohol-dependence medications given adjunctively with psychosocial treatment strategies improve drinking outcomes, yet adoption of these medical treatments in the broader addiction treatment community faces continuing obstacles, such as lack of medical personnel, incompatible treatment philosophy, or clinical ignorance of efficacy. Pharmacologic interventions that target reductions in drinking without aiming for abstinence may have difficulty gaining clinical traction in the generally abstinence-oriented world of traditional alcoholism recovery programs.

Meta-analytic evidence from multiple clinical trials suggests that of the FDA-approved pharmacotherapies, acamprosate's strongest effects are in achieving and maintaining complete abstinence, while orally administered naltrexone's most robust effects are in decreasing heavy-drinking days. These are the medications that should be used first-line.

Whereas subacute and maintenance pharmacotherapeutic interventions have been a mainstay of treatment for chronic opioid dependence, it is as yet unclear whether medications are of benefit in the long-term treatment of chronic alcohol dependence. Similarly, other characteristics have yet to be clearly established, such as the optimal dosages and effectiveness of available pharmacotherapies in clinical settings, the optimal psychosocial interventions with each medication, and which subpopulations respond best to which medication. It is hoped that pharmacotherapies for alcohol dependence may evolve into a more routine and widely used intervention as continuing evidence mounts demonstrating their effects in promoting abstinence and reducing drinking behavior.

Suggested Readings

Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *J Am Med Assoc*. 2006;295:2003–2017.

Garbutt JC, Kranzler HR, O'Malley SS, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *J Am Med Assoc*. 2005;293:1617–1625.

Gelernter J, Gueorguieva R, Kranzler HR, et al. Opioid receptor gene (OPRM1, OPRK1, and OPRD1) variants and response to naltrexone treatment for alcohol dependence: results from the VA Cooperative Study. *Alcohol Clin Exp Res*. 2007;31:555–563.

Heilig M, Egli M. Pharmacological treatment of alcohol dependence: target symptoms and target mechanisms. *Pharmacol Ther*. 2006;111:855–876.

Hughes JC, Cook CCH. The efficacy of disulfiram: a review of outcome studies. *Addiction*. 1997;92:381–395.

Johnson BA, Roache JD, Javors MA, et al. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. *J Am Med Assoc*. 2000;284:963–971.

Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for treating alcohol dependence. A randomized controlled trial. *J Am Med Assoc*. 2007;298:1641–1651.

Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev*. 2006;(1): Art. No.: CD001333. DOI: 10.1002/14651858. CD001333.pub2.

Ray LA, Hutchison KE. A polymorphism of the mu-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans. *Alcohol Clin Exp Res*. 2004;28:1789–1795.

Rosenthal RN. Alcohol Abstinence Management. In: Ruiz P, Strain EC eds. *Lowinson and Ruiz's Substance Abuse, A Comprehensive Textbook*. 5th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams and Wilkens; 2011:477–493.

24 Vaccines for Substance Use Disorders

Introduction

Vaccines for substance abuse offer a new and very different approach for treating cocaine, nicotine, methamphetamine, heroin, and phencyclidine (PCP) abuse. The basic concept for vaccine effects on the pharmacology of drugs is that antibodies can slow the rate of drug entry into the CNS, potentially reducing total drug concentrations. This is achieved through antibody binding of the substance in the bloodstream, since antibody molecules are too large to pass through the blood–brain barrier under normal conditions. This should result in a reduction in the reward sensations from drug ingestion, making the vaccinated user less susceptible to psychological and physiologic reinforcement responses, so that the bonds of addiction might be more easily loosened.

There are three distinct areas of limitation on vaccine effects relating to the influence on drug distribution and metabolism: the amount and persistence of antibody ordinarily elicited by vaccines, and the affinity of the antibody for the drug. The advantages of vaccines as a treatment for substance abuse, in contrast to conventional drug therapy approaches, are that if persistent, high levels of antibody can be elicited by a vaccine, compliance failures will be much less of a problem, and undesirable CNS side effects of the treatment itself would not be a concern, as they often are with small molecule agonists or antagonists. Vaccination resulting in long-term inhibition of the pharmacologic actions of abused drugs has great potential for assisting motivated addicts to begin and sustain abstinence from their specific abused substance.

Conceptual Basis for Drug Vaccines

Drugs associated with substance abuse enter the CNS following absorption or injection and occupy receptors that modulate neuron signaling, thus leading to the reward/reinforcement sensations associated with use of the specific drug. These sensations are dependent on the number of receptors occupied as well as, in many cases, the rate at which receptor occupation occurs. Cocaine, for example, targets dopamine transporters (DATs), and methamphetamine binds several different receptors, while morphine and heroin metabolites bind μ-opiate receptors (MORs). Preventing the rapid rise of receptor occupation in the brain will inhibit the maximal pleasurable and reinforcing effects of many abused drugs.

In order to influence drug pharmacodynamics, substance abuse vaccines must elicit high levels of specific immunoglobulin G (IgG) antibodies with good binding affinity, so that these antibodies can bind and hold most of the drug molecules within the circulation, reducing and

delaying drug access to the brain. Antibody binding to target antigens has been extensively studied over the past several decades, and small molecule (hapten) binding in particular is quite well understood. The interactions between a small molecule (such as a drug of abuse) and an antibody can thus be accurately characterized as predominantly a function of antibody quantity and affinity, because antibody binding to a hapten does not result in significant changes in the structure or subsequent function of the antibody, in contrast to antibody binding to complex antigens. In the latter case, binding can create immune complexes, with alterations in the structure of the heavy chain portion of the antibody exposing complement binding sites, leading to activation of the complement cascade. Such changes in structure also result in attachment of the bound antibody to antibody receptors on cells of the reticuloendothelial system so that these complexes can be cleared from circulation. This clearance process can also cause activation of other immune functions that may lead to inflammatory responses in various tissues. Since binding of abused drugs, for example, cocaine, methamphetamine, or morphine, does not cause alterations in antibody structure, the half-life of the antibody is essentially unaffected. In fact, the half-life of the drug is often significantly prolonged as a result of binding to the antibody, except in the case of cocaine (discussed later).

To determine the initial, necessary goals for vaccine elicitation of antibody in terms of quantity and binding properties (affinity), the simple model of mass action equilibrium can be used, where K_a represents the association constant, [A] the free antibody concentration, [H] the concentration of free hapten, and [AH] the concentration of bound complex of drug and antibody at one combining site:

$$K_a = \frac{[AH]}{[A]*[H]}$$

This equation is, for purposes here, sufficient to describe the basic interaction of a single drug molecule and a single antibody combining site, since the combining sites (two on IgG, for example) do not interact when bound with small molecules, either on the same antibody or between antibody molecules. At 50% occupancy of available antibody binding sites, the K_a predicted is accurate for IgG, the antibody isotype that dominates the antibody response with vaccines currently being studied. In order to evaluate this equation, one must know the expected concentrations of free drug that are typically found in substance abusers depending on the drug of interest. Most of the drugs used achieve peak concentrations in the 0.5 to 1 μM range drug, although in heavy abusers, concentrations can sometimes be much higher (e.g., with morphine).

From this information, and making reasonable assumptions about the expected binding affinity of the antibody responses, it is relatively straightforward to determine the amounts of antibody required for binding a desired proportion of administered drug. As compared with the usual antibody responses needed for complete protection against toxins and microbes using standard vaccines, such as those against tetanus (1 to 2 μg/mL) or the *Haemophilus influenzae* b bacterium (0.15 μg/mL), the concentrations of antibody required for drug binding are quite high, up to 100 μg/mL or more for higher doses of drug. However, these levels are achievable in only a proportion of human patients using standard vaccine techniques.

Simple binding to block uptake, however, is not the only consideration that affects drug pharmacodynamics. The speed with which the antibodies can bind to a drug will also influence its inhibition of drug entry into the CNS. As with many drugs of abuse, physiologic and subjective (the "rush") effects from smoked cocaine or methamphetamine are detectable within a few minutes of exposure. The antibody–antigen binding characteristics of haptens have been carefully studied over the years, and the initial attachment of an antibody combining site to its specific target molecule (the "on" rate) has been empirically determined in several model systems. Fortunately for substance abuse vaccine applications, these studies indicate that

such initial antibody binding rates for small molecules are quite rapid and should not prove a hindrance to the effectiveness of vaccines, if they elicit a sufficiently high concentration of antibodies. IgG antibodies will bind the target molecules in a fully mixed sample essentially to equilibrium in less than 1 second, and consequently for ordinary administration routes and doses, the on rate of antibody binding is expected to be fast enough that maximal possible drug binding will occur in the bloodstream well before transfer of the drug to the brain is expected to take place. Achieving the high-level responses necessary in vaccine recipients by optimizing vaccine design and administering with improved adjuvants should greatly reduce both the rate and the total drug accumulation in the brain from single doses.

Finally, although the above considerations do account for many of the clinical and experimental observations made with substance abuse drugs and vaccines thus far, some data from experimental animal studies suggest further effects of drug vaccines that are not fully understood. With nicotine vaccines in mice, for example, entry of a bolus dose of nicotine into the brain was blocked in vaccinated rats not previously treated with nicotine. Chronic nicotine treatment of such rats, however, which should result in some reduction of binding capacity of the antibody, showed lower levels of the nicotine bolus retained in the blood, but the mice still had a reduction in brain concentrations equivalent to the vaccinated mice without nicotine treatment. This might be explained in part by an increase in fat uptake, though the mechanisms for this observation remain obscure. Thus, some benefits of vaccination on drug pharmacodynamics may be operative, even at suboptimal antibody response levels.

Antibody Effects on Drug Pharmacodynamics and Pharmacokinetics

Most current ideas about reward from addictive substances combine aspects of "rate" and equilibrium binding pharmacologic theories to explain observations relating to drug action. The influence of both drug concentrations and pharmacodynamic features for cocaine, nicotine, methamphetamine, and opioids is important for their physiologic and subjective effects. Thus, a marked reduction in free-drug concentration in the blood by binding to specific antibodies would significantly inhibit drug action in the brain (e.g., if 75% to 90% of the drug is bound by high-affinity antibody), since IgG-bound drug cannot readily cross the normal, noninflamed blood–brain barrier. In addition, it is well known experimentally that the rate of increase in receptor occupation in the CNS has a profound influence on the subjective effects of each of these drugs. Thus, less dramatic binding of the drug even by lower affinity antibody (e.g., resulting in 50% binding, perhaps) could still have a substantial influence on the rate of entry of free drug into the CNS. Even if the eventual total accumulation in the brain is similar to what would be achieved in the absence of antibody, the subjective CNS effects of the drug may be substantially or completely blunted, since the rate of receptor occupancy would be significantly reduced.

The pharmacokinetics of antibody-bound drug is thus related to the effects of antibody binding on a drug's metabolism, tissue distribution, and elimination pathways, as well as the antibody's intrinsic half-life and the effect of drug binding on antibody half-life through changes in the antibody structure, if any. Antibody binding to morphine, for example, prolongs morphine's terminal half-life in the bloodstream of experimental animals two- to threefold, with essentially no effect on drug metabolism. In a vaccine study in rats, on the other hand, antibody binding of cocaine was shown to have little effect on cocaine half-life or metabolism, due in part to ongoing ester hydrolysis in the bloodstream, as well as no effect on clearance of the antibody.

Some antibodies can display catalytic properties, however. Selected monoclonal antibodies can enhance cocaine hydrolysis, thus speeding the metabolic degradation of this drug in vivo.

However, a vaccine that would elicit such catalytic antibodies from active immunization would be very difficult to design, given the broad variation in the structural features of the polyclonal antibodies elicited through immunization. Similar to morphine and in contrast to cocaine, antimethamphetamine antibodies have been shown to decrease methamphetamine clearance, prolong methamphetamine concentrations in serum, reduce conversion to amphetamine, and increase uptake in reticuloendothelial tissues like the liver. These features may well be related to the longer biologic half-life displayed by methamphetamine in comparison with cocaine, and especially to the fact that a substantial fraction of methamphetamine is not metabolized but rather excreted unchanged in the urine. Nicotine also has a longer half-life in the body than cocaine, and the effects of antibodies on nicotine pharmacokinetics have been shown to resemble those on methamphetamine, with higher plasma concentrations after nicotine doses, and a half-life that is prolonged three- to sixfold.

A theoretical concern is that the potentially high affinity of the antidrug antibodies for drug metabolites, if present in high concentrations, may reduce the amount of antibody available for native drug binding. This is particularly a concern with cocaine. Benzoylecgonine is produced by hydrolysis of cocaine's methyl ester moiety, is structurally very similar to cocaine, and is essentially inactive pharmacologically. Heavy use of cocaine will result in substantial concentrations of benzoylecgonine in plasma, up to 10-fold higher than peak cocaine concentrations. Other metabolites, such as ecgonine methyl ester and norcocaine, are present in concentrations lower than cocaine itself. The half-life of benzoylecgonine is longer than that of cocaine, contributing to the high concentrations observed. Nicotine and its major metabolites, for example, cotinine, also present concerns regarding antibody binding competition. On the other hand, significant cross-reactivity of antimethamphetamine antibodies with amphetamine, a major methamphetamine metabolite, would be very desirable since amphetamine itself is pharmacologically active. Similarly, heroin is rapidly metabolized to 6-acetylmorphine and morphine in both the periphery and in the CNS. Both of these heroin metabolites are pharmacologically active. Fortunately, morphine conjugate vaccines can elicit antibodies capable of recognizing all three compounds.

Nontraditional Vaccine Constructs

An alternative vaccine design is a completely synthetic, self-adjuvanting epitope-based vaccine, which is used to stimulate immune responses. The target epitope of the vaccine (in this case a substance abuse drug) is conjugated to a helper T (Th) cell epitope that also has the lipid moiety dipalmitoyl-*S*-glyceryl-cysteine (Pam2Cys) attached to it to function as the costimulatory signal for immune activation.

A number of candidate antibody-inducing vaccines based on this design have been constructed, such as epitopes of either luteinizing hormone releasing hormone, gastrin, or a neutralizing epitope of group A streptococcus, and each has shown good responses in animal models. Epitopes from influenza virus *Listeria monocytogenes* and tumor antigens that are recognized by cytotoxic T lymphocytes have been successful in demonstrating protection in various experimental animal systems. For antibody-inducing epitopes, the specific antibody levels elicited by the self-adjuvanting vaccine constructs in lab animals can be similar to that elicited by more traditional vaccines with standard adjuvants, such as complete Freund adjuvant (CFA), but without the toxicity associated with the latter agent. As a completely synthetic construct, the generic vaccine structure described here could have significant advantages in evaluation and development for rapid progression to human trials and clinical use.

Haptens like nicotine, cocaine, morphine, and methamphetamine are obvious potential immunogenic epitopes for such lipopeptide vaccine constructs using standard chemistries on

a peptide synthesizer. Early experiments have shown that vaccines against amphetamine and cocaine elicited satisfactory levels of antidrug antibodies in mice. Once effectively formulated, a novel antidrug lipopeptide vaccine construct of this type would be inexpensive to produce with likely fewer side effect risks than the potentially toxic additional adjuvants traditionally required for most other vaccines.

Status of Specific Drug Vaccines

Nicotine

Cigarette smoking kills almost 5 million per year worldwide and further contributes to a worse clinical outcome in a variety of diseases. Successful escape from nicotine addiction in long-term smokers remains low despite the availability of several medications, counseling programs, and other treatments. Polls have shown that an overwhelming majority of tobacco users would like to quit the habit, which is fueled mainly by a strong physical dependence on nicotine. Given the widespread prevalence, adverse health consequences, motivated population of addicts, and failure of currently available treatments, nicotine is a critical therapeutic target for an effective vaccine.

Significant strides are being made in the area of nicotine vaccines, which will provide a new therapeutic option to help motivated individuals to finally break free of nicotine addiction. Drug vaccines rely on the elicitation of specific antibodies that bind the drug in the bloodstream and thus prevent it from reaching specific receptors in the brain. This process effectively decouples the act of taking the drug and receiving the "reward" of the drug's effects. The antibodies must be present in sufficient quantities to deal with the majority of the drug amounts delivered. Whereas cocaine, heroin, and methamphetamine abuse is typically sporadic and taken in one bulk dose, nicotine is commonly delivered with frequent small doses. This can result in high plasma concentrations over a long duration. Furthermore, relapse to smoking after a period of abstinence frequently results from an ex-smoker being reacquainted with as little as a few puffs on a single cigarette, or even being in a smoky room occupied by current smokers. The presence of antibody at this precarious juncture could prevent any reward effect of the nicotine absorbed and thus help to prevent a relapse from occurring.

The effectiveness of eliciting antibodies targeting nicotine has been clearly demonstrated in animal models. In humans, three unique nicotine conjugate vaccines have completed Phase I clinical trials. All were well tolerated and able to elicit nicotine-specific antibodies, and cross-reactivity to human signaling molecules such as neurotransmitters was not observed. Following the NicVAX (Nabi Biopharmaceuticals) Phase I vaccine trial, a number of participants quit smoking for 30 days or more. This is particularly remarkable given that the trial was based around dosing and safety, not monitoring efficacy in smoking cessation. The majority of those individuals who quit were from the highest dose group, potentially linking dose/antibody response to successful smoking cessation. The NicVAX Phase IIB trial showed a 12-month continuous abstinence rate of 16% for the 400-μg schedule and 14% for the 200-μg schedule versus only 6% for the placebo group. Substantial antinicotine antibody levels were also achieved utilizing the NicQb/NIC002 vaccine (Cytos Biotechnology AG). This was illustrated in the impressive quit rates attained for the upper third of antibody responders when compared with the placebo group (57% vs. 31%). Data from the NIC002 Phase IIB trial were broken into three subgroups based on the antibody response to the vaccine: low, medium, and high responders. The 6-month continuous abstinence data showed 32% for the low, 32% for the medium, and 57% for the high responder groups compared with 31% for the placebo group, confirming the principle that only those with adequate antibody responses benefit significantly

from immunization. After 12 months, the groups exhibited a continuous abstinence rate of 26%, 21%, and 42%, respectively compared with the 21% of the placebo group. A second dose optimization trial, increasing the dose of conjugate from 100 to 300 μg, showed a 4.2-fold increase in specific antibody with up to 87% of patients achieving the antibody target level. The trial involving the TA-NIC vaccine (Celtic Pharma, London) showed a similar positive response when the 12-month quit rate was compared between the highest dose group and the control group (38% vs. 8%). These studies show that vaccination against the nicotine molecule has immense potential to aid in the vast numbers of people seeking smoking cessation, especially if the quantity of specific antibodies induced can be optimized.

Cocaine

Cocaine continues to be a major problem in the United States and elsewhere in the world, resulting in both individual and family difficulties from the medical and legal perspectives, and economic and political disruptions from the local to the international level are pervasive. At least 14.5% of Americans (35.9 million) have tried cocaine at least once in their lifetimes as of 2007, and 2.3 million admitted to cocaine use in the past year, including 2.1 million in the prior month. The societal costs of this abuse are considerable, but include the health-care costs for drug-related emergency room (ER) visits, as well as the direct health complications for individuals such as acute psychotic reactions, acute coronary syndromes, and strokes. Even though most individual abusers come to realize the dire consequences of their dependence, they often lack the ability to discontinue this highly addictive substance.

Medications to treat cocaine abuse have been sought for many years, but none has yet been sufficiently successful to achieve the status of approval. Behavioral therapies have been shown useful for some cocaine addicts, but it is clear that new approaches are needed to complement those treatment programs. A therapeutic vaccine could be just an additional treatment, with or without new medications that are currently under study, since a vaccine would function via an entirely different and potentially complementary mechanism of action. Studies in experimental animals have shown that cocaine-specific antibody will significantly inhibit the accumulation of cocaine in the brain of rats and mice, demonstrating a reduction in locomotor activity induced by pharmacologic doses of cocaine, as well as an inhibition of the reinstatement of cocaine self-administration (SA). This latter finding, as an accepted model of human cocaine addiction, may be the most pertinent for therapeutic applications of the clinical vaccine, since reinstatement of cocaine craving after a period of abstinence is one of the most difficult problems preventing the success of cocaine treatment programs. Complete avoidance of all exposure to the drug is certainly the best approach, but this is difficult to achieve, since even the most motivated individual may succumb to the temptation for cocaine use under a particularly stressful circumstance or in the context of social pressures for drug use. Thus, blocking the transient pleasure ordinarily felt from cocaine use may reduce or eliminate the craving response usually engendered in the previously abstinent individual.

A cholera toxin B conjugated cocaine preparation (TA-CD) has been developed and undergone preliminary clinical trials demonstrating safety and immunogenicity and some clinical effectiveness. A 14-week Phase IIA trial, in which 18 cocaine-dependent subjects in early recovery were studied, showed the vaccine was well tolerated at two dose levels (100 μg × 4 injections or 400 μg × 5 injections). Cocaine-specific antibodies were detectable in immunized individuals for at least 6 months. Those subjects receiving the higher dose of vaccine developed significantly higher anticocaine antibody titers than those in the low dose group and were also more likely to maintain cocaine-free urines. In the Phase IIB double-blind placebo-controlled trial, the TA-CD vaccine was able to stimulate specific antibody in almost all 57 immunized subjects (with none found in the 57 control subjects), but only about 30% of those immunized were able to produce levels of IgG antibody high enough to be expected to bind a major

fraction of the cocaine that would enter the circulation after administration of a typical abused dose of the drug. In addition, after booster dosing was completed at 12 weeks, antibody titers peaked at 16 weeks and then began an inexorable decline in virtually all subjects. Nonetheless, of those subjects who did achieve such antibody concentrations, a marked reduction in cocaine use was documented in thrice weekly urine tests for cocaine metabolites. For these subjects, more than 50% of their urine tests indicated no new use of the drug during the period when their antibodies were present. In contrast, subjects who did not develop high levels of anticocaine antibody had no significant change in their cocaine use in the same period of the study.

One concern regarding cocaine vaccines, as well as other substance abuse vaccines, is that a vaccinated individual might be tempted to use increasing doses of drug to overwhelm the antibody block in order to achieve adequate concentrations in the brain to get the high sought from the substance. Theoretically, such increasing doses might result in higher risks of drug overdose toxicity. Interestingly, higher cocaine use did not appear to happen in most of the individuals with high antibody concentrations as documented by quantitative benzoylecgonine monitoring of urine samples in the above study. This may indicate that cocaine vaccines will be best applied clinically to those individuals who are motivated to quit their substance abuse. The implications of these preclinical and clinical studies are that cocaine conjugate vaccines may have a significant role to play in reducing cocaine abuse for those who wish to quit, especially with improvements in the vaccine design or administration methods that result in higher and more persistent cocaine-specific antibody levels.

A novel complementary therapy for vaccines that produce specific antibody to cocaine has also been proposed. One of the two principal pathways for degradation of cocaine is through the enzyme butylcholinesterase, a nonspecific detoxifying hydrolase in circulation. This enzyme degrades cocaine by hydrolyzing the benzoyl ester of cocaine to produce benzoic acid and ecgonine methyl ester. Investigators have markedly enhanced the hydrolytic function of this enzyme. Recent work on this enzyme has resulted in enhanced activity up to 50,000 times faster than the native enzyme. Although passive administration of the enzyme can be overcome by increasing doses of cocaine, combining a vaccine to produce antibody to bind the drug, and gene therapy to produce low to modest levels of the enzyme might be sufficient to block CNS entry by even very high doses of drug. Such an approach, while still relegated to the future clinically, is being actively developed in animal models.

Phencyclidine

PCP ("angel dust"), an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is representative of a number of designer drugs that continue to be abused in some areas of the United States and around the world, despite the severe psychotic reactions that can occur with its use. Actual PCP dependence has been relatively uncommon, and as a result, vaccine development for PCP has been oriented primarily toward production of therapeutic antibodies, especially monoclonals, that can be used for passive, acute administration in emergency situations. The goal of eliciting monoclonal antibodies with a broad specificity for binding to a variety of PCP-related compounds has been challenging, although some progress has been made in that regard. Animal studies with PCP conjugate vaccines have shown that substantial quantities of induced antibodies can reduce the accumulation of PCP in the brain. Such antibodies can block the behavioral effects of PCP on locomotor activity and posturing, and passively administered polyclonal and monoclonal anti-PCP antibodies can also reverse the toxic effects of high PCP doses, suggesting that they may prove useful in treating patients who overdose on this drug. Unlike antibody blocking of other drugs thus far, infused monoclonal antibody against PCP has been found to block CNS effects of the drug much longer and at lower doses than would be expected based simply on predictions from drug pharmacokinetics and the antibody half-life. The mechanism by which this effect occurs remains unknown, although protection has been

shown to persist in experimental animals for up to a month after administration, despite doses of PCP administered far in excess of the antibody binding capacity.

Methamphetamine

Methamphetamine is a stimulant that is abused broadly in the United States, particularly in rural and suburban areas. The effects of methamphetamine to increase energy, a sense of well-being, and euphoria make this substance highly addictive, and once addiction is established, it is very difficult to overcome. Unlike cocaine, which is rapidly hydrolyzed to inactive compounds, methamphetamine has a long half-life and is in part demethylated to amphetamine, which is itself an addictive stimulant. Much of the parent compound and its major metabolite are cleared by the kidney with a biologic half-life of 9 to 15 hours, depending on urinary pH. The effects of this stimulant are complex, because it affects multiple neurotransmitters in the nervous system, including dopamine (DA), norepinephrine, serotonin, histamine, and γ-aminobutyric acid (GABA), both blocking monoamine transporters and causing the release of monoamines from synaptic vesicles. As a result, it is likely to be less amenable to a specific drug antagonist, or even a substitute agonist agent, than cocaine, heroin/morphine, or nicotine.

Although a very small molecule near the lower limit of size for recognition of epitopes by the immune system (molecular weight of 149), antibodies can be made against it as a hapten when conjugated to a carrier protein like the other drugs discussed in this chapter. When a monoclonal antibody preparation is administered to rats, it is able to reverse the effects of 1 mg/kg methamphetamine given 30 minutes before the antibody, as might be useful in a drug overdose situation. Furthermore, methamphetamine SA in rats and locomotor activity in rats given high-dose methamphetamine could also be inhibited by administration of monoclonal antibodies.

Active immunization with methamphetamine conjugate vaccines produces polyclonal antibodies, which will develop even with ongoing administration of methamphetamine, demonstrating that the immune responses to the conjugate vaccine were not inhibited by drug exposure during the vaccination process. This is particularly important considering the clinical application of the vaccines to active substance abusers. These experiments did not show inhibition of methamphetamine pharmacologic activity at the high doses administered; however, studies have demonstrated that some blockade of methamphetamine activity by active immunization can be achieved. In these experiments, a phenyl ring linkage to the drug was used to conjugate to fused peptides (C5a, a complement component fragment that binds to dendritic cells, and a tetanus toxoid peptide sequence recognized by Th cells). Rats were immunized with the conjugate vaccine weekly for 5 weeks, and in the absence of any other adjuvant, the resultant immune response showed modest antidrug IgG antibody by 6 weeks (1.7 μg/mL in sera). Nonetheless, vaccinated rats had to self-administer more methamphetamine than controls to overcome the presence of the antibody, which eventually became saturated with the drug, and the amount of measurable free antibody did not return to baseline until 34 days after administration of the drug was stopped. Conjugate vaccines constructed with more typical carrier proteins injected with conventional adjuvants, however, have been able to elicit much higher levels of specific antimethamphetamine IgG, up to 2 mg/mL, as measured by enzyme-linked immunosorbent assay (ELISA) at 16 weeks after the original immunization and a booster dose at 3 weeks.

Heroin and Morphine

The concept of immunization against drugs of abuse was first realized in experimental animals more than 35 years ago with morphine. However, the discovery and development of synthetic narcotic derivatives such as methadone and buprenorphine shortly thereafter, and the successful implementation of these drugs in heroin abuse treatment programs, reduced the enthusiasm for narcotic vaccines, at least in developed countries. Unfortunately, the cost of these programs,

and the resurgence of heroin/morphine abuse in recent years, especially in developing countries have clearly illustrated the limitations of this pharmacologic approach to the problem.

Narcotics abuse worldwide is dominated by heroin, especially, and morphine. In developed countries, however, there is an increasing problem with prescription drug abuse using synthetic narcotic derivatives. The number of related compounds with narcotic abuse potential and the activity of heroin metabolites, as well as the extremely broad dose range of these drugs when actively abused, pose special problems for a therapeutic immunization approach for these substances. Thus, the design of the conjugate vaccines in terms of linkage of the drug hapten to the carrier protein may be critical to their usefulness. Cross-reactivity with the major metabolites of heroin is crucial for antibody effects, since heroin is a prodrug that is rapidly converted to the pharmacologically active opiates 6-acetyl morphine and morphine by esterases present in both the periphery and the CNS. Early studies demonstrated that conjugate vaccines with a linkage through the 6-hydroxyl group elicited antibodies capable of binding heroin, 6-acetylmorphine, and morphine itself, the dominant compounds of interest, and similarly produced antibodies were later shown to bind glucuronide metabolites that also have significant narcotic activity.

Early studies of morphine conjugate vaccines through a derivative of its 6-hydroxyl group elicited a polyclonal antibody response that bound heroin and 6-acetylmorphine, as well as morphine itself. The bound drug could be displaced from this binding by later addition of new morphine, indicating that bound molecules are eventually released for metabolism and elimination. In these studies, the authors also demonstrated that the antibodies were saturable, so that higher doses of drug could overcome the binding capacity of circulating antibodies. Of most clinical relevance, SA of heroin was reduced in actively immunized rhesus monkeys. Sequestration of the drug in the blood by antibody binding prolonged morphine half-life to explain at least a part of this effect. A conjugate vaccine using morphine linked through its 6-hydroxyl moiety to tetanus toxoid was shown to be capable of binding both morphine and heroin sufficiently so that rat reinstatement behavior for either morphine or heroin was inhibited. The antibodies could bind in vitro to heroin, morphine, and the active metabolites, similar to the findings in earlier studies, but they showed no binding to synthetic narcotics used in treatment, such as methadone and buprenorphine. Conjugate vaccines to morphine through the 6-hydroxyl group are also able to elicit high levels of antibody that are also able to inhibit the nocioceptive action of morphine using hotplate assays in mice.

As discussed in the earlier section on antibody quantitation, the amount of antibody that may be expected from a very effective vaccine would be in the hundreds of micrograms/mL range, which, in molar concentration terms would be a few micromoles per liter. Owing to tolerance in heavy users, heroin doses of up to 1,600 to 1,800 mg can be "safely" injected by some subjects, which would result in up to a 2 mM acute concentration. As a result, the target population for vaccination in heroin/morphine abuse will have to be motivated addicts who have been withdrawn or are being withdrawn from opiates. Withdrawal leads to a reversal of tolerance so that the pharmacologically active drug dose will be within the range able to be inhibited by achievable antibody concentrations.

The well-known socioeconomic costs of narcotics abuse and especially the associated health complications of injected heroin abuse, including the spread of the HIV, the hepatitis C virus (HCV), and other sexually transmitted diseases (STDs) in many countries such as China, India, and Russia, have reestablished considerable enthusiasm for development of alternative therapeutic approaches for abuse of these substances, including active immunization. A successful vaccine against heroin abuse that could slow or even reverse the addiction would have profound effects on criminal behavior, social stability, and the transmission of HIV/AIDS and other blood-borne diseases or STDs.

Conclusion

A number of addictive drugs have pharmacokinetic and pharmacodynamic characteristics that make them viable targets for vaccine development. On a theoretical basis, from the known properties of antibodies and the drug concentrations in blood expected for the abused drugs discussed, the quantity and quality of antibody elicited by an effective vaccine should be sufficient to reduce or block drug effects, often by both reducing and slowing the accumulation of drug in the brain. Animal studies with several conjugate drug vaccines and human studies with nicotine and cocaine vaccines have all shown promising results. Blocking immediate behavioral and toxic drug effects is valuable in itself, but even more promising from the addiction perspective is the inhibition of drug reinforcement, or craving, which is necessary to help prevent relapse to drug use by individuals motivated to quit. According to some animal experiments, the effects on reinforcement may not require levels of antibody blocking as high as would be expected for inhibition of the acute drug effects, a property that could dramatically extend the benefits of this approach to therapy. Drug vaccines should also effectively complement current counseling programs and potential future small molecule medications that may be developed to treat the growing worldwide problems posed by the addictions. Advances in vaccine conjugate design, carrier protein use, and especially adjuvant optimization will significantly enhance the quantity and quality of the antibodies produced, allowing drug vaccines to become useful clinical tools for the treatment of substance abuse.

Suggested Readings

Anton B, Salazar A, Florez A, et al. Vaccines against morphine/ heroin and its use as effective medication for preventing relapse to opiate addictive behaviors. *Hum Vaccin*. 2009;5:214–229.

Cerny EH, Cerny T. Vaccines against nicotine. *Hum Vaccin*. 2009;5:200–205.

Duryee MJ, Bevins RA, Reichel CM, et al. Immune responses to methamphetamine by active immunization with peptide-based, molecular adjuvant-containing vaccines. *Vaccine*. 2009;27:2981–2988.

Kosten T, Owens SM. Immunotherapy for the treatment of drug abuse. *Pharmacol Ther*. 2005;108:76–85.

LeSage MG, Keyler DE, Pentel PR. Current status of immunologic approaches to treating tobacco dependence: vaccines and nicotine-specific antibodies. *AAPS J*. 2006;8:E65–E75.

Martell BA, Orson FM, Poling J, et al. Cocaine vaccine for the treatment of cocaine dependence: a randomized double-blind placebo-controlled efficacy trial. *Arch Gen Psychiatry*. 2009;66:1116–1123.

Orson FM, Kinsey BM, Singh RAK, et al. Substance abuse vaccines. *Ann N Y Acad Sci*. 2008;1141:257–269.

Orson FM, Kinsey BM, Singh RAK, et al. Vaccines for cocaine abuse. *Hum Vaccin*. 2009;5:194–199.

Pentel PR, Dufek MB, Roiko SA, et al. Differential effects of passive immunization with nicotine-specific antibodies on the acute and chronic distribution of nicotine to brain in rats. *J Pharmacol Exp Ther*. 2006;317:660–666.

25 Acupuncture

Acupuncture (derived from the word *aces*, meaning a sharp point, and *puncture*, meaning to pierce) can be defined as a technique of inserting and manipulating fine filiform needles into specific points on the body to relieve pain and for various therapeutic purposes. The original acupuncture technique uses up-and-down and rotating maneuvers, termed as manual needling. In modern times, new methods of stimulating the acupuncture points (acupoints) include applications of electric current to needles inserted in the acupoints (electroacupuncture, EA), skin electrodes placed over the points (transcutaneous electrical acupoint stimulation, TEAS), injections into the points, and finger-pressure massage of selected points (acupressure). In addition to the original 361 points, many new points have been described on specific body parts, leading to, for instance, scalp acupuncture, hand acupuncture, and ear acupuncture, also known as auricular acupuncture.

Although acupuncture and related acupoint therapies are most commonly known for their analgesic effects, it may be indicated for other medical applications such as nausea and vomiting of various etiologies. While a consensus on the clinical efficacy of acupuncture for the treatment of addictions has not yet been achieved unanimously, it has been amply demonstrated that acupuncture is an addiction treatment service now being sought by many potential patients.

Studies of Acupuncture for Analgesia

The use of acupuncture as a method of anesthesia and/or analgesia for surgery in China in the late 1950s raised a great deal of interest among the public and the biomedical community. This led to exploration of the biologic mechanisms underlying the actions of acupuncture. Starting in 1965, the Department of Public Health of China sponsored extensive research in this area. The discovery of morphine-like substances (endorphins) in the mammalian brain in 1975 had a great impact on modern concepts of pain and analgesia. It was soon clear that acupuncture (manual needling)-induced analgesia can be blocked by the opioid receptor antagonist naloxone, suggesting the involvement of endogenous opioid substances. Manual acupuncture or EA was shown to accelerate the production and release of endorphins, which could then interact with various opioid receptors to relieve or prevent pain. Endorphins are a group of peptides possessing a variety of specific characteristics. Among those peptides, β-endorphin and enkephalin are primarily agonists of the μ- and δ-opioid receptors, whereas dynorphin is the agonist for the κ-opioid receptors. Interestingly, electrical stimulation of different frequencies can specifically induce the release of different endorphins. For example, low-frequency (2 to 4 Hz) EA stimulates release of the enkephalins that interact with μ- and δ-opioid receptors, whereas high-frequency (100 Hz) EA can stimulate the release of dynorphin to interact with κ-opioid receptors. These findings

provided a biochemical explanation for the traditional acupuncture practice and suggested that the usefulness of acupuncture might be much broader than pain control.

From Pain Management to Opioid Dependence

It was natural to think that if acupuncture could release endogenous opioids in the brain to ease pain, why not make use of it to relieve opiate withdrawal symptoms? This idea was initially tested in rats made dependent on morphine. The withdrawal symptoms were significantly reduced by high-frequency (100 Hz) EA administered at the hind limbs. This effect was found to be much greater than that induced by low-frequency (2 Hz) stimulation. Encouraged by the experimental results, EA was applied clinically to previous heroin addicts to see if it suppressed withdrawal symptoms. Preliminary results were promising. However, it was soon found that it was not always feasible for patients to visit the clinic to obtain professional treatment one or more times a day, and, as a result, patients might drop out. Technology for self-administration (SA) of the stimulation was developed to see whether it would be possible for patients to treat themselves by using electrical acupoint stimulation without a needle, as part of the treatment program for their addiction problem.

Experimental findings obtained in the rat model showed that electrical stimulation applied to the surface of the skin overlying the acupoint could produce analgesic effects similar to those produced by EA through the penetrating needles. Satisfactory results were also obtained for the treatment of heroin withdrawal in humans using the same method of electrical acupoint stimulation via skin electrodes. Later, it was found that this device was also useful in suppressing the conditioned place preference (CPP) to morphine in the rat. This is an animal model mimicking craving for drugs of abuse. Subsequent human studies revealed that this form of stimulation could also inhibit the craving for heroin in addicted patients.

Acupuncture and Procedural Modifications

Manual Needling

Classical acupuncture involves the piercing of the skin by a sharp metallic needle and manipulation by up-and-down (plug-drag) and twisting (twirling) movements. The correct placement of the needle at the acupoint and the optimal manipulation are generally characterized by feedback from the patient concerning a subjective feeling called *de-qi*. This sensation, reported by patients to include heaviness, soreness, numbness, and sense of swelling, occasionally also involves the trembling of the local muscles. In the meantime, the operator of the needle (the acupuncturist) often has a feeling resembling that experienced during fishing when a fish is nibbling at or swallowing the bait. This is likely the result of the rhythmic contraction of muscle fibers surrounding the needle. According to the traditional acupuncturist, it takes years to really master the particular modes of manual stimulation, for example, to produce a feeling that is "warm" (like the whole mountain is burning), or, to produce a feeling that is "cold" (like the whole sky is freezing).

Electroacupuncture (EA)

It has been made clear that the analgesic effect induced by acupuncture can be completely blocked by local procaine injection deep into the acupoint, but not by its subcutaneous injection, suggesting that the signal of acupuncture originates mainly from nervous tissues (or tissues susceptible to procaine blockade) located in deep structures rather than in the superficial layer of the skin. Using single nerve fiber recording technique to record the afferent impulses

of the nerve innervating the site of stimulation, it was found that the nerve fibers responsible for transmission of acupuncture signals belong to the group II (Aβ) fibers. Since the analgesic effect induced by manual needling can be totally abolished by local nerve blockade or nerve transection, a neural mechanism is strongly implicated. It is thus rational to use electrical stimulation administered via the metallic needles in lieu of its mechanical movement. This has been called *EA*. The advantage of EA is that the frequency, amplitude, and pulse width of the electrical stimulation can be determined precisely and objectively, and therefore, it can be replicated by other acupuncturists or experimenters without any difficulty. Moreover, the procedure of inserting the needle at a precise skin location, and changing the direction and the depth of the needle to an optimal status to achieve a maximal *de-qi*, is just the same as in manual needling. It is only at the end of the needle-placement procedure that the patient is connected to the electrical stimulator in place of further manual stimulation. EA should optimally be given daily, or even several times per day during the period of detoxification, which may be difficult for outpatients who are at a distance away from the clinic. A procedure that can be operated by the patient at home under the supervision of the physician might be a desirable alternative to daily treatment in the clinic or inpatient care. In addition, because drug-addiction patients have a high incidence of blood-borne viral infections, it may be more convenient for invasive procedures to be replaced by noninvasive methods that do not produce sharp biohazardous waste.

Transcutaneous Electrical Acupoint Stimulation (TEAS)

An alternative to the use of EA is to take a transcutaneous route of electrical administration. However, since the skin has a very high impedance, which is more than 10 times that of the muscle tissue, it is necessary to use a constant current output device to assure a constant level of stimulation without being affected by the degree of moisture of the skin surface or the change of blood flow rate within the skin. Because the tip of the needle goes several millimeters or even centimeters below the skin, the placement of the skin electrodes should ensure the maximal stimulation of the deep structures underlying the acupoint. For example, to stimulate the Hegu point (coded as Large Intestine 4 [LI-4]) located in the thenar muscle of the hand, the correct placement of the skin electrodes should be one on the dorsal side and the other on the palm side of the point, so that the current is forced to pass through the thenar muscle with little deviation.

Regarding the frequency of stimulation, it is commonly accepted that conventional transcutaneous electric nerve stimulation (TENS) is based on the gate-control theory that high-frequency (e.g., 100 to 200 Hz) low-intensity stimulation is preferable to activate the large-caliber nerve fibers in order to suppress the pain mediated by the unmyelinated small-caliber fibers. On the other hand, "acupuncture-like" stimulation is characterized by low-frequency (e.g., 2 to 4 Hz) high-intensity stimulation. The new approach of TEAS attempts to combine the TENS-like and the acupuncture-like stimulation to create what is hoped to be an optimal mode of stimulation to maximize the release of both classes of endorphins. A device that possesses these features was designed and named Han's Acupoint Nerve Stimulator (HANS), and used in a series of animal and clinical experiments.

Neurobiology of Acupuncture Treatment

Physical Dependence

Systemic studies reveal that the mechanism of acupuncture analgesia is attributed mainly to the increased release of endogenous opioid peptides in the CNS. A rational extrapolation is that

the activation of endogenous opioid systems by acupuncture should be useful to ease opiate withdrawal symptoms.

Early in the 1970s, it was reported that transauricular electrostimulation suppressed the naloxone-induced morphine withdrawal syndrome in mice and in rats. It was shown that TENS with an intermittent high-frequency current effectively attenuated the abstinence syndrome in the rat after abrupt cessation of morphine administration. The mechanisms of action remained obscure. On the basis of findings that low-frequency EA (e.g., 2 Hz) accelerated the release of β-endorphin and enkephalin in the CNS, whereas high-frequency EA (e.g., 100 Hz) accelerated the release of dynorphin in the spinal cord, the effect of EA in a naloxone-precipitated morphine withdrawal model of the rat was tested. The results showed that 100-Hz EA was far more effective than 2-Hz in suppressing withdrawal syndrome. This outcome is hypothetically compatible with the previous reports that (a) 100-Hz EA accelerated the release of dynorphin in spinal cord and (b) spinal dynorphin can suppress the withdrawal syndrome in heroin-dependent humans and morphine-dependent rodents.

Studies have shown that chronic morphine treatment can result in damage to the dopamine (DA) neurons in the ventral tegmental area (VTA) of rats, manifested as shrinkage of the cell size, swelling of the rough endoplasmic reticulum, and blurring of the mitochondria. When 100-Hz EA was given to rats 24 hours after the last injection of morphine twice a day for 10 days, the morphine withdrawal syndrome was diminished, accompanied by a recovery of the VTA dopaminergic neurons, as compared with rats without EA treatment.

Psychic Dependence

There are several animal models that can be used to study the psychic dependence on drugs of abuse, which is a central issue in addictive disorders. CPP is one of the frequently used models. In a two-chamber or three-chamber experimental apparatus, the drug (unconditioned stimulus) is injected in the animal in one of the chambers. Thus, the drug effects become associated with the environmental stimuli unique to that chamber (e.g., color of the surroundings and texture of the floor). After repeated training, the rat will choose to stay longer on the drug-associated side than in a chamber associated with normal saline injection or no injection. The ratio between the time spent in the drug-associated side and the saline-associated side can be taken as an index for the degree of "craving." Using this model, experiments were conducted to test whether acupuncture suppresses the expression of CPP.

CPP was significantly suppressed by a single session (30 minutes) of EA at 2 Hz and 2/100 Hz, but not 100 Hz. The results suggest that it is the low-frequency component of the EA that suppressed the morphine CPP. Since the effect of EA can be completely reversed by the opioid receptor antagonist naloxone at a dose of 1 mg/kg, which is sufficient to block the opioid μ and δ, but not the κ, receptors, it seems evident that the effect of EA is mediated by endogenously released μ- and δ-opioid agonists, most likely endorphins and enkephalins, to ease "craving" for exogenous opioids (in this case, the morphine).

In practical life, craving and relapse can be easily induced by stress or by a very small dose (priming dose) of opioids. This phenomenon can be reproduced in animals using the CPP model, and this reinstated CPP can also be suppressed by EA.

For simplicity and clarity of analysis, previous studies observed only the effects produced by a single session of EA. However, in clinical practice, acupuncture or HANS is delivered daily in consecutive days or even several times a day. To mimic the clinical situation, animal experiments were designed using EA once a day for 3 or 5 consecutive days. In this case, not only 2-Hz but also 100-Hz EA was effective in suppressing morphine CPP. This finding suggests that the efficacy of EA to suppress morphine-induced CPP depends not only on the frequency of EA (2 Hz better than 100 Hz) but also on the total number of sessions of EA being administered (5 times > 3 times > single session). This may be related to the degree of activation of

the genes encoding opioid peptides. It was found that 2 and 100 Hz EA can selectively elevate preproenkephalin (PPE) and preprodynorphin (PPD) mRNA level, as well as an increase of the tissue content of DA in the nucleus accumbens (NAcc) of morphine-induced CPP rats.

Efficacy in Human Studies

Effect on Withdrawal Syndrome

For the treatment of the withdrawal syndromes in heroin addicts, HANS was used once a day for 30 minutes for a period of 10 days in a drug-addiction treatment center. Apart from the subjective answer to a standard questionnaire, two objective parameters were measured, that is, the heart rate and body weight of the patients.

Single Treatment

To observe the immediate effect of HANS on the heart rate of patients in withdrawal from heroin, the two pairs of output leads of the HANS were connected to four acupoints in the upper extremities —one pair at Hegu point (LI-4, at the dorsum of the hand on the thenar eminence) and Laogon (P-8, opposite to LI-4, on the palmar side), another pair on Neiguan (P-6, located at the palmar side of the forearm, 2 inches proximal to the palmar groove, between the tendons of the palmaris longus and flexor carpi radialis) and Waiguan (TE-5, on the dorsal surface of the forearm opposite the P-6). A "dense-and-disperse" mode of stimulation was administered, in which 2-Hz stimulation alternated automatically with 100-Hz, each lasting for 3 seconds. This mode of stimulation releases all four kinds of opioid peptides in the CNS. The control group received the same treatment, except that the electrodes were disconnected from the electronic circuitry. The average heart rate of the patients in opioid withdrawal was 109 beats per minute before treatment, significantly higher than the normal value of below 70. The dense-and-disperse mode stimulation for 30 minutes reduced the heart rate to 90 beats per minute. The full effect remained for only 20 minutes after the stimulation, and returned to its original level thereafter. So the effect was robust but short lasting.

Multiple Treatments

To observe the cumulative effect of multiple daily treatments with HANS, heroin-addiction patients were randomly divided into four groups, receiving HANS of 2, 100, or 2/100 Hz ("dense and disperse"). The control group received mock stimulation, with the electric circuitry disconnected. The treatment was delivered 30 minutes a day for 10 consecutive days. In the control group receiving mock HANS, heart rate did not come down to a level of 100 beats per minute until 8 days after the treatment. Repeated daily EA treatment was effective in reducing the tachycardia of heroin withdrawal, with an effective order of dense-and-disperse > 100 Hz > 2 Hz. This result is compatible with the findings obtained in rats that the withdrawal syndrome is more effectively reduced by 100 Hz rather than 2 Hz stimulation, while the dense-and-disperse mode is always the best because of synergistic interaction between opioids.

In order to obtain a quantitative estimate of the effect of HANS in reducing withdrawal syndrome, the following protocol was established: HANS was used three times a day for the first 5 days and reduced to twice a day for the second 5 days and then once a day for a total of 14 days. Buprenorphine (Buprenex) IM (intramuscular) was used as a supplement to HANS when the patient experienced withdrawal distress. To quantify the role of HANS in a combined HANS/buprenorphine treatment, 28 heroin-addiction patients were randomly divided into two groups, receiving only buprenorphine, or HANS plus buprenorphine. The results indicated that the total amount of buprenorphine used in the HANS group was only 8.3% of that needed

in the pure buprenorphine group. This can be taken as a quantitative estimate of the effect of HANS on opioid withdrawal symptoms. This is apparently a result of an accumulation of the therapeutic effect produced by repetitive treatments in the period of 14 days. Similar observations were made in another group of heroin-addicted subjects using a methadone reduction protocol as control group and HANS (2/100 Hz) plus methadone as the experimental group. The total dose of methadone used in the HANS group was only 25% of that in the control group.

Effect of HANS on Opiate Craving in Humans

To obtain a quantitative estimate of possible suppression of craving in response to acupuncture or related techniques, a visual analogue scale (VAS, 0 to 100 mm) to represent the degree of craving in a group of heroin-addicted patients who had completed the process of detoxification more than 1 month earlier was used. A total of 117 subjects with an initial VAS score higher than 20 were recruited, and were randomly assigned to four groups, receiving HANS treatment once a day for 10 days. This treatment period was preceded by a control pretreatment period for 10 days, and followed by another 10 days for the observation of after-effects. Three groups were subjected to HANS treatment at frequencies of 2, 100, or 2/100 Hz, respectively, and one group to mock HANS of minimal stimulation (using 5 mA threshold intensity at the beginning for 5 minutes and then switched off). There was a very slow decline of the VAS in the mock HANS control group. A dramatic decline of the degree of craving was observed in the groups receiving 2 or 2/100-Hz electric stimulation, but not in the group receiving 100-Hz stimulation. In summary, the results observed in humans coincided with the findings obtained in the rat that low-frequency HANS is more effective than high-frequency HANS in reducing the craving for opiates.

Drug- Free for 1 Year as a Standard for Successful Prevention of Relapse

Heroin addiction is characterized by a high rate of relapse even after a long abstinence. Without taking special measures, the chance of complete drug abstinence for a period of 1 year is minimal. On the basis of the findings shown in the previous study concerning the effect of HANS on opiate craving, detoxified addicted patients were encouraged to take with them a unit of portable HANS when they were discharged from the detoxification center. It was strongly recommended to have at least one session (30 minutes) before going to bed to facilitate sleep. It was also suggested that they use the device anytime when there was a strong drug cue or a robust episode of craving. The anticraving effect was usually reported to appear within 20 minutes.

A follow-up study was conducted on a group of 56 patients in Hainan Island of south China, who used HANS at home with weekly consultation and a urine check twice a month. At the end of 12 months, only 9 were drug-free based upon urine test results, so the 1-year relapse rate was 83.9% (16.1% success rate). A later study in Shanghai found a 1-year success rate of 26.8% (60 out of 224). Compared with a 95% to 99% relapse rate at the end of 1 year in the majority of reports on heroin addiction in China (without methadone maintenance), the above-mentioned results were encouraging.

Safety

Side Effects

Relatively few complications have been reported for acupuncture. Serious events including organ puncture and lung collapse are very rare, since most of the acupoints are located in the

extremities. In fact, acupuncture is well known for its low rate of aversive side effects and high safety, compared with many standard pharmacologic treatments. The risk of acupuncture-mediated infection is minimized by strict adherence to the instructions for single use needle. For those still concerned, the use of skin electrodes rather than needles will reduce this risk from minimal to zero. The serendipitous electric shock is prevented by the design of the stimulation device such that once the modulatory keys are set, the whole device will be locked to avoid the incidental touch of the parameter keys.

Dependence Liability

Given the established finding that acupuncture and related techniques would increase the release of opioid peptides in the CNS, one may be concerned that acupuncture per se might produce dependence. In an experimental setting in the rat, the hypothesis that if EA produces a pleasurable experience, repeated EA in a fixed experimental environment might cause CPP was tested. This was verified by the finding in rats that EA of 2 Hz indeed causes significant, although mild, CPP. Translating into human behavior, one may expect that acupuncture or a related technique would be welcomed by the patients, or at least to neutralize the possible inconvenience caused by needle punctures and to keep patients adhering to the acupuncture treatment schedule.

Special Considerations

Alcohol

Acupuncture was considered quite promising for the treatment of alcohol addiction in the 1980s. A study in which orthodox ear points were used, and points 3 to 5 mm apart were used as nonspecific points for control, showed promising results. However, these results could not be replicated. In a randomized, placebo-controlled study of auricular acupuncture, a large-scale clinical trial that included 503 cases showed that all groups had a significant improvement. The authors concluded that ear acupuncture did not make a significant contribution over and above that achieved by conventional treatment alone in the reduction of alcohol use.

Data show that the euphoric effect of alcohol is mediated by endogenous opioid peptides, and the opioid antagonist naltrexone has been used to assist cognitive–behavioral therapy for alcoholics. Therefore, modulation of the endogenous opioid system should be considered to be one of the approaches for the treatment of alcohol craving in alcoholic patients. EA at rat hind limb points zusanli (ST-36) significantly reduced the alcohol-seeking behavior, whereas the lumbar point Shenshu (BL-23) was not effective. The effect of EA stimulation at ST-36 was accompanied by an increase in DA level in the striatum, compared with that produced by EA at BL-23. These findings provide new information for understanding alcohol-drinking behavior and for treating human alcoholics. This was supported by a study on rats that showed special favor for alcohol consumption. EA applied at ST36 and SP6 of the rat with 2/100 Hz stimulation caused a significant reduction of alcohol consumption, which was reversed by naltrexone, a long-acting opioid receptor antagonist, suggesting that this effect is mediated by opioid receptors.

Smoking

A Cochrane review concluded that despite the relatively large number of studies, there was no consistent evidence that acupuncture was effective for smoking cessation. The efficacy of a standardized protocol of TEAS in alleviating the urge to smoke in nicotine-dependent individuals, during a 26-hour abstinence period, was evaluated. Electrical stimulation was applied on

the Hegu (LI 4)/Laogon (PC 8) points of the hand and Neiguan (PC 6)/Waiguan (TE 5) points of the upper arm using 2/100 Hz alternating frequency and 10 mA intensity as the effective stimulation, and no stimulation or intermittent 5 mA minimal stimulation as the control. The results showed that 10 mA stimulation, but not the minimal stimulation, significantly reduced the craving for smoking. The results warrant further large-scale clinical trial.

Cocaine

Cocaine addiction is one of the most important challenges of substance abuse treatment for two reasons. First, according to the 2007 WHO report, cocaine has approached heroin in terms of drug users in the whole world (14 vs. 16 million persons), and surpassed heroin in terms of illicit drug market (71 vs. 65 billion dollars). Second, there is no effective pharmacologic treatment available for cocaine addiction.

Compared with heroin addiction, cocaine addiction shows a minimal withdrawal syndrome upon cessation of use, yet more prominent and longer-lasting craving serves as one of the most important cues leading to its relapse. Therefore, the most important issue is whether acupuncture can have an effect in suppressing and/or preventing cocaine craving. Data obtained from animal experiments with cocaine are discussed first, followed by a discussion of results from clinical trials.

Experimental Studies

In the last three decades, the SA technique has commonly been used to assess the degree of psychic dependence to cocaine in rats. In recent years, CPP has also been used for this purpose. The expression of cocaine-induced CPP in rats, which was maintained for as long as 4 weeks at weekly checking, or for 13 days at a daily checking schedule, was studied. High-frequency (100 Hz) EA applied at hind leg points for 30 minutes was found to significantly reduce the CPP, whereas low-frequency (2 Hz) was without effect. This is in sharp contrast to opioid-induced CPP, where 2-Hz EA is much more effective than 100 Hz in suppressing its expression. The attenuation of cocaine CPP by 100-Hz EA may involve a κ-opioid mechanism. Indeed, the effect of 100-Hz EA can be blocked by the opioid antagonist naloxone only at a high dose (10 mg/kg). This dose is sufficient to antagonize all three subtypes of opioid receptors, including κ receptor. On the other hand, the lower doses (1 and 5 mg/kg) that are only able to inactivate μ- and δ-, but not κ-opioid receptors was not effective. These results may suggest a role for 100-Hz EA to reduce cocaine craving and to prevent relapse. Clinical trials of this approach are certainly warranted.

Clinical Trials

Ear acupuncture is often used for the treatment of cocaine addiction in the United States. A study of 226 cases of users of cocaine or crack cocaine found that 149 (65%) had more than 80% negative urine tests during the auricular acupuncture treatment period. While there was no control group, the success rate by itself was felt to be quite encouraging. This was supported by other observational studies, and encouraged by the aforementioned results, a randomized, controlled, single-blind, multisite large-scale clinical trial was conducted from 1996 to 1999. A total of 620 cocaine-dependent adults were randomly assigned to receive auricular acupuncture (four needles schedule), a needle-insertion control (four needles inserted into the helix of the ear), or a relaxation control. Treatments were offered five times weekly for 8 weeks. Main outcome measures were cocaine use during treatment and at the 3- and 6-month follow-up based on urine toxicology screening and retention in treatment. The conclusion was that within the clinical context of this study, acupuncture was not more effective than a needle-insertion or relaxation control in reducing cocaine use. The authors concluded that the results

do not support the use of acupuncture as a stand-alone treatment for cocaine addiction, yet it may play an ancillary role in the treatment of cocaine addiction. This conclusion is apparently in contrast to that derived from the animal experiments, as well as results from the preceding pilot work.

Finally, in the planning of future large trials of acupoint therapy for cocaine addiction, attention should also be directed to the results obtained in rat experiments showing that the therapeutic effect of EA is frequency-dependent, that is, 100-Hz, rather than 2-Hz stimulation can suppress the cocaine-induced CPP. Therefore, it may be worthwhile to include 100-Hz EA (and possibly body EA) stimulation in future trials of acupuncture-related therapy for the treatment of cocaine addiction.

Technical Comments on Using Acupuncture in the Treatment of Addiction

Ear Acupuncture versus Body Acupuncture

Although the ear concha is not included in the classical 14 meridians, there is no reason not to use ear points. On the other hand, there seems no reason to avoid the use of body points either. While the sensation produced by piercing the ear is almost pure pain, pain is not a component of the typical experience of *de-qi* in the body acupuncture. In other words, ear acupuncture and body acupuncture should have an equal chance of being used in the treatment of drug abuse.

Needle Staying versus Manual Needling

The results obtained in human studies suggest that manipulation of the needle produces a stronger physiologic effect than does needle staying (i.e., no manipulation) in the acupoint, at least when pain modulation is measured.

Acupuncture and Electroacupuncture versus Transcutaneous Electric Stimulation

A series of studies showed that the manipulation of the needle triggers a train of nerve impulses transmitted along the afferent nerve fibers to the CNS. The physiologic effects produced by acupuncture (e.g., the antinociceptive effect) can be readily blocked by the injection of local anesthetics deep into the acupoint, or along the afferent nerve. If nerve activation accounts for the transmission of the acupuncture signals, then similar effects should be induced whether nerve impulses are generated by manipulation of a needle (manual acupuncture, MA), or by electrical stimulation via the needles inserted into the point (EA), or even by electrodes placed on the surface of the skin over the point, forcing the current to pass through the underlying tissue (TEAS). In an experiment performed on the rat, the analgesic effects induced by EA (via needles) and by transcutaneous stimulation (via skin electrodes) were compared, and no significant difference was found between the two approaches in the antinociceptive effect. It is interesting to note that a similar mechanism seems to underlie the two analgesic effects. Thus, no matter whether the electrical stimulation is delivered via needles or skin electrodes, the opioid antagonist naloxone (2 mg/kg) produced a complete reversal of 2-Hz stimulation-produced analgesia, a partial reversal of 15-Hz stimulation-induced analgesia, and no reversal on 100-Hz stimulation-produced analgesia, unless the dose of naloxone is increased to 10 to 20 mg/kg.

Opioid versus Nonopioid Mechanisms

The mechanism of acupuncture or EA relies, at least partly, on the frequency-dependent release of opioid peptides in the CNS. For example, high-frequency (100 Hz) stimulation is more efficacious in reducing opiate withdrawal syndrome, whereas low-frequency appears to be more effective in reducing opiate craving. In contrast to opiate addiction, effects on cocaine addiction may work through a slightly different mechanism, such that CPP for cocaine in the rat, a rodent model of cocaine craving, can be suppressed only by 100-Hz, but not 2-Hz, stimulation. These findings should be considered in the future study.

Design of Appropriate Control Group

Acupuncture, as a procedure (or group of related procedures), is far more difficult to subject to a double-blind clinical trial than is a drug. In this respect, clinical trials of acupuncture should be compared with trials for different types of psychotherapy or surgical procedures, rather than drug trials. Considerable methodological progress has been made that will better answer many questions about acupuncture's efficacy. For example, the design of a mock needle that looks like it is penetrating the skin, but actually withdraws into a hollow space leaving a touch sensation on the skin mimics the *de-qi* experience. This is a single-blind design, because the acupuncturist knows the difference between the conventional needle and the mock needle.

To use EA at threshold intensity with intermittent trains is another option. For example, using a constant current device, the threshold intensity for a 4 × 4-cm skin pad is 5 mA for most subjects. A desirable intensity is two times the threshold, that is, 10 mA. On the other hand, one can use a minimal stimulation by (a) reducing the stimulation intensity to the threshold level (5 mA) and (b) reducing the time of stimulation by using an intermittent (on/off) schedule, that is, 10 seconds on and 20 seconds off, so that the stimulation time is cut by 2/3, yet the subject still feels the stimulations come and go.

Conclusion

Acupuncture is an emerging treatment for drug abuse. This approach is different from that of pharmacologic treatments. For example, while methadone maintenance treatment is aiming at long-term replacement of methadone for problematic and illicit opioid use, acupuncture or TEAS attempts to strengthen the endogenous opioid system and eventually end use of the drug. From a technical point of view, there is still considerable room for improvement, and more evidence of efficacy remains to be shown. For example, apart from the reduction of protracted withdrawal symptoms and craving, two further changes in body function help the patient to build confidence in maintaining abstinence. One is the disappearance of injection marks, and the other is the recovery of the depressed sexual function. The complicated network underlying drug abuse can be unraveled only through combined physiologic, neurobiologic, and psychological endeavors, and acupuncture may play a role at least as one of the tools in a comprehensive treatment approach.

Suggested Readings

Bullock ML, Kiresuk TJ, Sherman RE, et al. A large randomized placebo-controlled study of auricular acupuncture for alcohol dependence. *J Subst Abuse Treat*. 2002;22:71–77.

Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. *Trends Neurosci*. 2003;26:17–22.

Han JS, Zhang RL. Suppression of morphine abstinence syndrome by body electroacupuncture of different frequencies in rats. *Drug Alcohol Depend*. 1993;31:169–175.

Hu L, Chu NN, Sun LL, et al. Electroacupuncture treatment reverses morphine-induced physiological changes in dopaminergic neurons within the ventral tegmental area. *Addict Biol*. 2009;14:431–437.

Lambert C, Berlin I, Lee TL, et al. A standardized transcutaneous electric acupoint stimulation for relieving tobacco urges in dependent smokers. *Evid Based Complement Alternat Med*. 2009; 10:1–9.

Liang J, Ping XJ, Li YJ, et al. Morphine-induced conditioned place preference in rats is inhibited by electroacupuncture at 2 Hz: role of enkephalin in the nucleus accumbens. *Neuropharmacology*. 2010;58:233–240.

Margolin A, Kleber HD, Avants SK, et al. Acupuncture for the treatment of cocaine addiction: a randomized controlled trial. *J Am Med Assoc*. 2002;287:55–63.

Wang B, Zhang BG, Ge XC, et al. Inhibition by peripheral electric stimulation of the reinstatement of morphine-induced place preference in rats and drug-craving in heroin addicts. *J Peking University Health Sci*. 2003;85(3):241–247.

Wu LZ, Cui CL, Han JS. Han's acupoint nerve stimulator for the treatment of opiate withdrawal syndrome. *Chin J Pain Med*. 1995;1:30–35.

Wu LZ, Cui CL, Han JS. Reduction of methadone dosage and relief of depression and anxiety by 2/100 Hz TENS for heroin detoxification. *Chin J Drug Depend*. 2001;10:124–126.

26 Nicotine Treatment

Nicotine is recognized as the primary addictive ingredient in tobacco, and nicotine dependence has many characteristics that are behaviorally and physiologically similar to other addictions. Specific evidence-based treatments, particularly pharmacological treatments, used by the medical profession for treating nicotine dependence are a relatively recent phenomenon. The first tobacco cessation medication, nicotine gum, was approved by the FDA in 1984, and the next medication to be approved in the United States was the nicotine patch in 1993. The off-label usage of the antidepressant bupropion for nicotine dependence therapy began in the mid-1980s; FDA approval was given in 1996. These initial forays into pharmacotherapy were followed by other nicotine replacement medications, including the nicotine inhaler, nasal spray, and lozenge. Varenicline (a partial agonist at the nicotinic acetylcholine receptor [nAChR]) was approved for nicotine dependence treatment in 2006. There are now seven FDA-approved medications, three of which are available over the counter (nicotine gum, patch, and lozenge). In addition to clinic-based interventions, internet quit programs and telephone quitlines have greatly enhanced access to psychosocial treatments in the past two decades.

Nicotine Dependence Practice Guidelines

Nicotine dependence treatment begins by engaging the patient and assessing his or her readiness to change smoking behavior. Treatment should be tailored to the individual and his or her particular circumstances, motivational level, and other unique factors that influence him or her to use tobacco. This may include helping him or her increase motivation to quit and set a quit date, offering pharmacotherapy and psychosocial treatments, and helping him or her sustain abstinence and prevent relapse.

During the engagement phase, a careful assessment includes identifying the pattern of use and severity of dependence. The Fagerström Test for Nicotine Dependence, which assesses time to first cigarette of the day, the number of cigarettes smoked per day, and other smoking characteristics, can help to determine severity. Biochemical markers of tobacco use include cotinine levels in the blood and CO levels in expired air. Higher cotinine and CO levels are associated with an increased number of cigarettes per day and indicate the likely severity of nicotine withdrawal. For someone who regularly smokes 20 cigarettes per day, expired-air CO levels are typically in the 10 to 30 parts per million (ppm) range and cotinine levels in the 250 to 300 ng/mL range. The CO meter is easy to use and can be a useful motivational tool.

Assessment for history of prior quit attempts should include treatments used, if any, the length of abstinence, and the full context of relapse. Prior psychosocial treatments might include

group or individual treatment, American Lung Association and other community support groups, acupuncture, hypnosis, or Nic-A. An assessment should also be made of the person's current reasons for quitting, including his other motivation, commitment, and self-efficacy (perceived ability to quit). Another characteristic component of nicotine dependence treatment is helping the patient pick a "quit date" for when he or she will stop using tobacco products.

Pharmacology of Smoked Nicotine

Pharmacological approaches are an important component of smoking cessation treatment, and a brief understanding of the pharmacology of smoked nicotine helps understand medication strategies. The method by which nicotine is administered determines how quickly it crosses the blood–brain barrier and exerts psychoactive effects. Importantly, the strength of these effects is determined by how rapidly blood levels rise. Smoked tobacco is the most "efficient" method for delivering nicotine. Nicotine that is inhaled through a cigarette reaches the brain in less than 10 seconds and reaches peak arterial levels in 20 seconds. The half-life of nicotine is often given as 2 hours; however, it varies considerably from individual to individual, ranging from 1 to 4 hours. As a result of the short half-life, and because levels begin to fall only 15 to 20 minutes after a cigarette is smoked, nicotine plasma levels rise and fall rapidly many times throughout the day. As the blood levels fall, smokers experience withdrawal distress and an increased urge to smoke. As levels rise, withdrawal distress is alleviated and the urge to smoke diminishes. Thus, among dependent smokers, the subjectively felt "need" for nicotine is driven, to a large extent, by negative reinforcement mechanisms, which are especially potent on the account of the rapid rise in nicotine blood levels.

Nicotine-Based Medications

There are currently five FDA-approved nicotine-based medications and two FDA-approved non–nicotine-based medications. (Electronic cigarette, or e-cigarette, is available as an alternative to traditional smoked tobacco, but is not typically used as a treatment aid for quitting smoking.) The neurobiological targets of nicotine replacement therapy (NRT) are the same nAChRs that tobacco products target. However, NRT works without exposing people to either the other harmful ingredients of tobacco products or the extreme peaks and troughs in nicotine blood levels that contribute to and help maintain dependence. As a result, the abuse liability of NRTs is low. Among NRTs, the fastest peak plasma nicotine levels are achieved with the nasal spray (within 5 minutes), compared with the average cigarette in which peak arterial levels can reach 100 ng/mL within about 10 seconds. Therefore, smokers are able to titrate nicotine dose through smoking to keep within a certain peak/trough range that they prefer. Other nicotine replacement medications, including the lozenge, gum, and inhaler, are far slower acting, with peak levels reached after about 45 minutes for the lozenge, around 30 minutes for the gum, and around 10 minutes for the inhaler. Peak levels with transdermal nicotine are reached much more slowly, after about 3 to 4 hours. Interestingly, despite the wide range of time-to-peak absorption of nicotine, these products appear to have similar abilities to alleviate withdrawal distress and urges and help individuals remain abstinent in the long term. Another important factor to consider is how much nicotine is available for delivery with different products and medications. Of note, a typical cigarette contains about 13 mg of nicotine and the average smoker absorbs about 1 to 2 mg into the body. This information can be helpful, along with cotinine or carbon monoxide levels, in determining dosing titration of nicotine replacement medication. Other

factors that are used as surrogates for level of nicotine dependence and dosing of medication include time to first cigarette and number of cigarettes per day.

Non–Nicotine-Based Medications

The FDA has approved two non–nicotine-based smoking cessation medications, bupropion and varenicline. The pharmacological actions of bupropion that mediate its efficacy in smoking cessation treatment remain to be clarified. However, there are several hypothesized connections between bupropion and smoking cessation. First, bupropion acts as an antagonist at nAChRs, many of which are present throughout the mesolimbic system. Second, depletion of dopamine (DA) is believed to contribute to symptoms of nicotine withdrawal; animal studies suggest that chronic administration of bupropion increases DA concentrations, perhaps through an effect on the dopamine transporter (DAT). Third, the effects of bupropion on noradrenergic pathways may also attenuate withdrawal symptoms. Bupropion inhibits firing of noradrenergic neurons in animals and decreases whole-body turnover of norepinephrine in humans. Thus, the efficacy of bupropion in smoking cessation treatment may be due, in part, to its effects on the mesolimbic dopaminergic and possibly noradrenergic systems involved in drug withdrawal.

The pharmacological actions of varenicline that mediate its efficacy in smoking cessation treatment are likely a function of its competitive nAChR antagonist properties. Varenicline is also an $\alpha 4\beta 2$ nAChR partial agonist. As a partial agonist, the effect of varenicline on DA release is only about 35% to 60% compared with nicotine. Less DA activity reduces craving and withdrawal symptoms, which also decreases the reinforcing aspects of nicotine.

Medication Efficacy

There is abundant support for the efficacy of the FDA-approved medications for nicotine dependence. In clinical trials, about 14% of participants receiving placebo achieve long-term smoking abstinence of 6 months. The nicotine patch has been the most extensively investigated of the NRTs, and in meta-analyses, has been found to approximately double the odds that a smoker will achieve long-term abstinence. A similar odds ratio has been reported for the nicotine inhaler, lozenge, and nasal spray. Nicotine gum, used for up to 14 weeks, increased the odds of quitting by 50% compared with placebo. Interestingly, however, the odds of quitting doubled in trials of longer-term gum use.

Among the non–nicotine-based medications, bupropion has been the most extensively studied, and meta-analyses show that this medication also approximately doubles the odds of quitting. The odds of quitting with varenicline appear to depend on dosage. The 1-mg dose approximately doubles and the 2-mg dose triples the odds of achieving long-term abstinence. When compared with the nicotine patch, varenicline improves the odds of quitting by 60%. Finally, two second-line medications for smoking cessation, nortriptyline and clonidine, also approximately double the odds of achieving long-term abstinence.

A growing number of clinical trials have also investigated the efficacy of combinations of smoking cessation medications. Studies of two combinations in particular—patch and gum, patch and nasal spray—have produced the best results. Participants who received one of these combinations were 3.6 times more likely to achieve abstinence compared with placebo. Recognizing that tobacco dependence is a chronic relapsing disorder, researchers have also begun to investigate the efficacy of long-term medication treatment. As already noted, meta-analyses found greater efficacy of nicotine gum in studies in which the gum was used for more than

14 weeks compared with fewer than 14 weeks. In addition, one study has reported higher quit rates with long-term use of the nicotine patch.

Efficacy of Medication in Smokers with Psychiatric Disorders

Researchers are increasingly turning their attention to investigating the efficacy of smoking cessation treatments in smokers with psychiatric disorders, where rates of smoking are two to four times higher than in the general population. Randomized medication trials have been conducted with smokers with schizophrenia, and there is some evidence that suggests smokers on atypical antipsychotics are more likely to achieve abstinence following a quit attempt than those taking typical antipsychotics. There is little evidence that quitting smoking has an adverse effect on the symptoms of schizophrenia.

Studies have also investigated the efficacy of smoking cessation treatments with alcoholics in early recovery. In a meta-analysis of clinical trials of concurrent smoking and alcohol treatment, the mean quit rate at follow-up for both intervention and control conditions was 7%. Importantly, the preponderance of evidence does not indicate that smoking cessation compromises alcohol abstinence. However, there is some evidence that suggests that drinking status should be carefully monitored during a smoking quit attempt in this population.

Studies have investigated the effect of a quit attempt on the emergence of major depression among smokers with a past history of depression. While rates vary widely between studies, these smokers were more likely to develop major depression following a quit attempt compared with smokers without a past history. Close monitoring of smokers with histories of depression is warranted during smoking cessation treatment. However, clinicians and patients should understand that depressed mood is not uncommon among smokers following a quit attempt and that it often resolves within 1 to 4 weeks.

Optimal Use of the Medication, Including Safety Concerns

Medications are optimally used by individualizing a prescribed regimen to fit the patient's needs, including the amount of daily tobacco use and severity of nicotine dependence, comorbid psychiatric and medical conditions, concurrently-taken medications, and patient values and preferences. It is particularly important to educate patients about the appropriate use of medications. For example, "chewing" nicotine gum is a "bite and park" technique. A second example is that patients must understand the effect of acidic beverages on the buccal absorption of nicotine from the gum, lozenge, and inhaler. Two common ways to optimize the medications include the concurrent use of two medications for nicotine dependence (e.g., a patch and a short-acting NRT) and integrating behavioral and/or other psychosocial treatments with medications. Nicotine dependence treatment practice guidelines recommend the integration of nicotine treatment medications with behavioral and supportive psychosocial approaches.

Nicotine Gum

Nicotine gum is available in doses of 2 and 4 mg. Although the 2-mg gum is recommended for people who smoke fewer than 25 cigarettes per day and the 4-mg gum is recommended for people who smoke 25 or more cigarettes per day, many clinicians will just recommend the 4-mg dose during smoking cessation or forced abstinence situations (such as on an airplane). Smokers

should use at least one piece every 1 to 2 hours for the first 6 weeks but not exceed 24 pieces in a 24-hour period. The gum is typically used for 8 to 12 weeks, although some research has shown that longer duration of use is associated with greater efficacy. The gum is effective when it is used to maintain a steady plasma nicotine level; while it can also be used to cope with urges as they occur, it is unlikely to be effective when only used ad libitum.

Nicotine gum releases nicotine from an ion-exchange resin. The gum should be chewed slowly until a peppery taste is achieved (usually after two or three "chews") and then placed between the teeth and cheek for a few minutes. The process is then repeated until the taste dissipates (after about 30 minutes). The nicotine released has a medicinal effect only when it is absorbed through the oral mucous membranes. It should not be swallowed because absorption depends on the pH of the medium, and nicotine cannot be absorbed in a highly acidic medium. For this same reason, acidic beverages (e.g., coffee, soft drinks) should not be used for 30 minutes before or 30 minutes after gum use. Finally, nicotine gum is not recommended for patients with temporomandibular joint problems, dental problems, and dentures.

Side effects and adverse effects of nicotine gum can include local irritation in the mouth, tongue, and throat, mouth ulcers, hiccups, jaw ache, gastrointestinal symptoms (flatulence, indigestion, and nausea), anorexia, and palpitations. Chewing the gum too fast can cause lightheadedness, dizziness, hiccups, nausea, vomiting, or insomnia. Another frequently occurring side effect of chewing nicotine gum is the apparent constriction of the muscles of the throat. As nicotine constricts the blood vessels in the gums, use of nicotine gum for a longer period of time can lead to gum diseases, owing to inadequate blood flow. Heartburn can occur as a side effect of nicotine gum use if the nicotine containing saliva is swallowed rather than absorbed buccally.

Nicotine Toxicity

Nicotine toxicity, while rare, can occur if the individual continues the usual smoking patterns while also using NRT. Although concurrent use can occur with any type of NRT product with tobacco products, clinicians have been most careful when prescribing the NRT patch since this is a long-acting product. In most cases, individuals who start NRT patch might slip and also use a few cigarettes while trying to quit. This does not mean that the NRT should be discontinued; however, the clinician should work with the patient in an attempt to determine the ongoing triggers and whether some short-acting NRT (gum, lozenge, spray, or inhaler) might be added to the NRT patch or if there are some behavioral therapy (BT) strategies that could be helpful to manage ongoing cravings. Tobacco users try to avoid nicotine intoxication symptoms when smoking or using other forms of tobacco. Symptoms of nicotine overdose include chest pain, irregular heartbeat, nausea, vomiting, along with severe dizziness, blurring of vision, and seizures.

Nicotine Lozenge

The nicotine lozenge is available in 2- and 4-mg dosages. The 2-mg lozenge is recommended for tobacco users who are less heavily addicted (e.g., smoke their first cigarette of the day more than 30 minutes after waking in the morning). The 4-mg dose is recommended for more heavily addicted users. Suggested dosing is at least nine lozenges per day during the first 6 weeks of treatment, with one lozenge every 1 to 2 hours. The lozenges should be used for up to 12 weeks with a dose taper to one lozenge every 2 to 4 hours starting in week 7 and further tapering to one lozenge every 4 to 8 hours in weeks 10 to 12. Usage should not exceed 20 lozenges per day. As with the gum and inhaler, nicotine absorption occurs through the oral mucous membranes and users should be instructed to avoid acidic food and drink for 30 minutes before and after use.

Side effects and adverse effects of the nicotine lozenge can include irritation of the teeth, gums and throat, indigestion, diarrhea or constipation, flatulence, insomnia, hiccups, headache,

and coughing. The lozenges should be sucked slowly and gently, and not chewed or swallowed, as this may cause heartburn or indigestion. Nicotine toxicity may occur if not used as directed.

Nicotine Patch

Nicotine patches are available in 21-, 14-, and 7-mg dosages. A typical nicotine dependence treatment regimen can be 8 to 12 weeks, and one method starts the patient on a 21-mg patch for 1 month, followed by 2 weeks of the 14-mg dose and 2 weeks with a 7-mg dose. Some clinicians just prescribe the 21-mg dose for the full 8 to 12 weeks and do not taper to lower dose patches. The nicotine patch allows nicotine to be slowly absorbed through the skin. At the start of each day, the patient should place the patch on a relatively hairless, clean location (typically between the neck and waist), rotating the location every day to avoid local skin irritation. The patch may be removed at night if the patient experiences disruption of normal sleep. The nicotine patch provides continuous release of nicotine. Peak nicotine levels are reached after 4 to 6 hours and then gradually decline over the course of the rest of the day, dropping to very low but detectable levels during the night. The 21-mg patch provides the user with about 16- mg of nicotine over a 24-hour period. The transdermal patch does not allow for self-titration of dose, like the other NRT products (gum, spray, inhaler, and lozenge) which can be taken to help quell momentary craving or withdrawal distress.

Side effects and adverse effects of the nicotine patch can include local skin reactions or erythema (25%), itching, burning, or tingling when the patch is applied. This usually goes away within an hour, and is a result of nicotine coming in contact with the skin. Some patients complain of vivid and sometimes unpleasant dreams and/or insomnia with overnight patch use; this is more frequent with the 24-hour patch, and one remedy is to remove the patch while sleeping.

Nicotine Nasal Spray

The nicotine nasal spray contains aerosolized nicotine that is delivered to the nostril. Each spray contains 0.5 mg of nicotine. One dose consists of two sprays of 0.5 mg each, one to each nostril (1- mg of nicotine total). Each bottle contains enough nicotine for roughly 50 doses. Initial treatment should be 1 to 2 doses every hour, increasing as needed for relief of withdrawal symptoms. Minimum recommended dosage is eight doses per day. Usage should not exceed 40 doses per day. Recommended duration of therapy with the nasal spray is 3 to 6 months. Nicotine from the nasal spray is absorbed through nasal mucous membranes, resulting in more rapid absorption than NRTs absorbed through oral mucous membranes or transdermally. Therefore, the nasal spray may be appropriate for smokers who respond strongly to the "hit" of nicotine that cigarettes provide. Patients should avoid sniffing, swallowing, or inhaling through the nose while administering doses, as this may increase irritation. The spray is best administered with the head tilted backward slightly.

Side effects and adverse effects of the nicotine nasal spray can include local airway irritation (i.e., coughing, rhinorrhea, lacrimation, nasal irritation), though tolerance to these appears to develop relatively quickly. Systemic effects include nausea, headache, dizziness, tachycardia, and sweating. The spray replicates the repeated administration of nicotine seen in smokers, potentially resulting in reinforcing peaks. As such, an initial concern regarding the spray was the potential for abuse due to the relatively rapid time course to peak blood level, although cases of abuse have been rare.

Nicotine Inhaler

The nicotine inhaler consists of a perforated cartridge filled with 10-mg of nicotine and an additive to reduce irritation from inhaled nicotine. A draw from the inhaler is similar to the

average draw from a cigarette and produces about 0.1 μmol of nicotine at room temperature, with nicotine delivery decreasing sharply below 40°F. Similar to other NRTs, the recommended time on the medication is about 12 weeks and this might be extended depending on individual situation and need for tapering off. The inhaler must be "puffed" and, therefore, imitates the upper airway stimulation experienced while smoking, though absorption is in fact primarily through the oropharyngeal mucosa. As such, acidic foods such as coffee and soft drinks should be avoided for half an hour before and after use. Efficacy of the inhaler is optimized by frequent use. Users should consume at least six cartridges per day. Each cartridge delivers a 4-mg dose of nicotine over 80 inhalations.

Side effects and adverse effects of the nicotine inhaler are similar to those of the spray and can include local irritation, cough, headache, nausea, and dyspepsia. Local irritation in the mouth and throat was reported by 40% of patients using the inhaler as compared with 18% of patients on placebo. Coughing (32% active vs. 12% placebo) and rhinitis (23% active vs. 16% placebo) were also higher for those using the inhaler.

Bupropion SR (Zyban, Wellbutrin)

Bupropion is a heterocyclic, atypical antidepressant that blocks the reuptake of both DA and norepinephrine. It is a strong antagonist to the $\alpha_3\beta_2$ nicotinic receptor and weaker antagonist to the $\alpha_4\beta_2$ and α_7 nicotinic receptors. Treatment for nicotine dependence with bupropion SR should begin about 1 to 2 weeks before the patient's quit date. A dose of 150-mg should be taken each morning for 3 days, followed by a dose of 150-mg twice daily for the remainder of the treatment. From clinical experience, some patients benefit from a longer time period before the dose is increased to 300 mg per day. Dosage should not exceed 300 mg daily. Similar to other nicotine dependence treatments, the PDR recommends 12 weeks for treatment; however, individual situations may suggest using the medication for a longer period.

Bupropion SR's efficacy in nicotine dependence treatment is not due to its antidepressant properties, although it has been found helpful in patients with a history of depression. Of note, NRT has also been shown to be effective in helping people with a prior history of depression. If insomnia occurs with bupropion SR, taking the second daily dose earlier in the evening may be helpful. Alcohol should be used moderately while taking bupropion SR, and patients should be evaluated for alcohol dependence or any other substance use disorders (SUDs). Bupropion SR is contraindicated in patients with a history of seizures or eating disorders, and patients who have used a monoamine oxidase inhibitor (MAOI) in the past 14 days.

Side effects and adverse effects of bupropion are more limited with this medication in smoking cessation studies compared with studies of depressed patients, although the reason for this is not understood. Some of the common side effects include dry mouth, insomnia, nausea, and skin rashes. Less frequently, use of bupropion is also associated with hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. As a result of these concerns, the FDA requires a black-box warning about these possible adverse effects and recommends that the provider monitor any changes in patient mood or behavior while the patient is taking bupropion. This warning about neuropsychiatric problems is also present for varenicline. Finally, as noted, bupropion should not be used for patients who have an eating disorder or who have a history of seizures.

Varenicline (Chantix)

This is a partial agonist of the $\alpha_4\beta_2$ subtype of the nAChR and a full agonist at α_7 neuronal nicotinic receptors. Typical nicotine dependence treatment with varenicline involves an initial upward titration of dose. The patient should be instructed to take varenicline on a full stomach,

starting at 0.5 mg once daily for the first 3 days followed by 0.5 mg twice daily for 4 days. The patient then takes 1 mg twice daily for 3 months. The patient should be instructed to cease smoking on day 8 of the treatment, when the dosage increases to 1 mg twice daily. Varenicline is approved for up to 6 months of treatment. If insomnia becomes an issue, the second pill of the day should be taken at supper instead of bedtime. Dosage of varenicline in patients with significant kidney disease (creatinine clearance ≤30 mL/min) or who are currently on dialysis should be reduced.

Side effects and adverse effects of varenicline can include constipation; flatulence; headache; increased appetite; nausea; vomiting; vivid, strange or unusual dreams; insomnia; and taste changes. These were the most common adverse events, occurring at twice the rate as with placebo or in more than 5% of subjects. Less frequently, use of varenicline is also associated with hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. As a result of these concerns, the FDA requires a black-box warning about these possible adverse effects and recommends that the provider monitor any changes in patient mood or behavior while the patient is taking varenicline.

Psychosocial Treatment

Psychosocial treatments are an important component of nicotine dependence treatment. Unfortunately, psychosocial treatments are underutilized and most often not a component of treatment. Treatment is most likely to be medication only. There are many reasons for this, including poor reimbursement, lack of provider training in the techniques, and emphasis on medications due to direct-to-consumer advertising. All treatment guidelines recommend the use of psychosocial treatment.

The core psychosocial treatments for nicotine dependence are similar to those for other SUDs, including cognitive–behavioral therapy (CBT), motivational enhancement therapy/motivational interviewing (MET/MI), and 12-step facilitation. CBT and MET have been adapted and evaluated specifically for nicotine dependence, both as brief interventions in primary care and more intensive interventions in smoking cessation clinics. Internet- and telephone-based interventions are also broadly available and effective. In general, psychosocial treatments aid in smoking cessation by increasing patient awareness of the risks of tobacco use and the benefits of quitting; increasing motivation to quit, and engage in treatment; providing support for changes in behaviors and activities that will help sustain abstinence over time; and encouraging use of medications. Assessing motivation to quit smoking is important. The transtheoretical model describes five stages of motivational readiness to change a behavior: precontemplation, contemplation, preparation, action, and maintenance stages. There are outstanding resources available that provide detail on specific approaches for these different motivational levels.

Lower Motivated Patients

Many patients are lower motivated and do not initially want to stop using tobacco products. Different strategies can be used to help motivate these individuals, including MET, brief personalized feedback interventions, reducing barriers to accessing treatment, connecting to support groups or healthy living/wellness oriented groups, educating their family members, and recommending they speak to others who have quit. Some strategies to help patients prepare for quitting include suggesting they monitor their own tobacco use, which may lead to recognition of how much and in what situations patients are smoking, discussion about the benefits of quitting and risks of continued use, and assessing who could provide support and who or what might be the barriers to change.

MET strategies try to help the individual increase their motivation and commitment to quit. The approach gives the clinician a framework of maintaining empathy, optimism, and a nonconfrontational style in the context of lower motivation and lack of agreement on a goal of abstinence. MET works very well with the stages of change model, which recommends modifying the strategies based on the patient's readiness for change. When patients appear to have no internal motivation to quit, a confrontational style predictably elicits patient resistance and nonengagement in treatment. By "joining up" with patients and meeting them at their stage of change, clinicians are more likely to be able to develop realistic goals with the patient. These might be limited to increasing awareness about risks and benefits, providing knowledge about treatment options, and understanding the particular motivators for and barriers to change. As motivation increases, patients may feel more comfortable setting a goal to reduce or eliminate cigarette use only in a specific place (for instance, in the car or home) versus complete abstinence. Brief personal feedback interventions by a physician or other medical staff can increase the likelihood of treatment success two- to tenfold. Personalized feedback that has been shown to help increase motivation includes giving feedback on the patient's cost of cigarettes for 1 year, carbon monoxide score, and information on the relationship of the patient's own specific health concerns (e.g., cardiac, pulmonary, impotence, wrinkles, wound healing). Other helpful feedback includes discussing the interaction of a patient's medications with tobacco metabolism, and the negative effect on low-density lipids from smoking.

Higher Motivated Patients

The general approach to the motivated client is to initially engage with them by doing a comprehensive assessment, give them information on treatment options, confirm the motivation to quit, learn about potential barriers and strengths, and set a quit date. Helping them quit includes preparing for the quit date, selecting the medication option that they prefer, enlisting supportive friends or family, and engaging in some type of psychosocial treatment (individual, group, internet, quitline). This phase includes learning about cues and triggers and anticipatory guidance on how to manage these; about nicotine withdrawal and the appropriate use of medications to manage the symptoms; and about psychosocial strategies to help manage cravings, withdrawal symptoms, and triggers to use. CBT and BT, in general, are appropriate treatment options for most dependence issues, including nicotine dependence. BT involves the identification of affective, cognitive, and environmental cues that trigger tobacco use behavior. Awareness of these trigger cues is helpful in planning intervention strategies to prevent relapse upon their presentation. BT strategies often normalize the role of abstinence lapses during the progress of treatment ("slips") such that "falling off the wagon" is not viewed as an irreparable failure. Discussion of management techniques for withdrawal symptoms, such as sleep disturbance and irritability, can be useful and can allow individuals to learn techniques from others when performed in a group setting. This can also occur as part of a separate relapse prevention coping skills training. Stress management and relaxation training are often used as secondary interventions to buttress behavioral methods. Stimulus control strategies involve the removal or alteration of cues that have been strongly associated with tobacco use, for example, avoiding certain situations that are likely to increase craving. Problems with the group format include low compliance, lack of availability of groups, and a general reluctance to participate on the part of some patients. Problems with the individual format include higher cost and the need for more counselors per population.

Despite little controlled research examining psychosocial intervention with spouses and significant others or families, social support for individuals who are attempting to quit using tobacco appears to enhance treatment success. Immediate family and social circles can be involved in treatment via education about supportive roles and behaviors. Concerned others can be engaged as well, providing assessment information or helping to enhance patient motivation.

Conjoint sessions with family members may help with motivation, education, and sustaining changes. This may also address a barrier if a family member is a tobacco user.

Hypnosis, acupuncture, and laser therapy are approaches that some individuals believe have been beneficial in their efforts to stop using tobacco. The empirical evidence does not support use of these therapies, though poor study methodology makes a definite conclusion impossible to make. Hypnosis claims to reduce or even ameliorate the desire to use tobacco or to help solidify a commitment to quit. Acupuncture is a traditional Chinese therapy that aims to reduce the withdrawal symptoms associated with tobacco cessation through the insertion of needles into specific areas of the body. Laser therapy purports to operate under the same mechanisms of action as acupuncture using low-level lasers instead of traditional needles.

Many areas now have meetings of Nic-A groups that are structured similarly to Alcoholics Anonymous groups. These groups are based on the 12-step approach to recovery. Nic-A is a relatively new organization and does not therefore have the extensive network that other 12-step programs have developed over time. No formal controlled studies looking at the benefits obtained by attending Nic-A have been conducted. Written self-help materials such as those distributed within Nic-A can play a vital role in patient education, especially regarding the negative health effects of tobacco, the benefits of quitting, and the nature of the addiction. Self-help literature, internet resources, and Nic-A can be efficiently incorporated into formal treatments as well as brief interventions individual and group treatments.

Addressing Tobacco through Organizational Change

The better integration of nicotine dependence treatment into routine clinical practice requires system changes as well as training and education of staff and physicians. All the evidence-based practice guidelines also include information on doing system change. The Addressing Tobacco Through Organizational Change (ATTOC) model has been used in all types of clinical settings, including inpatient, outpatient, community-based outreach, mental health, addiction, general medical, and emergency room settings. The ATTOC model helps an agency/practice to develop specific patient, staff, and environmental goals that will help assure improved patient care, staff recovery, staff training, new policy development, communication, and environmental restrictions or campus tobacco-free initiatives. Staff training is not enough for changing the culture of clinical practice to integrate nicotine dependence treatment.

Conclusion

Nicotine dependence treatment is efficacious and cost-effective. Blending medications and psychosocial treatments improves clinical outcomes, as does the use of multiple medications for the more severely dependent. There are specific strategies for patients with different levels of motivation; using motivation-based treatment approaches may help patients create more realistic goals in which they are invested. In addition to individual and group counseling approaches, the use of internet sites and telephone quitlines allows for greater access to help for many.

Suggested Readings

Abbot NC, Stead LF, White AR, et al. Hypnotherapy for smoking cessation. *Cochrane Database Syst Rev*. 1998;(2): Art. No.: CD001008. DOI:10.1002/14651858.CD001008.

Etter JF, Stapleton JA. Nicotine replacement-therapy for long-term smoking cessation: a meta-analysis. *Tob Control.* 2006;15:280–285.

Hajek P, Stead LF, West R, et al. Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev*. 2005;(1). Art. No.: CD003999. DOI:10.1002/14651858. CD003999.pub2.

Hughes JR. Depression during tobacco abstinence. *Nicotine Tob Res.* 2007;9:443–446.

Keating GM, Siddiqui AA. Varenicline: a review of its use as an aid to smoking cessation therapy. *CNS Drugs*. 2006;20(1):945–960.

LeSage MG, Keyler DE, Pentel PR. Current status of immunologic approaches to treating tobacco dependence: vaccines and nicotine-specific antibodies. *AAPS J.* 2006;8(1):65–75.

Piper M, Smith S, Schlam T, et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Arch Gen Psychiatry.* 2009;66(11):1253–1262.

Prochaska JJ, Delucchi K, Hall SM. A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. *J Consult Clin Psychol*. 2004;72:1144–1156.

Stead LF, Perera R, Bullen C,et al. Nicotine replacement for smoking cessation. *Cochrane Database Syst Rev*. 2008;(1):CD000146 pub3.

White AR, Rampes H, Campbell JL. Acupuncture and related interventions for smoking cessation. *Cochrane Database Syst Rev.* 2006;(1): Art. No.: CD000009. DOI:10.1002/14651858. CD000009. pub2.

27 Psychosocial Treatments

Self-Help Groups

Self-help groups (SHGs), often called mutual help or support groups, are an important component of the system of care for individuals with substance use disorders (SUDs). SHGs are composed of individuals who share a common problem, such as a SUD, and who meet regularly to exchange support and information about how to manage and overcome that problem and lead more meaningful lives; in general, these groups do not have professionally trained leaders. SUD patients have high rates of posttreatment relapse and additional episodes of specialized care; participation in SHGs tends to improve the likelihood of achieving and maintaining remission and to reduce the need for further professional care. SHGs offer a safe, structured setting in which members can express their feelings, improve their communication and interpersonal skills, clarify the reasons for their substance abuse, learn self-control, and identify new activities and life goals.

Twelve-Step Self-Help Programs

The most prevalent substance use–focused self-help programs, including Alcoholics Anonymous (AA), Narcotics Anonymous (NA), and Cocaine Anonymous (CA), follow traditional 12-step principles. AA is a fellowship whose primary purpose is to help individuals with alcohol-related problems maintain sobriety. It is structured around the 12 steps (e.g., admission of powerlessness over alcohol, belief in a higher power) and 12 traditions (e.g., an emphasis on common welfare and recognition that personal recovery depends on AA unity). Other key aspects of AA involve open and closed group meetings.

NA is a fellowship of recovering individuals with drug use problems. NA grew out of AA and is similar to AA in that it provides a structured support network in which members share information about overcoming addiction and living productive, drug-free lives through adherence to the 12 steps and 12 traditions. NA encourages complete abstinence from all drugs, including alcohol, but, consistent with AA, accepts the use of prescribed medications for psychiatric and medical disorders.

CA is a fellowship open to individuals who want to stop using cocaine, including "crack" cocaine and other mind-altering substances. CA's program of recovery was adapted from AA, and like AA. Traditional 12-step SHGs may have some limitations for individuals who have both substance use and psychiatric disorders, in part because they may be less able to bond with other members who do not share experiences associated with psychiatric problems.

Alternative Self-Help Programs

Many individuals do not believe in 12-step principles or traditions and find it hard to accept the idea of submitting themselves to a Higher Power. This fact has led to the growth of several self-help programs that are not based on the 12 steps, including SMART (Self-Management and Recovery Training/SMART Recovery), Secular Organizations for Sobriety/Save Our Selves (SOS), LifeRing Secular Recovery (LifeRing), and Women for Sobriety (WFS).

SMART espouses a rational treatment orientation and focuses on teaching individuals new coping skills and more logical ways of thinking and acting. SMART's four-point program includes (1) building and maintaining motivation to abstain; (2) learning how to cope with urges; (3) managing thoughts, feelings, and behavior; and (4) balancing momentary and enduring satisfactions.

SOS provides support for individuals who seek to achieve and maintain sobriety, a forum to express thoughts and feelings about recovery, and a nonreligious or secular approach that does not depend on the 12 steps or traditions. Members are expected to acknowledge their addiction and take personal responsibility for achieving and maintaining sobriety.

LifeRing is another secular alternative to AA and NA. It is similar to AA/NA in that it is oriented toward abstinence; however, it is based on the belief that the positive social reinforcement of the group, rather than a Higher Power, can support individuals in their quest to lead a clean and sober life. Members are encouraged to rely on the group process to guide them toward the development of an individualized path to recovery.

Some women are alienated by the emphasis on powerlessness, humility, and surrender and/or express discomfort with face-to-face self-disclosure in group meetings populated mostly by men. These issues led to the development of WFS, which shares AA's focus on meditation and spirituality, but espouses the idea that sobriety depends on taking personal responsibility for one's behavior rather than on a Higher Power. WFS provides an alternative for women who prefer an emphasis on improving self-esteem, independence, and personal responsibility, and who wish to explore personal issues in groups with other women.

Self-Help Groups and Substance Use Outcomes

Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity) was a large clinical trial that compared the outcome of 12-step facilitation, cognitive–behavioral therapy, and motivational enhancement treatment for patients with alcohol use disorders. Patients who attended AA more often in each 3-month interval after treatment were more likely to maintain abstinence from alcohol in that interval. In addition, more frequent AA attendance in the first 3 months after treatment was related to a higher likelihood of abstinence and fewer alcohol-related consequences in the subsequent 3 months. Outpatients with SUDs who attended more 12-step SHG meetings in the prior 6 months were more likely to be abstinent at both 6-month and 5-year follow-ups. Individuals who attend SHGs over a longer interval are more likely to maintain abstinence than are individuals who stop attending. Patients who participated in a minimum of six meetings in the prior 6 months had better substance use outcomes at 6- and 30-month follow-ups. Attendance is an important indicator of participation, but it may not adequately reflect the depth of an individual's involvement in a SHG, as shown by such indices as number of steps completed, acceptance of 12-step ideology, and self-identification as a group member.

Maintaining attendance without significant involvement may indicate reluctance to fully accept 12-step group ideology and the goal of abstinence. Individuals who attend SHGs but are unable to embrace key aspects of the program are less likely to benefit from it. Thus, optional SHG attendance may be more closely associated with better substance use outcomes than is SHG attendance that is expected as part of a treatment program, perhaps because voluntary participation reflects more motivation for change than does expected or coerced participation.

Self-Help Groups and Quality of Life Outcomes

SHGs also appear to promote positive quality of life outcomes, as indicated by more personal and social resources and better social functioning. With respect to personal resources, participation in SHGs has been associated with increases in self-efficacy for abstinence, and decreases in distress, depression, and psychiatric symptoms. Affiliation with 12-step SHGs tends to promote more reliance on approach coping and less on avoidance coping. In this vein, compared with patients who had no continuing care after residential treatment, at a 1-year follow-up patients who attended 12-step SHGs tended to rely more on coping responses aimed at reducing substance use, such as stimulus control (e.g., removing reminders of drinking from home) and, counter-conditioning (e.g., engaging in physical activity instead of drinking). There is also a relatively robust relationship between SHG involvement and better social support and functioning. Similarly, individuals with drug use disorders who attended NA once a week or more had more friends and social resources than their peers who did not attend NA or attended infrequently.

Participation in Self-Help Groups and Treatment

Compared with individuals who initially entered only AA, individuals who entered both treatment and AA participated in AA as much or more in the subsequent 15 years. Individuals who stayed in treatment longer in the first year after initiating help-seeking subsequently showed more sustained participation in AA. More extended treatment later in individuals' help-seeking careers was not associated with later participation in AA, which suggests that treatment providers' referrals to AA have more influence in the context of an initial treatment episode.

There is also a more specific link in that, compared with patients who participate in treatment not oriented toward 12-step principles, patients who participate in 12-step facilitation treatment, which introduces patients to 12-step philosophy and encourages them to join a group and get a sponsor, are more likely to affiliate with 12-step SHGs. Similarly, patients with cocaine use disorders who receive individual drug counseling based on 12-step philosophy are more likely to attend and participate in SHGs than are comparable patients who receive supportive–expressive or cognitive treatment.

In Project MATCH, patients who developed a stronger alliance in treatment were more likely to attend AA during and after treatment. More generally, a supportive and spiritually oriented treatment environment can enhance participation in 12-step activities. In this vein, patients in more supportive treatment environments increased 12-step involvement during treatment; that is, they were more likely to acquire a sponsor and 12-step friends and to read 12-step literature. These findings suggest that participation in treatment tends to strengthen SHG affiliation, which may bolster the effects of treatment. A supportive treatment milieu and strong treatment alliance may enhance patients' motivation for recovery and strengthen the impact of counselors' recommendations to maintain affiliation with SHGs.

Treatment, Self-Help Groups, and Substance Use Outcomes

Participation in treatment and participation in SHGs have independent effects on substance use outcomes that tend to augment each other. In the long-term study of individuals with alcohol use disorders described earlier, individuals who participated in both treatment and AA were more likely to be remitted at both 1- and 16-year follow-ups than were individuals who received only treatment in the first year. Similarly, among clients with drug use disorders, longer episodes of treatment and weekly or more frequent SHG attendance have been independently associated with 6-month abstinence. Moreover, in a nationwide sample, alcohol-dependent individuals who participated in 12-step SHGs in addition to treatment were more than twice as likely to achieve an abstinent recovery as were individuals who obtained formal treatment alone.

Self-Help Groups and Health-Care Utilization and Costs

Involvement in SHGs can reduce the use and costs of health care. Compared with individuals who initially obtained professional outpatient care, individuals who entered AA had less income and education and experienced more adverse consequences of drinking at baseline, suggesting somewhat worse prognoses. Nevertheless, individuals who initially sought help from AA had alcohol-related and psychosocial outcomes comparable to those who initially obtained outpatient treatment, and they had 45% lower alcohol-related health-care costs over a 3-year period.

By increasing their patients' reliance on SHGs, professional treatment programs that emphasize 12-step approaches may lower subsequent health-care costs. In this vein, compared with patients treated in cognitive–behavioral programs, patients treated in 12-step programs were more involved in SHGs at both 1- and 2-year follow-ups after discharge from acute treatment. In contrast, patients treated in cognitive–behavioral programs received more inpatient and outpatient care after discharge, resulting in 64% higher 1-year and 30% higher 2-year annual health-care costs. Patients treated in 12-step programs also had higher rates of abstinence at both 1-year and 2-year follow-ups.

Personal Factors, Participation, and Self-Help Group Outcomes

In a search to identify individuals who may be especially well-suited for participation in SHGs, researchers have examined a range of personal factors, including severity and impairment related to substance use, and disease model beliefs and religious/spiritual orientation. In addition, some studies have considered the suitability of SHGs for individuals with substance use and psychiatric disorders, women, youth, and members of racial and ethnic minority groups.

Severity and Impairment

Individuals who are heavier substance users, have more substance-related problems, and are more dependent on substances are more likely to affiliate with SHGs. More impaired clients are also more likely to continue SHG attendance and less likely to drop out after treatment than less impaired clients are.

Compared with individuals with less severe substance use problems, those with more severe problems may benefit more from SHG involvement. For patients who had less severe problems, levels of SHG affiliation were not related to outcomes. Individuals with more severe problems may benefit more from the support and structure of SHGs because it helps to alleviate their distress and increase their self-control and interpersonal and coping skills. Consistent with these ideas, 12-step SHG attendance appears to be more effective for individuals who have relapsed than for those who have maintained interim recovery status.

Disease Model Beliefs and Religious/Spiritual Orientation

Individuals whose beliefs are more consonant with a 12-step orientation are more likely to affiliate with 12-step SHGs. More specifically, patients who believe in the disease model of substance use and have an abstinence goal and an alcoholic or addict identity tend to become more involved in SHGs and are less likely to drop out. Patients with both SUDs and posttraumatic stress disorders (PTSD) whose beliefs matched 12-step philosophy participated more in SHG activities; more participation was associated with less distress for these patients but with more distress for patients whose beliefs did not match 12-step principles as well.

Because of the emphasis on spirituality in 12-step SHGs, there has been speculation that less religious or spiritually inclined individuals may participate and benefit less from these

groups. In fact, individuals with stronger religious beliefs are more likely to attend and become involved in 12-step SHGs and are less likely to drop out.

Acceptance-based responding, or awareness of internal experiences that enable an individual to respond adaptively to stressors such as craving, may explain part of the effect of spirituality/religiosity on enhanced 12-step SHG involvement. In this vein, individuals who are higher on spirituality/religiosity tend to increase more in acceptance-based responding. In turn, acceptance-based responding has been linked to increased 12-step SHG involvement.

Individuals with Substance Use and Psychiatric Disorders

A high proportion of patients with SUDs have co-occurring psychiatric disorders. In general, except for individuals with psychotic disorders, dually diagnosed individuals appear to attend and benefit from substance use–focused 12-step SHGs as much as do individuals with only SUDs. A study of patients discharged from hospital-based residential treatment showed that dually diagnosed patients attended a comparable number of 12-step SHG meetings in the 3 months before 1-, 2-, and 5-year follow-ups as did patients with only SUDs. SHG attendance was similarly associated with a higher likelihood of 5-year remission for both groups of patients.

A few studies have focused on individuals with specific psychiatric disorders. Patients with SUDs and PTSD participated as much in 12-step SHGs after treatment as did patients with only SUDs. The dually diagnosed patients who participated more in SHGs were more likely to be abstinent and experienced less distress; they were also more likely to maintain stable remission. Some aspects of 12-step SHGs, such as their spiritual emphasis and provision of support, may be especially helpful to trauma survivors by lessening their sense of shame and hopelessness and providing an enhanced sense of purpose in life.

The situation may be different for individuals who have SUDs and co-occurring major depression. Compared with patients with only SUDs, those who also had major depression were less likely to become involved in 12-step SHGs after treatment. At a 2-year follow-up, the association between SHG involvement and abstinence was stronger for patients who had only SUDs than for patients who also had major depression. Depressed individuals may have interpersonal problems that make it harder to develop friendships and to acquire and relate to a sponsor; thus, they may need more support and guidance to become involved in and benefit from 12-step SHGs.

Some dually diagnosed individuals may do especially well in dual-focused 12-step SHGs, such as Double Trouble in Recovery (DTR). In fact, individuals who experience more severe consequences of drug use and more psychiatric symptoms are more likely to maintain attendance in DTR, which is associated with better adherence to medication regimens. With respect to outcomes, individuals who affiliate more strongly with DTR are less likely to continue to use substances and tend to improve more in self-efficacy for recovery, leisure time activities, feelings of well-being, and social relationships.

Women

Women with alcohol or drug use disorders are at least as likely as are men to attend SHGs and continue to participate in them. Participation in SHGs is also associated with as good or better outcomes for women as for men. In a comparison of women and men with alcohol use disorders, women were more likely than men to attend AA and went to more AA meetings in the first year after initiating help-seeking. More extended participation in AA was associated with a higher likelihood of remission for both women and men; however, the positive association between a longer duration of AA attendance and stable remission was stronger for women.

Compared with men, women may be more in tune with 12-step philosophy, which involves acceptance of powerlessness over the abused substance and dependence on a higher power to attain sobriety. Women with SUDs often report low self-esteem, an external locus of control, stable attributions for failure, and frequent substance use when feeling powerless or inadequate. These personal characteristics are congruent with 12-step ideology, which expects individuals with substance use problems to admit past wrongdoing, acknowledge inability to control substance use, and trust a higher power to achieve recovery.

Youth

Many adolescents attend SHGs after treatment, and those who do tend to experience better substance use outcomes. In a study that followed adolescents for 8 years, it was found that AA/NA attendance in the first 6 months and 12 months posttreatment was associated with a higher likelihood of abstinence at each subsequent follow-up. Attendance at just one meeting per week was associated with better outcomes, and attendance at three or more meetings per week was associated with complete abstinence.

More broadly, adolescents who have more severe alcohol and drug problems and are more motivated for abstinence are more likely to attend 12-step SHGs. Adolescents often attribute their relapses to social situations and the pressure to use substances. Therefore, they may benefit from contact with a sponsor who can be a role model, structure that helps them avoid high-risk situations, participation in substance-free social events, and the opportunity to try out a new lifestyle.

However, adolescents' attendance tends to decline over time, in part due to boredom and lack of perceived fit with the group. There are also important barriers to SHG participation for adolescents, including less severe substance use problems and less motivation for abstinence, practical problems arranging transportation to and from meetings, discomfort with the emphasis on spirituality, and issues that are quite different than those of older members, many of whom are concerned with marital and employment problems that are less relevant to adolescents.

Members of Racial and Ethnic Minority Groups

Compared with Caucasians, African Americans may be more likely to attend SHGs, increase their affiliation during treatment, identify as AA members, experience a spiritual awakening in AA, and do service at AA meetings; in addition, they appear to be less likely to drop out of SHGs after treatment. Certain characteristics of 12-step SHGs may especially appeal to African American patients, including the fact that meetings are widely available and open to anyone, are free of charge, and have a strong social and spiritual component.

In order to meet their unique recovery needs, African Americans appear to integrate cultural factors and a unique language and perspective in the process of affiliation with AA. African Americans are more likely to associate their problems with racism and economic disadvantage than with alcohol abuse; they are less likely to accept the disease concept of alcoholism. Nevertheless, they respond to modeling and support from mentors and sponsors, modify the moral aspects of AA to meet their spiritual needs, and adapt the AA world view to better fit their racial and cultural background.

Compared with non-Hispanic White individuals, Hispanic individuals may be less likely to attend AA after treatment, perhaps because they tend to turn to their existing family and community support system. Moreover, attendance at AA tends to be associated with decreased alcohol consumption among Hispanic individuals, just as it is among non-Hispanic Whites.

Twelve-step SHGs have been criticized as less well suited for American Indian groups because they entail the disclosure of personal problems, emphasize Western religious beliefs, and have a philosophy of powerlessness over alcohol that runs counter to the mores of many tribes on self-reliance and stoicism. Although self-help cannot be universally appropriate for all American Indian tribes, owing to the tribes' cultural diversity, it can be appropriate for some. Native American modifications of SHGs incorporate elements of the medicine wheel, purification sweat, and sacred pipe as healing devices. The 12 steps have been blended with the medicine wheel in the Wellbriety Movement, a culture-specific recovery approach for Native Americans.

Active Ingredients of Self-Help Groups

The effectiveness of SHGs in curtailing substance use is based largely on four key ingredients: (1) abstinence-specific and general support that emphasizes the value of identification with abstinence-oriented role models and strong bonds with family, friends, work, and religion; (2) the goal direction and structure of a consistent belief system that espouses a substance-free lifestyle; (3) involvement in rewarding activities that do not involve substance use, including helping others overcome substance use problems; and (4) an emphasis on bolstering members' self-efficacy and coping skills (36).

These critical factors appear to be common change factors that underlie long-term recovery from substance abuse. In support of this idea, a survey of SHGs, including traditional 12-step groups, SMART, SOS, and WFS, showed that active involvement in a support group was associated with a higher likelihood of long-term remission, irrespective of the particular group to which the individual belonged.

Abstinence-Specific and General Support

SHGs are an important source of abstinence-specific and general support, and may be especially effective in counteracting the influence of substance users in a social network. SHGs provide modeling of substance use refusal skills, ideas about how to avoid relapse-inducing situations, practical advice for staying sober, and helpful hints on how to address everyday life problems. Individuals who continue to attend AA more regularly after treatment are more likely to have social network members who support cutting down or quitting substance use than are individuals who attend AA less regularly. In fact, the increase in friends' abstinence-oriented and general support explains part of the positive influence of SHG involvement on remission.

Individuals who have fewer heavy drinkers in their social network, more people who encourage reduction in drinking, and more AA-based support for reducing drinking are more likely to initiate and maintain abstinence. In addition, the number of AA-based social network members who support reduced drinking tends to explain part of AA's effect on abstinence. Involvement in AA may also protect individuals from the potential negative influence of a "wet" social network.

Goal Direction and Structure

SHGs provide a context of goal direction and structure in the form of a shared ideology that enhances individuals' immersion into the group. The shared ideology, which is reinforced by explaining group beliefs in understandable terms, specifying changes needed to maintain sobriety, and providing the 12 steps as a guide for change, helps members negotiate the recovery process. AA norms appear to result in more personal and intimate self-disclosures, and less conflict, in AA groups than in non-AA support groups.

There is also a system of taking turns in AA that exemplifies its egalitarian nature and low levels of conflict. In this vein, members acknowledge and identify with previous speakers' contributions and do not openly confront or challenge them, thereby communicating acceptance, maintaining solidarity, and reducing the potential for disagreement. AA members tell life stories aligned with AA principles, which supports the development of shared identities characterized by dependence on AA and relevance to the 12 steps.

The emphasis on spirituality is a key aspect of the goal direction in 12-step SHGs. In this sense, AA can be seen as a spiritual recovery movement that rewards compliance with its norms by engaging individuals in a social system that promotes new meaning in their lives.

Rewarding Activities

Another active ingredient of SHGs involves their role in engaging members in rewarding substance-free social pursuits. Members who are more involved in group meetings and related activities, such as doing service and becoming a sponsor, are more likely to achieve and maintain abstinence. Involvement in community groups predicted 1-year abstinence among drug-dependent individuals independent of attendance at AA/NA and being a sponsor. Adolescents may also benefit from the substance-free and sober social events and activities and avoidance of high-risk social situations associated with SHGs. By helping their members become more socially integrated, SHGs increase the likelihood of sustained abstinence.

SHGs also provide members with an opportunity to help other individuals in need through service at meetings and other prosocial and altruistic behaviors. Recovering individuals who become sponsors or are otherwise engaged in helping other alcoholic individuals are less likely to relapse and tend to experience fewer depressive symptoms. Similarly, compared with DTR members who were less involved in sharing at meetings and helping other members, those who were more involved in these activities were more likely to remain abstinent. The type of helping that occurs in SHGs, which includes personal contact with peers who have similar problems, may be especially beneficial in that it enhances the helper's social status, social bonding, and sense of purpose.

Self-Efficacy and Coping Skills

Affiliation with AA tends to be associated with increases in members' motivation for abstinence and self-efficacy to avoid drinking. Findings from Project MATCH showed that self-efficacy predicted a higher likelihood of abstinence and explained part of the association between participation in AA and abstinence. In addition, AA attendance at 6 months posttreatment predicted self-efficacy at 9 months, which predicted abstinence at 15 months. Self-efficacy to avoid drinking explained part of the effect of AA attendance on abstinence for both less severe (type A) and more severe (type B) alcoholic individuals.

A study that assessed patients in 12-step treatment during treatment and at 1- and 6-month follow-ups focused on several common change factors, including commitment to abstinence, self-efficacy, and active cognitive and behavioral coping. More affiliation with AA in the month after treatment was associated with increases in these change factors and with better 1- and 6-month substance use outcomes.

These effective ingredients of SHGs reflect four critical factors that aid long-term recovery of SUDs: (1) forming bonds and obtaining social support from new relationships and role models, such as a new spouse/partner, friend, or sponsor; (2) supervision or monitoring, such as by a sponsor or spouse/partner, and the provision of positive consequences for continued remission; (3) involvement in rewarding activities that do not involve substance use, such as a program of exercise, spiritual or religious pursuits, or social and service activities that include

helping other people; and (4) affiliation with a group that provides a sustained source of hope and self-confidence.

Facilitating Participation in Self-Help Groups

In general, individuals participate much longer and more intensively in SHGs than they do in treatment. Many individuals with SUDs depend more on SHGs than on treatment as their dominant resource, probably because SHG meetings are accessible and free, entry is easy, and rewarding long-term social networks are likely to develop. However, there are many obstacles to participation, including lack of motivation and perceived need for help, and dropout rates may approach 75% in 12 months. Accordingly, treatment providers need to strengthen their efforts to help patients engage in these groups.

12-Step and Social Network Treatment

Treatment oriented toward 12-step principles increases the likelihood that an individual will participate and affiliate with 12-step SHGs. More specifically, 12-step facilitation treatment effectively promotes participation in 12-step SHGs among both alcohol- and drug-dependent clients. Adaptations of 12-step treatment have been developed for patients with substance use problems seen in nonspecialty care settings and for patients with substance use and other psychiatric disorders. An adaptation for dual diagnosis patients that includes medication compliance and social skills, on-site DTR groups, and case managers who help patients find and attend meetings appears to be successful in increasing 12-step SHG participation.

A socially focused treatment that tries to shape a patient's social network to reinforce sobriety in part by emphasizing the importance of AA can also increase participation in AA.

Briefer Interventions

There are also brief interventions, such as motivational interviews, that appear to help get patients engaged in SHGs. Clients who receive motivational enhancement interventions are more likely to participate in 12-step SHG meetings than do clients in usual care. Compared with patients in a standard referral condition, patients in the intensive referral condition were more likely to attend 12-step SHG meetings, read 12-step literature, provide service during a meeting, consider themselves to be a 12-step group member, celebrate a 12-step birthday, and have a sponsor.

Similarly, in a study of adolescent SUD programs, clinicians from sites at which clients had high SHG attendance rates were more likely to have used active strategies to connect youth with SHGs. These clinicians monitored clients' meeting attendance, prescreened sponsors, and taught clients how to find an appropriate sponsor. They also often worked with local members of AA or NA to conduct meetings at the treatment site; members helped clients find sponsors, arranged transportation to meetings, and linked adolescents to sober social activities within the recovery community.

Conclusion

A high priority for future research is to specify the characteristics of individuals who are most likely to benefit from SHGs and to consider the benefits and barriers to joining SHGs and beliefs associated with participation. We also need more information about the optimal duration and frequency of participation for individuals who vary in the severity of their disorder

and level of personal and social resources. Other issues to address include identifying personal and contextual predictors of dropout and of the duration of participation, and developing an integrative model of the role of SHGs and other life context factors as joint influences in the course of relapse and remission.

Most generally, the finding that a longer duration of participation in SHGs predicts better substance use outcomes indicates that SHGs are most beneficial when they become an ongoing supportive aspect of individuals' lives. Extended 12-step group engagement may initiate and maintain the personal and social changes needed to solidify stable remission, especially abstinence-specific and general support, goal direction and structure, involvement in rewarding substance-free activities, and enhanced self-efficacy and coping skills. SHGs represent an important part of the array of effective interventions that can change the enduring aspects of individuals' life contexts and increase the likelihood of a long-term course of recovery.

Alternative Support Groups

This chapter overviews five support groups for addictive behavior. These groups are in many aspects fundamentally different from and hence alternatives to 12-step groups such as AA. These groups are WFS, SOS, Moderation Management (MM), SMART, and LifeRing. This chapter is oriented toward providing information that would help professionals and their patients identify whether alternatives in general, and which alternatives in particular, might be helpful for a particular patient.

Groups not covered in this chapter are those with a religious orientation (e.g., Overcomers Outreach; Overcomers in Christ; the Calix Society; Jewish Alcoholics, Chemically Dependent Persons, and Significant Others), those which offer only a small number of meetings (e.g., Men for Sobriety), and Rational Recovery (RR).

History of Alternative Support Groups

The modern alternatives to 12-step groups are relatively young and unknown. AA, the original 12-step group, began in 1935. The oldest of the alternatives, WFS, began in 1976. Despite the continued predominance of 12-step groups in the United States, the alternatives slowly appear to be gaining recognition.

Although these alternatives arose in response to the perceived mismatch between some individuals and 12-step groups, the alternatives nevertheless have significant similarities with 12-step groups. All 12-step and alternative groups are without substantial empirical support of effectiveness. All offer 60- to 90-minute meetings at no charge but request donations. All are essentially self-supporting, primarily through member donations and the sale of recovery materials (including newsletters, books, workbooks, audio- and videotapes, and software, some of which may be produced by lay individuals or professionals not directly affiliated with the organization). All have recommended reading lists. All have an extensive official and/or unofficial Internet presence. This presence evolves as Internet communication evolves, and currently includes online meetings (text and/or voice), listserves, message boards, blogs, and chat rooms. All (except MM) are abstinence-oriented. All (except SMART and LifeRing) were founded by an individual who had a new perspective about recovery from addictive behavior. All are nonprofit corporations.

The differences between 12-step groups and alternatives with respect to meetings and meeting leaders are also substantial and numerous. All groups typically devote major portions of their meetings to discussion ("cross talk"). None have speaker meetings (although their leaders may give separate public presentations). All have, or prefer to have, small meetings

(approximately 6 to 12 members), to allow ample opportunity for individual participation. All have meeting formats, but tolerate (or even encourage) significant variation based on local custom or preference. None have extensive meeting rituals. All are led by a facilitator who guides the discussion. The facilitator is typically a peer, and a member of the group's recovery program (but a significant minority of facilitators in some alternatives are behavioral health professionals). Because of the responsibility involved in being a facilitator, all appear to experience difficulty finding facilitators. Because of the lack of a lifetime-membership requirement, all experience difficulty retaining facilitators. All aspire to international availability, as qualified facilitators can be identified.

The five alternatives differ from one another primarily on their view of addiction as a disease. WFS takes a disease approach. SOS and LifeRing leave this issue up to the individual, but emphasize physiologic aspects of addiction more than psychological ones. MM views addictive behavior as a learned maladaptive behavior, not a disease. SMART originally also viewed addiction as a learned maladaptive behavior, but in 2008 changed to accepting belief in addiction as a disease (or not) as a personal belief of the participant.

Description of Each Alternative Support Group

Women for Sobriety

History WFS was founded in 1976 by Jean Kirkpatrick, PhD, to address the unique problems of women alcoholics. She suggested that these problems include self-value, self-worth, guilt, and humiliation. Kirkpatrick's own experience was that AA was only partially helpful to her as a woman alcoholic.

Despite professional treatment and AA attendance, Kirkpatrick had a 30-year drinking history, including hospital and mental hospital admissions, hit-and-run accidents (during blackouts), and jail time. She had recurring episodes of depression and attempted suicide several times. She nevertheless earned a doctorate in sociology from the University of Pennsylvania by age 50. She died in June 2000, at the age of 77.

Kirkpatrick's AA experience was one that she believed was typical for women. The recounting of the harm caused by drinking seemed to be good for men in AA and reminded them of their reasons not to relapse. For her, however, recounting painful and often humiliating past drinking experiences seemed to make even more difficult the task of accepting herself and gaining mastery of her life. Additionally, AA did not address how societal views of women (vs. men) alcoholics posed additional challenges for recovering women.

Program WFS has two primary publications. The WFS newsletter is *Sobering Thoughts*. WFS is intended for women alcoholics (including those who also have prescription medication problems). Kirkpatrick suggested that for some women AA may be more effective at achieving initial sobriety, because initially a woman may be overwhelmed by the complexity of the WFS program.

WFS views alcoholism as a physical disease that a woman can grow beyond by learning new self-enhancing behavior via:

1. Positive reinforcement (approval and encouragement)
2. Cognitive strategies (positive thinking)
3. Letting the body help (relaxation techniques, meditation, diet, and physical exercise)
4. Dynamic group involvement.

Meeting Format WFS meetings are led by a certified moderator. Certification is based on having at least 1 year of continuous sobriety. Meetings are open to all women alcoholics. Newcomers are given a packet of introductory information. Meetings begin with a reading of the Statement of Purpose, followed by introductions ("Hello, my name is Jean, and I'm a

competent woman"). Most of the meeting is devoted to discussion of members' concerns, and how the "New Life" Acceptance Program can be applied to them. Following discussion, each member is asked to describe something positive she has accomplished in the past week.

The meeting closes with the members standing, holding hands, and saying, "We are capable and competent, caring and compassionate, always willing to help another, bonded together in overcoming our addictions."

Secular Organizations for Sobriety/Save Our Selves

History SOS was established in 1985 by Jim Christopher, in Hollywood, California. Christopher had been sober since 1978, initially using AA. He separated from AA early in his recovery, because he wanted an approach that was based on personal responsibility rather than reliance on a higher power. In 1985, he wrote "Sobriety without Superstition" for *Free Inquiry*, a leading U.S. secular humanist journal. Because of the strong positive response to the article, he founded SOS.

Program Originally intended for alcoholics, SOS has been extended to the full range of addictive behavior (both substance and activity addictions), and in some cases to family members as well. SOS is for individuals who desire recovery but are uncomfortable with the spiritual content of 12-step groups and would prefer a personal responsibility approach. Specialized groups for family members, youth, or youth in dysfunctional families are also allowed. The only requirements of an SOS meeting are that it be secular and promote total abstinence.

SOS views the cycle of addiction as having three elements: physiologic need for the substance, the learned habit of using and all the associations to using, and the denial of both the need and the habit. Over time, the addiction becomes the highest priority, and it begins to destroy the rest of life. However, the cycle of addiction can be replaced by the cycle of sobriety: acknowledgment of the addiction, acceptance of the disease or habit, and making sobriety the highest priority in life (the "sobriety priority"). The sobriety priority is a cognitive strategy to be applied daily, to weaken associations to using, and to allow new associations to develop. SOS accepts that participants may use a wide variety of techniques or approaches in recovery. SOS emphasizes that it concerns itself only with helping participants accomplish the sobriety priority, and not with transforming the rest of life. With sobriety secured, participants are in a much better position to grow as individuals, but this remains a personal matter.

Meeting Format The suggested meeting format includes an opening statement summarizing the purpose of the meeting, announcements (e.g., the availability of new literature), anniversaries (of sobriety), the reading of the Suggested Guidelines for Sobriety, and introductions of all present. The meeting proper is next ("This meeting is now open. We ask that you try to keep your sharing to a reasonable length of time so that everyone can participate."). The closing includes passing the hat, and a ritual ("Let's close by giving ourselves a hand for being here to support and celebrate each other's sobriety.").

The members of each SOS group are allowed to create a meeting structure that meets their needs. Most SOS meetings have an active exchange of information, experiences, and ideas.

Moderation Management

History MM was founded in 1993 by Audrey Kishline to support individuals who desire to moderate their alcohol consumption. Her own experience had been that it was difficult to obtain support for this goal.

During her 20s, Kishline's drinking increased to the level of a moderate problem. She eventually sought treatment. Ultimately, this treatment included two inpatient stays, an aftercare program, and consultation with at least 30 alcoholism treatment professionals, all of whom diagnosed her as

"alcoholic." She also attended AA regularly for several years, attending hundreds of meetings. Her initial reaction to treatment was that her drinking became more severe. She suggested that at least in part this increase was a self-fulfilling prophecy based on what she had learned about alcoholism as a disease over which she was powerless. She also suggested that over several years she gradually matured out of her drinking problem, as she became more involved in the responsibilities and activities of life (e.g., marriage, children, homemaking, college courses, hobbies, and friends). As this maturing occurred, her beliefs about herself also evolved. Rather than believing herself to have a disease, she chose to abstain because of the kind of life she wanted to lead. Kishline chose to return to moderate drinking. She asserted that she was misdiagnosed initially, and that moderation of her alcohol consumption had been overlooked as an option for her. She founded MM in the hope that the moderation option would not be overlooked for others in similar situations.

Program MM is intended for individuals who fit the description "problem drinker" rather than "alcoholic." There are two fundamental requirements for membership: a willingness to accept responsibility for one's own behavior and a desire to moderate (or stop) drinking. MM is not aimed at individuals who have experienced significant withdrawal symptoms from alcohol, who have medical conditions exacerbated by alcohol (e.g., heart disease, diabetes, gastrointestinal problems, and so on), or who are experiencing other relevant conditions including pregnancy or desired pregnancy, a behavioral health disorder, being on medications that interact negatively with alcohol, or being in personal crisis. Lastly, MM is not designed for individuals who are already abstaining successfully after a history of severe dependence.

MM recommends that as early as possible in their MM involvement, members abstain for 30 days, during which time they examine how drinking has affected their lives; write down their life priorities; consider the quantity, frequency, and circumstances of their past drinking; and learn the moderation guidelines MM suggests. Members might also complete the Drinker's Checkup, a free interactive program available on the MM website, or the Short Alcohol Dependence Data Questionnaire (SADD), also available on the MM website. On the SADD, scores from 1 to 9 suggest low dependence on alcohol, 10 to 19 medium dependence, and 20 or higher (maximum score 45) high dependence. Individuals who score below 16 are considered good candidates for MM. Those who score between 16 and 19 are encouraged to obtain professional assessment before attending a moderation program. Individuals who score 20 and above are encouraged to pursue abstinence. Even individuals with low scores are not discouraged from pursuing abstinence, but are offered the alternative of MM as a means to abstain.

MM hopes to reach problem drinkers early in their problem drinking career by offering an approach that appeals to common sense and does not require excessive effort (relative to the intensity of the problem). MM is therefore partly a prevention program (see Section 8). If an individual is not successful following MM's moderation guidelines, the individual is encouraged to pursue abstinence.

MM views drinking problems as arising from bad habits, rather than being the manifestations of a disease. MM is based on empirically supported cognitive–behavioral moderation training.

MM understands moderate drinking to be (for men) no more than 4 standard drinks per day, no more than 4 drinking days per week, and no more than 14 standard drinks per week. A standard drink is the amount of alcohol in a 12-ounce bottle of beer, a 5-ounce glass of wine, or a 1.5-ounce shot of liquor, all of which, because of differing concentrations, have approximately equal amounts of pure alcohol. For women, moderate drinking is understood to be no more than three standard drinks per day, no more than four drinking days per week, and no more than nine standard drinks per week. Both sexes are encouraged not to drink and drive, or to drink in situations where the drinker or others might be endangered.

Meeting Format Meetings are led by a moderator, and begin with the reading of an opening statement describing the purpose of MM, followed by a reading of the nine steps and ground rules

for members. Visitors (the meetings are open) and newcomers are invited to introduce themselves. Anyone who recently completed the recommended initial 30 days of abstinence is acknowledged.

The first working section of the meeting is devoted to giving every member the opportunity to update the group on the member's activities since the member's last meeting. Feedback by others may be offered. The next working section is general discussion. If no one has a topic to discuss, the moderator suggests one, which would typically be one of the ideas or techniques covered in the MM book. The meeting ends with the reading of a closing statement.

SMART Recovery

History SMART incorporated as a nonprofit organization in 1992 under the name Rational Recovery Self-Help Network. The organization entered into an agreement with Jack Trimpey, the founder and owner of Rational Recovery Systems, to use the name RR and to operate RR support groups. Trimpey took the leading role in establishing and incorporating the organization.

Program SMART assumes that there are degrees of addictive behavior, and that all individuals to some degree experience it. Individuals for whom the negative consequences of addictive behavior have become substantial are the ones likely to be considering or desiring abstinence.

The SMART program is consistent with a cognitive– behavioral perspective, which does not require a belief in addiction as a disease. However, just as participants are free to have any conception (or not) of a higher power, they are similarly free to have any understanding of addiction as a disease.

There are four primary goals for an individual in the SMART program: motivational maintenance and enhancement, effective urge coping, rational thinking (leading to effective emotional and behavioral management), and lifestyle balance. In service of these goals, many cognitive–behavioral and other psychological techniques are taught.

Meeting Format Meetings are open unless closed by local custom. Meetings begin with an opening statement by the facilitator. The statement describes the four primary goals of the SMART program, and outlines the meeting to follow. Participants check in and establish an agenda for who will be the primary focuses of the discussion. The major portion of the meeting follows, consisting of discussion guided by the facilitator on the four primary goals of the SMART program, and the Tools SMART continues to evolve to accomplish these goals, as they apply to the individual situations discussed. One of the principal approaches is to consider "activating events" volunteered by the members. Activating events can include urges, life circumstance changes, thoughts, social interactions, or other experiences that lead or potentially lead to undesired emotions or behavior, including addictive behavior.

LifeRing Secular Recovery

History LifeRing began as the Northern California set of SOS meetings. In 1999, a federal court ruling prohibited SOS from using that name in Northern California. Representatives of the Northern California meetings, on May 23, 1999, adopted the name LifeRing Secular Recovery. During 2000, LifeRing emerged as an organization independent of SOS. A constitutional congress ratified bylaws on February 17, 2001. Some former SOS meetings from outside of Northern California are now affiliated with LifeRing.

Program Recovery is the process of reinforcing and building connections between the sober selves until they merge into a resilient and predominating sober self. Each participant is encouraged to develop a Personal Recovery Program.

LifeRing uses the "three-s" philosophy of sobriety, secularity, and self-help. Sobriety is understood as complete abstinence from alcohol and other drugs. Another LifeRing motto

is "we do not drink or use, no matter what." LifeRing welcomes adherents of any religious belief or none. Religious or spiritual beliefs are not part of the LifeRing program (secularity), which focuses on enhancing human effort to overcome addiction. LifeRing meetings focus on reinforcing the participant's striving to maintain sobriety. Individual motivation and effort are understood as the foundations of change (self-help).

The LifeRing program suggests that there are as many ways to get sober as there are individuals. No single approach will work for all. A successful recovery plan probably involves some learning by experimentation. Therefore, the LifeRing publications emphasize a wide range of tools, including changing one's self-image, understanding the effects of substances, eating well, exercising, and recalling the bad effects of one's use.

Meeting Format Meeting facilitators are termed convenors. Convenors are normally required to have 6 months of recovery. Meetings typically focus on answering the question "how was your week?" Convenors aim to foster a discussion that is informal, supportive, and conversational. The discussion focuses on the challenges to recovery the participants have faced in the previous week, and the ones they expect to face in the upcoming week.

Evidence of Efficacy

With respect to experimental evidence of efficacy, alternatives and 12-step groups are similar. Although the 12-step literature is substantially larger, neither has definitive evidence of efficacy. However, the ultimate justification of a support group will not be established by an efficacy study. Millions have attended 12-step groups despite their lack of evidence of efficacy. Although alternatives have lower attendance, they continue to exist, in one instance for more than 30 years. Support groups exist because recovering individuals choose to attend them.

The majority of the evidence about alternatives addresses the issues of who might differentially benefit from one support group versus another, and who attends these groups. Penn found comparable outcomes for participants in a 12-step or SMART-oriented day-treatment program for the addicted mentally ill. The investigators needed to make the 12-step arm of the study more client-centered (as SMART already is) in order to reduce the subject dropout rate. Nonreligious subjects were less likely to participate in 12-step groups. Religious respondents were less likely to participate in SOS. Religiosity had little impact on SMART participation.

As to who is attending WFS and why, Kaskutas studied women who attended only WFS, or both WFS and AA. Their responses support the suggestion that women may need a different approach to recovery. Women who attended only WFS reported that they did not feel that they fit in at AA, that AA was too negative, that they disliked the "drunkalogues" and the focus on the past, and that AA is better suited to men's needs than to women's needs. Women attended WFS for support and nurturance, for a safe environment, for discussion about women's issues, and for the emphasis on positives and self-esteem. Attending WFS for 1 year was associated with an increase in self-esteem. For women who attended both WFS and AA, insurance against relapse and AA's availability were frequently cited reasons for attending AA. Respondents were primarily white, educated, middle-aged, and middle- or upper-class. Most had also participated in individual psychotherapy.

MM participants are white, middle-class, and well-educated. They appreciate the nondisease approach to recovery, and find the emphasis on choice and self-control a better match for their values. MM tends to attract more women and younger participants. There are mixed findings about the level of physical dependence on alcohol. Individuals who inquire about MM and then actually attend MM have more serious alcohol problems than those who simply inquire. Perhaps as MM has become better known, it has attracted more women and individuals with higher levels of alcohol problems.

SMART participants have a significantly higher level of internal locus of control than do AA members. LifeRing presents the results of a membership survey on its website. The membership is comparable to the other alternatives.

How Alternative Support Groups Are Optimally Used?

If an individual has no experience with addictive behavior support groups, sampling all that are available would seem most sensible. Further research may provide guidance regarding the initial matching of individuals to addictive behavior support groups. However, given the general paucity of *treatment* matching findings, we might expect to discover that it is difficult to predict which individuals will do better in which support groups. The wisest course of action in practice, until clear findings suggest otherwise, would appear to be encouraging patients to sample the available support groups and make their own choices.

If an individual has no strong preferences, 12-step groups would seem more desirable than the alternatives simply because of their availability and size (which increase the likelihood that suitable models of success would be identified). If alternatives are preferred, and more than one is reasonably proximate and not inappropriate for one's gender (WFS) or goal (MM), on what basis might one be selected over another?

Special Considerations

Serious ethical and legal issues may arise when an individual, for considered and responsible reasons, chooses to pursue an alternative approach to recovery, but a treatment provider or third party insists on 12-step–group attendance and/or 12-step–oriented treatment. It would appear to be unethical to insist that an individual use a 12-step approach to recovery if the individual wishes to pursue another approach.

If the third party is the government, then a series of U.S. Federal Circuit Court decisions that began in 1996 is relevant. These five decisions (2nd, 3rd, 7th, 8th, and 9th Circuit) have held that government-required 12-step attendance violates the establishment clause of the U.S. Constitution's First Amendment. Although the distinction between a religious and spiritual approach is widely made in the 12-step community (with 12-step groups being considered of the latter type), these decisions have held that 12-step groups are religious enough that a citizen cannot be ordered by the government to attend one. The U.S. Supreme Court has already declined to hear an appeal of the decision in the 2nd Circuit. It appears likely that further decisions around this precedent will be in lower courts, perhaps for the purpose of awarding damages. Given the frequency with which judges and probation and parole officers order individuals in the criminal justice system to "attend AA," the ramifications of these decisions, for alternative support groups in particular and the addiction treatment community in general, are just beginning to be recognized.

Conclusion

A fundamental conclusion about alternative support groups is that they could be highly valuable resources for many individuals, but awareness of their existence is slight and growing very slowly. This conclusion gives rise to a number of questions. Will enough individuals attend alternatives so that one or more may come to exist as equal members of the recovery community, and not merely as "alternatives?" Will widespread awareness of the existence of alternatives increase the number of individuals involved in support groups (or recovery or treatment) or will they draw their participants only from those who otherwise would have attended 12-step

groups? How much time will be needed before there is widespread awareness of these recovery resources? What are the root causes of the slow growth of awareness about alternatives, and what can be done to address these causes? If awareness continues to grow too slowly, would some form of affirmative action be appropriate, and who would sponsor this affirmative action?

Suggested Readings

Atkins RG, Hawdon JE. Religiosity and participation in mutual aid support groups for addiction. *J Subst Abuse Treat*. 2007;33:321–331.

Humphreys K, Moos R. Encouraging post-treatment self-help group involvement to reduce demand for continuing care services: two-year clinical and utilization outcomes. *Alcohol Clin Exp Res*. 2007;31:64–68.

Kelly J, Moos R. Dropout from 12-step self-help groups: prevalence, predictors, and counteracting treatment-related effects. *J Subst Abuse Treat*. 2003;24:241–250.

Kishline A. *Moderate Drinking: The Moderation Management Guide for People Who Want to Reduce Their Drinking.* New York, NY:Crown 1996.

Magura S. Effectiveness of dual focus mutual aid for co-occurring substance use and mental health disorders: a review and synthesis of the "double trouble" in recovery evaluation. *Subst Use Misuse*. 2008;43:1904–1926.

28 The Therapeutic Community

The therapeutic community is a drug-free, self-help program, a highly structured, family-like environment where positive peer interaction assumes center stage. The therapeutic community is different from other drug treatment approaches, mainly in its use of the community as the key agent of change. The therapeutic community believes that drug abuse is not in itself a disease but merely a manifestation of underlying problems that the addicted need to overcome with the encouraging support of a caring community. The therapeutic community impresses upon the drug abusers that "only you can do it, but you cannot do it alone."

Multidimensional Approach to Healing

The basic premise of the therapeutic community is that the person (substance abuse client) "enjoys" a disorder that affects all aspects of his or her life. It is a disorder of the whole person. Individual attitudes and behaviors, emotional management, and one's personal values, all these are slated for change. Such a multidimensional goal can be negotiated in a communal setting. Throughout the years, the therapeutic community has enhanced substance abuse treatment, intervention, prevention, and educational services for both adolescents and adults. It has emphasized a holistic approach to healing, using interdisciplinary staff, proven paraprofessionals, as well as family members to provide a wide variety of services to accommodate the need portfolios of adolescents as well as of adults. It utilizes multiple approaches in responding to the changing needs of its clients.

The therapeutic community also recognizes the need to engage other agencies, utilizing a cross-reference system, embracing different approaches in an effort to provide a holistic, healthy structure for substance abuse clients in recovery. In dealing with the substance abuse clients, one needs to consider an approach that is centered upon the partnership of family, school, and community forces. There is a strong need to address the interrelatedness of the differing systems of the larger community in order to have an effective treatment program. According to the African saying that "it takes a whole village to raise a child," correspondingly "it takes a whole community to raise an integrated person." In the therapeutic community, there is strong emphasis upon the need for rebuilding a sense of community, or village, in which everyone reasserts his or her shared responsibility in the process of nurturing the substance abuse clients.

Healing through a Caring Family Environment

Family is vital in the life of substance abuse clients. It is the setting where the valuable aspects of self-esteem, self-acceptance, and sense of responsibility are nurtured. Although ideally the

family is where these should be in play, the fact is that there are many substance abuse clients who do not enjoy stable and healthy families. These clients are numbered "among the damaged" because their families have been severely wounded and stand clearly in need of healing. It is impossible to learn these tasks when one lacks a healthy, functioning family setting. It is true that "the therapeutic community can never [fully] replace the functional family, [but] it is a temporary place enjoying the support with the natural family." In this case, the therapeutic community is a place where the family can also relearn and refashion itself.

The therapeutic community recognizes the importance of healing not only for the wounded clients in treatment but for the families as well. The therapeutic community has given evidence of some success by virtue of its efforts in soul-caring by providing the quintessential nourishing family environment, which, more often than not, has been found wanting in the original familiar situation. The English word "care" comes from the Latin word "*cura*," which connotes, among other things, attention and healing. This consideration stands at the portals of the therapeutic community, a formula for living that encourages individuals and families to embrace one's soul-life as the inner core of their being. The process of healing (care of self and one's soul) is not accomplished in isolation but, rather, in the collective journey traveled through family with each member supporting the other.

Herein lies the root of the therapeutic community outreach to families of substance abuse clients, which serves to heal relationships between members within the family unit. It aspires to increase the solidarity of the family while promoting its own well-being. The therapeutic community family outreach opens up avenues for confronting tensions, conflicts, and consequent maladjustments in the vast sea of family tensions through efforts of reorganization and reintegration. The therapeutic community offers innovative approaches for understanding the soul-life of the family unit as well as the blueprints for organizing families in support of each other. This approach in promoting the well-being of the family is an example of family systems theory. It represents a holistic approach, which positions every part of family life in terms of the "family as a whole."

Healing through Caring Peers

The therapeutic community requires a multiplicity of role models (roommates, older and younger residents, as well as senior and junior staff) to maintain the integrity of the community while ensuring the promotion of individual growth and healthy relationships.

William Glasser, who is recognized as "the father of reality therapy," contends that human beings have some basic needs that must be satisfied in order to exist in a reasonably satisfying life. The first is the need for a relationship of mutual respect and affection with at least one other person. Glasser argues that when one is unable to fulfill the needs for love and worth, one experiences pain, loneliness, and discomfort. The therapeutic community fulfills these two basic needs, particularly by providing a caring setting where residents feel nurtured and supported, physically and psychologically safe, as well as understood and accepted by others. It is a place that fulfills the essential need to be connected and to belong. The therapeutic community is set apart from other approaches by means of the strategic use of healthy peer relationships to facilitate change and growth.

Healing through Caring Mentors

In the therapeutic community, members are expected to serve as role models for purposes of "maintaining the integrity of the community as well as of ensuring the wide acceptance of social learning." A greater investment of responsibility is expected from staff and senior members of the community who serve as "caring mentors" for newer members. Staff and senior residents act as guides in assisting others in their recovery. The credentials of therapeutic community

mentors are their own experiences in self-help recovery. When new members walk through the doors of a therapeutic community residence, they are not met by doctors, professors, or priests. Someone equally wounded greets them. That someone has been where the new members now find themselves at entry, and that someone has successfully traveled the path toward recovery. These therapeutic community mentors serve as caring guides for new members through the processes of self-discovery and change. They ensure that new members of the community receive exposure to a range of growth experiences through positive interactions with others. To serve as caring mentors in the lives of younger residents is a paramount responsibility of staff and senior residents.

Healing through Honesty and Responsible Concern

O. Hobart Mowrer maintains that the practice of honesty, responsible love, and concern is intrinsically therapeutic. The therapeutic community provides honesty with a new dimension: radical self-disclosure and transparency. It is here where one discovers healing and wholeness. When a resident feels "nurtured, supported, and safe as well as accepted by others," he or she is more likely to participate in the community and risk the challenge to change. The "tough love and rugged honesty" of the therapeutic community is always within the context of a caring and nurturing setting. Carl Rogers, the "father of client-centered therapy," explained that the healing outcome from the environment of the therapeutic community springs from the encounter process that is at the heart of that caring environment. "Shame, fear, anger, guilt, confusion, despair, and aloneness" are some of the early pains experienced by members of the community, and these are "associated with circumstantial stress, pressures, and psychological injuries" of the past, as well as from isolation. However, the therapeutic community offers an environment that fosters nurturing and caring, along with physical and psychological safety as well as social relatedness.

Healing through Responsibility

In exploring the meaning of responsibility, Bratter argues that the English word "response" appears to be less proactive than the French term "*repondre*," or the German "*antworten*." He explains that the German term "*verantwortung*" appears more comprehensive. It suggests answering for one's actions. "Ability" connotes being able to accomplish a task that coincides with the therapeutic community's overall definition of "responsibility." He defines the word "responsibility" where the emphasis is placed on the person's ability to respond to external challenges with reasonable judgment.

In the therapeutic community, the residents and staff are immersed in dialogue on how to be responsible through the continual, candid feedback of the group. This is the goal of psychotherapy, according to Bratter, to help the individual assume responsibility for self, in the sense of recognizing the active, responsible force in one's life; being capable of making decisions; and assuming consequences. Along with this acceptance, the recognition of responsibility toward others follows upon a readiness to discover the obligations arising from the values one holds, whether they relate to one's children, parents, friends, employees, colleagues, the community, or one's country.

In the therapeutic community, responsibility is regarded as an essential part of a mutually dependent relationship between the individual and the society. Being part of the community means taking on the full responsibilities of membership while accepting the consequences when these responsibilities do not bear fruit. One cannot be satisfied with a passive, noncontributing membership style. On the contrary, one must be aware of his or her role in accepting full responsibility in the larger community. "Accountability and responsibility are integral tools for interrupting self-defeating lifestyles" while facilitating the recovery process in the community.

The therapeutic community encourages its members to care for and support each other. "I am my brother's/sister's keeper," the Christian principle holds, while in the therapeutic community, it reaches further, "in helping my brothers/sisters, I, also, help myself!" Helping each other includes helping peers to struggle. Helping others becomes a key component in the process of helping oneself.

Healing through One's Woundedness

The dynamics of the therapeutic community encourages and empowers individuals to embark upon a journey into self-knowledge and personal growth. Recognizing the difficulties on the path to gathering a candid picture of oneself, just as the eye cannot reflect upon itself, the therapeutic community itself serves as a complete reflection of a member's potential. At the same time, it surfaces patterns of denial, hypocrisy, manipulation, and self-deception where they exist. Entering the therapeutic community in itself is a cry for help. The experience becomes a form of grasping at one's limitations, maladaptive behaviors, fears, and negative attitudes. In another sense, the community becomes a holding environment that provides the individual with a safe place to accept imperfection, to develop a vision of life, and to implement a curative way of living in which those imperfections can be constructively addressed.

Therapeutic Community: The Wounded Healer

The therapeutic community was born out of the crying need of a suffering and an anguished group of social outcasts "who forged an instrument for change that came to be known as the 'therapeutic community.'" The therapeutic community founders soon discovered that peer group influence was extremely effective in bringing on change and in learning how to live again. Through peers, wounded people were able to relate deeply and emotionally on the basis of shared experience, a common ground of woundedness, and on this premise they moved forward in an historic effort to assist each other to reclaim their lives via mutual support and peer modeling.

The therapeutic community actualizes the paradox of the wounded healer. Its members can be described as the "twice-born" mentioned in *The Varieties of Religious Experience* of William James: "The 'twice-born' have known tragedy, failure, and defeat and they have named them as such; but they also have a new sense of possibility of somehow rising above such experience … It is only in the embracing of our torn self, only in the acceptance that there is nothing 'wrong' with feeling 'torn,' that we can hope for whatever healing is available and can, thus, become as 'whole' as possible. Our own brokenness allows us to become whole."

The community represents a living paradox that embraces the human condition as "both/and" (both a wounded warrior and a healer, both a saint and a sinner) rather than "either/or" (either a wounded warrior or a healer, either a saint or a sinner). The healing experience of the therapeutic community transcends its own boundaries. The therapeutic community staff and facilitators need to recognize their own woundedness to be able to heal the wounds of others.

Conclusion

The central inquiry of this chapter is to discuss the healing components of the therapeutic community. It proposes that the therapeutic community offers an effective healing approach in dealing with wounded substance abuse clients. For people who do not fall into this labeled "wounded" category, it serves to confirm and strengthen positive traits of character. The therapeutic community rebuilds a person's self-esteem, self-image, self-respect, and self-dignity. It

restores a sense of hospitality to self and to others. The therapeutic community assumes a certain maturity through responsible concern for peers.

The therapeutic community affirms the fundamental values common to all religions, but particularly to the Christian faith. It stands as a model for the holistic and multidimensional treatment approach in addressing the needs of the substance abuse client as a whole person. The therapeutic community is a paradigm for comprehensive treatment programs that incorporates partnership with families, schools, and other community forces in a common effort to promote a healthy and caring environment for their clients. It offers other helping agencies a pattern for building small communities through caring peer relationships, which facilitate change and growth through honesty, responsible concern, and responsibility. The therapeutic community recognizes the necessity of being in touch with one's vulnerability, one's "woundedness," and this provides helping professionals and educators with a framework for ministering more effectively to wounded substance abuse people. The journey of fashioning and refashioning peoples' lives remains the crowning moment of the community effort. The therapeutic community is in many ways a *koinonia* where the "wounded" are healed through the embrace of an *agape* and caring community. As a young Daytop graduate declared, "The therapeutic community is truly an Easter place!"

Suggested Readings

Albers R. Families and substance abuse. In: Anderson H, Browning D, Evison I, et al., eds. *The Family Handbook*. Louisville, KY: Westminster John Knox Press; 1998:187–191.

Brieland C. *Triumph over Tragedy: The Story of the Therapeutic Community*. Milford, PA:Promethean Institute and Division of Daytop Village; 1993.

De Leon G. *The Therapeutic Community: Theory, Model and Method*. New York, NY: Springer Publishing Company; 2000.

Kooyman M. The history of therapeutic communities: a view from Europe. In: Rawlings B, Yates R, eds. *Therapeutic Communities for the Treatment of Drug Users*. Philadelphia, PA: Jessica Kingsley Publishers Ltd; 2001: 59–78.

Nouwen H. *The Wounded Healer*. New York, NY: Image Books, Doubleday; 1990.

29 Individual Psychotherapy

A great deal of addiction treatment is conducted in groups, and the relative expense of individual sessions can lead to downplaying their value. However, such sessions can play a key role in promoting the engagement and retention that is associated with positive substance abuse treatment outcomes. It is imperative that the therapists have familiarity with the stages and tasks of recovery and have the ability to tailor interventions accordingly. Individual therapy with a clinician familiar with addiction and recovery can make a significant contribution to the patient's quality of life at all stages.

No single definition allows us to distinguish between therapists and counselors, but historically the terms have been used to indicate level of training and scope of practice. Therapists, by custom and by law in many states, have advanced degrees in psychiatry, psychology, or social work and corresponding state licenses to practice autonomously. Counselors working in substance abuse treatment programs may or may not have credentials, and usually have circumscribed roles that include case management, exploring current obstacles to recovery efforts, and teaching of early recovery skills. They may conduct individual sessions, depending upon particular organizational licenses and state laws.

Therapists and Counselors within a Specialty Treatment Program

Individual therapists and counselors have a variety of roles, depending on whether they are in specialty programs or private practice, and whether they are licensed or not. Both counselors and therapists in specialty programs may be utilized to do a comprehensive assessment, but whether this includes a precise evaluation of a mental disorder that coexists with the addictive disorder depends on whether the clinician has the training and appropriate license to do so. Although it can be difficult to get an accurate diagnosis, uncontaminated by substance-induced symptoms, it is nonetheless important to make a provisional diagnosis or a sufficiently clear description of symptoms to allow for treatment planning. This diagnosis can be revised as further information emerges.

Entry into a specialty program is often precipitated by a crisis, and this is often best managed in individual sessions. It is tempting for family members and outside therapists to breathe a sigh of relief once the patient is admitted to a residential or inpatient program, but engaging family members and outpatient therapists at this stage gives an excellent opportunity to promote their involvement in the treatment episode and in the patient's long-term recovery. Even a single meeting with family members permits the therapist to work more effectively with the

patient toward good resolution of the current crisis. Some desirable outcomes of the crisis intervention are relief from stress and fear, enhancing the patient's confidence in the utility of professional help, harnessing the opportunities in the crisis, and increasing awareness that the alcohol and other drug use is only one element that needs to be addressed.

Structured programs rely heavily on group interventions, and these have some distinct advantages. Indeed, some staff may take the position that individual sessions undermine group participation. However, individual sessions have strategic value in promoting engagement, particularly for patients who are not yet comfortable disclosing important issues in a group format. It is important that therapists repeatedly encourage patients to bring important issues to the group as soon as they surface, and fears of further disclosure can be addressed.

Licensed therapists usually have strong clinical skills to bring to this effort. Individual sessions offer more time to explore issues related to motivation, work on ambivalence about abstinence, discuss incidents where behavioral strategies appeared to break down, and focus on the interplay between alcohol and other drug use and other psychiatric disorders that may be present. Although all of this can be done in the group setting, time constraints can preclude the kind of thorough discussion that improves results.

Therapists in Independent Practice

The task of finding a therapist who is competent to assess and treat substance abuse issues is more complicated than one might assume. Unfortunately, academic degrees and professional licenses may not accurately represent specific skills to address substance abuse. Graduate or medical schools do not necessarily integrate thorough training in the assessment and treatment of addictive disorders into their core curricula, nor are their supervisors always prepared to address these issues in clinical training settings. Indeed, the older and more "seasoned" the clinical supervisor, the less the likelihood that he or she has had formal training in addressing substance abuse. Some seek it out, but many assume their basic training will serve them with only modest modifications and underestimate the importance of specialized knowledge. Licensed professionals have been known to be too wedded to their theoretical models, or their temperament may hamper their ability to revise their practices in the light of emerging evidence.

The issue of the therapist or counselor's recovery status has been debated for decades. Many patients indicate that having a therapist in recovery increases their confidence that they will be understood and be given helpful guidance. However, some recovering people, like some licensed professionals, can be quite rigid and may find sophisticated ways to blame the patient if the treatment is not working. In the psychotherapy literature, therapist variables (the quality of the relationship, therapist effects such as positive regard) account for 18% of the variance, and the specific treatment method accounts for 5% to 8%.

In selecting good therapists for referral, it is helpful to consider

- Evidence of basic knowledge, through course work or continuing education activities.
- Recent updates in training.
- Good relationship skills, as reflected in patient and colleague feedback and patient satisfaction surveys.

Finding a Specialty Program

Therapists in the community are in a prime position to intervene early on developing problems with alcohol and other drugs, and if they are proficient, they may save the patient decades of self-destructive behavior. However, the patient may reach a point where more structure is

needed than a private practitioner can provide, and referral to a specialty program is in order. General considerations when choosing a program should include

- Whether the program has a current license from the Commission on Accreditation of Rehabilitation Facilities (CARF) or the Joint Commission (aka the Joint Commission on the Accreditation of Health Care Organizations) or another certifying entity recognized by the state where the program is located.
- If not part of a local medical center, whether the program has a close relationship or current referral agreement with local primary and specialty care, including detoxification if needed.
- If the program involves family members in therapy and recovery planning. This means that geographical considerations should usually take precedence over prestige, unless financial resources permit participation no matter what the location.
- If the program uses evidence-based practices and explains them clearly to family members.
- If the program either provides or has access to medications, including psychotropic medications and medications used to treat addiction (such as buprenorphine or methadone). The program should not discriminate against patients needing specific types of medications. It is especially important that programs do not discourage patients needing opioid agonists or partial agonists from utilizing such medication as part of a comprehensive program of recovery.
- If the program is willing to maintain a collaborative relationship with the therapist in the community and include the therapist when possible in recovery planning meetings.

It is very important to assess financial resources and plan for a long-term recovery process. In private sector programs, what is offered as data on outcomes often originates from the marketing department, and the average patient or family member is not equipped to evaluate the data they are shown. Interestingly, public sector programs are under more pressure to utilize evidence-based practices and document outcomes, and are often subject to third-party scrutiny. High prestige programs are often touted as the most desirable, and some families mortgage their retirement in order to send their loved one for a month or more. The key question is what resources will be needed for the long term? What services will need to be continuous? For example, a patient with complex medical and psychiatric problems will possibly need a team that includes several physician specialists and a therapist, one of whom must agree to coordinate the care over the long term. The choice of inpatient or residential treatment should rest on whether the patient will get the needed services there, and what is offered in the brochure may not correspond to what is readily available once the patient enters the program. Inpatient/residential treatment may be an excellent way to sort out the patient's different problems, but the long-term structure and treatment plan will determine success. Unfortunately, the patient who has regular crises can elevate the anxiety of family members and even the therapist, resulting in magical expectations for specialty treatment. Not all essential activities need to be provided by professionals. There is a growing emphasis on a recovery-management approach that provides long-term supports and recognizes multiple pathways to healing.

Strengths and Limits of Office-Based Therapy

There are distinct advantages to office-based therapy, and challenging disadvantages. Social stigma and the possibility of severe negative consequences to admitting substance use cause many individuals to avoid or delay seeking help for extended periods of time, especially in group settings. An office setting affords far greater reassurance of privacy and confidentiality. It is a far less threatening point of entry into treatment, and for those already in psychotherapy, there is an excellent opportunity to avoid the full-blown consequences of a substance

use disorder (SUD) through identification and early intervention by a therapist who is already trusted. There is a greater possibility of flexible, individualized care. Most addiction treatment programs rely heavily on group interventions, for very good reasons. They often do a comprehensive assessment, but are limited in their ability to offer individualized treatment.

Office-based treatment may have significant limitations, especially for the practitioner who does not have strong connections to other resources, including specialty addiction treatment programs. It is important for the therapist to identify an addiction medicine specialist to identify, evaluate, and treat addiction-related medical conditions. Early psychosocial treatment typically requires multiple visits each week, and patients may not be able to afford this, or their insurance may not cover anything but licensed addiction treatment programs. Individuals whose alcohol or other drug use is severely out of control usually require the firm structure of an inpatient, residential, or intensive outpatient specialty program to be launched into a successful recovery process. This is especially true if the patient is a suicide risk, or at risk of harming others. Therapists may be unwilling or unable to provide drug and alcohol testing in the office, and unable to find a monitoring program in the community.

In summary, the therapist in the community is in an ideal position to do early intervention, provide assistance to those with mild-to-moderate problems, and prepare patients to enter a specialty treatment program if that becomes appropriate.

Unique Features of the Treatment Approach

The issue of harm reduction versus abstinence as a treatment goal can be a significant aspect of the therapeutic encounter in individual psychotherapy for a patient with a SUD, and the therapist should be familiar with these concepts and their own stance on this feature of treatment. Harm reduction is a public health strategy intended to reduce the impact of particular behaviors on individuals, families, and communities. Abstinence is on one end of the continuum of harm reduction and controversy exists about the merits of intermediate goals.

We know that abstinence-oriented treatment produces a small percentage (possibly 20%) of continuous, unbroken abstinence over a period of many years. Nonetheless, it yields significant benefits of reduction of alcohol and other drug use, reduction of drug-associated crime, improvement in family, medical (including psychiatric) status, and family functioning.

We know that abstinence-oriented programs, despite their imperfections, produce substantial harm reduction. We do not know whether harm reduction programs produce equivalent harm reduction. These important studies still need to be conducted.

Patients seen in private practice may be possible candidates to choose their own harm reduction goals. These should be consistent with health guidelines on consumption, for example, limits on alcohol (www.niaaa.nih.gov/FAQs). There are no sure methods for selecting who will do well with a harm reduction approach, but a short personal history of substance use, no family history of problematic substance use, and no physical dependence on the substance are commonly used criteria. Disqualifiers include pregnancy, medical and psychiatric conditions exacerbated by use, and hazardous interactions with prescribed medications. In the case of illicit drugs, the risks of procuring, possessing, and using the substances are a consideration. Therapist neutrality should be carefully communicated so that the therapist is not seen as endorsing these behaviors.

Preparing the Patient for Specialty Treatment if Needed

Patients do not greet the recommendation to specialty treatment with enthusiasm for a variety of reasons. Many resent the pressure to give up their drugs and do not yet have strong enough

incentives to undertake the task. Many communities do not have an appropriate program. For example, working patients often seek an intensive outpatient program with evening sessions, but residential treatment is the only option. The patient may lack insurance coverage or other financial resources for payment. Some large public sector programs offer specific programs for higher functioning patients who can pay, and these are typically less expensive than other high-profile programs that advertise extensively. However, they may provide excellent treatment, particularly since their funding requires attention to evidence-based practices.

It should be noted that recovery is a long-term process that may or may not require continuing professional treatment, so families must manage their resources with this long-term view. It is common for therapists and family members to be anxious and exhausted coping with the alcoholic or drug user, and reach for residential/inpatient treatment as the only acceptable solution. Skillful advertising promotes the idea that high-end treatment can be the "cure" for addiction, and families can spend hard-earned savings to provide this level of service. It is important that an addiction specialist makes a careful assessment to determine which actual services will meet the needs of the patient.

Connecting Presenting Problems with Alcohol and Other Drug Use

Many patients do not connect their alcohol and other drug use with the troubles that propel them to seek therapy, so the therapist must help them make that link. This requires familiarity with the different drugs of abuse, not only their short-term effects but also the longer-term consequences that unfold days or weeks after the episode of use, or after the patient has gone from occasional to regular use. The therapist should not attempt to "prove" that the patient's problems are the result of drinking and/or using, but should make the connection and encourage the patient to think about it, including keeping a journal to promote closer observation.

Setting Goals

Patients entering a specialty addiction treatment program usually do so with the expectation that they accept abstinence as a goal. However, it is important to make room for an ongoing discussion of ambivalence, which is always present to some degree. For some patients, a wavering commitment to abstinence surfaces once they feel better and begin to convince themselves that they "can handle it now." Others harbor fantasies of controlled use from the outset. Some treatment programs convey the impression that ambivalence is somehow a sign of failure or lack of commitment to recovery and thus discourage disclosure. It is important to convey that ambivalence is normal and open discussion can provide insight and encouragement. This is an excellent opportunity to reinforce the idea that cravings or feelings do not have to be acted upon.

A variety of programs, especially those designed for the severely mentally ill and those addressing HIV/AIDS, provide low-threshold admission in which the goal is to engage the patient and focus on whatever goals are acceptable to reduce harm to self and others. In these programs, setting specific goals that are realistic, incremental, and achievable is important. Early successes increase motivation and engagement, and some patients eventually find themselves committing to total abstinence even when they had no intention of doing so when they entered the program.

Regardless of program orientation, some risk factors require immediate attention. Imminent danger to self and/or others must be addressed immediately. Vigorous intervention is required for patients who are suicidal, homicidal, psychotic, or at risk for serious violence at home or elsewhere. Other dangers include driving while intoxicated, having unprotected sex with strangers, or patterns of self-mutilation. Patients may also need a medically managed

withdrawal. Drugs such as cocaine, methamphetamine, or marijuana can be discontinued immediately without medical consequences. Alcohol may require a medicated withdrawal; this should be assessed by a physician before stopping abruptly. Benzodiazepines and other sedative–hypnotics require physician assessment and management for withdrawal. Withdrawal from opiates is not in itself life-threatening, but the stress of withdrawal can be dangerous to patients with other medical conditions, such as heart disease.

Establishing Abstinence: Stabilization Phase

Mastering the Behaviors of Abstinence

Cognitive–behavioral and contingency management strategies have been extensively researched and can be employed as a component of psychotherapy to assist patients to establish and maintain abstinence. Early recovery skills include the ability to anticipate and manage cravings and urges. As stated in the popular video series *Beat the Street*, "Avoid if you can; cope if you must." Assertiveness is often a problem, and a variety of approaches teach patients how to assert themselves without being apologetic, how to refuse alcohol and other drugs, how to extract themselves from compelling but dangerous situations, and how to establish a protective structure that will facilitate progress. It is important to identify family members and others who can be relied upon to provide support in the recovery process. Often, it takes effort to reconnect with such people, or develop new relationships, and the therapist can provide an arena to discuss difficulties and make a plan to address them.

Identifying and Addressing Co-occurring Disorders

Although there is general consensus that psychotherapy should focus on discontinuing drug use before addressing other issues, in practice this may not work. Patients may insist that their traumatic experiences haunt them and they cannot be expected to give up their alcohol and other drug use until they make some progress toward putting their feelings to rest. Women in domestic violence situations who seek treatment in substance abuse settings may not be able to focus on their substance abuse until they receive some help for the threats from their relationship. Those in battering relationships may be ready to make changes in their exposure to violence before they are fully receptive to substance abuse treatment. The clinician who offers meaningful help is in a good position to engage the patient about the substance use. Treatment priorities should not be determined by rigid formulas, but the therapist can work within a recovery-oriented framework and address topics consistent with where the patient is in the recovery process. Thus, specific content can be discussed at any time, but the goals can shift from engagement, to stabilization (symptom management), to mastery.

Facilitating the Use of Self-Help Programs

One of the most important tasks of the therapist is to facilitate the use of the self-help system. These programs fill a variety of needs that cannot be met by professional treatment alone: a community that supports the recovery process, a wide range of role models, structured activities to fill the gaps left by the absence of alcohol and other drug use, and a process for personal development that has no financial barriers. It is not interchangeable with professional therapy or substance abuse treatment, but complements and augments its effects.

Ongoing Recovery Issues

While individual psychotherapy can be useful in the early stages of substance abuse treatment, it also has great potential to improve the quality of recovery by addressing issues that remain after a period of extended abstinence. Patients usually need to improve their ability to identify, modulate, tolerate, and appropriately express their feelings. They need to learn to manage their feelings without being self-destructive. In collaboration with a skilled therapist, they need to learn to distinguish between strong but appropriate feelings, feelings that represent a pathologic condition such as major depression (that may need medication), and ones that may be detrimental to their psychological health. Recovering people may be intolerant of affects, but they may also be too reluctant to seek psychotropic medications, as "using a pill to feel better" is understandably a charged issue. The appropriate use of medications is not only important for a satisfying recovery, but it can also play a key role in preventing relapse.

Interpersonal issues are usually an important focus in ongoing recovery, as key relationships have usually been distorted by alcohol and other drug use. The selection of a mate while drinking and using usually raises issues about the durability of the relationship once abstinence is stable. During the using phase, the more intact partner or spouse often takes over key functions, such as parenting and management of finances. Recovery often brings dissatisfactions with power imbalances in relationships, which need to be carefully renegotiated on a realistic timetable. Even changes for the better raise anxiety levels and the therapist can be an important anchor as well as guide through the turmoil. Other common issues include separation and individuation, self-esteem, and issues related to childhood trauma or other sources of posttraumatic stress disorder (PTSD).

A wide range of psychotherapies can be beneficial during extended abstinence, but it is crucial that the therapist have an appreciation of relapse potential once the patient begins to explore anxiety-provoking material. It is particularly easy to underestimate vulnerability in patients who are articulate and high functioning. Patients typically do not want to disappoint their therapists by announcing that relapse has occurred. Therapists should work with the patient to make a list of relapse warning signs for that individual and should inquire periodically about fantasies or cravings about drugs, or "exceptions" such as a drink here and there. Carelessness about attire, getting inadequate sleep, and loss of a previously regular exercise schedule can also be indications of a relapse state of mind or an actual relapse.

Conclusion

Individual therapy has been studied because it allows for better control in trials on specific interventions, such as motivational enhancement or cognitive–behavioral therapy, but far too little is known about its optimal use in addiction treatment and recovery. Since it is relatively expensive to provide, it is important to understand when it is essential, desirable, unnecessary, or even contraindicated in a specialty program. Patients often report that having individual attention allows them to settle into treatment and make a sustained commitment, but it is not possible at this time to disentangle the relative contributions of different activities. For therapists working in private practice in the community, it is crucial to appreciate what must be done to effectively address alcohol and other drug use within the ongoing therapeutic relationship. It is also important to know how to prepare a patient for specialty treatment if needed. Interventions have been developed that show efficacy in controlled trials, but these are rarely used by private practitioners in the community. Manuals exist for treatments with a strong evidence base, but little work has been done on how to disseminate them among private

practitioners and train such clinicians in their use. Inasmuch as most patients with alcohol and other drug problems do not seek help in specialty settings, it is important to understand how best to strengthen the ability of community practitioners to address this issue.

Suggested Readings

Denning P, Little J, Glickman A. *Over the Influence: The Harm Reduction Guide for Managing Drugs and Alcohol*. New York, NY: Guilford Press; 2004.

Johnson JE, Finney JW, Moos RH. End-of-treatment outcomes in cognitive–behavioral treatment and 12-step substance use treatment programs: do they differ and do they predict 1-year outcomes? *J Subst Abuse Treat*. 2006;21:41–50.

Leichsenring F, Rabung S. Effectiveness of long-term psychodynamic psychotherapy: a meta-analysis. *JAMA*. 2009;300(13):1551–1565.

Rounsaville BJ, Carroll KM, Beck SE. Individual psychotherapy. In: Ries RK, Fiellin DA, Miller SC, et al., eds. *Principles of Addiction Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:769–785.

Washton AM, Zweben JE. *Treating Alcohol and Drug Problems in Psychotherapy Practice: Doing What Works*. New York: Guilford Press; 2006.

30 Group Therapy

The history of group therapy adopted specifically for treating substance use disorders (SUDs) is not easily traced, but over the past several decades, group therapy has evolved into the most prevalent form of substance abuse treatment in the United States. Group therapies are used for treating all types of SUDs (including those involving the use of alcohol, cocaine, opioids, sedatives, marijuana, and various combinations of these and other substances) and for individuals suffering from co-occurring psychiatric and addictive disorders. A broad spectrum of group therapy models (e.g., cognitive/behavioral, psychoeducational, motivational, interpersonal, 12-step, psychodynamic) are utilized by substance abuse treatment programs and practitioners operating from differing theoretical orientations. Most group-based interventions for SUDs incorporate a variety of therapeutic strategies and techniques consistent with recent trends toward integrative rather than monolithic approaches.

Group therapy is defined as treatment delivered to a preselected cohort of addicted individuals in the context of regularly scheduled group therapy sessions led by a professionally trained group leader—typically an addition therapist, counselor, or other mental health professional with relevant training and experience.

Efficacy

Although group therapy has emerged as the most popular treatment modality for SUDs, empirical evidence of its clinical efficacy is sparse. Most studies have compared the effectiveness of different models of group therapy, but only a handful have compared group to individual therapy, and results are inconsistent.

It has been noted that alcohol-dependent patients who received couples therapy in a group format showed greater reductions in alcohol consumption at 6-month follow-up than patients who received couples therapy individually. In addition, there was some indication that couples treated in the group format reported more improved marital adjustment and higher ratings of relationship satisfaction than couples treated individually.

Outpatient delivery of the same 12-session cocaine relapse prevention (RP) program in group has been compared with individual therapy formats. Although the proportion of patients producing cocaine-free urine samples at the end of treatment did not differ between formats, group RP patients reported using cocaine on significantly fewer days during treatment and experienced fewer cocaine-related problems than did individual RP patients. Follow-up data collected at 12 and 24 weeks posttreatment revealed no significant differences between formats

regarding cocaine use or any other outcome measures, leading the authors to conclude that the efficacy of RP interventions is not strongly influenced by delivery format.

Additionally, it has been found that in patients struggling with concurrent bipolar and SUDs, integrated group therapy designed to address both disorders was more effective than group drug counseling alone in reducing both drug use and psychiatric symptoms. It has moreover been reported that substance abusers in a soup kitchen who received motivationally enhanced group counseling were significantly more likely than others who received concrete services only (i.e., information, referral, advocacy) to show reduced drinking and increased participation in some type of substance abuse intervention (e.g., formal treatment and/or 12-step groups) during the follow-up period. The comparison of the effectiveness of four psychosocial treatments for cocaine-dependent outpatients indicated that patients receiving a combination of group drug counseling plus individual drug counseling were more likely to show decreased drug use over time than patients who received only group drug counseling or group drug counseling plus individual psychotherapy.

An extensive study involving 7,815 patients from 63 publicly funded outpatient substance abuse treatment programs has provided perhaps the strongest empirical evidence to date of the efficacy of group approaches. This study found that the type of treatment, defined as proportion of group to individual therapy, was strongly and positively associated with various treatment performance measures, including completion of treatment and achievement of treatment goals.

Although these studies provide some empirical support for the effectiveness of group-based treatment interventions, more extensive research in this area is sorely needed.

Despite the absence of a solid empirical base for utilizing group therapy as the treatment of first choice for addiction, the current popularity of group interventions appears to be based largely on its historically long-standing use as the mainstay of addiction treatment programs in the United States, on its cost-effectiveness, and on the apparent goodness of fit between certain clinical needs/characteristics of addicted individuals and the combination of therapeutic forces that group therapy uniquely provides.

Advantages of Group Therapy

From an economic standpoint, group therapy is more cost-effective to deliver than individual therapy is, making it increasingly attractive in current efforts to reduce health-care costs. Due to limited resources, most treatment programs, especially those supported by public funds, are unable to make individual therapy routinely available to their patients. As compared to individual therapy, group therapy allows a larger number of patients to be treated by fewer clinicians on a given workday. Importantly, group therapy enjoys a high rate of patient acceptance and desirability among individuals seeking treatment for SUDs. In fact, patients seeking addiction treatment often prefer group to individual treatment.

One of the most striking therapeutic benefits of group-based interventions for SUDs is readily apparent to clinicians who routinely provide this type of treatment, namely, that groups often have a unique ability to empower clients to change even after individual therapy and/or other interventions have failed. When people struggling with a common adversity join together in pursuit of a common goal, a variety of potent forces are mobilized, which motivate and inspire them to overcome the adversity. This same phenomenon is evident, for example, in how people cope with the aftermath of natural disasters and other severely traumatic or life-threatening situations.

Group therapy incorporates a unique combination of therapeutic forces not available in other forms of treatment. Groups provide therapeutic opportunities for (a) mutual identification and reduced feelings of isolation and shame; (b) peer acceptance, support, and role

modeling; (c) confrontation and realistic feedback; (d) peer pressure, social support, structure, and accountability for making positive changes; (e) acquisition of new coping skills; (f) exchange of factual information; and (g) instillation of optimism and hope. The gathering together of people who share a common problem often creates a bond between them, stemming from a sense of mutual identification and an expectation of being intuitively understood. This is critically important in counteracting the intense feelings of isolation, shame, and guilt that addicted individuals often experience. The social stigma of addiction and profound humiliation of having lost control over one's behavior make rapid acceptance into a peer group all the more important for newcomers. The group instills optimism and hope by giving newcomers a chance to make contact with others who are succeeding in making positive changes and by instantly supplying newcomers with a positive support network committed to the pursuit of common goals. Groups often enhance treatment retention as a by-product of the bonding that develops between group members. Groups provide a forum for developing better coping abilities and avoiding common pitfalls in recovery. Because groups typically place high value on self-disclosure, active participation, compliance with group norms (e.g., abstinence, punctuality, attendance, honesty), a spirit of cooperation among group members, and facing rather than avoiding problems, it is difficult for resistant or noninteractive patients to "hide out" in small groups because all members are expected to routinely participate in group discussions.

Limitations of Group Therapy

Given the numerous advantages of group therapy, what might be some of its limitations, and when might individual therapy be preferable? First, unlike individual therapy in which patients enjoy total privacy and confidentiality, group therapy inevitably requires patients to disclose their identity and personal problems to strangers. This can be a problem especially for patients who live in small communities where the chances of encountering people who might know them can be substantial. While maintaining strict confidentiality regarding group members' identities and the content of sessions is a cardinal rule of group therapy, there is no way to control what group members might say or do outside of group sessions. Despite increasing public enlightenment about addiction as a widespread disorder affecting people from all walks of life, unwanted disclosure of information about an individual's alcohol or drug problem still holds the potential to damage careers, reputations, and relationships.

A second limitation of group therapy is that the content and pace of the treatment is determined by the group as a whole and not by the needs of any one individual. Inevitably, there are times when group therapy is out of step with the needs of some members while appropriately addressing the needs of others. This limitation is most evident in open-membership groups where new members are admitted throughout the life of the group as others leave. Each time newcomers enter an ongoing group, the continuity of treatment is interrupted as attention shifts back to newcomer issues. By contrast, individual therapy allows the therapist to address the patient's issues as they arise and to spend as much time within a session or as many sessions as necessary to deal with these issues.

A third limitation of groups is that typically only a small portion of the therapy time is devoted to the needs of any one individual. This is offset to some extent by the benefits that group members may derive indirectly from participating in discussions that focus on the issues of other members. Nonetheless, individual therapy devotes 100% of the therapy time to the needs of one person, which may be more likely to engender change or perhaps do so more rapidly.

A fourth limitation is that group therapy may not be suitable or appropriate for all addicted individuals. While many, if not most, can benefit from group therapy and prefer it to other forms of treatment, others are simply not good candidates for group treatment. Patients

with severe borderline personality disorders often find the intense interpersonal interaction and scrutiny in group sessions intolerably stressful. Similarly, patients who are avoidant, shy, or schizoid may be unable to participate actively in group discussions or form meaningful connections with other group members. Apart from psychiatric impairment, some patients simply do not want to be in group therapy for whatever reasons and flatly refuse to participate, preferring individual therapy instead. Although further exploration of this unreceptive stance may help to allay certain commonly held fears and misconceptions about group therapy (e.g., expectations of harsh confrontation by peers), some patients remain adamant about not wanting group therapy, and it is important for clinicians to respect these patients' wishes.

Group Therapy Versus Self-Help Groups

Group therapy and self-help groups such as Alcoholics Anonymous (AA) are not good substitutes for one another. Each forum provides a unique form of help and, ideally, they should be seen as synergistic rather than competing activities. Self-help groups have many advantages, but the in-depth attention given to psychological and personal issues that take place in professionally led recovery groups is simply not available in self-help meetings. Many individuals are not comfortable revealing personal details of their lives in the public forum of a self-help meeting and are more inclined to do so in the smaller, more intimate setting of a group therapy session. In group sessions, members are strongly encouraged to give objective feedback to one another, whereas in self-help meetings giving feedback (known as "cross talk") is not permitted. These are not criticisms of self-help groups, which contain their own unique blend of therapeutic forces, but fundamental differences between these two very different forms of help for people struggling with the problem of addiction. Unlike group therapy, self-help meetings are characterized by peer rather than professional leadership, an absence of screening or exclusion criteria, unlimited size of membership, widespread availability, and an absence of time limits on the length of participation which may extend over a participant's lifetime.

Patient Selection Factors

A formal selection process is required to ensure that patients are placed in groups best suited to meet their needs. Ideally, screening of potential group members should be conducted by the clinician who leads the group. No matter how rigorous the selection process may be, it is sometimes impossible to ensure that the composition of patients placed in a group is ideal for conducting the group's therapeutic work. The goal of patient selection should be to achieve a reasonable degree of homogeneity and heterogeneity among group members. It is important that all group members find a basis for identifying with one or more of the other members because admitting a newcomer into the group who shares few characteristics with other members may create problems for that individual and for the group as a whole. At the same time, diversity enhances the richness of the group experience. Group members can differ in age, gender, race, socioeconomic status, educational level, and other variables as long as one member is not the lone "outlier." Generally, newcomers will fare better when there are at least one or two other group members with whom they can readily identify. Individuals who are different from all other group members in one or more important respects (e.g., one woman among a group of men, one gay person among heterosexuals, one seriously impaired person among highly functional people) are likely to feel out of place in the group, not participate actively in group discussions, and/or drop out prematurely.

Group membership should not be limited only to patients who have the same primary drug of choice, considering that the addictive disorder, not the drug use itself, is the focus of treatment. Heterogeneity in this regard can help group members realize that different substances often lead to the same constellation of problems and that changes required to deal effectively with these problems are very similar, regardless of a person's substance(s) of choice. When a newcomer happens to be the only person in a group with a particular drug of choice, identification and bonding with other group members can be compromised. Despite similarities, however, the group should not ignore some of the unique problems associated with the use of different types of substances such as residual cognitive impairments following chronic alcohol use, lingering withdrawal symptoms of depression and insomnia following cessation of opioid use, and sexual acting-out behaviors often associated with cocaine and methamphetamine use. Addressing substance-specific issues straightforwardly, proactively, and whenever they arise can help to promote group cohesiveness and induct patients with different substances of choice into the group.

In addition to the above, other important patient selection factors include the patient's desired treatment goals, motivation or reasons for entering the group, and stage of readiness for change. Individuals committed to the goal of total abstinence from all psychoactive substances usually do not mix well in groups with those who choose nonabstinence goals such as harm reduction, moderation, or partial abstinence (i.e., abstinence from the most problematic substance, but not others). Those pursuing a goal of total abstinence from all psychoactive substances often feel irritated and unsafe in groups where others are not committed to the same goal and may feel that the presence of these group members not only adversely affects their own motivation to refrain from all substance use but also distracts the group from its primary mission of supporting abstinence. Similarly, those not choosing total abstinence are likely to feel criticized and out of place in a group where all other members are committed to abstinence. Thus, patients with incompatible or opposing goals are not likely to work well together in groups and their seemingly irreconcilable differences can consume too much of the group's time and thwart the therapeutic work. Traditionally, substance abuse treatment groups have restricted membership to patients who are committed to total abstinence or at least willing to comply with an abstinence requirement during their tenure in the group. Recognizing that many patients who seek help for SUDs are not ready or willing to accept total abstinence as their goal, harm reduction and moderation groups have emerged as alternatives for these patients, whether or not abstinence is their ultimate goal.

Groups for Different Stages of Recovery

Phase-Specific Groups

Work on the application of the stages of change model to group therapy indicates that substance abuse treatment groups function best when all members are in a similar stage of change. Ideally, groups should be composed of individuals either in the early stages of precontemplation, contemplation, and preparation or those in the latter stages of action and maintenance. The types of therapeutic interventions that work best in the treatment of addiction often depend on what phase of recovery or stage of change the person is in. Individuals grappling with addiction typically progress through a series of phases as they move from active use toward sustained abstinence and recovery. Accordingly, many treatment programs offer phase-specific groups that focus on the tasks and goals most relevant to each stage. This may include motivation enhancement or pretreatment induction groups for those who need preparatory

work before making an abstinence commitment or participating in a formal treatment program, early abstinence groups for those in the process of breaking free of alcohol/drug use, and RP or continuing care groups for those in the middle and later stages of recovery. This stratification of groups offers a number of clinical advantages: (a) it focuses the group work on the specific problems, tasks, and goals relevant to each phase; (b) it provides predefined progress markers that give group members a sense of personal accomplishment as they complete one phase and move on to the next; (c) it makes it easier for individuals to identify and relate to stage-specific issues being addressed in the group and to bond with other group members who are dealing with similar issues; and (d) it facilitates patient placement into a group best suited to meet his or her needs at each stage of the recovery process. The rationale for stratification is based on the assumption that matching treatment interventions to meet the specific needs of patients as they progress through different stages of recovery is likely to enhance clinical outcomes. There is a natural progression from an initial focus on breaking free of substance use, to securing abstinence, to preventing relapse, and eventually to addressing a variety of psychological issues. The dividing lines between different stages are somewhat arbitrary and the rate of progression through each stage varies from person to person.

Mixed-Phase Groups

Despite the numerous advantages of phase-specific groups, there are also drawbacks. One significant disadvantage is that the group composition may change too frequently and become disruptive as members move from one phase to the next. Another limitation is that private practitioners or small treatment programs may not have sufficient caseloads or manpower to reliably maintain different groups for patients in each phase of treatment, and thus, mixed-phase groups may be the only feasible alternative. In a mixed-phase model, participants stay in a group as long as needed to achieve their treatment goals and/or as long as their participation in the group remains productive. Individuals struggling with addiction move through the change process at such different rates that it is not possible to specify in advance how long it will take for a given group member to achieve his or her treatment goals. As compared to phase-specific groups, mixed groups contain a broader array of patients at different phases of recovery: some in the early phases, others farther along in the process, and still others somewhere in between. All have an opportunity to interact with one another in a group setting and derive mutual benefits from doing so.

Early Recovery Groups

Early recovery groups focus on issues most relevant to the beginning stages of treatment: helping members to establish initial abstinence, stabilize their overall functioning, acknowledge and accept their addiction problem, work through initial ambivalence and reluctance about giving up alcohol/drug use, establish a social support network, become bonded to other members and integrated into the group, overcome early relapses and other setbacks without dropping out, deal effectively with both immediate and delayed consequences of their addiction, and begin the process of identifying and changing some of the dysfunctional self-defeating cognitions, emotions, and behaviors intertwined with their addiction. This is an ideal wish list and certainly not every group member will achieve all of these goals during their tenure in the group. In the absence of financial constraints that limit length of stay, tenure in a group varies according to how quickly patients progress toward achieving their goals, ranging usually from several months to as much as a year, if circumstances permit.

Newcomers struggling to establish or maintain initial abstinence usually need specific guidance and support from other group members on early recovery issues such as

(a) discarding all drug supplies and paraphernalia; (b) avoiding contact with dealers, users, parties, bars, and other high-risk situations; (c) learning how to recognize self-sabotaging behaviors and other "setups" for drug/alcohol use; and (d) learning how to manage urges and cravings. Once initial abstinence is established, the focus predictably shifts to stabilization of the individual's functioning. Often, a profound sense of disappointment emerges in the newly abstinent patient soon after the patient realizes that life is still fraught with problems despite having given up alcohol/drugs. This realization may lead the patient to seriously question whether the struggle of staying abstinent is really worthwhile, especially if and when delayed consequences of prior substance use such as financial, legal, and relationship problems begin to surface while the patient is actually doing well. Support and advice from established group members who have "been there" can be extremely helpful at this point to counteract the newcomer's tendency to impulsively self-medicate their resentment, anxiety, and fear.

Relapse Prevention and Continuing Care Groups

The essential tasks and goals of RP and continuing care groups are to help patients strengthen their commitment to abstinence, work through residual ambivalence about giving up alcohol and drugs, and both learn and practice RP strategies. Although RP is the primary focus of this phase, the group should not focus exclusively on substance use but on a wider range of issues in greater depth. These issues may include the recovery tasks of repairing damaged relationships, forming new ones, working toward resolving the lingering impact of developmental and traumatic issues, enhancing self-esteem, and creating a reasonably satisfying lifestyle that is free of alcohol and other drugs. Relapses that occur after abstinence has been firmly established and practiced for at least several months are frequently caused not so much by environmental triggers (which is more typical during the early phases) as by failure of the patient to cope adequately with negative emotions generated by interpersonal conflicts and other types of life problems and stressors. Research on the relapse process indicates that the most common precipitants of relapse are negative mood states, interpersonal conflict, and social pressures to use alcohol/drugs. Among the many topics addressed in this phase of treatment are how to identify negative feelings; how to manage anger; how to avoid impulsive decision-making; how to relax and have fun without drugs; how to give and receive constructive criticism; how to be assertive without being aggressive; and how to deal with problems in interpersonal relationships.

In addition to providing coping skills training, it is equally important to sensitize patients to relapse warning signs so that appropriate measures can be taken to "short-circuit" what is often a progressive backsliding in attitudes and behaviors. Explaining the relapse dynamic as a progressive identifiable process that is set in motion long before returning to substance use empowers group members to interrupt what otherwise might be an insidious slide toward relapse, which they are unable to recognize while it is happening. Moreover, group members must be alerted to the possibility that flare-ups can occur many months (or even years) after stopping alcohol and drug use.

RP groups should also address psychological issues that go beyond the basic cognitive and behavioral factors that promote a return to substance use. This involves exploring in detail the inner emotional life of each group member and interpersonal problems that repeatedly give rise to the compulsive desire to "self-medicate." Patients with long, destructive histories of substance use often lack the ability to identify, manage, tolerate, and appropriately express feelings. The ultimate goal here is not merely the acquisition of self-knowledge and insight but fundamental change in the individual's characteristically maladaptive patterns of thinking, feeling, behaving, and interacting.

Group Management Considerations

Leadership Roles and Responsibilities

The group leader serves a variety of essential functions. These include (a) establishing and enforcing group rules in a caring, consistent, nonpunitive manner to protect the group's integrity and progress; (b) screening, preparing, and orienting potential newcomers to ensure suitability and proper placement in the group; (c) keeping group discussions on track and focused on important issues to maximize the therapeutic benefit for all group members; (d) emphasizing, promoting, and maintaining a caring, nonjudgmental, therapeutic climate in the group that both counteracts self-defeating attitudes and promotes self-awareness, expression of feelings, honest self-disclosure, and adaptive alternatives to drug use; (e) managing problem members who are disruptive to the group in a timely and consistent manner to protect the membership and integrity of the group; and (f) educating patients about selected aspects of alcohol/ drug use, addiction, recovery, and related issues.

Effective leadership of an addiction recovery group demands that the leader adopt a certain posture in the group that differs significantly from that of traditional psychodynamically oriented psychotherapy groups, particularly in the early stages of recovery. In traditional groups, the therapist gently guides and focuses the attention of group members on matters pertaining to group process, group dynamics, and the complicated interpersonal interaction among group members. With the exception of carefully timed comments, the therapist may remain quiet and nondirective in the customary mode of psychodynamic psychotherapy. By contrast, in early abstinence groups the therapist must work actively to keep the group focused on concrete here-and-now issues that pertain directly to addiction-related issues. The therapist plays a very active and directive leadership role that includes questioning, confronting, advising, and educating group members on relevant issues. The therapist keeps the group task-oriented and reality-based, and serves as the major catalyst for group discussion. Addressing substance-related issues is always the number one priority of the group, and the therapist must always be sure to keep the group focused on this task.

It is not the group leader's role to direct or control the group discussion, but rather to facilitate a process whereby members learn how to interact with one another in an increasingly open, honest, empathetic manner that promotes positive change. When a group is working properly, the leader functions as a coach or guide, staying in the background while the group takes responsibility for the therapeutic work. When the group is not working properly, the leader is doing a lot of talking and/or spending a lot of time exhorting members to participate more actively in group discussions. Well-functioning groups require deliberate and persistent intervention by the group leader to return maximum responsibility for what goes on in sessions to the group's members, consistent with the psychotherapeutic principle of analyzing resistance before dealing with content. It is much more important to help group members recognize their passivity than it is to try to drag them into doing the therapeutic work. As compared to early recovery groups, where the group leader plays a much more active role, later stage groups should be helped to focus increasingly on group process and become reliably self-correcting when the discussion strays off track or becomes unproductive.

Preparing New Members for Group Entry

Preparing new patients for group entry involves not only orienting them to basic group ground rules but also establishing realistic goals and expectations. Before admitting new patients to a group, the group leader should ideally meet individually with each prospective newcomer for

at least one or two sessions to assess motivation, clarify myths and misconceptions about group therapy, and address resistances to group participation. Prospective members should also be informed about how the group works, how to give useful feedback, and how to refrain from unhelpful group behaviors. Before newcomers attend a first group meeting they should agree in writing to adhere to the group ground rules.

Managing Peer Confrontation and Feedback

Peer confrontation can be extremely effective in helping group members achieve a more realistic assessment of their maladaptive attitudes and behaviors. But heavy-handed, excessive, and poorly timed confrontation can be countertherapeutic and damaging. Some patients enter groups with the mistaken idea that humiliation and aggressive confrontation are the ways to force resistant group members to face reality. Sometimes, harsh confrontations are rationalized as attempts to be "truly honest" with members who are seen as "resistant" or not conforming to group expectations and norms. Group members typically have less tolerance for negative attitudes and obfuscations than do group leaders, especially when these attitudes are reminiscent of their own problems. Likely targets for attack are members who repeatedly relapse, those who are experienced as defiant, superficial, or insincere, and those who minimize their problem and make little attempt to bond with other members. The group leader should not allow unpopular, frustrating, resistant, or severely troubled group members to be verbally scapegoated and bludgeoned by their peers, even when the content of what is being said is entirely accurate. Harsh or excessive confrontation must not be used as a means to push unpopular or troubled members out of the group and discourage them from coming back. It is often the style rather than content of peer confrontation that determines its impact on the recipient. The main goal of confrontation is to make the person more receptive to change without eliciting defensiveness or destructive acting-out behavior.

Managing Common Problems

Among the most common problems that arise in group therapy are the following: chronic lateness and absenteeism, hostility and other disruptive behaviors, lack of active participation, superficial presentations, proselytizing and hiding behind AA, and playing cotherapist. Because of space limitations, these problems are touched on only briefly here.

Lateness and Absenteeism

An atmosphere of consistency and predictability is essential for group therapy to be effective. Because most patients have histories of irresponsible behavior during active addiction, when this type of behavior arises in the group it should not be ignored. A pattern of repeated lateness and/or absenteeism adversely affects group morale and cohesion. It is almost always a sign of ambivalence about being in the group and should be addressed as such.

Hostility and Other Disruptive Behaviors

Sometimes, the content of what a member says in a group session is less important than the way he or she says it. The group leader must attend the session continuously to affect body language, voice intonation, and overall communication style of group members. Some members are chronically antagonistic, argumentative, and sarcastic. They repeatedly devalue the group, complain about how poorly it is run, point out minor inconsistencies, and reject advice or suggestions offered by other group members or the group leader. The group leader should not ignore these types of negative behaviors.

Silence and Lack of Participation

Some group members sit quietly on the sidelines as observers of the group discussion, glad to have the focus of attention not be on them. Silent members may secretly harbor feelings of ambivalence, resentment, and annoyance about being in treatment, and doubt whether they need to be in the group at all. Some members are just shy and need gentle coaxing and encouragement from the group to open up.

Superficial Presentations

Terse or superficial presentations that focus on facts rather than feelings and reveal little or nothing about the presenter are another forms of patient resistance to the group's therapeutic work. Similarly, some group members present lengthy stories recounting external events and circumstances full of irrelevant details and devoid of emotional content. This is often indicative of a member who is just going through the emotions of being in treatment to satisfy a spouse, employer, or mandate.

Proselytizing and Hiding behind AA

This is one of the most difficult problems to address in group therapy for addiction. In almost every recovery group, there are likely to be some members solidly linked into AA or other 12-step programs who insist with unwavering conviction that AA is the one and only pathway to successful recovery. They may be openly intolerant of other members who do not embrace AA and take it as their mission to proselytize the benefits of AA in the hopes of converting nonbelievers. Additionally, they may complain that there is not enough "recovery talk" in the group and that the format of group sessions does not sufficiently parallel that of an AA meeting. These individuals will often polarize the group into opposing factions: those who embrace AA enthusiastically and wholeheartedly versus those who are more tempered in their posture toward AA or reject it completely. If this polarization is not addressed, it will ultimately destroy group cohesion, create an unsafe climate in the group, divert valuable attention from other important issues, and stall the group's therapeutic work.

Playing Cotherapist

Some group members play the role of therapist's helper that serves (unconsciously) as a diversion or smokescreen for dealing with their own issues. They often try to perform certain of the group leader's functions such as keeping the group discussion on track, confronting other members on inappropriate behaviors, and reinforcing group norms. Because their input is often very helpful to the group, it is easy for other members and sometimes the group leader to overlook the fact that the self-appointed "cotherapist" spends so much time being a helper that his or her own issues are rarely, if ever, addressed.

Responding to a Group Member's Substance Use

When a group member reports that he or she has used alcohol/drugs since the last group session, the group must give first priority to addressing this issue. In doing so, the group leader should adopt a direct, compassionate, nonpunitive response. The group leader's task is to help the group utilize the discussion of a member's use as an opportunity to learn something useful. Suggested guidelines for dealing with a group member's recent alcohol/drug use are as follows: (a) Ask the individual to give the group a detailed account of the sequence of feelings, events, and circumstances that led up to the use. (b) Invite others to ask the patient about early warning signs, self-sabotage, and other factors that may have preceded the actual substance use. (c) Ask others to share any suggestions or feedback they can offer the patient about the use and how

to prevent it from happening again. Also ask them to share their feelings about the episode, reminding them to avoid any tendency they may have to scapegoat the patient or to act out feelings of anger and frustration with negative comments. (d) With the patient's active participation, ask the group to develop a list of suggested strategies and behavioral changes to guard against the possibility of further substance use.

Although most group members respond supportively to a fellow member's substance use, there is an unspecified limit as to how many times this will happen. When a group member shows little evidence of using previous suggestions about how to prevent further use, other members may start to become intolerant and feel that this individual may be jeopardizing the integrity of the group. Peer confrontation can become very intense when dealing with relapse issues and the group leader must guard vigilantly against the group's tendency to scapegoat or ostracize the struggling member.

Conclusion

We addressed the efficacy, advantages, and limitations of group therapy as well as various practical considerations involved in group formation and leadership. Group therapy has evolved over several decades into the treatment of choice for addiction. Stage-specific groups that address the changing needs of patients as they move through different phases of recovery help to enhance patient-treatment matching and clinical outcomes. Although clinically effective, group therapy is not the best or only treatment option for every individual with an addiction problem. Group therapy should not be used as a stand-alone treatment but ideally as just one component of a more comprehensive multimodality treatment approach. Group leaders serve many important and complex functions, including deciding which patients to bring together in a group, keeping group discussions focused on relevant topics, and handling various types of problems that arise during group sessions. In addition to its therapeutic benefits for patients, groups provide a valuable source of personal and professional growth, even for the most seasoned clinician.

Suggested Readings

Morgan-Lopez AA, Fals-Stewart W. Analytic complexities associated with group therapy in substance abuse treatment research: problems, recommendations, and future directions. *Exp Clin Psychopharmacol*. 2006;14(2):265–273.

Panas L, Caspi Y, Fournier E, et al. Performance measures for outpatient substance abuse services: group versus individual counseling. *J Subst Abuse Treat*. 2003;25:271–278.

Spitz HI, Brook DW. *The Group Therapy of Substance Abuse*. New York, NY: Haworth Medical Press; 2002.

Washton AM. Outpatient groups at different stages of substance abuse treatment: preparation, initial abstinence, and relapse prevention. In: Brook DW, Spitz HI, eds. *The Group Therapy of Substance Abuse*. New York, NY: Haworth Medical Press; 2002:99–119.

Washton AM, Zweben JE. *Treating Alcohol and Drug Problems in Psychotherapy Practice: Doing What Works*. New York, NY: Guilford Press; 2006.

31 Family/Couples Therapy

Historically, alcoholism and drug addiction have been viewed by the majority of treatment providers and researchers, as well as by the public at large, as problems of the "individual." In turn, intervention approaches focused largely or exclusively on the diagnosed individual. During the last four decades, this conceptualization has slowly given way to a greater awareness of family members' crucial roles in the etiology and maintenance of, not to mention the long-term recovery from, various kinds of addictive behaviors. Consequently, treatment providers and researchers alike have placed greater emphasis on understanding drinking and drug use from a family systemic perspective and, in turn, on exploring how consideration of partner and family dynamics may be understood and used to address individuals' substance abuse.

As it turns out, the preponderance of available evidence reveals that marital and family therapy approaches are among the most efficacious in terms of prevention, change initiation, and treatment of substance use disorders (SUDs). Indeed, some have argued that these intervention approaches are the most effective methods for treating alcoholism and drug abuse, principally because of the substantial improvements seen across a very broad range of outcomes (e.g., substance use reduction, improved child functioning, reduced domestic violence).

We will (a) present a brief history of couple- and family-based perspectives and treatment approaches; (b) describe the unique features of these treatment approaches that differentiate them from other models; (c) discuss the various partner-and family-involved approaches for substance use that focus on treatment engagement and active therapeutic models, and review the available evidence of efficacy for these approaches; (d) present optimal implementation techniques used by the most efficacious couple- and family-based approaches; and (e) identify special considerations that clinicians and researchers alike may be likely to encounter when conducting couples- and family-based treatment with substance-abusing couples. Lastly, we will conclude with an exploration of possible future directions with respect to partner- and family-involved therapies with substance-abusing patients.

History of Family- and Couples-Based Approaches

The traditional framework from which SUDs are viewed is succinctly captured in the commonly stated axiom among treatment providers: "Alcoholism and drug abuse are individual problems best treated on an individual basis." It is a long-standing clinical philosophy that had held sway in the substance abuse treatment community for much of the last half century and had a very powerful influence on the treatment of alcoholism and other drug use disorders. By the early 1970s, there was an acknowledgment among many providers that the focus on the individual

was necessary, but not sufficient, since it did not adequately consider the contextual factors that served to support patients' continued use or relapse. Despite the very dominant individual-focused paradigm, the family and home environments were simply too important to ignore. This shift toward consideration of the family when treating addictive behavior was legitimized in a special report given to the U.S. Congress in the early 1970s by the National Institute on Alcohol Abuse and Alcoholism (NIAAA); that body described couple and family therapy as "one of the most outstanding current advances in the area of psychotherapy of alcoholism" and recommended funding of controlled studies to test the effectiveness of these promising methods.

Since that time, the call to examine family-based treatment approaches for substance abuse has been answered by many different research groups, initially with small-scale studies and, as evidence of effectiveness accumulated, followed by large-scale randomized clinical trials. Results of this programmatic line of research yielded findings that were both consistent and highly positive; compared to individual-based therapies, partner- and family-involved interventions were more efficacious in terms of substance use reductions, improvements in patients' psychosocial adjustment, and amelioration of serious family problems, such as domestic violence and children's maladjustment. As a result, an increasing number of treatment providers and the programs in which they work began intervening with the family as a way to reduce or eliminate abusive drinking or drug use by one or more of its members. In the last decade, the Joint Commission on Accreditation of Health Care Organizations (JCAHCO) standards for accrediting substance abuse treatment programs in the United States required that an adult family member who lives with an identified substance-abusing patient be included at least in the initial assessment. Thus, in the last 50 years, some involvement of the family in the treatment of substance abuse moved from being viewed in most circles as inappropriate all the way to a component of competent standard practice.

Family Treatment: Unique and Defining Features

Definitions: Marriage and Family

When considering what makes partner- or family-focused interventions for alcoholism and drug abuse unique, a deceptively simple answer is that these treatments focus on or otherwise involve intimate partners or other family members. Although certainly true, how does one define terms like "marriage" and "family?" In many important respects, what defines these terms has been and very much remains in a state of flux. To gain appreciation of this, one needs to only reference headlines or watch the news about the heated debates among those who favor or are opposed to same-sex marriage. How our society and our culture, as well as other societies and cultures, define and operationalize these terms is among the great sociopolitical debates of our generation. Simply stated, there is no encompassing definition of *family* or *marriage*; this has always been the case. Different societal norms and attitudes influence definitions of such cultural constructions, and because cultures and beliefs change over time, the definition of what is meant by marriage and family changes in concert.

However, at least for the purpose of operationalizing these terms to identify an "intervention unit," it nonetheless seems possible to distill certain qualities and characterizations of these institutions that are somewhat consistent under a variety of circumstances and conditions. In the most inclusive sense, family or marriage (or at least an intimate relationship—marriage carries legal elements as well as sociocultural ones) implies an enduring involvement in an emotional level with other people. For practical purposes, family can be defined according to the individual's closest emotional connections, of which marriage is a subset. In other words, the individual constructs who is his or her family or his or her partner(s), which is not to be confused, of course, with those persons the individual "likes." Thus, our definition moves beyond the pure

genetic, biologic, or legal definitions, but also encompasses emotional and behavioral connections defined by the individual who identifies "partner" and "family." As a practical consideration, it is common for providers to identify a romantic partner as one with whom the patient has married or lived with for at least a year. For individuals who work with broader family systems, such systems are often partially defined by those with whom the patient currently lives (e.g., married partner and children) or lived with while growing up (e.g., family-of-origin members, such as parents and siblings). From this perspective, we see the family can take many different forms, including, but not limited to, (a) a traditional nuclear family in which members are cohabiting in household (where either one or both parents are working); (b) a household or family headed by a single parent; (c) a "blended" family resulting from divorce, separation, and remarriage; (d) a same-sex couple with or without custodial children; (e) a multigenerational household, including grandparents, parents, and children; and even (f) long-term cohabiting partners who are not romantically linked but define themselves as a family. Depending on the need of the patient, any of these can ultimately become the familial unit of intervention.

The Interplay between Substance Use and Marital/Family Maladjustment

Compared to traditional individual-focused interventions for alcoholism and drug abuse, family-based approaches try to understand these disorders from a systems perspective. People interact with others in their social and environmental networks; they influence those networks, and those networks influence them. Although there are certainly many social networks (e.g., work, school, church, etc.), the family is very often the most proximal, influential, and powerful. Proponents of family-based intervention approaches universally hold that the power of the family can be used to help bring about healthful behavioral change.

The interconnection between substance use and familial distress appears to be marked by what can be best described as "reciprocal causality." Certain commonly observed characteristics and behaviors of alcoholics and drug abusers (e.g., denial of problems, checking out of interactions and general cognitive distortion of information) are not conducive to positive family environments. In turn, these characteristics contribute high relationship and family distress, which makes for an environment that serves to promote (inadvertently or otherwise) continued use or relapse. Thus, the link between substance use and relationship problems is not unidirectional, with one consistently causing the other, but rather each can serve as a precursor to the other, creating a "vicious cycle" from which couples who include a partner who abuses drugs or alcohol often have difficulty escaping.

There are several family environment, antecedent conditions, and reinforcing consequences of substance use. Couples, marital, and family problems (e.g., poor communication and problem-solving, arguing, and financial stressors) often serve as precursors to excessive drinking or drug use, and unfortunately, resulting family interactions can inadvertently help to facilitate continued drinking or drug use once these behaviors have developed.

Lastly, the family is an extremely important molding influence for children, with deleterious effects on children's emotional and behavioral functioning well-established in both the scientific and the lay press. As part of the family of the substance-abusing patient, children in the home become caught in the dynamics of the "vicious cycle" created by substance abuse within the family. Distress within the couple spills over into their parenting and the family environment to impact children; sometimes, in turn, children's distress may feed back into the family's functioning. For example, alcoholic parents are less likely than nonalcoholic parents to monitor what their children are doing, which can lead to affiliation of their adolescent children with drug-using peers, creating another source of family conflicts. Parental substance abuse thus often has direct and serious physical, emotional, behavioral, and economic consequences on parenting and children. Moreover, the ancillary short- and long-term negative influences

created within the family are often no less destructive. Exposure to violence, interparental conflict, and stress, which are comparatively high in families with an alcoholic or drug-using family member, compromises children's functioning, and may increase their likelihood of becoming substance users in adolescence. Although researchers and providers tend to think of the deleterious effects of parenting and parental substance misuse on children (which are indisputable), it is also clear that stress in the family that can be created by children helps to provide a family context conducive to continued use or relapse.

Foundational Frameworks of Couples/Family

The strong interrelationship between substance use and family interaction supports the use of interventions that address both substance misuse and family functioning. Approaches to relationship- and family-focused treatments for substance abuse take many different forms, but most are founded largely or exclusively on one of three foundational frameworks. The best known of these and the most widely used is the *family disease approach*, which views alcoholism and other drug abuse as an illness experienced by the family, suffered not only by the substance user but also by family members.

Interventions founded on this perspective, such as Al-Anon and related approaches, focus on the patient and his or her detachment from family members during the recovery process. Family members are taught that there is nothing they can do to stop the substance user besides stopping enabling behaviors, and instead are encouraged to focus on their own recovery. As such, any family member involvement in treatment, if it occurs, is conducted in parallel to that of the substance-abusing individual, rather than as an integrated part of the patients' treatment. In many ways, although interactions are considered, this framework remains most closely tied to individual-based conceptualizations of substance use, which place the primary responsibility of change within the individual patient.

The *family systems approach* applies the principles of general systems theory to families, with particular attention paid to ways in which families maintain a dynamic balance between substance use and family functioning and whose interactional behavior is organized around alcohol or drug use. From this perspective, the family system provides a context that enables excessive drinking and/or drug use. Alcoholism and other addictive disorders are diseases that flourish in and are enabled by family systems. Family members react to the identified patient with particular behavioral patterns. They may enable the substance misuse to continue by shielding the patient from the negative consequences of his or her actions. Such behaviors are referred to as *codependence*. In this way, the person with the drug or alcohol use problem is said to suffer from the *disease of addiction*, whereas the family members suffer from the *disease of codependence*.

In a general sense, treatment evolving from a family systems perspective aims at identifying the function that substance use within the family serves, and then restructuring interaction patterns associated with drinking or drug use to make that maladaptive behavior unnecessary in the maintenance of the family system functioning. Structural and strategic theory and therapy methods fall within this broader systems framework.

The *behavioral model* assumes that family interactions serve to reinforce alcohol- and drug-using behavior. The goal of couple and family therapy from this perspective is to eliminate reinforcement for substance use by the family, which is often unintentional, and to promote reinforcement of behavior conducive to abstinence.

Family-based behavioral models are the foundation for the most commonly used interventions with alcoholic and drug-abusing couples. From this perspective, three general reinforcement patterns are typically observed in couples with a substance-abusing partner: (a) reinforcement for substance-using behavior in the form of attention or caretaking, (b) shielding the substance user from experiencing negative consequences related to his or her drinking or

drug use, and (c) punishing substance use behavior. Behaviorally oriented treatment focuses on changing spousal and other family members' interactions that serve as stimuli for abusive substance use or that trigger relapse. More adaptive and reinforcing interaction antecedents, such as improving communication and problem-solving abilities and strengthening coping skills, are developed in ways that reinforce sobriety.

Efficacy of Couples- and Family-Involved Approaches

During the last several decades, many different couples-based and family therapy approaches have been developed (or at least modified) to engage and treat substance-abusing patients; a large and growing body of research evidence supports their effectiveness. Because of the multiple forms of family-based approaches that have been used to address substance abuse, and the wide array of outcomes explored by both treatment providers and investigators, it is well beyond the scope of this chapter to discuss them all. Among the most frequently referenced in the research and clinical literatures include (a) community reinforcement and family training (CRAFT), (b) behavioral couple therapy (BCT), (c) solution-focused couple therapy (SFCT), (d) brief strategic family therapy (BSFT), (e) multisystemic family therapy (MST), and (f) multidimensional family therapy (MDFT). In some cases, some of these are minor variations of each other, although many would argue that some of the nuanced differences may have a great influence on treatment response and outcomes for a given patient and his or her family.

For reasons that are more pragmatic than conceptual or theoretic, family-involved therapeutic interventions for alcoholism and substance abuse have been categorized as either *partner-focused approaches* (that include intimate partners as part of the intervention) or *family approaches* (that address larger family systems that may or may not include the dyadic system). Of course, in practice and research, this distinction often becomes blurry; for example, some partner-involved therapies for substance abuse have also incorporated substantial elements of parent training to improve children's adjustment. Nonetheless, such distinctions between couples- and family-involved therapies offer some organizational structure to any discussion of such treatment methods and how they may be used to engage or treat substance-abusing individuals within these families.

Partner-and Family-Involved Approaches to Engagement

Treatments developed to help substance-using individuals to recognize problem behavior and seek help to change have involved both partners and other family members. The Community Reinforcement Approach (CRA) is based on an assumption that by shifting patterns of reinforcement and contingencies across environmental influences and events, an individual substance abuser's behavior can change. Within this broad community framework, the family is one of many critical environmental influences of interest. Given the importance of family, CRA was modified to focus on the family. The resulting CRAFT aims to teach family members (most often spouses of substance abusers) how to (a) encourage the substance abuser to evaluate whether or not drinking or drug use is problematic, (b) support sobriety, (c) seek out and encourage treatment for substance abuse, and (d) participate in that treatment in a way that is most beneficial.

A more coercive approach, the *Johnson Institute Intervention,* commonly referred to as an "Intervention," involves training family and significant others to confront an alcohol or drug abuser, request that he or she seek treatment, and impose consequences for not seeking help. The goal of this program is treatment engagement by the substance abuser. The approach is controversial (on practical and ethical bases), and there is limited evidence of effectiveness with the widely diverse population of individuals with alcohol use disorders.

Unilateral family therapy (UFT) is used to help family members develop or strengthen coping skills, to enhance healthful family functioning, and to help create a family environment that is conducive to sobriety or at least reduced drinking and drug use. UFT outlines a series of graded steps that families can use prior to initiating any sort of confrontation with the substance abuser to recognize his or her problem and seek formal treatment. Although research is limited, in a small-scale trial, participation in UFT was associated with significantly greater likelihood that individuals with drinking problems would enter treatment or reduce their drinking.

It is also important to mention certain related approaches that, rather than focus on initiating change, emphasize self-healing. For example, J. E. Dittrich has developed a *group program for wives of treatment-resistant substance abusers*. Following the family disease framework, this treatment is designed to help partners cope with their own emotional distress rather than trying to motivate the substance-abusing partner to seek help or otherwise change. This particular approach borrows heavily from Al-Anon, the most commonly used source of support for family members of substance abusers, which advocates family members detach from the substance abusers in a loving way, accept they are powerless to control the substance abuser, and seek support from other Al-Anon members.

Results of randomized clinical trials have compared some of these approaches in terms of their efficacy in engaging patients in treatment. One investigation compared the CRAFT, Al-Anon, and Johnson Institute Intervention approaches for effectiveness in getting individuals with drinking problems into formal treatment. The highest overall treatment rate for the alcoholic family members was associated with the CRAFT therapy (64%). The majority of families in the Johnson Institute condition chose not to complete the intervention; in fact, 70% failed to follow up with the critical confrontation session. Because Al-Anon is not designed to facilitate entry into treatment, it is not surprising that this was not a common outcome.

Couple-Based Approaches to Treatment

The majority of couple- and family-involved approaches to substance abuse have focused on efforts to treat the substance abuser to attain and adjust to sobriety, and to maintain these gains. Two commonly referenced couple approaches, BCT and SFCT, dominate the research and practice areas of couple therapy, respectively.

BCT has, to date, the strongest empirical support for its effectiveness. When using BCT with a married or cohabiting alcoholic or drug-abusing patient, a therapist treats the partners together and works to build support from within the dyadic system for abstinence. In a global sense, emphasis is placed on increasing reinforcement with the dyadic system for abstinence. To accomplish that goal, BCT seeks to strengthen the relationship by improving partners' communication and having partners participate in relationship-enhancement exercises (e.g., participating in mutually shared rewarding activities, and observing and recognizing caring behaviors). As the relationship strengthens, partners are taught skills and engage in exercises to positively reinforce aspects of sober living.

Empirical support for the effectiveness of BCT with alcoholic and drug-abusing couples is extensive. Multiple studies have compared drinking and relationship outcomes for alcoholic patients and their partners treated with BCT to various forms of therapy that involve only the individual patient (e.g., individual counseling sessions and group therapy). Results of these investigations have been very consistent, revealing a pattern of less frequent drinking, fewer alcohol-related problems, happier relationships, and lower risk of marital separation for alcoholic patients who received BCT than for patients who receive only individual-based treatment.

Although the research on the effects of BCT for married or cohabiting patients who abuse drugs other than alcohol is more recent, the outcomes have been no less impressive than those obtained for alcoholic couples. Compared to individual treatment only for the substance-abusing partner, BCT for drug-abusing men and their non–substance-abusing female partners resulted in fewer days of drug use, fewer drug-related arrests and hospitalizations, a longer time

to relapse after treatment completion, and more positive relationship adjustment. Although BCT studies with alcoholic and drug-abusing patients have recruited samples that consisted largely or exclusively of married or cohabiting male patients and their non–substance-abusing female partners, preliminary investigations with married or cohabiting female patients and their non–substance-abusing male partners have yielded positive results similar to those for substance-abusing men. Interestingly, the use of BCT with alcohol- and drug-abusing couples also has important effects on other aspects of family functioning that are not primary targets of the intervention, including improvements in custodial children's emotional and behavioral adjustment (even though the children did not participate in BCT nor was parenting an emphasis of the intervention) and reductions in domestic violence.

SFCT primarily emphasizes solutions to the presenting issue or concern, rather than the origins of the problem. Simply stated, SFCT is a strengths-based, solution-focused brief therapy approach to couple distress and substance use. The basic conceptualization of relationship problems in SFCT is that distressed couples (a) are locked into a negative mindset, (b) are stuck in problem talk, (c) have inherent strengths but are not seeing or utilizing them, and (d) are not noticing the exceptions to when the problem occurs. In SFCT, problem talk is completely discouraged; the goal of the therapist is to help the couple identify and coconstruct active solutions to the problem, often found in the exceptions (i.e., those times when the problem does not occur), and identify small achievable goals that may enhance optimism for further behavioral change. The therapy is brief, sometimes lasting only 1 to 2 sessions, and rarely more than 10.

Family Approaches to Treatment

As noted, no one family-involved intervention has come to dominate family therapy for alcoholism and drug addiction. Upon reflection, this is not a surprise; as opposed to partner-involved therapy (which inherently narrows the intervention unit to intimate partners), family therapy has a much larger field of family types and, relatedly, family issues that it is called upon to address. The bulk of the controlled clinical research trials that include a family component in substance abuse treatment examines adults with partners in couple-based approaches. However, it is also important to consider the role of family and significant others in the treatment of adolescents who struggle with alcohol problems. Thus, in addition to the models listed above, three other approaches that have been developed for use primarily with substance-abusing adolescents and their families are reviewed: (a) BSFT, (b) MDFT, and (c) MST. Each of these approaches integrates structural and strategic theory and principles within a family systems perspective, and although highly intensive, has developed a strong base of empirical support.

In BSFT, substance-abusing behavior is seen to develop in response to unsuccessful attempts at dealing with developmental challenges. Rigid family structures are also believed to contribute to the development of adolescent substance abuse. The therapist attempts to intervene in the system through the parents by changing parenting practices, improving the parent–adolescent relationship, and teaching conflict resolution skills. A series of randomized trials has demonstrated empirical support for BSFT at engaging and treating substance-using adolescents and their families, including Hispanic youth and families; a multisite effectiveness trial is currently under way.

MDFT views adolescent substance abuse as a result of multiple interacting factors, which may include failure to meet developmental challenges as well as other forms of abuse or trauma. The primary goals of treatment are to improve adolescent, parental, and overall family functioning, which in turn will impact the substance-abusing and other problematic behaviors. MDFT is a very flexible approach; the treatment length is determined by the treatment provider, setting, and family and may include a combination of individual and family sessions. MDFT begins with a thorough multisystem assessment of both developmental ecologic risk and protective factors. This information is then used to create an MDFT case conceptualization, which identifies the strengths and weaknesses in the adolescent's multiple systems and

becomes the basis of treatment. MDFT has demonstrated strong efficacy in reducing substance use and delinquency with juvenile justice–involved adolescents.

MST is based on Bronfenbrenner's social ecologic model of behavior, seeking to understand the substance-abusing behavior within a broader, real-world context. MST assumes that substance abuse is influenced by variables from multiple systems, targeting change in other areas (e.g., arrests, out-of-home placements, and mental health) as well as substance use. Thus, one of the goals of treatment is to assess the strengths and needs of each system and their relationship to the presenting problem. Family members play a large role in determining treatments goals. MST focuses on the present and targets a broad set of specific and well-defined problems through the use of daily and weekly assignments. The MST therapist is responsible for addressing and overcoming any barriers that may result during the course of treatment.

With its broad, ecologic, and family focus, MST was not originally designed to target substance use specifically. As such, initial studies examining substance-related outcomes of MST among violent and chronic juvenile offenders showed long-term effects on substance use–related outcomes through adulthood (e.g., drug-related arrests or convictions), though less consistently valid substance use reductions. Recent pilot and larger trials that integrate MST with other contingency management strategies aimed specifically at reducing substance use suggest promising effects on both self-report and biologic substance use reductions.

Optimal Implementation of Family-Based Treatment

There is considerable debate among providers about how to implement family-based treatments as part of an overall package to address alcoholism and substance abuse. It is sometimes asserted among some providers that participation in family treatment should not occur until the identified patient has been sober for at least a year. There are at least three problems with that recommendation: (a) given that so many patients who received treatment in substance abuse treatment settings relapse during the year after leaving treatment, only a limited number of patients would actually be sober for a year and be eligible for family-involved treatment; (b) if patients remains sober for a year, they often will not meet the necessary diagnostic criteria for a substance abuse treatment program to be able to provide services (in many states, a current diagnosis of an SUD is required for admission); and (c) there is no empirical support that delaying family treatment enhances efficacy.

Optimally, it is important to include a family member or members in the intervention package as early as possible. In our experience, family members often bring a different perspective than the patient on the family and its role in the etiology and maintenance of the patient's drinking and drug-use behavior. They can also give providers a sense of whether or not the family will be functionally supportive of the patient's efforts to maintain a sober lifestyle, as well as how much focus will need to be placed on the family as treatment unfolds. As a general rule of thumb, the best time to implement family-focused treatment for substance abuse is as soon as possible. An early assessment can inform providers about the possible role of the family in the patient's treatment.

Lastly, in an ideal situation, there should be family therapy providers who do "family work" with patients, which is provided as a complement to individual-focused treatments by yet another provider. Such staffing allows for certain therapeutic boundaries to exist between partner- and family-focused therapy sessions and individual-focused sessions. In reality, many programs do not have the resources to enjoy the luxury of having separate providers for family therapy. Nonetheless, it is often out of necessity that a single provider serves as the individual counselor and the family counselor. In our experience, one person can effectively serve as the individual counselor and the family counselor. When that is the only way that family therapy can be provided, it is important to establish confidentiality boundaries between what is discussed in family therapy and what is discussed in individual therapy. Typically, the contents of the individual sessions are kept confidential from the family therapy sessions.

Special Considerations

There are several clinically significant considerations in implementing effective family intervention with substance abusers that may challenge its use. One that is commonly encountered among couples and families with a substance-abusing member is violence. In situations where the risk of types of violence that are severe (i.e., aggression that has the potential to result in serious injury or is life-threatening), the immediate intervention goal is safety; in these situations, partner and family therapy is contraindicated. For some families, there may, in fact, be legal restrictions (i.e., restraining orders or no-contact orders) that preclude conjoint family sessions.

Another factor to consider is whether more than one actively substance-abusing family member is present—particularly if these individuals have formed a drinking or drug use partnership of some type. Sometimes referred to as "double-trouble couples," these family systems may support continued use versus abstinence. Research on family-based approaches for these situations is lacking, and it is often recommended that individual therapy be used prior to engaging family members in these circumstances.

Another critical consideration is the existence of high levels of blame and rumination from family members (usually the partner) toward the substance-abusing individual. There may also exist important practical barriers to partner or family intervention; these include (a) geographic distances among family members or among family members and the treatment provider; (b) family members who are divorced, incarcerated, or otherwise separated; (c) coordination of family members' and treatment providers' schedules; and (d) securing reimbursement for services delivered to multiple individuals in the context of formal treatment.

Conclusion

As has been well documented in the scientific and lay press, the emotional, economic, and societal toll of alcoholism and drug abuse is incalculable. The effects of SUDs affect not only the patients but also those around them; in fact, those emotionally closest to the substance-abusing patient often suffer the most. Partner- and family-involved approaches have had such well-documented success because such methods view outcomes across multiple dimensions of functioning that go well beyond the frequency of substance use toward outcomes like child and family adjustment, family violence, relationship quality, and so forth. By seeking to foster family environments conducive to abstinence, marital and family approaches have great potential to help maintain long-term and even multigenerational healthful change.

Suggested Readings

Birchler GR, Fals-Stewart W, O'Farrell TJ. Couple therapy for alcoholism and drug abuse. In: Gurman AS, ed. *Clinical Handbook of Couple Therapy*. 4th edn. New York, NY: Guilford; 2008;523–544.

Fals-Stewart W, O'Farrell TJ, Birchler GR. Behavioral couples therapy for substance abuse: rationale, methods, and findings. *Sci Pract Perspect*. 2004;2:30–41.

McCrady BS. Family and other close relationships. In: Miller WR, Carroll KM, eds. *Rethinking Substance Abuse: What the Science Shows and What We Should Do about It*. New York, NY: Guilford Press; 2006.

Powers M, Vedel E, Emmelkamp P. Behavioral couples therapy (BCT) for alcohol and drug use disorders: a meta-analysis. *Clin Psychol Rev*. 2008;28:952–962.

Robbins MS, Szapocznik J, Horigian VE, et al. Brief strategic family therapy for adolescent drug abusers: a multi-site effectiveness study. *Contemp Clin Trials*. 2009;30:269–278.

32 Cognitive–Behavioral Therapy

Cognitive–behavioral treatments are among the most well-defined and rigorously studied psychotherapeutic interventions for substance use disorders (SUDs). Cognitive, behavioral, and motivational therapies are applicable across a broad range of SUDs. These approaches were developed from well-founded theoretical traditions with established theories and principles of human behavior. These approaches are highly flexible and can be implemented in a wide range of clinical modalities and settings. Moreover, they are compatible with a variety of pharmacotherapies and, in many cases, foster compliance and enhance the effects of pharmacotherapies, including methadone, naltrexone, and disulfiram. Finally, these approaches are relatively brief/short-term and highly focused approaches that emphasize rapid, targeted change in substance use and related problems. In this manner, they are very compatible in a health-care environment that is increasingly influenced by managed care, best clinical practice models, and professional accountability.

At the most simple level, cognitive–behavioral therapy (CBT) attempts to help individual patients recognize, avoid, and cope, that is, recognize the situations in which they are most likely to use drugs or alcohol, avoid those situations when possible or appropriate, and learn to cope more effectively with a range of problems and problematic behaviors associated with substance use. CBT has two critical components and defining features: first, a thorough functional analysis of the role alcohol and illicit drugs play in the individual's life. For each instance of substance use the patient experiences during treatment, the therapist and patient will identify the patient's thoughts, feelings, and circumstances before the substance use, as well as the patient's thoughts, feelings, and circumstances after the episode of substance use. Early in treatment, the functional analysis plays a critical role in helping the patient and therapist assess the determinants, or high-risk situations, that are likely to lead to substance use, as well as shed light on some of the reasons the individual may be using drugs or alcohol. The second critical component of CBT is skills training. In CBT, this consists of a highly individualized training program that helps substance users change old habits associated with their drug use and learn or relearn more adaptive skills and responses.

History

Cognitive–behavioral treatments have their roots in classical behavioral theory and the pioneering work of Pavlov, Watson, Skinner, and Bandura. Pavlov's work on classical conditioning demonstrated that a previously neutral stimulus could elicit a conditioned response after being paired repeatedly with an unconditioned stimulus. Furthermore, repeated exposure to the

conditioned stimulus without the unconditioned stimulus would eventually lead to extinction of the conditioned response. The power of classical conditioning was demonstrated in drug abuse by Wikler, who confirmed that opioid addicts exhibited conditioned withdrawal symptoms upon exposure to drug paraphernalia. Today, classical conditioning theory is the basis of several behavioral approaches to substance use treatment, such as cue exposure and stimulus avoidance as an early component of many addiction counseling approaches. Second, Skinner's work on operant conditioning demonstrated that behaviors that are positively reinforced are likely to be exhibited more frequently. The field of behavioral pharmacology, which has convincingly demonstrated the reinforcing properties of abused substances in both humans and animals, is grounded in operant conditioning theory and principles. Behavior therapies assume that drug use and related behaviors are learned through their association with the positively reinforcing properties of the drugs themselves as well as their secondary association with other environmental stimuli. CBT attempts to disrupt this learned association between drug-related cues or stimuli and drug craving or use by understanding and changing these behavior patterns. A wide range of behavioral interventions, including those that seek to provide alternate reinforcers to drugs use or reduce reinforcing aspects of abused substances, also are based on operant-conditioning theory.

CBTs conceive SUDs as complex, multidetermined problems, with a number of influences playing a role in the development or perpetuation of the disorder. These may include family history and genetic factors; the presence of comorbid psychopathology; personality traits such as sensation seeking or impulsivity; and a host of environmental factors, including substance/drug availability and lack of countervailing influences and rewards. Though CBTs primarily emphasize the reinforcing properties of substances as central to the acquisition and maintenance of substance abuse and dependence, these etiologic influences are seen as heightening risk or vulnerability to the development of substance use problems. For example, some individuals may find substances unusually highly rewarding secondary to genetic vulnerability, comorbid depression, a high need for sensation seeking, the modeling of family and friends who use substances, or environments devoid of alternative reinforcers.

CBTs also reflect the pioneering work of Ellis and Beck that emphasizes the importance of the person's thoughts and feelings as determinants of behavior. CBT evolved in part from dissatisfaction with the extreme positions of radical behaviorism (e.g., emphasis on overt behaviors) and classical psychoanalysis (emphasis on unconscious conflicts or representations). CBT emphasizes how the individual perceives and interprets life events as important determinants of behavior. A person's conscious thoughts, feelings, and expectancies mediate an individual's response to the environment. CBT also seeks to help patients become aware of maladaptive cognitions and then learn to challenge and change them.

Just as CBT assumes that many individuals essentially "learn" to become substance users over time, through complex interplays of modeling, classical conditioning, or operant conditioning, each of these principles is invoked in CBT to help the patient stop using drugs and alcohol. For example, modeling is used to help the patient learn new behaviors (e.g., how to refuse an offer of drugs, how to break off or limit a relationship with a drug-using associate) by having the patient participate in role plays with the therapist during the treatment. That is, the patient learns to respond in new, unfamiliar ways by first watching the therapist model those new strategies and then practicing those strategies within the supportive context of the therapy hour.

Operant-conditioning concepts are used in several ways in CBT. First, through a detailed examination of the antecedents and consequences of substance use, the therapist attempts to develop an understanding of the reasons the patient may be more likely to use in a given situation and to understand the role that drugs or alcohol play in their life. This "functional analysis" of substance use is used to identify the high-risk situations in which the patient is likely to use drugs and thus to provide the basis for learning more effective coping behaviors in those situations. Second, the therapist attempts to help the patient develop meaningful alternate reinforcers

to drug use, that is, other activities and involvements (relationships, work, hobbies) that serve as viable alternatives to drugs and alcohol use and help the patient remain abstinent. Finally, a detailed examination of the consequences, both long- and short-term, of their substance use, is used as a strategy to build or reinforce the patient's resolve to reduce or eliminate their substance use.

Classical-conditioning concepts also play an important role in CBT, and particularly in interventions directed at reducing some forms of craving for drugs. Just as Pavlov demonstrated that repeated pairings of a conditioned stimulus with an unconditioned stimulus could elicit a conditioned response, he also demonstrated that repeated exposure to the conditioned stimulus without the unconditioned stimulus would, over time, result in extinction of the conditioned response. Thus, the therapist attempts to help the patient understand and recognize conditioned craving, identify his/her own idiosyncratic array of conditioned cues for craving, avoid exposure to those cues, and cope effectively with craving when it does occur without using the drug so that conditioned craving is reduced and eliminated over time.

Learning serves as an important metaphor for treatment process throughout. CBT therapists tell patients that a goal of the treatment is to help them "unlearn" old, ineffective behaviors and "learn" new ones. Patients, particularly those who are demoralized by their failure to change their substance use, or for whom the consequences of addiction have been severe, are frequently surprised to think about substance use as a type of skill, as something they have learned to do over time: In effect, they have learned a complex set of skills that enabled them to acquire the money needed to buy drugs and alcohol (which often led to another set of licit or illicit skills), avoid detection, and so on. Patients who can reframe their self-appraisals in terms of being "skilled" in this way can often see that they also have the capacity to learn a new set of skills, this time, though, skills that will help them remain abstinent.

Unique Features

Durability

While CBT is not necessarily more effective than other evidence-based therapies for SUDs, where it appears to stand out is in its durability. An important development in our conception of SUDs is that they are chronic relapsing disorders and thus treatment should be conceived of as producing behavior change and maintaining it over the lifespan, rather than brief, disjointed, acute episodes of care. Thus, a major disadvantage of many addiction pharmacotherapies in this context is that they can be very effective while the patient is taking them, but relapse is common once the medication stops.

CBT, however, is associated with particularly durable effects. Several studies have documented a "sleeper effect" in which patients exposed to CBT continue to improve even after they leave treatment. The durability of effects from CBT is found in its applications to other areas as well, and may be associated with its emphasis on conveying effective, generalized skills that may benefit the individual long after they leave treatment.

Unique and Common Factors of CBT

All behavioral or psychosocial treatments include both common factors as well as unique factors or active ingredients. Common factors refer to dimensions of treatment that are shared across most therapies. These common factors include the provision of education, a convincing rationale for the treatment, enhancing expectations of improvement, the provision of support and encouragement, and in particular the quality of the therapeutic relationship. A positive therapeutic relationship, or alliance, has repeatedly been associated with better outcome in a range of

psychotherapies, including those for SUDs. A positive working relationship is an essential component of virtually all therapies, but, by itself, is not necessarily sufficient to produce change.

Unique factors refer to a treatment's "active ingredients" or those techniques and interventions that distinguish or characterize particular psychotherapies. While common factors are shared, unique factors are those that are not shared across different therapies. CBT, like most therapies, consists of a complex combination of common and unique factors. For example, in CBT mere delivery of skills trainings without grounding in a positive therapeutic relationship leads to a dry, overly didactic approach that alienates or bores most patients and ultimately has the opposite effect of that intended. It is important to recognize that CBT is thought to exert its effects through this intricate interplay of common and unique factors, and a major task of the therapist is to achieve appropriate levels of balance between attending to the relationship and delivering skills training. For example, without a solid therapeutic alliance, it is unlikely that a patient will either stay in treatment, be sufficiently engaged to learn new skills, or to share successes and failures in trying new approaches to old problems. Conversely, empathic delivery of skills training as tools to help the patient manage his/her life more effectively, with the therapist giving the message of "I see you really struggling with your craving for cocaine [for example], I think we can come up with some effective ways to help you understand what is happening better and help you deal with it," may form the basis of a strong working alliance.

To specify CBT in terms of its common and unique factors and to clarify the range of therapist interventions that are consistent and inconsistent with this approach, CBT interventions will be described in terms of the system recommended by Waltz and colleagues: first, CBT's essential and unique interventions, that is, active ingredients that are specific or unique to CBT; second, CBT's recommended interventions, those that are thought to be "active" and important, but which are not necessarily unique to CBT; third, interventions, behaviors, or processes that are acceptable within the therapy but are not essential or unique; and finally, interventions, behaviors, or processes that are proscribed, or not consistent with this approach. Each of these has been explicated in a detailed process-rating system and validated in several randomized clinical trials of CBT.

Essential and Unique Interventions of CBT

In CBT, the key active ingredients that distinguish it from other therapies and the elements that must be delivered in order for the patient to be considered as being "adequately exposed" to CBT include

- Conducting functional analyses of substance use
- Providing individualized skills training in strategies such as recognizing and coping with craving, monitoring, challenging, and changing thoughts about substance use, problem-solving skills, planning for emergencies, recognizing seemingly irrelevant decisions, and refusal skills
- Examining the patient's cognitive processes related to substance use
- Identifying and debriefing the past and future high-risk situations
- Encouraging and reviewing extrasession implementation of skills (homework)
- Practicing skills within sessions

Recommended Interventions

Interventions that are essential but not necessarily unique to CBT include the following:

- Discussing, reviewing, reformulating the patient's goals for treatment
- Monitoring substance use and craving
- Monitoring general functioning
- Exploring positive and negative consequences of substance use

- Exploring the relationship between affect states and substance use
- Providing feedback on urinalysis results
- Setting a clear agenda for each session
- Making process comments as indicated
- Discussing the advantages of an abstinence goal and exploring the patient's ambivalence
- Meeting resistance with exploration and a problem-solving approach
- Supporting patient efforts to institute behavior change, assessing the level of family support

Acceptable Interventions

Interventions that are not required or strongly recommended as part of CBT but are not incompatible with this approach include

- Being involved in self-help activities as a coping skill
- Identifying means of self-reinforcement for abstinence
- Exploring discrepancies between patient's stated goals and actions
- Eliciting concerns about substance use and consequences (e.g., decision balance)

Proscribed Interventions

Interventions that are proscribed because they are distinctive of other forms of empirically validated approaches to treatment include the following (note, however, that CBT can be combined effectively with other approaches):

- Extensive self-disclosure by the therapist
- Use of a confrontational style or a confrontation-of-denial approach
- Requiring the patient attend self-help groups (as in 12-step facilitation)
- Use of disease-model language or slogans (as in 12-step facilitation)
- Extensive exploration of interpersonal aspects of substance use (as in interpersonal or supportive-dynamic approaches)
- Extensive discussion or interpretation of underlying conflicts or motives (as in supportive-dynamic approaches)
- Provision of direct reinforcement for abstinence (e.g., vouchers, tokens, as in contingency-management [CM] approaches)

Evidence of Efficacy

CBT has been shown to be effective across a wide range of SUDs, including alcohol dependence, marijuana dependence, cocaine dependence, and nicotine dependence. CBT has also been shown to be compatible with a number of other treatment approaches, including pharmacotherapy and traditional counseling approaches and thus can be implemented in a wide range of settings. These findings are consistent with evidence supporting the effectiveness of CBT across a number of other psychiatric disorders as well, including depression, anxiety disorders, and eating disorders.

Another particularly exciting development in the field of drug dependence treatment has been the very strong empirical support for CM approaches, where participants receive incentives (i.e., vouchers redeemable for goods and services, chances to draw prizes from a bowl) contingent on demonstrating acquisition of treatment goals (e.g., submitting drug-free urine specimens, attending treatment sessions). Given that CM has strong immediate effects but those effects tend to weaken after the contingencies are terminated, while CBT tends to have more modest effects initially but is comparatively durable, several investigators have begun

to evaluate various combinations of CBT and CM, reasoning that the relative strengths and weaknesses of these may be offset by combining them. For example, Rawson and colleagues recently compared group CBT, voucher CM, and a CBT/CM combination in conjunction with standard methadone maintenance treatment for cocaine-using methadone maintenance patients. During the acute phase of treatment, the groups assigned to CM had significantly better cocaine use outcomes than the group assigned to CBT. However, during the follow-up period, a CBT "sleeper" effect emerged again, where the group assigned to CBT essentially caught up to the CM groups by the 52-week follow-up. Similar results were found for a parallel study conducted among a large sample ($N = 171$) of stimulant-dependent individuals treated as outpatients, where CM was associated with better retention and substance use outcomes during treatment, but outcomes for CBT and CM were comparable at 1 year.

Optimal Use, CBT Techniques, and Strategies

At the most simple level, most CBT approaches attempt to help individual patients recognize the situations in which they are most likely to use, avoid those situations when appropriate, and cope more effectively with a range of problems and problematic behaviors associated with substance use by implementing a range of cognitive and behavioral coping strategies. Specific techniques vary widely with the type of cognitive–behavioral treatment used, and there are a variety of manuals, protocols, and training programs available that describe the techniques associated with each approach.

As noted earlier, two key defining features of most cognitive–behavioral approaches for SUDs are (a) an emphasis on a functional analysis of drug use, that is, understanding drug use with respect to its antecedents and consequences, and (b) an emphasis on skills training. Cognitive–behavioral approaches include a range of skills to foster or maintain abstinence. These typically include strategies for:

- **a.** Understanding the patterns that maintain drug use and developing strategies for changing these patterns. This often involves self-monitoring of thoughts and behaviors that take place before, during, and after high-risk situations or episodes of drug use.
- **b.** Fostering the resolution to stop substance use through exploring positive and negative consequences of continued use (also known as the decisional balance technique).
- **c.** Understanding craving, craving cues, and the development of skills for coping with craving when it occurs. These include a variety of affect regulation strategies (distraction, talking through a craving, "urge surfing," and so on).
- **d.** Recognizing and challenging the cognitions that accompany and maintain patterns of substance use.
- **e.** Increasing awareness of the consequences of even small decisions (e.g., which route to take home from work), and the identification of "seemingly irrelevant" decisions that can culminate in high-risk situations.
- **f.** Developing problem-solving skills, and practicing application of those skills to substance-related and more general problems.
- **g.** Planning for emergencies and unexpected problems and situations that can lead to high-risk situations.
- **h.** Developing skills for assertively refusing offers of drugs, as well as reducing exposure to drugs and drug-related cues.

These basic skills are useful in their application to helping patients control and stop substance use, but it is essential that therapists also point out how these same skills can be applied to a range of other problems. For example, use of a functional analysis can be used to understand the determinants of a wide range of behavior patterns, skills used to cope with craving

can easily be applied to other aspects of affect control, the principles used in the sessions on seemingly irrelevant decisions can easily be adapted to understanding a wide range of behavior chains, and substance use refusal skills can easily be transferred to more effective and assertive responding in a number of situations. We think it is essential that, when therapists teach coping skills, they emphasize and demonstrate that the skills can be applied immediately to control substance use, but can also be used as general strategies that can be used across a wide range of situations and problems the patient may encounter in the future.

Broad-spectrum cognitive–behavioral approaches, such as those described by Monti and colleagues and adapted for use in Project MATCH, expand to include interventions directed to other problems in the individual's life that are seen as functionally related to substance use. These interventions may include general problem-solving skills, assertiveness training, strategies for coping with negative effect, awareness of anger and anger management, coping with criticism, increasing pleasant activities, enhancing social support networks, and job-seeking skills, among others.

In comparison to many other behavioral approaches, CBT is typically highly structured. That is, CBT is generally brief (12 to 24 weeks) and organized closely around well-specified treatment goals. Usually, an articulated agenda exists for each session, and the clinical discussion remains focused around issues directly related to substance use. Progress toward treatment goals is monitored closely and frequently, with frequent monitoring of substance use through urine toxicology screens, and the therapist takes an active stance throughout treatment. Generally, sessions take place within a weekly scheduled therapy "hour." In broad-spectrum cognitive–behavioral approaches, sessions often are organized roughly in thirds (the 20/20/20 rule), with the first third of the session devoted to the assessment of the patient's substance use and general functioning in the past week and report of current concerns and problems; the second third is more didactic and devoted to skills training and practice; and the final third allows time for therapist and patient to plan for the week ahead and discuss how new skills will be implemented. The therapeutic relationship is seen as principally collaborative. Thus, the role of the therapist is one of consultant, educator, and guide who can lead the patient through a functional analysis of his/her substance use, aid in identifying and prioritizing target behaviors, and consult in selecting and implementing strategies to foster the desired behavior changes.

While structured and didactic, CBT is a highly individualized and flexible treatment. That is, rather than viewing CBT treatment as cookbook "psychoeducation," the therapist carefully matches the content, timing, and nature of presentation of the material to the individual patient. The therapist attempts to provide skills training at the moments the patient is most in need of them. That is, the therapist does not belabor topics such as breaking ties with cocaine suppliers with a patient who is highly motivated and has been abstinent for several weeks. Similarly, the therapist does not race through material in an attempt to "cover" all of it in a few weeks; for some patients, it may take several weeks to master a basic skill.

Extrasession Practice as a Possible Mediator of CBT

In CBT, therapists encourage patients to practice new skills; such practice is a central and essential component of treatment. The degree to which the treatment is a "skills training" over merely a "skills exposure" approach has to do with the degree to which there is opportunity to practice and implement coping skills, making extrasession practice and homework all the more important. It is critical that patients have the opportunity to try out new skills within the supportive context of treatment. Through first-hand experience, patients can learn what new approaches work or do not work for them, where they have difficulty or problems, and so on. There are many opportunities for practice within CBT, both within sessions and outside

of them. Within each session, there are opportunities for patients to rehearse and review ideas, raise concerns, and get feedback from the therapist.

As noted earlier, there has been growing interest in understanding not only what treatments work, but how they work. Understanding the mechanisms of action of CBT and other empirically validated therapies has heretofore received very little attention in the literature, but is an area of great importance. Understanding treatment mechanisms can not only advance the development of more effective treatment strategies, but also result in more powerful, efficient, and ultimately less-expensive treatments.

The converging evidence suggesting that CBT is a particularly durable approach has led to increased focus on unique or distinctive aspects of CBT that might account for its durability. Encouraging clients to implement and practice skills outside of sessions via homework assignments is one possible mechanism for this effect. Homework encourages practice of skills outside sessions and possibly generalization of skills to other problems, and emphasis on extrasession practice assignments is a unique feature of CBT. Moreover, investigators evaluating CBT in non–substance use psychiatric disorders have noted the importance of homework in CBT's effectiveness.

The relationship of homework compliance, skills acquisition, and outcome in CBT has received comparatively little attention in the substance abuse literature. Thus, in a recent trial for cocaine dependence treatment, we evaluated homework completion in detail, collecting data on the specific type of homework assigned and how well it was done (e.g., fully, partially, no attempt made) at every session. We found strong relationships between homework compliance and outcome. Compared with the participants assigned to CBT who did not do homework or who did it only rarely, the participants who did homework consistently *stayed in treatment significantly longer, had more consecutive days of cocaine abstinence* (a strong predictor of long-term outcome), and *fewer cocaine-positive urines during treatment*. Similar effects were found for the subset of participants who completed treatment in this study, suggesting that the effects of homework compliance on better substance use outcomes were not completely accounted for by differential retention. In addition, we found strong relationships between homework compliance and acquisition of coping skills, as well as between homework completion and participants' ratings of their confidence in avoiding use in a variety of high-risk situations. Participants who completed homework had significant increases over time in their self-reported confidence in handling a variety of high-risk situations, while scores for the subgroup that did not do homework did not change over time.

Farabee and colleagues evaluated the extent to which cocaine users reported engaging in a series of specific drug-avoidance activities (e.g., avoiding drug-using friends and places where cocaine would be available, exercising, using thought-stopping) after CBT versus alternate treatments (e.g., CM and a control condition). They found that, by the end of treatment, participants assigned to CBT reported more frequent engagement in drug-avoidance activities than participants in the comparison treatments. Furthermore, the frequency of drug-avoidance activities was strongly related to better cocaine use outcomes over the 1-year follow-up. Taken together, these studies suggest that CBT interventions that foster the patients' engagement in active behavior change may play a key role in CBT's comparative durability.

Special Considerations

Training and Competence in CBT

The growing evidence base for CBT and the increased emphasis on incorporating empirically supported therapies into clinical practice has also led to greater focus on training and dissemination. Although standard methods used to train clinicians to use CBT in clinical efficacy trials

have generally been associated with high levels of treatment fidelity and comparatively small levels of variation in treatment delivery, these methods (intensive didactic workshop training plus structured feedback on supervised training cases) had not been empirically evaluated, nor are they commonly used in training clinicians to use novel approaches.

Addressing Limitations of CBT

Despite CBT's emerging empirical support, future research is needed to address its limitations. CBT is a relatively complex approach, in that it is comparatively complicated to train clinicians to use this approach or to implement it effectively in clinical practice. As a result, competent delivery of CBT has been shown to be very rare in clinical practice. Independent review of clinician audiotapes from the "treatment as usual" condition in a multisite trial supported by the National Institute on Drug Abuse (NIDA) Clinical Trials Network indicated that, although the clinicians professed using a high level of CBT in their clinical work, interventions associated with CBT (e.g., skill training, focus on cognitions) were extremely rare.

Another relative weakness of CBT may be the cognitive demands it places on patients, in that they are asked to learn a range of new concepts and skills, including to monitor and remember cognitions and inner states, implement new skills while in stressful situations, and so on. Recent data suggests that substance users with higher levels of cognitive impairment may have poorer outcome in CBT than those who are less impaired. This suggests that clinicians using CBT strategies should monitor the cognitive skills of their patients, and in cases where the patients may have memory, attention, or impulse control problems, to adapt the implementation of CBT accordingly, with slower progression through concepts, frequent repetition of material and checking back with the patient to assess understanding, and providing more structure on extrasession assignments.

Potential strategies for addressing these issues include greater emphasis on understanding CBT's mechanisms of action so that ineffective components of CBT can be removed and treatment delivery simplified. A more novel strategy is to harness the ability and breadth of technology to standardize CBT and make it more widely available to those who may benefit from it. We have developed a computer-assisted version of CBT, called CBT4CBT (computer-based training in CBT). The content of CBT4CBT is based closely on our NIDA CBT manual, but it is delivered in six sessions, or modules, and makes extensive use of the multimedia capabilities of computers to convey CBT principles and illustrate implementation of new cognitive and behavioral strategies. That is, key CBT concepts are taught through short movies, or vignettes, which feature engaging characters in realistic settings confronting a number of challenging situations as well as a number of interactive games and exercises to teach CBT strategies. Thus, users are able to see multiple examples of how CBT principles can be implemented, rather than hear sometimes too abstract or incomplete presentations from their therapists.

In a clinical trial where CBT4CBT was delivered in addition to standard outpatient treatment, exposure to the program was associated with significantly fewer drug-positive urine specimens submitted and longer durations of abstinence during treatment. In addition, data from a 6-month follow-up indicated the durability of these effects in that the "sleeper effect" of CBT appeared to extend to its computer-based version, which appeared to have been mediated by significantly higher levels of skill acquisition among those who used the CBT4CBT program. Finally, participants' level of neuropsychological functioning did not appear to be associated with outcome in the CBT4CBT program, perhaps because little or no reading of text was required, users can control the rate of speed of material presented, can repeat material as often as they wish, and they can select the types of exercises and issues they would like to address, thereby reducing the "cognitive load" of CBT. Although CBT4CBT and other computer-assisted programs have great potential to make empirically supported therapies more

widely available and to broaden the base of substance abuse treatment, and some of the early data on their effectiveness is very encouraging, substantially more testing and evaluation is needed before they can be widely distributed.

Conclusion

CBT is a behavioral approach that has strong theoretical and empirical support with a variety of substance abusing populations, as well as a broad range of disorders that tend to co-occur with addiction, including depressive and anxiety disorders. Moreover, these approaches can be combined and integrated effectively with a range of other empirically supported behavioral therapies as well as pharmacotherapies. CBT also appears to be particularly durable, an important feature among the addictions, which are characterized by frequent relapse. In recent years, clinical researchers have recently emphasized moving these approaches more broadly into the clinical community, and thus a range of practical resources (e.g., books, videotapes, manuals, training resources, and programs) for implementing them effectively in clinical practice are available, and data from recent trials evaluating computer-assisted version of CBT have been promising. Thus, due to its comparatively strong evidence base, flexibility, broad applicability across a range of patient types and settings, and durability, CBT should be a component of all substance abuse clinicians' repertoire.

Suggested Readings

Carroll KM, Nich C, Sifry R, et al. A general system for evaluating therapist adherence and competence in psychotherapy research in the addictions. *Drug Alcohol Depend*. 2000;57:225–238.

Donovan DM, Anton RF, Miller WR, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence (The COMBINE Study): examination of posttreatment drinking outcomes. *J Studies Alcohol Drugs*. 2008;69:5–13.

Dutra L, Stathopoulou G, Basden SL, et al. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry*. 2008;165:179–187.

Hollon SD. Does cognitive therapy have an enduring effect? *Cognit Ther Res*. 2003;27:71–75.

McLellan AT, Lewis DC, O'Brien CP, et al. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA*. 2000;284:1689–1695.

33 Contingency Management

Substance use disorders (SUDs) are highly prevalent in the United States, as they are in virtually all other developed countries, and tremendously costly both economically as well as in terms of personal loss. While there has been a great deal of progress in developing evidence-based treatments for SUDs, there is no question that new and more effective interventions are needed. One widely recognized need is for interventions that are explicitly designed to increase the likelihood of initiating and sustaining behavior change over time, that is, interventions to combat the waxing and waning of commitment or motivation over time, which is a hallmark of SUDs. The focus of this chapter is on contingency management (CM), a treatment approach that is particularly well suited to that task.

CM interventions involve the systematic application of reinforcing or punishing consequences to promote and sustain behavior change. When used in the treatment of SUDs, CM interventions are usually focused on increasing abstinence from drug use, but also can address areas such as increasing clinic attendance, adherence to medication, and other therapeutic regimens. Investigators have been exploring the use of CM interventions for treatment of SUDs since the 1960s, but there has been tremendous growth in this area of investigation in the past two decades. The level of growth is striking and, as will be characterized below, associated with a high degree of efficacy across different types of SUDs, special populations, and therapeutic targets.

There are sound scientific rationales for the use of CM in treating SUDs. CM is based on the principles of operant conditioning, that is, the study of how environmental consequences alter the future probability of voluntary behavior. Behavior that is followed by reinforcing consequences increases in future probability, while behavior that is followed by punishing consequences decreases. There is overwhelming scientific evidence that drug use, including drug use by those with SUDs, conforms to the principles of operant conditioning. Additionally, an emerging area of behavioral economic research on delay discounting documents that individuals with SUDs exhibit a greater discounting of the value of temporally delayed reinforcement than do matched controls without SUDs. Considering that most of the naturalistic reinforcements for discontinuing drug use (improved physical health, family life, employment) are delayed in time while those derived from drug use are relatively immediate, it makes sense that systematically providing substitute reinforcement contingent on therapeutic progress as is done in CM might be helpful in bridging the temporal gap between discontinuing drug use and reaping naturalistic rewards for doing so. Moreover, chronic drug use can directly diminish frontal-lobe cortical functions (executive functions) that underpin effective goal-directed behavior across time and one's ability to focus on longer-term outcomes. Such diminished frontal-lobe functioning quite plausibly leaves individuals with SUDs more vulnerable to the mesolimbic-based, relatively immediate reinforcement that drug use represents. CM appeals to

that same mesolimbic brain-reward system to promote recovery from SUDs—that is, CM uses the same processes that drive addiction, but to promote recovery. A final rationale is that in addition to increasing activity in mesolimbic brain areas, response-contingent incentives increase activity in brain regions associated with top-down cortical functions underpinning attention, error monitoring, and other executive functions that are important to successful long-term goal seeking and are often diminished among those with SUDs.

Voucher-Based CM

This chapter is focused on voucher-based CM, which is the most thoroughly researched form of CM used in the treatment of SUDs. With this approach, patients earn vouchers exchangeable for retail items, or a comparable monetary-based consequence, contingent on meeting therapeutic goals—usually abstinence from drug use, but sometimes attendance at therapy sessions or compliance with medication regimens. Interventions involving vouchers exchangeable for backup prizes or where cash payments were used are included as part of the voucher-based literature in this chapter.

Basic Elements of Voucher-Based CM

Behavioral Principles and Core Procedures

In this section, we review some basic elements of implementing an effective CM intervention. All CM interventions involve the systematic use of the basic behavioral science principles of positive or negative reinforcement and positive or negative punishment. Voucher-based CM emphasizes positive reinforcement involving the delivery of a reinforcing stimulus (e.g., voucher) contingent on the occurrence of a therapeutic goal. The other principle used in voucher-based CM is negative punishment, which involves the removal of a reinforcing stimulus (e.g., special privileges) contingent on the occurrence of an undesirable response. As is outlined further below, this punishment component of voucher-based CM is in the form of a reset contingency wherein the value of vouchers that can be earned is reduced contingent upon evidence of recent drug use or failure to attend a scheduled test to confirm compliance with the contingency. In summary, then, voucher-based CM relies largely on systematic and frequent use of positive reinforcement and a modest use of negative punishment to increase abstinence, to deter relapse, and to encourage compliance with scheduled assessments and other therapeutic targets.

Effective voucher-based CM interventions usually include the following features: (1) a well-articulated contract, in writing when possible, to stipulate what behavior change is expected of the patient, what the consequences will be when the behavior change does and does not occur, and the start and stop dates of the intervention; (2) an operationally defined therapeutic target that allows for independent observer agreement on the occurrence or nonoccurrence of the target; (3) use of an objective means of verifying occurrence of the target behavior whenever possible; (4) a well-specified schedule for monitoring compliance with the contract; (5) a schedule that includes frequent opportunities for the patient to interact with and learn from the reinforcement contingencies; (6) a minimal number of behaviors that are simultaneously being targeted for change; (7) short temporal delays between verifying compliance with the therapeutic target and delivering the programmed consequences; and (8) a consequence of sufficient magnitude, intensity, or value to function as an effective reinforcer. Importantly, the last two points (delay in delivering consequences and magnitude/intensity/value of the consequence) are fundamental to

the effective use of reinforcement and were demonstrated to be statistically significant moderators of treatment effect size in our prior meta-analysis on voucher-based CM.

An Exemplar of Voucher-Based CM: Smoking Cessation in Pregnant Women

To provide a concrete example of an effective voucher-based CM program, in this section we describe the intervention and related results from a study on smoking cessation among pregnant women. This study was selected to serve as the exemplar because the voucher program used is relatively prototypical and the results achieved provide an excellent example of the substantial improvements in outcomes that can be achieved through effective use of the voucher-based CM approach.

Participants in this study were 82 women who were still smoking upon entering prenatal care. They were randomly assigned to an abstinence-contingent voucher condition wherein vouchers exchangeable for retail items were earned contingent on biochemically verified abstinence from recent smoking or to a noncontingent control condition wherein vouchers were delivered independent of smoking status. The details of the voucher conditions were described in the written consent form, which was supplemented by discussion with staff upon treatment assignment, and all study participants had to pass a brief written quiz designed to document understanding of the voucher contingencies before commencing with treatment. In addition to the vouchers, women received whatever was usual care for smoking cessation through their obstetric providers.

Women began their cessation effort on a Monday and reported to the clinic daily for 5 consecutive days for abstinence monitoring. The frequency of abstinence monitoring decreased to twice weekly in week 2 where it remained for the next 7 weeks, then decreased to once weekly for 4 weeks, and then to every other week until delivery. This schedule provided ample opportunity for frequent reinforcement of abstinence. During the postpartum period, abstinence monitoring was increased to once weekly again for 4 weeks related to the increased risk of relapse postpartum, and then decreased to every other week through 12 weeks postpartum at which point the voucher program was discontinued. Voucher values in the abstinence-contingent condition began at $6.25 for a negative test on the first day of the cessation effort and escalated by $1.25 for each consecutive negative specimen up to a maximum of $45.00 where it remained through the remainder of the intervention save for positive results or a missed visit. These values were tested in an earlier pilot trial and shown to be effective. Positive test results or failure to provide a scheduled specimen reset the value of vouchers back to their initial low level, but two consecutive negative tests restored the voucher value to the pre-reset level consistent with the punishment component noted above. If a woman abstained completely throughout the antepartum and postpartum periods, she could earn approximately $1150 in purchasing power; mean voucher earnings in this condition was $461 ± 456. Women in the non–contingent-voucher condition received vouchers independent of smoking status and at values of $15.00 per visit antepartum and $20.00 per visit postpartum, which were estimated based on our earlier pilot study to be comparable to average earnings in the contingent condition. Mean voucher amount provided to women in the noncontingent condition was $413 ± 163, which did not differ significantly from earnings in the contingent condition. Smoking status was biochemically verified based on breath CO specimens ≤6 ppm during the initial 5 days of the intervention and urine cotinine (≤80 ng/mL) from week 2 through the remainder of the study. Because of cotinine's relatively long half-life, it cannot be used to verify smoking status in the initial days of the quit attempt. Two ultrasound examinations were performed at approximately 30 and 34 weeks' gestation for the purpose of estimating fetal growth.

Biochemically verified 7-day point-prevalence abstinence was significantly greater among women in the contingent- compared to the non–contingent-voucher conditions at the

end-of-pregnancy assessment (41% vs. 10%) and 12-week postpartum assessments (24% vs. 3%). Mean weeks of continuous abstinence during the antepartum period was also significantly greater in the contingent- than the non–contingent-voucher conditions, with those in the former achieving 9.7 ± 1.9 weeks compared to 2.0 ± 0.8 weeks among those in the latter. Additionally, a significantly greater percentage of women assigned to the contingent- than the non–contingent-voucher conditions sustained abstinence through the third trimester (27% vs. 3%), which is the trimester where fetal growth appears to be especially impacted by maternal smoking. Treatment effects were no longer significant at the 24-week assessment (8% vs. 3%) in this trial whereas they had been in the prior trial (27% vs. 0%). Collapsing across trials, a treatment effect is discernible at the 24-week assessment (16% vs. 2%), but that should be confirmed in future trials that are better powered to estimate treatment effects after the intervention is discontinued.

Ultrasound assessments of treatment effects on fetal growth showed there was a significantly greater increase in estimated fetal weight in the contingent compared to the noncontingent treatment conditions. In addition, estimated growth rates for two of the three individual parameters used to compute fetal weight (fetal femur length, fetal abdominal circumference) were significantly greater in the contingent than in the noncontingent conditions. We consider these fetal-growth effects to provide important physical evidence of the substantive contributions that CM can make to improving treatment outcomes among pregnant women with SUDs.

Overall, the increases in abstinence and fetal growth observed in this trial are quite promising. This work is being followed up with further scientific efforts to improve outcomes with pregnant smokers and with plans to extend the approach into community practice.

Extending the Intervention to Additional SUD

While once the major trend in this area of investigation, extension of voucher-based CM to new types of SUDs is only a small part of current research efforts. In the present review, only two examples of this type of research were identified. One involved trials further establishing the efficacy of voucher-based CM in the treatment of marijuana dependence and the other extending its efficacy to treatment of methamphetamine dependence. Evidence on the efficacy of voucher-based CM in treating methamphetamine dependence surfaced initially in trials among mixed samples of cocaine- and methamphetamine-dependent patients.

Extending the Intervention to Special Populations

The use of voucher-based CM to treat SUDs in special populations is a trend that was discernible in the prior review and that continues to gain momentum in the period covered by the present review. For example, nine reports in the present review described results from studies testing the efficacy of voucher-based CM for smoking cessation in special populations, including adolescents, college students, pregnant women, and individuals enrolled in treatment for other SUDs, and one with individuals residing in rural areas isolated from usual smoking-cessation services. All reported significant treatment effects.

Other studies in special populations identified in the review further supported a well-established application of contingent vouchers to increase participation in vocational training among chronically unemployed, intravenous drug abusers. Two randomized clinical trials were identified supporting the efficacy of contingent vouchers for increasing adherence with antiretroviral medications in HIV-positive illicit drug–dependent individuals while the incentives were in place, although effects dissipated following termination of the intervention. The studies on adherence with antiretroviral medications suggest that some form of contingent-vouchers

maintenance therapy may be an important future direction to investigate with that population as well.

Extending the Intervention into Community Clinics

An important research effort has been on moving voucher-based CM from university-based research clinics into community clinics. This research effort is important because with lower-value incentives, community clinics operating on limited budgets are likely to be more open to adopting this evidence-based intervention. Important to keep in mind, though, and often misunderstood, is that there is overwhelming evidence that the size of the treatment effect obtained with voucher-based CM decreases as the value of the incentives decreases.

Sometimes overlooked but quite impressive are successful efforts by other investigators to use lower-value CM programs in community clinics. Again, there is no evidence to suggest that these investigators have devised a method for producing treatment effect sizes comparable to those achieved at higher voucher values but at a more affordable cost, but, rather, they are showing that costs can be lowered to more affordable levels and still retain significant benefit in terms of improving treatment outcomes.

Another research development relevant to the successful dissemination of voucher-based CM into community clinics in the United States and abroad is a project conducted in Spain wherein vouchers exchangeable for goods donated by community businesses were efficacious in treatment of cocaine dependence.

Important to mention in this section are three additional international examples relevant to the goal of integrating CM into community practices. First, a project is currently under way in the United Kingdom (UK), examining the feasibility of nationwide adoption of voucher-based CM for the treatment of SUDs, following a recommendation in that direction from the National Institute on Clinical Excellence, an independent body in the UK responsible for providing national guidance on health promotion. Second, voucher-based CM specifically for smoking cessation among pregnant women has been implemented into routine clinical practice in certain locations in the UK. For example, a program entitled "Give it up for Baby" in Tayside, Scotland uses vouchers exchangeable for grocery items to promote smoking cessation with economically disadvantaged mothers, the group most at risk for smoking during pregnancy. Third, while not targeting SUDs, some mention of conditional cash transfer (CCT) programs warrants mention in any discussion on dissemination of CM into community practices. CCT programs are aimed at eliminating chronic poverty and are operating in many low- and middle-income countries worldwide. In these programs, mothers earn cash supplements contingent on adherence with infant inoculations, supplemental feeding, and school enrollment and attendance, among other health-related goals. Tens of millions of families are participating in these programs, which, without question, represent the largest CM effort ever undertaken.

Combining the Intervention with Pharmacotherapies

A clear trend involving studies with voucher-based CM and medications is evident in the present literature review, with some studies examining the relative efficacy of voucher-based CM and medications, others investigating combined effects, and still others looking at whether CM can enhance compliance with medications known to be efficacious but where adherence is problematic. Eight of the 10 trials report results supporting the efficacy of the CM intervention, but beyond that the results from this emerging and potentially very important area of investigation are quite mixed. Perhaps the clearest finding is showing that the efficacy of voucher-based CM for cocaine abstinence among opioid-dependent patients enrolled in substitution therapy was conditional on an adequate dose of the medication. That study provided important experimental confirmation of what was long part of voucher-based CM for treating opioid-dependent

populations. Results from a trial offer a suggestion that combining bupropion therapy with CM for treatment of cocaine dependence facilitates the efficacy of the medication.

This area of investigation is currently lacking any programmatic direction that is readily discernible, but certainly appears to have great potential.

Investigating Longer-term Outcomes

From early in the development of the voucher-based CM approach to treatment of cocaine dependence, there has been interest in its longer-term outcomes. Research on how to directly improve longer-term outcomes has taken two complementary directions that are discernible in the results of the present review. The first seeks to build on correlational data suggesting that key to fostering longer-term abstinence is increasing during-treatment abstinence. The second direction of research on this topic of improving longer-term outcomes is focused on voucher-based maintenance therapy.

Conducting Parametric Studies

As is appropriate and necessary in treatment development, many studies in the CM literature address various parametric questions about this treatment approach. The focus of these studies ranges broadly, but includes a wealth of potentially important, creative, and essential investigations about how to optimize and further expand this efficacious treatment approach. Examples include experiments on prototypical voucher-based CM combined with computer delivered therapy, Internet-based CM delivered alone and without regular in-person interaction, different scheduling arrangements to optimize outcomes, and the possibility of using group rather than individual reinforcement contingencies. Some of these studies offer important but clearly incremental advances, while others offer novel advances. All are important and underscore the health of this area of research.

Conclusion

Voucher-based CM is an efficacious approach to the treatment of SUDs that is based on a clear and compelling set of scientific principles and evidence-based rationales. The approach also has a set of reasonably well-articulated recommended practices for effective CM treatment that we reviewed above. By coupling our review of those core principles and recommended practices with a detailed example of how they can be put into action in the form of a voucher-based CM treatment for pregnant smokers, we hope that readers interested in adopting this approach may be able to gain helpful practical insights from this chapter on how to do so.

The use of voucher-based CM with special populations is an exciting and growing area with potentially important contributions being made with pregnant women, adolescents, and those with other psychiatric disorders, among other groups. Recent developments with pregnant cigarette smokers and in vocational training with dually diagnosed veterans appear to hold particular promise in terms of this treatment approach becoming widely used in clinical practice. An area where we see unrealized potential is in the use of voucher-based CM in treating pregnant women dependent on illicit drugs.

Efforts to move voucher-based CM into community clinics have been tremendously successful in terms of demonstrating efficacy in those settings. Where progress has been slower is in adoption of the practices into routine clinical care, especially in the United States. As was noted above, efforts are under way exploring broad implementation in the UK, where they have a single-payor health-care system, but in the US system, how to pay for incentive-based

interventions remains a major obstacle to broad dissemination into community SUDs clinics. Important to recognize, though, is that there are other important community venues for intervening on SUDs besides treatment clinics. Indeed, employment settings, drug courts, other criminal justice settings, community agencies such as Women, Infants, and Children (WIC) offices, and community health centers may eventually prove to be a better match with the voucher-based CM approach than with community SUDs treatment clinics.

Progress is being made toward using voucher-based CM to improve longer-term outcomes. There is strong evidence that voucher-based CM interventions produce effects that carry over into the posttreatment period and progress is being made in how to improve upon that situation by increasing during-treatment success. The development of longer-term or maintenance CM interventions is a parallel and essential effort that is also progressing well. Indeed, when one considers the broad agreement that SUDs are chronic relapsing disorders, the need for maintenance interventions is obvious. Again, it may be the case that the venues for implementing such longer-term interventions end up being something other than or at least in addition to conventional community SUDs treatment clinics.

Also rather clear is the importance of effectively combining voucher-based CM with pharmacotherapies, but as yet nothing is particularly promising other than the use of voucher-based CM in methadone and other opioid-substitution clinics.

Last, but by no means least, we see promising growth in the use of voucher-based CM as a research tool. That was evident in trials on neuropsychological factors as well as the effects of initial abstinence on relapse risk. This remains a highly underutilized strength of voucher-based CM, but the trend from the present review shows growth in this area that is likely to continue as evidence accumulates on the scientific advantages of doing so.

Suggested Readings

Bickel WK, Miller ML, Kowal BP, et al. Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes. *Drug Alcohol Depend*. 2007;90(suppl 1):S85–S91.

Higgins ST, Silverman K, Heil SH, eds. *Contingency Management in Substance Abuse Treatment*. New York, NY: The Guilford Press; 2008.

Lussier JP, Heil SH, Mongeon JA, et al. A meta-analysis of voucher-based reinforcement therapy for substance use disorders. *Addiction*. 2006;101:192–203.

Muller J, Dreisbach G, Goschke T, et al. Dopamine and cognitive control: the prospect of monetary gains influences the balance between flexibility and stability in a set-shifting paradigm. *Eur J Neurosci*. 2007;26:3661–3668.

Volpp KG, Troxel AB, Pauly MV, et al. A randomized, controlled trial of financial incentives for smoking cessation. *N Engl J Med*. 2009;360:699–709.

34 Motivational Interviewing and Enhancement

One of the true innovations in the field of substance abuse treatment in the past 15 years has been the adoption of sophisticated motivational interventions. Lack of motivation to change is common in substance abuse, stemming from the capacity of substances to create habitual addictive patterns of behavior that include physiologic and psychological dependence. This has led some to call addictions "diseases of denial" and to suggest that confrontation, experiencing severe consequences, and "hitting bottom" are the most effective methods for breaking through the addicted individual's denial. For the most part, this perspective has changed dramatically over the past 15 years. There is growing recognition that a lack of motivation is not simply a problem of addiction but is a part of all human intentional behavior changes. Motivation is multidimensional, involving a series of tasks that include creating concern, decision-making, firm intentions, commitment, planning, and sustained implementation. These tasks are not new and are critical for understanding individual behavior change, whether it happens through self-change or with the assistance of treatment or mutual-help programs.

Motivational interviewing (MI) was developed as an intervention style and a set of strategies based on motivational principles to address the typical motivational conundrum faced by treatment providers: most treatments are action-oriented, but most patients are ambivalent, unmotivated, and not ready for change. MI is best thought of as an intervention that attempts to empower the individual and evoke change rather than an intensive treatment. This chapter will describe the MI approach, offer some evidence for the efficacy of this treatment, and describe how it can be used in substance abuse treatment.

History of Motivational Interviewing

MI was born out of two converging lines of research that emerged at the end of the 1970s and the beginning of the 1980s. For instance, it was advanced that brief interventions of advice and information were as effective as more extensive formal treatments when used with a broad range of individuals with alcohol problems. These findings spurred to begin developing and evaluating brief interventions for excessive drinking. Such interventions, like the Drinker's Check-Up, were designed to influence problem drinkers to change their drinking behavior using an assessment format that included objectively and empathically delivered feedback. Early on, minimal interventions were viewed as more relevant for problem drinkers rather than heavier or dependent drinkers. This was influenced by the belief that "true alcoholics" would not be able to benefit from these interventions because dependence compromised and crippled motivation. Nevertheless, evaluations of the Drinker's Check-Up program indicated that many

individuals with serious alcohol problems were able to moderate, if not quit, drinking. Interest grew among providers in using minimal, motivational interventions for substance abuse, primarily for alcohol abuse and dependence.

At the same time, the transtheoretical model, which described intentional behavior change in a series of stages that individuals negotiated using a number of behavior-change principles or processes. This model was proposed as an integrative, eclectic framework that could make sense of the puzzling outcomes of many treatment comparison trials indicating that different types of therapies seemed to produce equivalent outcomes when evaluated in clinical trials. This model delineated preaction stages (precontemplation, contemplation, and preparation/decision-making) indicating that there were tasks and steps that were necessary to get individuals ready for action. This research also indicated that there may be separate sets of strategies that could be used to influence early-stage transitions, which might differ from action-oriented strategies that would be more important in the later action stages (action and maintenance). It should be noted that many researchers were focusing on decision-making as well as beliefs and intentions contributing to the zeitgeist that led to the creation of cognitive–behavioral treatments that focused both on cognitive variables as well as on behavioral-learning principles as critical ingredients for change. Although originally focused on addictions, this approach came to be used for a variety of health-behavior problems. MI also became an integral intervention component for developing screening, brief intervention, referral, and treatment (SBIRT) approaches for early intervention in drug abuse and other problematic health behaviors. In addition, MI interventions were developed into an independent, brief treatment called motivational enhancement treatment (MET). Today MI is being used in pretreatment interventions as a component of a larger integrated approach, as a free-standing treatment (MET), and as a basic brief intervention used by a multidisciplinary and heterogeneous group of providers. Most importantly, the emergence of MI has reflected and promoted a dramatic change in perspective about how to approach and interact with individuals with substance abuse and how to engage motivational considerations in a constructive, respectful, and empowering manner.

Unique Features of Motivational Interviewing

MI is not a complete therapy intended to provide support, coping skills, and problem solving over a long period of time. As its name indicates, it is a way of talking and interacting with an individual that is designed to activate the person's concern, considerations, and intentions to change and to support the individual's sense of confidence and efficaciousness in making the change. It is specifically intended to help resolve ambivalence, to promote consideration of values, to reevaluate the current status quo and the potential for change, and to support realistic self-efficacy and planning to make a change. It consists of a *style* of interacting that can be used throughout the provider's encounter with a substance abuser as well as a series of *strategies* that can be used to address various obstacles and considerations that hinder the flow of motivation and change for specific clients. In addition, specific skills are needed for practitioners to be able to implement these strategies.

The style or spirit of MI is marked by critical attitudes and values that underlie the entire approach. The key dimensions of the MI-style are collaboration, evocation, and autonomy. Important elements that characterize an MI encounter between the provider and the client are empathy, respect, a collaborative relationship, belief in the capacity for change, and elicitation of motivational considerations, commitment, and change language from the client. Spirit and style are core elements that distinguish MI from other approaches that are more expert-oriented, openly directive, confrontational, and therapist-dominated. Many of the core MI elements are similar to those described in a good therapeutic or working relationship between

therapist and client. However, MI-style is a unique combination of elements from nondirective approach, from humanistic/existential therapy, and from emerging scientific principles of communication, interpersonal interaction, engagement, and motivation.

The core MI strategies include expressing empathy, using open-ended questions, listening reflectively, summarizing and clarifying client thoughts and experiences, affirming client strengths and capacity, eliciting change talk, rolling with resistance, asking permission before giving advice, and presenting a menu of options. The objective of the use of these strategies and techniques is to elicit and promote "change language" from the client. Change language consists of any client statements and expressions that reflect a desire, ability, reasons or need to change, or a commitment to take some action to change (DARN-C language). On hearing any DARN-C language, providers are expected to emphasize them and encourage exploration by reflecting on these client expressions using reflective listening techniques or highlighting them in various types of summaries (collecting, linking, and transitional).

The style, strategies, and skills that comprise MI may come more naturally to some health practitioners than to others. The style requires a respectful, empowering attitude toward the client and the intervention process. MI is intended neither to undermine the role of the provider as a professional, who has important knowledge and specific skills and aids, nor to blur the boundary between client and professional. However, an MI practitioner would need to have attitudes and communication skills that are consonant with collaboration, empathy, listening before speaking, tolerance of client ambivalence and lack of motivation, and the ability to collect, understand, reflect, and summarize what is being said in the encounter. The ability to listen and pay attention not only to clients' words but also to their demeanor, emotions, and language is at the heart of being able to engage in reflective listening and to offer accurate and provocative reflections. Minimizing assumptions and prejudgments of client capacity, motivation, and ability to change is also critical to eliciting change talk and being affirming. Although many practitioners indicate that they are using MI in their practice, fewer seem to be using the entire scope of style, strategies, techniques, and skills that are outlined and demonstrated by the developers of the MI approach. Simply using open-ended questions and reflections do not encompass the broad scope of knowledge, skills, and behaviors needed to fully implement MI. Because of its popularity, there are many adaptations of MI (AMI) that do not include all of the elements and are not executed with the rigorous skill development, feedback and supervision, and detailed analyses of taped sessions that reflect a more comprehensive and faithful application of MI.

Efficacy of MI with Different Populations

Techniques of MI may be more efficacious when addressing preaction motivational tasks and engagement with the intervention. One multisite drug-abuse treatment study found that MI strategies integrated into the initial intake and evaluation sessions of outpatient treatment were associated with significantly better treatment retention at 28-day follow-up. However, the intervention did not impact self-reported overall substance use at either 28-day or 84-day follow-up. Limited exposure to MI especially when joined with a more extensive treatment does not appear to be effective to produce differential changes in substance use behavior compared to active controls among a heterogeneous group of treatment-seeking substance abusers. However, AMIs did demonstrate some positive effects on treatment engagement and retention in inpatient or outpatient substance abuse programs. Studies focused on specific substances of abuse may provide a better test of potential efficacy of MI approaches. These are reviewed below, with the caveat that additional research is needed on the efficacy of MI for the treatment of specific substances of abuse, particularly illicit substances.

Alcohol

MI interventions for alcohol abuse and dependence have been studied more extensively than for any other addictive behavior. A large number of studies examined MI and AMI types of interventions for alcohol use, abuse, and dependence and found that AMI interventions had a moderate advantage compared with either other interventions or no intervention at all.

The strongest conclusion was that MI was significantly more effective in reducing alcohol consumption at a 3-month follow-up among nondependent drinkers when compared with no-treatment controls. When compared to other treatments, results were mixed. MI had greater efficacy than a standard care or treatment-as-usual (TAU) control in four studies. In five studies, MI was more effective than a comparison treatment (cognitive–behavioral therapy [CBT], skills-based counseling, and directive-confrontational counseling), but in three other studies, MI was equivalent to an alternative treatment. One of these was the large-scale, multisite alcohol treatment study, Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity), in which researchers utilized, with high fidelity, a treatment condition comprised of four comprehensive MET sessions and found it produced comparable results to two other more extensive 12-session treatments. The review concluded that MI was useful as a brief intervention and more successful when the client was a young adult who was a heavy drinker rather than an older adult with more severe dependence. It is notable, however, that in none of these studies was MI found to be less effective than other treatments or a no-treatment control.

Group differences in efficacy tended to be greater at 3-month compared to 6-month follow-ups, perhaps suggesting that its effects may fade with time. This does not always seem to be the case, however, since other studies have found support for sustained reductions in alcohol-related problems as well as reductions in the quantity and frequency of drinking at 12-month follow-up interviews. Studies of reduction in drinking with AMI interventions have also shown support for its use in screening and brief interventions across a number of settings.

In alcohol studies examining MI as a treatment option compared to no treatment, MI fared well. Heavy-drinking participants receiving one individual sessions of MI reduced their drinking throughout the 6-week follow-up period. Another study showed both MI and control groups reducing their drinking over a 2-month follow-up period, with subjects in the MI condition significantly reducing their binge-drinking above and beyond the comparison group.

In summary, MI has demonstrated efficacy compared to no treatment, TAU, and some comparison treatments for alcohol abuse and dependence. Results appear to be strongest with younger and less-dependent drinkers. There are also some indications that these brief interventions may produce effects that fade in some groups of drinkers. The research supports use of MI for brief interventions and for outpatient treatment for individuals with a range of excessive drinking problems. However, the exact parameters of who can most benefit from these types of interventions and in which settings they are most effective have not yet been definitively determined.

Opiates

Randomized controlled trials (RCTs) involving AMI with opiate abusers, either as brief interventions or strategies included throughout treatment, demonstrate inconsistent evidence of treatment efficacy. Out-of-treatment heroin users who received a single, brief motivational intervention during a routine medical visit showed higher rates of abstinence from heroin 6 months later. However, in another RCT examining methadone maintenance treatment retention street-recruited injection drug users who received four sessions of MI aimed at entering drug treatment and reducing drug use did not stay in treatment longer than those receiving a four-session risk-reduction intervention aimed at safer injection and sex behaviors. Earlier studies of MET have also found little support for efficacy in the treatment of opiate users in terms of outcomes and mixed effects on treatment engagement.

Amphetamines or Stimulants

There are few studies of MI with amphetamine or stimulant users that were RCTs. However, in one RCT, it was compared to the effectiveness of two treatment conditions containing one initial MI session followed by either two or four CBT sessions with a control group receiving only a self-help booklet to reduce amphetamine use. Participants in both treatment groups were significantly more likely than those in the control group to report abstinence from amphetamines, although not confirmed with urinalyses. Abstaining participants also reported less benzodiazepine use, tobacco smoking, polydrug use, injecting risk taking behavior, criminal-activity level, psychiatric distress, and depression.

Cocaine and Crack

Few RCTs have evaluated MI with cocaine users. However, in the same RCT examining heroin use, it was found that out-of-treatment cocaine users who received a single, brief MI session during a routine medical visit showed higher rates of abstinence from cocaine at 6-month follow-up, findings consistent with prior reviewed studies of motivational interventions for cocaine use with less-motivated participants.

Tobacco

In a meta-analysis of controlled trials examining efficacy of AMIs, it was concluded that there was not yet enough evidence to support MI for smoking cessation. Few studies met their criteria for an AMI-controlled trial. Since that review, however, it has been found a moderate effect size for the reduction of self-reported tobacco use at 3-month follow-up compared to an education-only group for a single MI session with over 200 young persons (aged 16 to 20) using alcohol, cannabis, and/or tobacco. Conversely, another study compared abstinence rates across four treatment groups of African American light smokers (<10 cigarettes per day) and found that receiving more directive, advice-oriented health-education counseling combined with either nicotine gum or placebo gum was associated with higher cotinine-verified abstinence rates at 6 months compared to a treatment that included an MI component.

For older adult patients in the CARES program, there was some support for MET tailored for smoking cessation and delivered by nurses during home-care visits to patients who smoke. A sample of these patients showed more than twice the abstinence rates and significantly more quit attempts and fewer cigarettes smoked per day than those who received only the Agency for Health Care Policy and Research (AHCPR) guideline smoking cessation treatment. Although there are not many RCTs in this area, MI strategies are often incorporated into smoking cessation interventions in primary care, quitlines, and group formats.

Cannabis

The evidence is mixed for efficacy of MI or MET use in treatment of cannabis abuse or dependence. Few RCTs focus on cannabis use alone, and studies vary widely with regard to the number of sessions (1 to 12), length of posttreatment follow-up periods (3 to 15 months), and populations (adolescents and young adults, with or without non–acute psychotic disorders or other substance dependencies). Two multisite RCTs involved in the Cannabis Youth Treatment (CYT) used MET in combination with CBT as part of three of the five treatment options studied. MET was delivered in 2 individual sessions, followed by either 3 CBT group sessions in the first condition (MET/CBT5) or 10 CBT group sessions in the second (MET/CBT12). A third treatment option, called the Family Support Network, added parent education meetings, home visits, and case management. The fourth and fifth treatment options involved case management,

10 to 14 sessions with a therapist, and additional skills training. All five CYT interventions showed significant, positive posttreatment clinical outcomes, measured as rates of abstinence and community functioning up to 12 months later. Minimal differences were found between the conditions, and the MET/CBT5 and MET/CBT12 were found to be among the most cost-effective interventions.

Another study found greater reductions in cannabis use after a nine-session treatment combining MET with CBT compared with a two-session treatment of MET alone. The populations involved in these studies of MI interventions for cannabis treatment differ from traditional substance treatment studies: psychiatric populations, adolescents, and pregnant women.

Efficacy of Motivational Interviewing with Special Populations

MI has also been used and evaluated with special populations with a variety of substance abuse problems. Special populations, as the title suggests, bring to treatment special considerations that can influence the efficacy of MI-style interventions. In the context of substance use, these populations often experience unique psychosocial, developmental, or contextual factors that can impact change in a variety of ways. Such factors can influence the dose and strategies of motivational interventions that are needed as well as evaluations of efficacy. Empirical studies of these populations warrant separate discussion.

Psychiatric Populations

Two RCTs involving larger doses of MI incorporated throughout treatment for drug abuse showed positive effects of MI on substance use outcomes in dual diagnosis or psychiatric treatment settings. One study of 129 stabilized outpatients meeting DSM criteria for drug dependence (cocaine, heroin, or cannabis) and serious mental illness (schizophrenia, schizoaffective disorder, or major affective disorders) evaluated the efficacy of behavioral treatment for substance abuse in severe and persistent mental illness (BTSAS), a multicomponent intervention that included a session MI at baseline, 3 months, and 6 months during treatment, social skills training, and urinalysis evaluation with monetary contingency management for abstinence. Compared to a sample of patients receiving supportive discussion treatment, BTSAS participants showed significantly higher percentage of clean urine samples throughout the intervention, longer time to drop out, and higher ratings on self-reported community functioning and quality of life.

Although general effectiveness for smoking cessation is not established, brief MI interventions may be effective for promoting smoking cessation among patients with serious mental illness. A single MI session with a sample of tobacco smokers with schizophrenia or schizoaffective disorder produced higher rates of contacting tobacco treatment providers and attending a first counseling session for smoking cessation, as compared to educational interventions or advice alone. Such findings are promising considering the exceptionally high rates of smoking among adults with severe mental illness (SMI).

Adolescents

In addition to the positive findings of studies using MI with cannabis using adolescents, recent studies have demonstrated effectiveness in promoting modification of smoking behavior among adolescents. In a multisite RCT conducted in 37 high schools, specially trained school nurses

delivered four one-on-one MI, style smoking cessation interventions to students who smoked in the past month *and* were interested in quitting. Students in the MI condition reported significantly greater abstinence rates and likelihood of quitting at both 6-week and 3-month follow-up compared to a TAU group. One MI session in a medical setting given to non–treatment-seeking adolescent smokers demonstrated greater reductions in smoking at 3-month follow-up, biochemically confirmed, as compared to those who received only standardized brief advice to quit smoking. Finally, MI used with adolescent problem drinkers demonstrated a sustained decrease in the average number of drinking days per month and frequency of high-volume drinking over a 12-month period compared to controls. There is solid support for using MI approaches with adolescents for harm reduction, prevention, and intervention.

Pregnant Women

MI-style interventions have shown promise in helping pregnant smokers to quit or reduce smoking and move along the stages of change, using brief interventions as well as more extensive and manualized interventions. However, recent RCTs have produced nonsupportive findings when examining substance use outcomes. MI added to standard health-care information researchers, health care provided at home by specially trained midwives did not produce reduction or cessation compared to the standard care. Four sessions of individually delivered MET provided to pregnant smokers in methadone maintenance in a hospital-based prenatal program were not more effective than standard care for smoking cessation. Another study of drug-abusing pregnant women (cocaine, marijuana, amphetamine or methamphetamine, alcohol, or phencyclidine [PCP]) compared substance use outcomes between two groups of women referred for treatment. Both groups received TAU and either three sessions of MI or an educational control treatment. Treatment condition had no effect on retention or substance use outcomes in this trial. In contrast, cost-effectiveness research comparing MI to usual care has demonstrated an estimated savings in maternal medical costs, quality-adjusted life years, and life years by selecting MI interventions for relapse prevention among low-income pregnant smokers over other special clinical interventions.

Conclusion

The evidence for the efficacy of MI across substances of abuse and special populations is supportive overall. However, a number of studies have results that are equivocal or fail to support the superiority of this approach. In areas where it has been evaluated more extensively (alcohol, cannabis, and some health behaviors), there is evidence that it is a viable brief intervention, is more efficacious than some comparison treatments, and is usually better than standard care at least for shorter-term outcomes. With other substances, like opiates and cocaine, evidence is less available and what exists is partially supportive. There also seem to be important problem and population dimensions that impact efficacy and effectiveness. Greater severity seems to decrease efficacy of brief interventions, as would be understandable. Some problem areas, like smoking, have yet to demonstrate superiority of MI approaches for cessation, but there is promising evidence for reduction with younger populations. AMIs also seem useful with special populations and can be used with psychiatric and adolescent populations, but the evidence for use with pregnant women is mixed and may depend on the outcome desired and the multiple problems faced by this population.

Overall, MI has received empirical support (a) as brief interventions, (b) as an adjunct to other treatments, and, (c) sometimes, as a free-standing treatment, depending on the type of substance, severity of the problem, and the multiplicity of client problems. It has also been

successfully used with various special populations, including those with psychiatric problems and with adolescents. Its utility with pregnant women seems more problematic in stringent tests of the intervention. Evidence for the superiority of MI to other credible and viable interventions and treatments, however, has yet to be established in many areas. The utility of AMI approaches for treatment engagement and retention is promising but also needs additional controlled research.

How the Treatment Is Optimally Used

Since MI is predominantly a style of interacting that includes a number of strategies and techniques, it can take many different forms and be adapted for use in many different settings. It seems to have been used most successfully as an intervention to address ambivalence and defuse resistance to change in brief interventions. However, this approach has been adapted for use in a more extensive, though still rather brief, format, including MET, and also incorporated as a component in combination treatments with cognitive–behavioral approaches. As noted in the review above, there is evidence for effectiveness for each type of use with one or another of the substances of abuse. Optimal use of MI would depend on the type of problem and population, the objective of the intervention, the skill and training of the providers, and the nature of the intervention setting. We will describe and reference applications that have been used in various studies.

It has been concluded that the state of the current research was such that very little is known about precisely how MI works to elicit various treatment outcomes. Some research indicates that the impact may be mediated by the motivational style of warmth and empathy communicated by the counselor, or the effect of offering tailored assessment feedback, or by promoting treatment participation which then affects behavioral outcomes. Nonetheless, it appears that both brief and more extensive MI-style treatments show efficacy. Following are descriptions of the unique features of each MI treatment that has shown significant effects in at least one of the following outcomes: substance use, substance-related problems, treatment engagement, retention or compliance, quality of life, and general functioning. Developers of these various MI-style interventions have been working to better understand the optimal combination of MI dose and strategy for promoting change in substance abuse.

Brief Interventions

Brief motivational interventions tend to take place in one-to-four sessions either as a substitute for treatment, a brief motivational intervention in an opportunistic setting or moment, or as a part of a screening brief intervention, referral, and treatment protocol. Brief interventions are administered instead of, or early in, treatment and sometimes as a pretreatment intervention to engage a client in treatment. These interventions focus on applying the styles, strategies, and select techniques of MI in order to help the client resolve ambivalence about change and move toward reducing or abstaining from substance use. Brief MI interventions also can be used to promote engaging in treatment creating a supportive environment for the client through empathy and active listening. Variations depend upon the setting and client goals.

Primary-Care/Medical/Health-Care Settings

Although patient-centered communication is becoming a standard element of medical student education, MI offers a very specific way to interview and negotiate change with patients

particularly about chronic disease risk behaviors, including smoking, diet, cancer screening, physical activity, and alcohol and drug use. Brief health-behavior change interventions (from 5 to 20 minutes) by general and specialty medical practitioners or other health-care providers (nurses, physician assistants, or behavior-change specialists) often have incorporated MI strategies in their design. These interventions can be structured and well defined like the five A's for smoking cessation: *a*sk about current substance use, *a*dvise clients to consider reducing or quitting their substance use, *a*ssess their readiness to quit, *a*ssist client in finding options for treatment or change plan, and *a*rrange for a follow-up. These interventions can also consist of a semiscripted individual interview during a routine medical visit and have also been incorporated in home health-care visits for elderly and for pregnant women.

Screening and brief interventions for alcohol and drug abuse that often incorporate an MI-style and one or more of the strategies and techniques (open-ended questions, reflective listening, summarizing, and choice) are being used in many different opportunistic as well as substance abuse treatment settings. The amount of time allocated to these types of interventions ranges from 20 minutes to roughly an hour in a single session; settings range from emergency rooms or trauma centers to rural health-care centers; and treatment can be focused on alcohol or drug use behaviors with patients including college students, young adult, and heavy or hazardous drinkers. Slightly longer brief MI-based interventions consisting of a couple of sessions or with additional feedback and/or contact by phone or mail have also been used with various populations in health-care settings.

Pretreatment and Addictions Treatment

MI strategies have also been incorporated into one, 2-hour assessment and evaluation session or in pretreatment sessions at the beginning of substance abuse treatment programs. MI has also been extended into a stand-alone treatment that has been manualized for use in alcoholism treatment in the form of MET that consists of four one-and-a-half-hour sessions spread over 12 weeks. This treatment has been used in other treatment trials (UK alcoholism treatment trial, UKATT) and has been adapted for use with various types of substances. However, more frequently, AMI have combined it with other forms of treatment either by making MI-style and strategies part of the entire program or by combining MI sessions with additional CBT sessions or combining the two types of treatment into an eclectic mix. MI has also been combined with other treatments for managing substance abuse problems in individuals with mental illness.

Special Considerations

There are a number of important considerations and concerns about MI that affect evaluations and recommendations for use. We will describe these in the following categories: fidelity and training, evaluations challenges, and barriers to effective use of MI.

Fidelity and Training

Many practitioners have been exposed to MI in presentations, workshops, and trainings. Some of the assumptions, principles, and techniques are familiar and similar to what practitioners believe are basic skills already learned in their formation as clinicians (empathy, listening, and respect for clients). However, the familiarity is deceptive and the ease of implementation is overestimated by many. What individuals mean when they assert that they are using MI varies

greatly. The developers have been very cognizant of the need for screening and extensive training of practitioners. They have also used detailed evaluations of taped interactions to assess fidelity to the MI approach in various research studies. Evaluating MI-consistent and -inconsistent behaviors of practitioners seems to be critical for fidelity and effectiveness, with the inconsistent behaviors predictive of worse outcomes. Although style and strategies/techniques have been taught, the essential skills needed to execute MI approaches with fidelity have not been clearly delineated. It does seem that clinicians who have difficulty being or appearing empathic or being nonjudgmental about the specific behavior being discussed, have difficulty sitting back and listening, cannot tolerate ambivalence, or get hooked by resistance behaviors will have a difficult time using MI. Adequate training and selection of practitioners is a critical consideration for implementing MI with fidelity.

In professional communications and evaluations, it is also important to be clear when using or assessing MI approaches. Practitioners and programs should clearly identify how they are using MI in their program. Are they incorporating only the style and spirit, only some strategies, or are they trying to adopt the entire approach? MI is primarily motivational. What are they doing to assist and support other dimensions of behavior change for their clients? When combining MI with other approaches, how are practitioners making sure these treatments are compatible, and what is the explicit strategy for integration or combination of MI with the other approaches? These are critical questions for implementation and especially for evaluation of MI as a brief or more extensive interventions technique.

Evaluation Challenges

In addition to fidelity of implementation and the skill and practices of the individual practitioners who are using MI in the various settings described above, there are a number of other challenges for accurate evaluation of MI. Caution should be used in reading studies and evaluations in the literature. It is not clear what the appropriate outcomes for evaluating MI interventions are. Behavior change is often the intervention goal, yet MI is focused on the motivational dimensions of change and empowerment of the individual to choose to change. Goals of clients and goals of interventions vary greatly. An abstinence-based alcoholism treatment program could have a client with a personal goal of moderation, and successful MI would be marked by reduction in use and not necessarily abstinence. A variety of other outcomes would be appropriate beyond drinking or drug use: stage movement, harm reduction, treatment engagement and retention, general functioning, quality of life, and reduction of substance-related consequences. In fact, some studies have shown that results may include some of these outcomes, like reduction in consequences, without necessarily seeing differences in drinking levels.

Another important dimension to be considered in the evaluation of MI is the heterogeneity of the individuals included in the intervention. Dramatic differences were observed in the ages, gender, problem severity, consequences, and sociodemographic characteristics of participants in the previously reviewed studies. Results often indicate that sometimes individuals with less severe problems and sometimes those with more consequences benefit most from MI. Studies with adolescents, who might be considered good candidates for this approach because of adolescent oppositionality, have had positive but mixed findings. Initial indications are that MI works equally well for men and women, but there are a number of smoking cessation studies with pregnant women where these women have not responded to this approach. When treatment goals include behavior changes needed to address multiple problems or health behaviors, most interventions find this challenging, and MI is no exception. Motivation for each problem area may be distinct, and brief interventions are more problematic with reciprocally complicating conditions. In terms of populations and settings, the critical dimensions of with whom and how MI works have not yet been resolved.

A final consideration about the evaluation of MI pertains to researchers conducting the studies. Studies conducted by proponents of MI produced higher effect sizes, on average, than other studies. This could be due to investigator allegiance effects and/or execution of MI in terms of training and supervision, or the intense monitoring involved in these studies. However, a practical implication of this observation is that well-implemented and supervised MI has greater efficacy.

Barriers to Implementing MI

There are a number of barriers that practitioners and trainers of MI approaches should address in their work, and the following seem to be among the most important:

- Most clinics use closed-ended questions during intake procedures to establish diagnosis and treatment options. Although often necessary for efficient triaging of patients, this type of interaction is contrary to the spirit and strategies of MI. Shifting between intake mode and MI mode presents a challenge, since interactions with the client have been established in the intake that are difficult to change. Efforts must be made to distinguish intake mode from MI intervention to reduce confusion.
- MI promotes client talk and provider listening. During brief interventions, providers are often fearful that promoting client talk will extend the session beyond what is feasible, allowable, reimbursable, and practical. Providers who have only limited time need to be taught not only how to promote client conversation but also how to direct and manage client conversations to meet the demands of the setting and the time allocated for this intervention. Using transitional and closing summaries, skillful messaging about having heard the client's concerns, and effective management of boundaries imposed by limits of time are critical to health-care providers implementing and keeping brief interventions brief.
- Standardizing MI interventions is difficult, and creating manuals that over determine provider behaviors and responses are problematic. Programs that want to include MI have to provide for some structure as well as some flexibility in implementation.
- MI is not nondirective. Individuals beginning to learn MI often mistake reflective listening as never giving advice or setting limits. Nothing could be further from the truth.

Conclusion

MI is an innovative style of interacting with individuals who have substance abuse problems that includes a set of strategies and techniques and also demands a specific skill set. Although not a complete therapy designed to intervene intensively during the entire scope of the change process from lack of interest and ambivalence to sustained change, its style and principles can be used to engage, motivate, and guide individuals throughout the change process. MI can be used as a brief intervention or combined with multiple other types of treatments either as a backdrop or as a companion treatment. There is a growing body of research that indicates efficacy for a variety of populations and problems. However, supporting evidence is not unequivocal, and there is a need for additional research on the scope of its effectiveness. Practitioners can incorporate MI-style and strategies with benefit, especially in addressing the needs of less-motivated clients. Careful implementation while paying attention both to the limitations and the multiple potential ways of integrating MI into both prevention and treatment of substance abuse is recommended.

Suggested Readings

Beckham N. Motivational interviewing with hazardous drinkers. *J Am Acad Nurse Pract*. 2007;19:103–110.

Carroll KM, Ball SA, Nich C, et al. Motivational interviewing to improve treatment engagement and outcome in individuals seeking treatment for substance abuse: a multisite effectiveness study. *Drug Alcohol Depend*. 2006;81:301–312.

DiClemente CC. Mechanisms, determinants and processes of change in the modification of drinking behavior. *Alcohol Clin Exp Res*. 2007;31:13s–20s.

Rollnick S, Miller WR, Butler CC. *Motivational Interviewing in Health Care: Helping Patients Change Behavior*. New York, NY: Guilford Press; 2008.

Ruger JP, Weinstein MC, Hammond SK, et al. Cost-effectiveness of motivational interviewing for smoking cessation and relapse prevention among low-income pregnant women: a randomized controlled trial. *Value Health*. 2008;11:191–198.

35 Relapse Prevention

Substance use disorders (SUDs) represent a serious public health problem in the United States. They are associated with many serious medical, psychiatric, family, occupational, legal, financial, and spiritual problems. SUDs not only cause impairment and suffering on the part of the affected individual but also create a significant burden for the family and society. The conceptual model of addiction as a chronic disorder requiring long-term management has been widely accepted within the substance abuse treatment field. Despite the fact that longitudinal studies have repeatedly demonstrated that substance abuse treatment is associated with major reductions in substance use, other studies have shown that the majority of individuals relapse at some point following a treatment episode and many of them subsequently reenter treatment. To better understand addiction, it is useful to take a "life course perspective" in which substance use, treatment, relapse, and recovery are not viewed as discrete and single events but rather as stages in a chronic and cyclical process where drug use patterns and treatment episodes influence later experiences. Relapse prevention (RP) is a cognitive–behavioral approach with the goal of identifying and addressing high-risk situations for relapse, and assisting individuals in maintaining desired behavioral changes. RP strategies are often incorporated into individual and group treatment manuals. RP techniques may be supplemented by other treatments for SUDs, such as pharmacotherapy or mindfulness meditation.

This chapter provides an overview of relapse and RP. We define lapse, relapse, and recovery, and review treatment outcome studies, empirical studies of RP approaches, relapse precipitants, models of RP, and the recent conceptualization of relapse as a dynamic process. Finally, we briefly discuss future research directions and their relevance to clinical care.

Overview of Lapse, Relapse, and Recovery

The term *lapse* refers to the initial episode of alcohol or other drug use following a period of abstinence, whereas the term *relapse* refers to failure to maintain behavior change over time: "a breakdown or setback in the person's attempt to change or modify a target behavior." Other conceptualization of relapse includes complex multidimensional composite indices of outcome/relapse, taking into account the different aspects of return to problematic behavior and the presence or absence of related consequences that go beyond the simple concept of abstinence–lapse–relapse and fit more into the concept of a harm-reduction approach. So relapse can be viewed not only as the event of resumption of a pattern of substance abuse or dependence but also as a process in which indicators or warning signs appear prior to the individual's actual substance use.

A lapse may end quickly or lead to a relapse of varying proportions. For example, it was reported that 63% of smoking lapsers who called a Stay-Quit line were smoking 2 weeks later; only 37% were able to stop their lapses. Other studies had shown that a lapse does not necessarily lead to a full-blown relapse in users of opiates and tobacco. Based on different conceptualization and methodologic approaches to understanding relapse, relapse is better understood as both a dichotomous outcome and a process involving a series of prior related events and the predictors of these events interfering with behavior change. A dynamic conceptual and clinical assessment model would better capture all the variables of relapse as it unfolds across time. The effects of the initial lapse are mediated by the person's affective and cognitive reactions. A full-blown relapse is more likely with the individual who has a strong perception of violating the abstinence rule (self-blame and loss of perceived control that individuals experience after the violations of self-imposed rules). Although some individuals experience a full-blown relapse and return to pretreatment levels of substance abuse, others use alcohol and drugs problematically, but do not return to previous levels of abuse or dependence and suffer less-harmful effects as a result. Relapsers vary in the quantity and frequency of substance use as well as in the medical and psychosocial sequelae that accompany a relapse.

Recovery

Most researchers implicitly define "recovery" only in terms of substance use and most often as abstinence, either total abstinence or from the specific substance under study. Several terms have been used such as remission, resolution, abstinence, and recovery. The emphasis on abstinence and equating it with recovery has been connected with the influence of abstinence-based 12-step recovery principles, and it has been also embraced by the American Society of Addiction Medicine definition of recovery as "overcoming both physical and psychological dependence to the psychoactive drug while making a commitment to sobriety." Recovery was generally described as a process rather than an end point, and even among participants who did not define recovery in terms of substance use, abstaining from all mood-altering substances was perceived as a prerequisite to the other benefits of recovery. Specific changes and improvements vary among people with SUDs and can occur in any of the following areas of functioning: physical, psychological, behavioral, interpersonal, family, social, spiritual, and financial. It is generally accepted that recovery tasks are contingent on the stage or phase of recovery the individual is in. Recovery is mediated by the severity and degree of damage caused by the SUD, the presence of a comorbid psychiatric or medical illness, and the individual's perception, motivation, gender, ethnic background, and support system. Gender similarities and differences have been more recently explored in the treatment, relapse, and recovery cycle. Women are one-third less likely to transition from one status to another (recovery, treatment, incarceration, and using), and predictors of transitioning to different statuses vary by gender. Numerous longitudinal studies have shown that on average, people reached sustained abstinence only after three to four episodes of different kinds of treatments over a number of years. Over a 2-year period, 82% of drug users transitioned one or more times between use, incarceration, treatment, and recovery. An average of 32% changed over 90 days, with movement in every direction, and treatment increased the likelihood of getting to recovery. The risk of relapse is particularly problematic in the first 3 years of abstinence and never completely goes away. Although some individuals may achieve full recovery, others achieve a partial recovery. The latter may experience multiple relapses over time.

Recovering from a SUD involves psychoeducation, increasing self-awareness, developing coping skills for sober living, and following a program of change. The program of change may involve professional treatment, participation in self-help programs (Alcoholics Anonymous [AA], Narcotics Anonymous [NA], Cocaine Anonymous [CA], Crystal Meth Anonymous [CMA], Rational Recovery, Self-Management and Recovery Training [SMART], Men or Women

for Sobriety, or Dual Recovery Anonymous [DRA]), psychotherapy, pharmacotherapy, case management, and self-management approaches. The information and skills learned as part of RP offer an excellent mechanism to prepare for the maintenance phase of recovery. In the earlier phases of recovery, the individual typically relies more on external support and help from professionals, sponsors, or other members of support groups. As recovery progresses, more reliance is placed on oneself to handle problems and the challenges of living a sober lifestyle.

Treatment Outcome Studies

Numerous reviews of the treatment outcome literature, as well as studies of specific clinical populations receiving treatment, document variable rates of relapse among alcoholics, smokers, and drug abusers. Despite the high relapse rates reported in some studies, treatment has a positive effect on multiple domains of functioning for treated alcoholics and drug-dependent individuals. Outcome is best viewed by considering multiple domains: substance use, as well as social, familial, and psychological functioning. SUDs are not unlike other chronic or recurrent medical or psychiatric conditions in that recovery is not a linear process and relapses do occur, yet significant improvements are often made. Relapse rates were lowest among opiate addicts who graduated from a therapeutic community in which they resided for a minimum of 18 to 24 months. The Comprehensive Assessment and Treatment Outcome Research (CATOR) group, an independent evaluation service for the substance abuse field, followed 8087 patients from 38 inpatient programs and 1663 patients from 19 different outpatient programs for 1 year. Sobriety rates at 1 year were 60% for inpatient, and 68% of outpatient subjects successfully contacted at 6 and 12 months. Even when these rates are adjusted and assume a 70% relapse rate for missing cases, sobriety rates at 1 year are 44% and 52% for the inpatient and outpatient cohorts. Numerous reports by the National Institute on Drug Abuse (NIDA) and the Center for Substance Abuse Treatments document the following positive outcomes for treatment of alcohol and drug abuse: cessation or reduction of substance use; decreases in posttreatment medical care and medical costs; decreases in work problems, including absenteeism and working under the influence; decreases in traffic violations and other arrests; and improvement in psychological, social, and family functioning.

Individuals who relapse do not always return to pretreatment levels of substance use. The actual quantity and frequency of use may vary dramatically. A cocaine or heroin addict who injected large quantities of drugs on a daily basis for years may return to substance use after treatment. Yet this individual may not return to daily use, and the quantity of drugs used may be significantly less than the pretreatment level. Because drug and alcohol use is only one outcome measure, an individual may show improvement in other areas of life functioning despite an actual lapse or relapse to substance use. Patients who remain in treatment the longest have the best outcomes. A recent review exploring gender differences in alcohol and substance abuse relapse showed that for women, marriage and marital stress were risk factors for alcohol relapse and among men, marriage lowered the relapse risk. Recent research is attempting to identify predictors of treatment performance and outcome.

Empirical Studies of RP

A study of inpatient alcoholic veterans found that results consistently favored veterans receiving RP over those receiving a discussion group. Subjects in the RP group drank less, had fewer episodes of intoxication, experienced less severe lapses for shorter periods of time, and stopped drinking significantly sooner after a relapse compared to subjects in the discussion

group. Another study of alcoholics receiving inpatient treatment found that there was greater treatment adherence and satisfaction, reduced lengths of inpatient treatment, and fewer alcohol-related arrests among patients receiving RP compared to patients receiving other treatment modalities. A study of hospitalized male alcoholics found that patients treated with RP compared to interpersonal process therapy drank on fewer days, drank less alcohol, completed more aftercare, and had a slightly higher rate of continuous abstinence at 6-month follow-up.

Two large studies comparing the effectiveness of cognitive–behavioral therapy (CBT) to other active treatments that emphasize the use of 12-step fellowship have demonstrated no difference between conditions at follow-up. Results of Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity), a large-scale multisite, randomized clinical trial of three manual-driven treatments (CBT; motivational enhancement therapy, MET; twelve-step facilitation therapy, TSF), showed significant reductions in days of alcohol use and drinks per day at both the 1- and 3-year follow-up periods. The second study was naturalistic, involved veterans, and showed that patients in all three conditions (CBT, TSF, or a combination of both) performed equally well at 1-year follow-up.

Recent randomized controlled trials support the reported efficacy of combined CBT-like therapies and naltrexone for alcohol-dependent individuals. The COMBINE (Combined Pharmacotherapies and Behavioral Intervention) study suggested that medical management of an alcohol-dependent patient with a physician providing treatment with naltrexone and basic advice and information is as effective as CBT. That trial enrolled 1,383 alcohol-dependent subjects and randomly assigned them to one of eight groups that could include naltrexone, acamprosate, or both of the drugs, with or without what was identified as a cognitive–behavioral intervention (CBI). One group received the CBI alone without the placebo. The patients who received a medication also received medical management that was fairly rigorous (9 appointments over 16 weeks), during which a physician or a nurse discussed the patient's diagnosis and progress and suggested attendance to AA. Those who got the CBI received up to 20 sessions, which was comparable with a streamlined version of outpatient alcoholism treatment. Subjects receiving medical management with naltrexone, CBI or both, fared better on drinking outcomes, whereas acamprosate showed no evidence of efficacy, with or without CBI. Putting it more into clinical implications, the percentages of subjects with a good clinical outcome were 58% for those who received only medical management and placebo, 74% for those who received medical management with only naltrexone, 74% for those who received medical management with naltrexone and CBI, and 71% for those who received medical management with placebo and CBI. The subjects were followed for a year after the 16-week treatment, and although the patterns of efficacy remained much the same, there were appreciable falloff for all groups.

The empirical literature on evaluating RP strategies for cannabis dependence has incorporated other strategies. A multisite study involving 450 marijuana-dependent individuals demonstrated that an integrated CBT and motivational interviewing (MI) was more effective than MI alone, which in turn was more effective than a delayed treatment-control condition. There are no efficacy studies evaluating RP specifically for abuse of club drugs, hallucinogens, inhalants, and steroids.

The most recent meta-analysis that focused solely on smoking and included 42 studies of controlled trials with at least 6 months follow-up, most of which used skills training approaches, showed small and no significant effects for the behavioral interventions. These findings are in contrast with the strong meta-analytic evidence for the efficacy of interventions consistent with RP for smoking cessation reported in the U.S. Public Health Services Clinical Practice Guideline.

Several studies have included spouses in the RP intervention. A study of the first relapse episodes and reasons for terminating relapses for men with alcoholism who were treated with their spouses found that the relapses of patients receiving RP in addition to behavioral–marital therapy were shorter than those of patients not receiving the RP. In a study of married

alcoholics, it was found that in couples assessed to be in "high distress," abstinence rates were highest for those who received behavioral–marital therapy in combination with RP. Alcoholics who received RP after completing behavioral–marital therapy had more days of abstinence, fewer days of drinking, and improved marriages than did those who received only behavioral–marital therapy. A more recent study evaluated conjoint treatments in 90 men with alcohol problems and their female partners. Couples were followed for 18 months after treatment. Across the three outpatient treatments (alcohol behavioral couples therapy: ABCT; ABCT/RP; ABCT with interventions encouraging AA involvement: AA/ABCT), drinkers who provided follow-up data maintained abstinence on almost 80% of days during follow-up with no differences in drinking or marital happiness outcomes between groups.

There are limitations to studies on RP. First, some studies have used RP as the single-treatment intervention for cessation of drinking rather than for maintenance of change once drinking was stopped. Second, studies usually do not differentiate between subjects who are motivated to change substance use behavior and those who have little or no motivation to change. Third, in some studies, sample sizes are small and there is not enough power to detect statistical differences between experimental and control conditions. Fourth, studies do not always use random assignment or operationalize the therapy being compared against RP, making it difficult to determine what factors contribute to treatment effects. And last, the follow-up period is often short-term (6 months or less). Despite these limitations, however, there is empirical evidence that RP strategies enhance the recovery of individuals with SUDs. Furthermore, RP is now listed on SAMHSA's (Substance Abuse Mental Health Service Administration) National Registry of Evidence-based Programs and Practices (NREPP) Web site (www.nrepp.samsha.gov) as an "Evidence-based Practice."

Relapse Determinants

Efforts have been made to classifying relapse for alcoholics, smokers, heroin addicts, gamblers, and overeaters in two broad categories, intrapersonal and interpersonal determinants. Intrapersonal determinants contributing to relapse include emotional states, coping, outcome expectancies, self-efficacy, craving, and motivation. According to this research, the category that most frequently affected relapse of alcoholics, smokers, and heroin addicts was negative emotional states. Thirty-eight percent of alcoholics, 37% of smokers, and 19% of heroin addicts relapsed in response to a negative affective state that they were unable to manage effectively.

Intrapersonal Determinants

1. *Emotional States*: In the original relapse taxonomy and in the replication of the taxonomy, negative affect was the best predictor of outcomes. Research efforts have recently identified negative affect as the primary motive for drug use. According to this model, excessive substance use is motivated by positive and negative affective regulation such that substances provide negative reinforcement when they provide relief from negative affective states. Thus, clinicians should incorporate interventions to help patients regulate their emotions and decrease negative emotional states.
2. *Coping*: Coping has been shown to be a critical predictor of substance use treatment outcomes and is often the strongest predictor of behavioral lapses in the moment. Several types of coping have been identified such as stress, temptation, cognitive and behavioral coping, as well as approach and avoidance coping. Active cognitive and behavioral coping strategies have been shown to be significantly related to abstinence outcomes, whereas the use of avoidance coping tends to be associated with negative outcomes.

3. *Outcome Expectancies*: Outcome expectancies are typically described as an individual's anticipation of the effects of a future experience. Anticipation of the effects of a substance has been identified as one of the primary cognitions related to substance use and relapse. Outcome expectancies may be affecting substance use behavior via the relationship between negative emotional states and beliefs about substances relieving negative affect. Both negative and positive expectancies are related to relapse, with negative expectancies being protective against relapse and positive expectancies being a risk factor for relapse. Individuals endorsing positive expectancies at the beginning of treatment may benefit from an intervention challenging them.
4. *Self-efficacy*: Self-efficacy is defined as the degree to which an individual feels confident and capable of performing a certain behavior in a specific situational context. Self-efficacy is a predictor of outcomes across all types of addictive behaviors, including gambling, smoking, and drug use. Increased self-efficacy following RP intervention was related to improved outcomes. Most likely, the relationship between self-efficacy and outcomes is bidirectional, meaning that individuals who are more successful report greater self-efficacy and individuals who have lapsed report lower self-efficacy. The mechanism by which self-efficacy influences outcome is not clear. Thorough assessment of self-efficacy during treatment and interventions designed to strengthen it are major components of any RP intervention.
5. *Motivation*: Motivation may be related to the relapse process in two distinct ways: the motivation for behavior change and the motivation to engage in the problematic behavior. This illustrates the issue of ambivalence experienced by many patients attempting to change an addictive behavior. The ambivalence is related to both self-efficacy and outcome expectancies. The transtheoretical model of change incorporates five stages of readiness to change: precontemplation, contemplation (ambivalence), preparation, action, and maintenance. Each stage characterizes a different level of readiness for change, with precontemplation indicating the lowest level of change. Motivation to change is transactional, reflected in and affected by interpersonal interaction. The transtheoretical model of change provides a framework for understanding the change process and MI provides a means of facilitating the change process. Thus, assessment of motivation and commitment to change during treatment and interventions such as MI designed to resolve ambivalence and strengthen motivation are critical components of any RP intervention.
6. *Craving*: Craving is possibly the most studied and poorly understood construct in the field of SUD research. Addiction research did not show any significant association between subjective craving and objective measures of relapse.

Interpersonal Determinants

Interpersonal precipitants of relapse include relationship conflict, social pressure to use substances, and positive emotional states associated with some type of interaction with others. Functional social support or the level of emotional support is highly predictive of long-term abstinence rates across several addictions. The quality of social support or the level of support from non–substance abusers has also been related to relapse. Research efforts have provided an overview of interpersonal dynamics as a high-risk situation for relapse. However, the relationship between interpersonal factors and relapse is not entirely clear. Clearly, the role of social support is a critical component of RP. An extension of RP that involves spouses or significant others in conjoint therapy, such as behavioral–marital therapy, has strong empirical support.

Overview of Models of RP

The Cognitive–Behavioral Model of Relapse

The cognitive–behavioral model of the relapse process centers on identifying high-risk situations and the individual's response to the situations. A high-risk situation is defined as a circumstance in which an individual's attempt to refrain from a particular behavior (ranging from any use of a substance to heavy use) is threatened. The high-risk situation is defined as any experience, emotion, setting, thought, or context, and varies from person to person and within each individual. High-risk situations often arise without warning. If the individual lacks an effective coping strategy and/or confidence to deal with the situation (low self-efficacy), the tendency is to give in to temptation. The decision to use or not use is then mediated by the individual's outcome expectancies for the initial effects of using the substance. Individuals who decide to use the substance may be vulnerable to the "abstinence violation effect," which is the self-blame and loss of perceived control that individuals experience after the violation of self-imposed rules, which undermines their commitment to abstinence goals. The lapse is more likely to lead to a full-blown relapse if the individual perceives it as an irreparable failure.

The Cognitive–Behavioral Model of Relapse, Revised

This reconceptualized cognitive–behavioral model of relapse focuses on the dynamic interactions between multiple risk factors and situational determinants. Seemingly insignificant changes in levels of risk (e.g., slight decrease in mood ratings) may kindle a downward spiral of increased craving, leading to a lapse episode often initiated by a minor cue. For example, increased level of stress may trigger a high-risk situation in which a decrease in coping ability considerably increases the likelihood of the person's using an ineffective coping response, thereby leading to an increased probability of a lapse.

Clinical RP Interventions

This section discusses practical RP interventions that can be used in multiple treatment contexts. These interventions reflect the approaches of numerous clinicians and researchers who have developed specific models of RP and/or written patient-oriented RP recovery materials and the authors' experience working with patients with alcohol dependence and drug addictions, including patients with comorbid psychiatric conditions. The interventions reflect the models of RP discussed earlier. Whereas some of these interventions can be used by the patient as part of a self-management recovery program, other interventions involve eliciting support or help from family members or significant others. The literature emphasizes individualizing RP strategies, taking into account the patient's level of motivation, severity of substance use, gender, ego functioning, and sociocultural environment.

The use of experiential learning (e.g., role playing, fantasy, behavioral rehearsal, monodramas, psychodrama, bibliotherapy, use of workbooks, interactive videos, and homework assignments) is recommended to make learning an active experience for the patient. In treatment groups, action techniques provide numerous opportunities for the clinician to elicit feedback and support for individual patients, identify common themes and issues related to RP, and practice specific interpersonal skills. The use of a daily inventory is also recommended. A daily inventory aims to get patients to continuously monitor high-risk situations and identify relapse risk factors, relapse warning signs, or significant stressors that could contribute to a lapse or relapse.

Help Patients Understand Relapse as a Process and as an Event

Patients are better prepared for the challenges of recovery if they are cognizant of the fact that relapse occurs within a context and that clues or warning signs typically precede an actual lapse or relapse to substance use. Although a relapse may be the result of an impulsive act on the part of the recovering individual, more often than not, attitudinal, emotional, cognitive, and/or behavioral changes usually manifest themselves prior to the actual ingestion of substances. An individual's clues or warning signs can be conceptualized as links in a relapse chain. Many relapsers reported to the authors that their warning signs appeared days, weeks, or even longer before they used substances. Patients under treatment for the first time can benefit from reviewing common relapse warning signs identified by others in recovery.

Help Patients Identify Their High-Risk Situations and Develop Effective Coping Strategies to Deal with Them

The need to recognize the risk of relapse and high-risk factors is an essential component of RP. High-risk factors, or critical incidents, typically are those situations in which patients used alcohol or other drugs prior to treatment. High-risk factors usually involve intrapersonal and interpersonal situations. Because the availability of coping skills is a protective factor reducing relapse risk, the clinician should assess coping skills and help the patient develop new ones as needed.

Numerous clinical aids have been developed by researchers and clinicians to help patients identify and prioritize their individual high-risk situations and develop coping strategies to aid in their recovery. For some patients, identifying high-risk factors and developing new coping strategies for each are inadequate, because they may identify large numbers of risk factors. Such patients need help in taking a more global approach to recovery and may need to learn specific problem-solving skills.

Help Patients Identify and Manage Alcohol or Drug Cues as well as Cravings

There is a growing body of research suggesting that patients' desire or craving for alcohol or other drugs can be triggered by exposure to environmental cues associated with prior use. Cues such as the sight or smell of the substance of abuse may trigger cravings that become evident in cognitive (e.g., increased thoughts of using) and physiologic (e.g., anxiety) changes. The advice given in AA, NA, CA, and CMA—"avoid people, places, and things" associated with substance abuse—was developed as a way of minimizing exposure to cues that trigger cravings that can be so overwhelming that they contribute to a relapse. A practical suggestion is to encourage patients to remove from their homes substances as well as paraphernalia (pipes, mirrors, needles, etc.) used for taking drugs. Cue exposure treatment is one method used to help reduce the intensity of the patient's reactions to cues. This treatment involves exposing the patient to specific cues associated with substance use. Cue exposure also involves teaching or enhancing coping skills (e.g., systematic relaxation, behavioral alternatives, visual imagery, and cognitive interventions) to improve the patient's confidence in his or her ability to resist the desire to use.

Because it is impossible for patients to avoid all cues that are associated with substance use, the clinician can teach the patient a variety of practical techniques to manage cravings. Patients should learn information about cues and how they trigger cravings for alcohol or other drugs. Monitoring and recording cravings, associated thoughts, and outcomes can help patients become more vigilant and prepared to cope with them. Helpful cognitive interventions for managing cravings include changing thoughts about the craving or desire to use, challenging euphoric recall, talking oneself through the craving, thinking beyond the high by identifying

negative consequences of using (immediate and delayed) and positive benefits of not using, using AA/NA/CA/CMA recovery slogans, and delaying the decision to use. Behavioral interventions include avoiding, leaving, or changing situations that trigger or worsen a craving, redirecting activities or getting involved in pleasant activities, getting help or support from others by admitting and talking about cravings and hearing how others have survived them, attending self-help support group meetings, or taking anticraving medications such as naltrexone or acamprosate. It has been recommended that ex-smokers carry a menu card that lists various ways to cope with a craving to smoke, a strategy that can also address alcohol or other drug cravings. Another effective way to cope with urges to use substances is a meditation imagery technique known as "urge surfing." To help patients deal with the urge to use without giving in, they are taught to visualize the urge as a rising ocean wave that they will learn to "surf" without getting "wiped out" by the craving.

Help Patients Understand and Deal with Social Pressures to Use Substances

Direct and indirect social pressures often lead to increased thoughts and desires to use substances, as well as anxiety regarding one's ability to refuse offers to drink alcohol or use other drugs. The first step is to identify high-risk relationships (e.g., living with or dating an active drug abuser or alcoholic) and situations or events in which the patient may be exposed to or offered substances (e.g., social gatherings where people smoke cigarettes or drink alcohol). The next step is to assess the effects of these social pressures on the thoughts, feelings, and behaviors of the patient. Planning, practicing, and implementing coping strategies is the next step. These coping strategies include avoidance and the use of verbal, cognitive, or behavioral skills. Using role playing to rehearse ways to refuse offers of drug or alcohol is one very practical and easy-to-use intervention. The final step of this process involves teaching the patient to evaluate the results of a given coping strategy and to modify it as needed. Pressures to use alcohol or other drugs may result from relationships with active drug users or alcoholics. The patient needs to assess his or her social network and learn ways to limit or end relationships that represent a high risk for relapse.

Help Patients Develop and Strengthen a Supportive Recovery Social Network

RP has been addressed from a broader perspective that involves the family or significant others. Involvement of immediate families or significant others in the recovery process provides them with an opportunity to deal with the impact of substance use on their lives as well as their own issues (e.g., enabling behaviors, preoccupation, feelings of anger, shame, and guilt). Families are then in a much better position to support the recovering member. It has been observed that family members sabotage the recovery of the addicted member in a multiplicity of overt and covert ways. Such behavior is usually an indication that they have not had an opportunity to deal with their own issues or heal from their emotional pain.

Patients can be encouraged to get involved in AA, NA, CA, CMA, or other support groups. Sponsors, other recovery and personal friends, and employers may become part of an individual's RP network. Patients generally should not try to recover in isolation, particularly during the early stages of recovery. Suggested steps for helping patients develop a RP network: The patient needs to identify whom to involve in or exclude from this network. Others who abuse substances, harbor extremely strong negative feelings toward the recovering person, or generally are not supportive of recovery usually should be excluded. The patient should then determine how and when to ask for support or help. Behavioral rehearsal can help the patient practice ways to make specific requests for support. Rehearsal also helps increase confidence

as well as clarifies thoughts and feelings regarding reaching out for help. Many patients, for example, feel guilty or shameful and question whether or not they deserve support from others. Yet others have such strong pride that the thought of asking others for support is very difficult to accept. Rehearsal may also clarify the patient's ambivalence regarding ongoing recovery, and it helps better understand how the person being asked for support may respond. This prepares the patient for dealing with potential negative responses from others. Patients should be advised to emphasize that recovery is ultimately their responsibility. An action plan can then be devised, practiced, implemented, and modified as needed. Some patients find it helpful to put their action plan in writing so that all of those involved have a specific document to refer to. The action plan can address the following issues: how to communicate about and deal with relapse warning signs and high-risk situations; how to interrupt a lapse; how to intervene if a relapse occurs; and the importance of exploring all the details of a lapse or relapse after the patient is stable so that it can be used as a learning experience. Having a plan can make both the recovering person and family feel more in control even if faced with the possibility of an actual relapse. Additionally, it helps everyone take a proactive approach to recovery rather than sit back passively and wait for problems to occur. The authors' clinical experience has been that patients and families who are involved in such discussions are much more likely to intervene earlier in the relapse process than those not involved in these discussions.

Help Patients Identify and Develop Effective Coping Strategies to Manage Negative Emotional States

Negative affective states are associated with relapse across a range of addictions. It has been reported that depression and anxiety are major factors in a substantial number of relapses. Coping responses for high-risk situations are less effective for smokers who were depressed. Other negative affective states associated with relapse include anger, anxiety, and boredom. The acronym HALT used in 12-step programs (which stands for "Don't get too hungry, angry, lonely, or tired") speaks to the importance of the recovering alcoholic's or drug addict's not allowing himself or herself to get too angry or lonely. These two emotional states are seen as high-risk factors for many.

Helping patients improve their ability to identify and manage their emotions is a helpful treatment strategy. Interventions for helping patients develop appropriate coping skills for managing negative emotional states vary, depending on the sources, manifestation, and consequences of these emotions. For example, strategies for dealing with depression that accompanies the realization that addiction caused havoc in one's life may vary from those for dealing with depression that is part of a bipolar or major depressive illness that becomes manifest after the patient is substance-free and creates significant personal distress.

Help Patients Identify and Learn Strategies to Cope with Cognitive Distortions

Cognitive distortions or errors in thinking are associated with a wide range of mental health and SUDs. These distortions have also been implicated in relapse to substance use as well. Twelve-step programs refer to cognitive distortions as "stinking thinking" and suggest that recovering individuals need to alter their thinking if they are to remain alcohol- and drug-free. Teaching patients to identify their cognitive errors (e.g., black-and-white thinking, "awfulizing," overgeneralizing, selective abstraction, catastrophizing, or jumping to conclusions) and evaluate how these affect the relapse process is often very helpful. Patients can then be taught to use counter thoughts to challenge their faulty beliefs or specific negative thoughts. The authors provide patients with a sample worksheet to help them learn to change and challenge relapse thoughts.

This worksheet has three directives: (a) list the relapse-related thought; (b) state what is wrong with it; and (c) create new statements. A list of seven specific thoughts commonly associated with relapse is used to prompt patients in completing this therapeutic task. These examples include "Relapse can't happen to me"; "I'll never use alcohol or drugs again"; "I can control my use of alcohol or other drugs"; "A few drinks, tokes, pills, lines won't hurt"; "Recovery isn't happening fast enough"; "I need alcohol or other drugs to have fun"; and "My problem is cured." Patients seldom have difficulty coming up with additional examples of specific thoughts that can contribute to a relapse. Many of the AA, CMA, and NA slogans were devised to help alcoholics and drug addicts alter their thinking and survive desires to use substances. Slogans such as "this, too, will pass," "let go and let God," and "one day at a time" often help the individual work through thoughts of using.

Help Patients Work toward a Balanced Lifestyle

In addition to identifying and managing high-risk relapse factors, recovering individuals often need to make more global changes to restore or achieve a balance in their lifestyle. Development of a healthy lifestyle is seen as important in reducing stress that makes one more vulnerable to relapse. The patient's lifestyle can be assessed by evaluating patterns of daily activities, sources of stress, stressful life events, daily hassles and uplifts, balance between wants (activities engaged in for pleasure or self-fulfillment) and shoulds (external demands), health and exercise patterns, relaxation patterns, interpersonal activities, and religious beliefs. Helping patients develop positive habits or substitute indulgences (e.g., jogging, meditation, relaxation, exercise, hobbies, or creative tasks) for substance abuse can help to balance their lifestyle.

Help Patients Develop a Relapse Management Plan

Since addiction has been clearly identified as a chronic relapsing illness, it is highly recommended that patients have an emergency plan to follow if they lapse so that a full-blown relapse can be avoided. If a full-blown relapse occurs, however, the patient needs to have strategies to stop it. The specific intervention strategies should be based on the severity of the patient's lapse or relapse, coping mechanisms, and prior history of relapse. Helpful interventions include getting patients to use self-talk or behavioral procedures to stop a lapse or relapse, asking family, 12-step sponsors, friends, or professionals for help, carrying an emergency card with names and phone numbers of others who can be called on for support, or carrying a reminder card that gives specific instructions on what to do if a lapse or relapse occurs. Developing a relapse contract with patients that outlines specific steps to take in the event of a future relapse could be useful. The aim of this contract is to formalize or reinforce the patient's commitment to change. Analyzing lapses or relapses is a valuable process that can aid ongoing recovery. This helps to reframe a "failure" as a "learning" experience and can help the individual prepare for future high-risk situations.

Consider the Use of Pharmacologic Intervention as an Adjunct to Psychosocial Treatment

Because some patients benefit from pharmacologic interventions to attenuate or reduce cravings for alcohol or other drugs, enhance motivation to stay sober, and increase confidence in their ability to resist relapse, a therapist should consider using a pharmacologic intervention as an adjunct to psychosocial treatment. None of the medications approved for the treatment of alcohol

dependence has proven effective without some form of concurrent behavioral intervention. In addition, research shows that the combined effects of the pharmacologic and behavioral treatment are additive for smoking cessation. Medications can also be very helpful in preventing relapse to opioid dependence. Unfortunately, despite a significant number of clinical trials with good outcomes, medications are still underutilized by physicians treating patients with addictions.

Assess Patients for Co-occurring Psychiatric Disorders and Facilitate Specialized Treatment if Needed

Numerous studies of community samples, psychiatric treatment populations, and substance abuse treatment populations evidence high rates of dual diagnoses (SUD co-occurring with a psychiatric disorder). Dual-diagnosis patients are at higher risk for substance use relapse than those with only a substance use diagnosis resulting from the effect of psychiatric symptomatology on motivation, judgment, and functioning. In addition, dual-diagnosis patients who resume substance use frequently fail to adhere to psychiatric treatment and comply poorly with pharmacotherapy, psychotherapy, and/or self-help program attendance. In a quality-assurance/-improvement study conducted with 25 substance abusers with mood disorders and 25 substance abusers with schizophrenia who were rehospitalized as a result of significant worsening of psychiatric condition, it was found that alcohol and drug abuse relapse played a significant role in 60% of these psychiatric relapses. In a study comparing psychiatric patients with (n = 127) and without (n = 102) substance abuse comorbidity, it was found that the patients with co-occurring disorders were significantly more likely to relapse and be hospitalized. RP strategies can be adapted and tailored to the specific problems and symptoms of the patient's psychiatric disorder. Monitoring target moods or behaviors, participating in pleasant activities, developing routine and structure in daily life, learning to cope with persistent psychiatric symptoms associated with chronic or recurrent forms of psychiatric illness, and identifying early warning signs of psychiatric relapse and developing appropriate coping strategies are helpful interventions for dual-diagnosis patients.

Negative mood states that are part of an affective disorder (major depression, bipolar disease, etc.) or anxiety disorder (phobia, panic disorder, etc.) may require pharmacotherapy in addition to psychotherapy and involvement in self-help programs. Patients on medications for these or other psychiatric disorders may also benefit from developing strategies for dealing with well-meaning members of self-help programs who encourage them to stop their medications because it is perceived as detrimental to recovery from their SUD.

Facilitate the Transition to Follow-Up Outpatient Treatment for Patients Completing Residential or Hospital-Based Treatment

Many patients make significant gains in structured, hospital-based or residential substance abuse treatment programs only to have these negated as a consequence of failure to adhere to ongoing outpatient or aftercare treatment. Interventions used to enhance treatment entry and adherence that lower the risk of relapse include the provision of a single session of motivational

therapy prior to discharge from inpatient treatment, the use of telephone or mail reminders of initial treatment appointments, integrating motivational interventions in early recovery, and providing reinforcers for appropriate participation in treatment activities or for providing drug-free urines. Studies of patients with schizophrenia and a SUD or patients with mood and SUDs show that providing a single motivational-therapy session prior to hospital discharge leads to a nearly twofold increase in the show rate for the initial outpatient appointment. Patients who show for their initial appointment and successfully "enter" outpatient treatment have a reduced risk of treatment dropout and subsequent psychiatric and/or substance use relapse.

Conclusion

Relapse is complex, dynamic, and unpredictable. A variety of RP clinical treatment models have been developed for patients with alcohol, tobacco, or other addictions. Many of the cognitive and behavioral interventions described in these RP approaches can be adapted for use with patients who have additional problems, such as other compulsive disorders, impulse control disorders, or comorbid psychiatric illnesses. RP interventions aim to help patients maintain change over time and address the most common issues and problems raising vulnerability to relapse. Studies indicate that RP has efficacy in reducing both relapse rates and the severity of lapses or relapses. RP strategies can be used throughout the continuum of care in primary rehabilitation programs, dual-diagnosis hospital programs, residential programs, halfway houses, or therapeutic community programs, as well as in partial hospital, outpatient, and aftercare programs integrated with other treatments such as pharmacotherapy. In addition, family members can be included in educational and therapy sessions and involved in the development of RP plans for members with SUDs. Many of the RP approaches already described could play an important role in the development of short-term or brief interventions such as MI. Incorporating the RP techniques within the brief intervention will be beneficial for patients attempting to abstain or reduce their substance use after treatment and they can be provided in individual or group sessions, making them attractive and cost effective. RP techniques need to be studied more rigorously in diverse samples of populations, including ethnic minority groups and adolescents. Future research should focus on refining the understanding of the dynamic reconceptualization of the relapse process and developing better data analytic methods for assessing behavior change. Clinical researchers should focus their efforts on better dissemination of RP strategies to community-based providers of drug and alcohol services. Neuroimaging studies are needed to better understand the underlying neuronal substrates of craving, decision-making, and the implications for RP.

Suggested Readings

Daley DC, Marlatt GA. *Overcoming Alcohol and Drug Problem: Effective Recovery Strategies*. Therapist Guide. 2nd edn. New York, NY: Oxford University Press; 2006.

Grella CE, Scott CK, Foss MA, et al. Gender similarities and differences in the treatment, relapse, and recovery cycle. *Eval Rev*. 2008;32(1):113–137.

Gwantley CJ, Shiffman S, Balabanis B, et al. Dynamic self-efficacy and outcome expectancies: prediction of smoking lapse and relapse. *J Abnorm Psychol*. 2005;114(4):661–675.

Laudet AB. What does recovery mean to you? Lessons from the recovery experience for research and practice. *J Subst Abuse Treat*. 2007;33(3):243–256.

McLellan AT, McKay JR, Forman R, et al. Reconsidering the evaluation of addiction treatment: from retrospective follow-up to concurrent recovery monitoring. *Addiction*. 2005;100(4):447–458.

36 Management of Associated Medical Conditions

Maternal and Neonatal Complications of Alcohol and Other Drugs

This chapter summarizes the literature regarding the maternal and neonatal complications of licit (alcohol, nicotine, benzodiazepines, prescription opioids, and inhalants) and illicit (heroin, cocaine, amphetamines, hallucinogens, and marijuana) substances. Unfortunately, the political and regulatory distinction between legal and illegal substances has led the public to erroneously assume that there is a relationship between the legality of a substance and its ability to negatively impact fetal development and growth. As will be illustrated in this chapter, if substances were ranked in terms of the severity of their devastating consequences to fetal and maternal health, the two legal substances of alcohol and tobacco would likely decidedly trump the negative consequences associated with illicit substances such as cocaine, heroin, and marijuana.

Prevalence

According to U.S. national survey data from pregnant women of childbearing age (between 15 and 44 years of age, inclusive), 5.1% reported using illicit drugs in the past month. This rate is similar to the rates reported since 2003 among pregnant women. However, this rate was significantly lower than the rate (9.8%) for nonpregnant women in the same childbearing age group. When this age group is categorized into subgroups, the same pattern of less reported use among pregnant than nonpregnant women was observed, except among girls 15 to 17 years of age. In this latter subgroup, those girls who were pregnant had a higher rate of reported substance use in the past month relative to those girls who were not pregnant, that is 21.6% versus 12.9%. There is evidence to suggest that illicit drug use decreases over the course of pregnancy, with 7.2%, 5.0%, and 2.8% of pregnant women reporting past month use of illicit drugs in the first, second, and third trimesters, respectively.

On examining the classes of substances used by pregnant women in the last month, it was found that 3.8% used marijuana, 0.8% used opioids (including heroin, OxyContin, and pain relievers), 0.4% used cocaine, and 0.2% used inhalants. Alcohol use in the past month was reported by 10.6% of pregnant women, while 4.5% reported binge drinking, and 0.8% reported heavy alcohol use. Similar to illicit drug use, these rates were significantly lower than the rates reported for their same-age nonpregnant counterparts, 54.0%, 24.2%, and 5.5%, respectively.

Among childbearing-age women, past-month cigarette use was lower among pregnant (16.4%) than nonpregnant (27.3%) women. Similar to the patterns seen with past-month illicit drug use, the pattern of fewer pregnant than nonpregnant women reporting use was seen in each age subgroup with the exception of 15- to 17-year-old girls, for whom the rate of cigarette smoking appeared somewhat higher for pregnant than nonpregnant girls (20.6% vs. 14.7%). Moreover, the same pattern of decreasing numbers of women reporting cigarette use over the trimesters was also evident.

Social Characteristics

When addressing the complications of maternal drug abuse or dependence during pregnancy, it is important to understand the overall context in which maternal drug abuse usually occurs. In the early 1980s, issues of maternal drug dependence was addressed within the context of the fundamental role gender plays in defining identity; coping skills; psychological, social, and cultural realties; and available resources. Drug-dependent women most often suffer from low self-esteem, depression, and anxiety; are usually the primary caregivers for their children; have a high incidence of victimization; and are involved in relationships with men who are also drug dependent. Although the actual prevalence varies across studies, the consistency in the data allows for a general characterization. Overall, substance abusing pregnant women tend to have completed approximately 11 years of education, are most likely to be unmarried, have a history of substance abuse in their families, have a history of physical and sexual victimization, have significant health and/or mental health problems, have current problems with criminal justice, have current and/or past involvement with Child Protective Services, lack stable housing, and are unemployed with poor vocational training.

These actions frequently deter women from seeking prenatal care and treatment for their substance use disorders (SUDs). Their chaotic lifestyle and lack of prenatal care result in an array of medical and obstetrical complications, reducing the chances of a healthy pregnancy outcome regardless of the effects of the drug(s) they are abusing.

Effects of Prenatal Exposure to Alcohol on the Neonate

Considerable research has consistently shown the adverse physical and behavioral effects on children whose mothers consumed alcohol during pregnancy. The early literature on this topic described a fetal alcohol syndrome (FAS) that included three defining aspects. The first aspect consists of facial malformations that can include small eyes, inner epicanthal folds, a thin upper lip, a long smooth philtrum, and midfacial hypoplasia. The second aspect is notable delays in growth and growth restriction (in head size and physical height). These delays are evident prenatally and there is typically failure to catch up at any point in life postnatally. The third aspect is central nervous system (CNS)/neurodevelopmental abnormalities (e.g., neurologic hard or soft signs, behavioral problems, learning disabilities as appropriate for age). Because there are some individuals who were prenatally exposed to alcohol who exhibit some but not all FAS aspects, newer terms have been developed to refine the characterization of their problems. These terms include alcohol-related neurodevelopmental disorder (ARND), alcohol-related birth defects (ARBD), and the largest umbrella term, fetal alcohol spectrum disorder (FASD). FASD encompasses all adverse effects demonstrated in individuals prenatally exposed to alcohol. FASDs are estimated to occur in 2% to 4% of all live births and are associated with severe cognitive, behavioral, adaptive, social, and emotional regulatory outcomes. These primary problems can set the occasion for vulnerabilities in childhood- or adult-onset secondary problems, particularly in the domains of psychiatric illnesses, including SUDs, social relations, school performance, and legal issues.

Information for Clinicians Regarding Alcohol Exposure during Pregnancy

Ideally, the use of alcohol during pregnancy should be avoided as no "safe" amount of alcohol has been identified. While some women are able to spontaneously quit their use of alcohol before or upon pregnancy awareness, other women are not in a life position to accomplish this behavior change. Thus, it is important to identify as early as reasonably possible pregnant women who are drinking in order to provide them with opportunities for intervention to change their drinking behavior.

Following a positive screen for at-risk drinking, pregnant women need to be assessed for current dependence on alcohol. Those women who are determined to be dependent need treatment in specialty centers. For those women who are not dependent, research shows the benefits of brief interventions, administered by health professionals in the context of care visits, for reducing at-risk drinking. American Congress of Obstetricians and Gynecologists (ACOG) also offers a FASD tool kit for assisting health-care providers in screening, intervention, and assistance for pregnant patients with at-risk drinking.

Effects of Prenatal Exposure to Opioids on the Neonate

Although there are a number of drugs classified as opioids, including buprenorphine, codeine, fentanyl, heroin, hydrocodone, methadone, meperidine, morphine, and oxycodone, the primary opioids used/abused by pregnant women are heroin, oxycodone, methadone, and buprenorphine. Opioids are not categorized as a teratogen, but they do easily cross the placenta. Infants exposed to opioids in utero are born passively dependent, and neonatal abstinence occurs in 55% to 94% of newborns.

Neonatal abstinence is characterized by signs and symptoms of CNS hyperirritability; gastrointestinal (GI) dysfunction; respiratory distress; and vague autonomic symptoms that include yawning, sneezing, mottling, and fever. Infants generally develop tremors, which may progress to the point where they occur spontaneously without any stimulation. A high-pitched cry, hyperactive Moro reflex, increased muscle tone, sleep disturbances, and irritability are also present. Respiratory dysregulation is indicated by nasal stuffiness and rapid respiration. The rooting reflex is increased and infants often suck frantically on their fists or thumbs, yet have difficulty feeding because of an uncoordinated sucking reflex. Additional GI dysfunction is characterized by regurgitation and diarrhea.

Infants undergoing withdrawal must be assessed to determine the severity of the withdrawal and whether to initiate pharmacotherapy to treat it. The most widely used assessment instrument used in U.S. hospitals is the Neonatal Abstinence Score, commonly referred to as the Finnegan score. Whatever scoring system is utilized, the purpose is to objectively assess the onset, progression, and diminution of abstinence symptoms. It provides a mechanism for determining if pharmacotherapy is indicated, monitoring the infant's response to treatment, and initiating a taper when control is achieved.

There is significant variability in the onset and duration of neonatal abstinence. The time of onset of withdrawal ranges from shortly after birth to 2 weeks of age, but on average, occurs within 72 hours after birth. In addition to individual variability, abstinence due to methadone exposure is more prolonged and more severe than for heroin exposure. Although the data to date are quite limited, there is also some suggestion that abstinence due to buprenorphine exposure requires less medication and a shorter hospital stay than for methadone-exposed infants. There are relatively no data to date on the characterization of neonatal abstinence from oxycodone exposure. Variability in neonatal abstinence can also be due to concomitant drug use. Benzodiazepine use among methadone maintained pregnant women has been found to increase the length of treatment for neonatal abstinence by an average of 14.4 days. Nicotine has also

been reported to increase the duration of neonatal abstinence in infants born to methadone-maintained women.

Information for Clinicians Regarding Opioid Exposure during Pregnancy

Different opioids manifest different clinical issues for opioid-dependent pregnant women. Heroin use is illegal and is characterized by a chaotic lifestyle; medical complications associated with parenteral opioid use can include hepatitis, HIV, septicemia, and cellulitis. Obstetrical complications are related to a lack of prenatal care. Moreover, the effects of heroin last only 3 to 5 hours, so the fetus is subjected to repeated episodes of opioid withdrawal, increasing the risk of morbidity and mortality. It is essential that efforts be made to engage pregnant heroin-dependent women in treatment.

Methadone is a synthetic opioid medication that is used in the treatment of opioid dependence and methadone maintenance is recommended as the standard of care in the management of opioid dependence during pregnancy. Effective methadone maintenance prevents the onset of withdrawal for 24 hours, reduces or eliminates craving, and blocks the euphoric effects of other opioids. In pregnancy, methadone prevents erratic maternal opioid drug levels, and protects the fetus from repeated episodes of withdrawal. Additionally, through regulation, it ensures that prenatal care will be available. In the United States, methadone may only be prescribed for maintenance within a licensed opioid treatment program (OTP). Under federal methadone regulations, 42CFR8.12, pregnant women must be given priority for admittance to an OTP and the program must, at a minimum, coordinate prenatal care with a medical provider if they do not have the capacity to provide obstetrical services. When effective methadone maintenance is provided with a comprehensive program that includes prenatal care, the incidence of obstetric and fetal complications and neonatal morbidity and mortality can be reduced.

One of the most contentious clinical issues in providing methadone maintenance to pregnant women is the question of dose. A prevailing concern has centered on whether there is a dose response to the severity of neonatal abstinence. Recommendations have often proposed low methadone doses in an attempt to reduce or eliminate neonatal abstinence. Although there have been many studies that have investigated the relationship between dose and severity of withdrawal, the findings are contradictory. While a number of studies have reported significant relationships, the majority found no relationship. As such, there is no compelling evidence to reduce maternal dose to avoid neonatal abstinence. Conversely, there is evidence that higher doses are associated with less illicit drug use and reducing methadone dose may lead to illicit substance use, and hence increase risk to both mother and fetus.

Although methadone has been used for the treatment of opioid dependence for over 40 years, recent concerns have emerged regarding an association between methadone and QTc interval prolongation, with torsade de pointes associated with very-high-dose methadone. There have been a number of publications with recommendations such as obtaining a pretreatment ECG, a follow-up ECG within 30 days, and annually. For patients with QTc interval greater than 500 msec, it has been recommended that consideration be given to discontinuing or reducing methadone dose. To date, there are no data on QTc intervals in pregnant opioid-dependent women maintained on methadone, so this presents a unique challenge for clinical care in this population.

Buprenorphine, a partial μ-opioid agonist, was approved for use in the treatment of opioid dependency in the United States in 2002; however, it was not approved for use in pregnancy. Nevertheless, there are many instances in which a woman has been successfully maintained on buprenorphine when she becomes pregnant. In such cases, the prescribing physician and patient may decide that the benefits of remaining on the current medication outweigh any risk.

The presence of methadone or buprenorphine in breast milk has been an important question in the clinical management of opioid dependence during pregnancy. There are limited data

regarding buprenorphine, but the evidence indicates that only small amounts of buprenorphine pass into breast milk and the well-established poor oral bioavailability of buprenorphine suggests that absorption via breast milk may be low.

Effects of Prenatal Exposure to Cocaine on the Fetus and Neonate

Cocaine is an alkaloid prepared from the leaves of the *Erythroxylum coca* plant. It blocks the presynaptic reuptake of the neurotransmitters norepinephrine and dopamine (DA), producing an excess of transmitter at the postsynaptic sites. Activation of the sympathetic nervous system by this mechanism produces vasoconstriction, an acute rise in arterial pressure, tachycardia, and a predisposition to ventricular arrhythmias and seizures. Cocaine use rose dramatically in the 1980s and was accompanied by ubiquitous media coverage due to numerous high-profile deaths and the shift from expensive cocaine powder to the far cheaper crack cocaine. The minimal cost and potent euphoria that crack cocaine provided gave rise to the "cocaine epidemic," including significant use among pregnant women. This led to major concerns on the effects on the fetus and neonate as cocaine easily crosses the placenta. The animal and adult literature on the effects of cocaine on the cardiovascular system provided support for such concern as did the potential for the potent vasoconstrictive properties of cocaine to cause congenital malformations.

Information for Clinicians Regarding Cocaine Exposure during Pregnancy

Women who use cocaine during pregnancy have a complex array of obstetrical/medical risks, including a high incidence of alcohol, tobacco and marijuana use, syphilis, gonorrhea, and hospitalizations related to violence, making their obstetrical management difficult. To date, there are no specific medical treatments for cocaine use in pregnancy; referrals should be made to either outpatient or residential treatment programs.

Effects of Prenatal Exposure to Amphetamines on the Fetus and the Neonate

Amphetamine and methamphetamine are commonly known stimulants. They have a somewhat different mechanism of action from cocaine. Amphetamine and methamphetamine reverse the action of the monoamine transporters. They also stimulate DA, norepinephrine, and serotonin release and increase the availability of these neurochemicals at the postsynaptic receptor. Methamphetamine is a known potent drug with neurotoxic effects. A review of the effects of prenatal exposure to amphetamines and methamphetamines concluded that cleft palates, cardiac anomalies, and deficits in fetal growth are evident in both animal studies and documented human-exposure cases.

Information for Clinicians Regarding Amphetamine Exposure during Pregnancy

The identification of amphetamine use during pregnancy can be challenging, and no self-report tools exist that are specific for pregnant women. There are biologic tests available that can detect the recent use of amphetamines and methamphetamine. At delivery, biologic matrices such as umbilical cord, meconium, urine, and hair have been used to determine the presence of these drugs at birth. While it is possible to identify a pregnant woman and her in utero

exposed neonate and to characterize the detrimental effects of this substance exposure on her and her child, treatment interventions to reduce or eliminate such use are needed. To the best of our knowledge, there are no specific behavioral or medication treatments that have been designed and/or have evidence to support their use in pregnant women who use amphetamine or methamphetamine. Ensuring prenatal-care attendance, regular assessment for fetal growth, and intervention with other substance use (e.g., concurrent alcohol use is prevalent in these stimulant users) seem especially important for these pregnant women.

Inhalants

A diverse group of chemicals are known as organic solvents (frequently known as inhalants). These chemicals have multiple household and industrial uses. Most people encounter solvents in their daily life with the use of items such as cleaning fluids and glues (containing aromatic hydrocarbons like toluene or benzene), paint stripper or correction fluid (containing alkyl halides like 1,1,1-trichloroethane [TCE]), fuels or lighter fluids (aliphatic hydrocarbons like propane, gasoline, butane), air fresheners (aliphatic nitrites like isoamyl), nail polish remover (like ketones), and nitrous oxide, which was used in pressurized whip cream dispensers and is still used in medical and dental settings. With awareness and proper use, most individuals experience only low-level exposure to these chemicals. There are infrequent occasions when industrial accidents have exposed individuals to acute, high levels of these chemicals. There are also individuals who voluntarily expose themselves to repeated high-levels of organic solvents. The voluntary exposure or abuse of organic solvents is typically performed by inhaling vapors to become intoxicated. The various inhalation routes include "bagging" (inhaling fumes after spraying into a bag), "huffing" (inhaling solvent fumes from a cloth placed over nose and mouth), "sniffing" or "snorting."

Associated Effects of Prenatal Exposure to Abused Inhalants on the Neonate

While there are numerous types of organic solvents that have been reported to be abused, there are few data about abuse of these inhalants during pregnancy. As such, only those organic solvents with the most human–prenatal exposure data are discussed below. While little is known about the specifics of abused inhalants during pregnancy, it is known that these types of substances are quite toxic and can be fatal if misused.

Toluene

The initial report concluding an association between inhalant abuse during pregnancy and negative birth outcome was published in 1979. It was in this report that the term "fetal solvent syndrome" was used to describe the constellation of physical effects including low birth weight, small head size, and facial dysmorphology that were present in children born to mothers with known abuse of toluene during pregnancy. Since that time, there have been numerous other case reports describing the effects of prenatal exposure to abused inhalants on the child.

Given the similarities between toluene and alcohol, a direct comparison of the teratologic effects of prenatal toluene and alcohol exposure has been undertaken. There were both overlapping and unique anomalies associated with prenatal exposure to either substance. Similar features included a thin upper lip, midfacial hypoplasia, and small palpebral fissures. Head and facial features that appeared unique to toluene were micrognathia, ear anomalies, a narrow bifrontal diameter, abnormal scalp hair patterns, down-turned corners of the mouth, and a large

fontanelle. Craniofacial features unique to fetal alcohol exposure included a more pronounced hypoplasia of the philtrum and nose. The reasons underlying the similar physical alterations may be either similar mechanisms of action of the two drugs, the restricted range of craniofacial abnormalities that can occur at birth, and/or the fact that the toluene-exposed children may have also been prenatally exposed to alcohol during gestation.

Gasoline

There is at least one report of two infants born to a mother who repeatedly sniffed gasoline during pregnancy. Both neonates had low birth weight, and were small in length and head circumference for their gestational age. Following delivery, they exhibited hypotonia followed by hypertonia. At later follow-up, they were observed to have minor facial and physical abnormalities.

It is important to remember the complexities of the lives of women who abuse substances while pregnant, and the inhalant literature, like other in utero literature, often minimizes the possible contribution of multiple factors such as nutrition, licit substance use (nicotine and alcohol), stress, and psychiatric comorbidities that may play important yet undefined roles in exacerbating or mitigating the effects on maternal and neonatal outcomes.

Information for Clinicians Regarding Inhalant Abuse during Pregnancy

Signs and symptoms of toluene or other solvent abuse can include stains (e.g., paint) on the body or clothing, a noticeable chemical odor, sores around the mouth and/or nose, irritated eyes and/or nose, drunken appearance, nausea, anorexia, irritability, or excitability. More recently, solvent withdrawal signs have been discussed in the literature and may include fatigue and difficulty concentrating, fast heartbeat, depressed mood, trembling, or twitching. Given the short duration of action, it is unlikely that tests of bodily fluids will be able to detect the use of inhalants or their metabolites. Thus, asking questions to women suspected of abusing inhalants during pregnancy about the amount and frequency of their inhalant use in a nonjudgmental and neutral manner may be the most effective method for determining abuse.

Renal tubular acidosis is one of the most frequent signs of solvent abuse. The effects of acidosis on pregnancy outcome are concerning. Maternal acidemia has been shown to decrease blood flow and oxygenation, which can compromise fetal development. While a reversible complication, renal tubular acidosis can result in hypokalemia, hypophosphatemia, hypomagnesemia, hypocalcemia, and rhabdomyolysis. Chronic use can result in neurotoxic damage with cerebellar degeneration and cortical atrophy. Hypokalemia and hypophosphatemia can result in debilitating muscle weakness. Further, hypokalemia may also result in cardiac arrhythmias. Hypomagnesemia can result in severe hypocalcemia and a related parathyroid hormone suppression.

In terms of the neonate, there have been reports of a neonatal withdrawal following prenatal exposure to abused solvents. However, standardized measures to evaluate such withdrawal are lacking. It might be expected that mothers showing signs of intoxication at delivery should have neonates monitored for alcohol-like withdrawal signs so that appropriate intervention can be provided to the neonate.

Effects of Prenatal Exposure to Marijuana on the Fetus and Neonate

Reports and studies of the effects of in utero exposure to marijuana have shown modest and inconsistent effects. A prospective study characterizing prenatal marijuana exposure showed

significant effects on birth weight adjusted for gestational age and length at birth. In contrast, the Infant Development, Environment, and Lifetime study demonstrated that marijuana use was not significantly related to the examined fetal growth parameters of gestational-age-adjusted birth weight and being SGA.

Interestingly, several studies have reported a mixture of negative and beneficial effects of in utero exposure to marijuana even in those studies that controlled for maternal weight gain due to marijuana's appetite-stimulant effects.

Information for Clinicians Regarding Marijuana Exposure during Pregnancy

While the majority of the evidence supports minimal to no effects associated with prenatal exposure to marijuana on birth outcomes, the literature is limited by methodologic challenges such as reliance on self-report, few prospective studies assessing exposure over the entire pregnancy, and controlling for multiple environmental and individual factors that could relate to the outcomes observed.

Although the current literature does not support a consistent negative pattern of effects on birth outcomes following prenatal exposure to marijuana, this absence of evidence should not be taken as reassurance that prenatal exposure to marijuana is without risks. There is accumulating evidence showing that the endocannabinoid system plays a major role in CNS patterning. This patterning occurs in areas that are relevant for mood, memory, and reward. A recent review suggested a possible association with in utero marijuana exposure and genetic changes of neural systems that are relevant to endocannabinoid function.

There are also data to support the conclusion that prenatal marijuana exposure has a negative relationship with executive functioning which is largely mediated by the prefrontal region of the brain which develops somewhat later in childhood maturation.

Effects of Prenatal Exposure to Tobacco Products on the Fetus and Neonate

Like alcohol, considerable attention has focused on characterizing and understanding the adverse effects on children born to mothers who smoke cigarettes or use other nicotine-containing products during pregnancy. The rates of cigarette-smoking women who continue to smoke cigarettes after finding out that they are pregnant decreased in the United States for several decades and have now plateaued. Women who smoke cigarettes during pregnancy are more likely to be younger, single, have less academic success and/or employment stability, and depend on governmental medical assistance compared to their nonsmoking counterparts. Women who continue to smoke cigarettes and/or tobacco products during pregnancy are more likely to have spontaneous abortions, ectopic pregnancies, premature rupture of membranes, placenta previa, placenta abruption, fetal-growth restriction, preterm birth, and sudden infant death syndrome (SIDS) relative to women who do not smoke during pregnancy. The adverse effects of secondhand smoke are also evident with increases in the risk for SIDS and infant respiratory distress.

While the exact mechanisms underlying the negative prenatal and neonatal effects of smoking have yet to be elucidated, it is known that nicotine binds to nicotinic acetylcholine receptors (nAChRs). These receptors are ligand-gated ion channels that are present throughout the fetal nervous system. Preclinical studies have shown that nicotine and its activation of nAChRs results in alterations in neuronal activity and life. However, the presence of other chemicals in addition to nicotine makes it difficult to disentangle the in utero effects of nicotine relative to the other chemicals in human exposures.

Information for Clinicians Regarding Tobacco Exposure during Pregnancy

Given the negative effects on both mother and fetus associated with prenatal exposure to tobacco products, there is a need to examine the current treatments for tobacco cessation in pregnant women.

The cessation of cigarette use during pregnancy can result in beneficial effects, with quitting smoking as late as the last trimester resulting in a near normal–birth weight infant. Currently, uncertainty exists about the use of nicotine replacement therapy during pregnancy, given the modest ability of these medications to achieve smoking cessation in pregnant women while also minimizing harm to the fetus and children exposed to these type of medication. Other medications such as bupropion, which acts to inhibit the presynaptic reuptake of DA and norepinephrine, may hold promise for reducing both smoking and depression, which is a frequent comorbid disorder found in pregnant smokers.

Given that any medication has some associated risk, and definitive efficacy and safety data are lacking for medication treatments, behavioral interventions should be the first line of treatment for smoking cessation during pregnancy. One of the most promising interventions for reducing tobacco use in pregnant women is voucher-based reinforcement therapy that is delivered contingent upon smoking abstinence. This intervention has been shown to effectively reduce cigarette smoking and improve fetal growth. However, the optimal choice of treatment for cigarette smoking during pregnancy depends on multiple factors including the patient's desire for a particular treatment, her previous treatment response, and any patient-specific medical precautions/contraindications.

Effects of Prenatal Exposure to Benzodiazepine on the Fetus and Neonate

Benzodiazepines are among the most frequently prescribed medications to pregnant women. Commonly prescribed benzodiazepines are diazepam (Valium), alprazolam (Xanax), lorazepam (Ativan), clonazepam (Klonopin), and chlordiazepoxide (Librium). Benzodiazepines affect the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and appear to act on the limbic, thalamic, and hypothalamic levels of the CNS to produce sedative and hypnotic effects, reduction of anxiety, anticonvulsant effects, and skeletal muscle relaxation.

The only benzodiazepine that has been systematically studied among pregnant women is diazepam. Initial reports found an increased incidence of cleft lip and cleft palate with exposure to diazepam during pregnancy, but prospective studies do not support these findings and most reviewers have concluded that diazepam is not teratogenic.

Neonatal abstinence syndrome has been reported for infants with prolonged interuterine exposure to diazepam with symptoms closely resembling opioid withdrawal. Symptoms include hypertonia, irritability, abnormal sleep patterns, inconsolable crying, tremors, bradycardia, cyanosis, poor sucking, apnea, diarrhea, vomiting, and risk of aspiration of feeds. If treatment is indicated, phenobarbital is the recommended medication.

Information for Clinicians Regarding Benzodiazepine Exposure during Pregnancy

While benzodiazepine use during pregnancy may be indicated for treatment of specific medical problems, they have a high potential for abuse when used with other depressants such as alcohol and opioids. Benzodiazepine dependence is one of the major challenges faced by clinicians providing methadone maintenance for opioid dependence and it is especially problematic

in the treatment of pregnant women. The abuse of benzodiazepines in methadone-maintained patients has the potential to increase the CNS depressant effects of methadone and as such is considered a risk factor for fatal overdose. Exacerbating this risk is that abuse of benzodiazepines is associated with poor psychological functioning and less reduction in illicit drug use. Management of benzodiazepine use is further complicated both by the potential for seizures in rapid withdrawal and by patient resistance to a benzodiazepine taper due to fear of seizures. Withdrawal from benzodiazepines should be conducted by a prolonged gradual taper accompanied with extensive psychological support.

Infants born to women maintained on methadone who use/abuse benzodiazepines require significantly longer treatment for neonatal abstinence than infants born to methadone-maintained women who do not use benzodiazepines. Effective management of the abstinence is made more difficult because of possible delayed onset of benzodiazepine withdrawal, which can occur as late as 12 to 21 days after birth. In addition, opioids used in the treatment of neonatal abstinence have no effect on withdrawal from a nonopioid. While phenobarbital is recommended as a drug of choice for non–opioid-related withdrawal, the optimal treatment for infants with concomitant opioid and benzodiazepine withdrawal is not known.

Breast-feeding is contraindicated for mothers using diazepam as diazepam has the potential to cause lethargy, sedation, and weight loss in infants. There is little data on breast-feeding while taking alprazolam, but based on available evidence of a case report and a cohort study of five cases, caution is indicated. No adverse effects have been reported with the use of lorazepam or chlordiazepoxide during breast-feeding. However, as previously discussed, breast-feeding is contraindicated with any illicit drug use, and in the case of misuse of prescription drugs, it would be prudent to follow this same guideline.

Effects of Prenatal Exposure to Hallucinogens on the Fetus and Neonate

Hallucinogens, including lysergic acid diethylamide (LSD), peyote, and phencyclidine (PCP), cause serious negative psychological effects, and because of their erratic nature, their use can be dangerous (e.g., "bad trips" and flashbacks associated with LSD use, and seizures and coma associated with high doses of PCP). Despite severe adverse outcomes related to these drugs, there is very little data on their effect in pregnant women. The limited data that exist include a few small retrospective studies, case reports, and one prospective study examining perinatal outcome associated with maternal PCP use.

In a study that screened over 2,000 pregnant women for PCP use early in pregnancy, a verbal history of use was reported by 149 pregnant women and current use documented by urine drug screens was identified in 23 pregnant women. Data collection was completed for 94 study patients, including 14 with confirmed current use, and 94 matched controls. The control group was unique from most studies in that they differed from the study group only in PCP use and the mean number of other drugs used; both groups frequently abused marijuana, cocaine, barbiturates, alcohol, and glue. Significantly more abnormal neurobehavioral findings, that is, decreased attention and depressed neonatal reflexes, were associated with maternal PCP use, both in the sample which included all users and the subsample of confirmed users. Moreover, multiple regression analyses showed the number of abnormalities was related to PCP use and no other drugs. No significant relationships were found between abnormal anatomic findings and maternal PCP use. The authors qualify their results with the caution that while this study suggests PCP is not an anatomic teratogen, it does not confirm it. The abnormal neurobehavioral findings are consistent with a case study that reported two infants whose mothers used PCP during pregnancy to have symptoms similar to opioid withdrawal, that is, jitteriness, hypertonia, and hyperreflexia. As with most of the drugs discussed in this chapter, there are no

specific treatment interventions to reduce or eliminate PCP use during pregnancy. For infants who exhibit moderate to severe CNS hyperirritability, treatment with phenobarbital is suggested. Breast-feeding is contraindicated as PCP has been found in breast milk.

Conclusion

As previously discussed, information for each class of drug was presented independently for purposes of organization, but most pregnant women with an SUD use/abuse multiple drugs. The use of multiple drugs may have additive or synergistic effects on both the mother and the neonate.

It is also important to understand that while the focus of this chapter is on the use of alcohol and other drugs during pregnancy, the substance use almost always precedes the pregnancy. All too frequently, the situation reflects a woman with a chronic SUD who becomes pregnant, and thus brings to the pregnancy multiple biopsychosocial problems that may impact on the health and well-being of both herself and her child.

As such, the effect of drug use during pregnancy is often confounded by numerous factors, including multiple drug use, psychiatric comorbidities, exposure to violence and victimization, lack of prenatal care, poor nutrition, and living in an impoverished community. Attention to the use of drugs during pregnancy should be viewed within the context of multiple risks, the need to eliminate vulnerabilities, stigma and prejudice, and the need to provide comprehensive care to promote a healthy outcome for both mother and child.

Suggested Readings

Jones HE, Johnson RE, Jasinski DR, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Depend*. 2005;79(1):1–10.

Odendaal HJ, Steyn DW, Elliott A, et al. Combined effects of cigarette smoking and alcohol consumption on perinatal outcome. *Gynecol Obstet Invest*. 2009;67(1):1–8.

Paley B, O'Connor MJ. Intervention for individuals with fetal alcohol spectrum disorders: treatment approaches and case management. *Dev Disabil Res Rev*. 2009;15(3):258–267.

Sarkar S, Donn SM. Management of neonatal abstinence syndrome in neonatal intensive care units: a national survey. *J Perinatol*. 2006;26(1):15–17.

Seligman NS, Salva N, Hayes EJ, et al. Predicting length of treatment for neonatal abstinence syndrome in methadone-exposed neonates. *Am J Obstet Gynecol*. 2008;199(4):396.e1–396.e7.

37 Medical Complications of Drug Use/ Dependence

Medical illness takes a heavy toll on drug users. Four principal factors contribute to drug users' higher risk for many medical conditions. Direct toxicities of illicit drugs are responsible for a wide variety of medical sequelae (e.g., cocaine-related cardiotoxicity). Behaviors associated with drug use (injection, exchanging sex for money or drugs) place drug users at elevated risk for specific conditions (such as endocarditis and sexually transmitted diseases [STDs]). Socioeconomic disadvantage and poverty engender life circumstances (e.g., congregate housing) that confer increased environmental risk for infections such as tuberculosis. Finally, diminished access to and effective use of care, and disruption of daily routines by active drug use (impeding self-care behaviors such as adherence with medication or appointments) adversely affect clinical outcomes.

Care for Drug Users with Medical Conditions

The Doctor–Patient Relationship and Principles of Care

To gather from patients the information needed to provide effective care, the relationship between patient and clinician must be grounded in trust. Physicians should avoid critical remarks regarding ongoing drug use, as patients often respond by withholding clinically important information they think might provoke such reactions in the future. Like other chronic illnesses, substance use is a persistent condition typically characterized by exacerbations and remissions. When a drug user resumes drug use after a period of abstinence, however, clinicians often become discouraged or angry. Clinicians who accept relapse as a common clinical presentation of drug use, and who are aware of available treatment options, are likely to remain more successfully engaged with the drug-using patient, enhancing the quality and continuity of care provided. The issue of confidentiality frequently arises when caring for the drug-using patient. The physician must be familiar with the laws governing confidentiality of patients' substance abuse behaviors and treatment.

Overlapping Symptoms and Syndromes

A clinical challenge that arises when assessing and caring for the drug-using patient is distinguishing symptoms and signs related to drug use itself from those of comorbid medical and psychiatric conditions.

Constitutional symptoms, while frequently related to drug use and withdrawal, may also reflect systemic illness. Thus, fever after drug injection may reflect use of an impure drug mixture or the first sign of endocarditis. Myalgias, chills, nausea, vomiting, and diarrhea—all hallmarks of withdrawal from narcotics and alcohol—may likewise reflect gastroenteritis or another infectious process, or the side effects of interferon treatment for hepatitis C infection. Weight loss, commonly associated with heavy cocaine use, must also prompt consideration of systemic infection (e.g., tuberculosis), malignancy, or HIV infection. Dyspnea in the crack smoker may be caused by chronic pulmonary dysfunction related to drug inhalation, or to asthma, or to community-acquired or HIV-related pneumonia. Seizures may occur in the context of drug withdrawal (e.g., alcohol or benzodiazepines) or as a result of prior trauma or intercurrent infection. The same principles apply to the overlap between many psychiatric syndromes and syndromes of intoxication or withdrawal.

Prevention of Complications

Disproportionate emphasis is often placed on drug treatment over prevention of the potential adverse consequences of use. Harm reduction takes a different approach, placing priority on minimizing the negative sequelae of drug use and promoting healthy behaviors, and acknowledging that abstinence may not be an immediate goal for all patients.

Injection Drug Use

Injection drug use, through the use of shared injection equipment, remains an important driver of the HIV/AIDS and hepatitis C virus (HCV) epidemics. Over one-third (36%) of AIDS cases in the United States, and the majority of cases among women, can be attributed directly or indirectly to injection drug use. HCV is the most common blood-borne infection in the United States, and injection drug use is the leading risk factor for transmission. The majority of these infections can be prevented through the once-only use of syringes and other injection equipment, as recommended by the U.S. Department of Health and Human Services (DHHS).

Overdose

Drug overdose is a leading cause of death among young adults, second only to motor-vehicle accidents in deaths due to unintentional injury. In 2005, the latest year for which data are available, there were over 22,000 drug-overdose deaths, far exceeding the number of deaths due to homicide in the United States. In recent years, drug-overdose deaths have risen dramatically, increasing by 68% between 1999 and 2004.

Sexual Risk Behavior

Because of the disinhibiting effects of many drugs, the stimulant effects of others, and the relationship of drug procurement to risky sexual behavior, substance users are also at higher risk for STDs, including HIV. Substance users are more likely to encounter circumstances where they have less authority over their sexual activity, because of engagement in commercial sex work, exchange of sex for drugs, and intimate partner violence.

Stimulant use is associated with increased sexual risk behavior among heterosexuals as well as men who have sex with men (MSM). It is strongly correlated with HIV incidence among MSM, with users of methamphetamine and crack cocaine reporting higher numbers of sexual partners and exchanging sex for drugs or money, and those who use drugs during sex being more likely to engage in unprotected intercourse and other high-risk sexual behaviors.

Immunization

Active substance users are at high risk for a number of vaccine-preventable infections. Substance users should receive annual vaccination against influenza. Tetanus booster vaccination every 10 years is recommended for the general population, and should be strictly observed for injection drug users (IDUs), given the association of tetanus with injection drug use. Pneumococcal vaccination is recommended for individuals with unhealthy alcohol use, HIV, and other chronic conditions (including heart, lung, or liver disease, diabetes, sickle cell disease), and thus is indicated for many substance users. All illicit drug users who lack immunity to hepatitis A should be vaccinated. Hepatitis B vaccination is explicitly recommended for IDUs by the Centers for Disease Control and Prevention (CDC).

Cardiovascular Disease and Cancer: Confluent Risks and Associated Outcomes

Leading Health Indicators

The leading causes of mortality in the United States are heart disease and cancer, which together account for nearly half of all deaths annually. Stroke (cerebrovascular diseases, 6%), chronic lower respiratory tract diseases (including chronic obstructive pulmonary disease [COPD], 5%), and accidents (5%) complete the top five causes of death. Each of these conditions are strongly associated with addictive disorders, with tobacco and alcohol making the greatest contribution overall but drugs such as opioids, cocaine, and amphetamine taking a heavy toll as well.

Cardiovascular Disease

Tobacco and Cardiovascular Disease

Tobacco-control efforts are based on well-understood causal associations between smoking and both heart disease as well as malignancy. For the most part, tobacco-addiction prevention and treatment takes place largely outside of the domain of the traditional addiction-treatment delivery system. The importance of addressing smoking cessation among patients presenting with other substance use disorders (SUDs) cannot be overstated as the comorbidity of tobacco dependence with alcohol, opioids, and stimulant abuse and dependence is exceptionally high.

Nicotine, the principal addictive component of both inhaled and smokeless tobacco, is a CNS stimulant and associated with increases in blood pressure and heart rate. Nicotine itself, however, has not been clearly implicated as a cause of atherosclerosis, lipid abnormalities, sudden cardiac death, or stroke in humans. Consistent with this finding is the fact that nicotine replacement therapy (NRT) has not been linked to increased cardiovascular disease (CVD) events or death. Rather, NRT is a mainstay of secondary CVD prevention among smokers following myocardial infarction or other cardiac events. The cumulative effect of cigarette-smoke compounds on the chronic user is an intravascular environment of hypoxia, inflammation and decreased immune function, abnormal lipid metabolism, and platelet, thrombotic, and vasomotor dysfunction, all of which act synergistically to initiate and promote atherothrombotic disease progression.

Alcohol and Cardiovascular Disease

Unique among addictive substances, alcohol relates to CVD risk and mortality. Multiple large epidemiologic studies have observed a similar relationship: moderate alcohol use is protective

against cardiac events, including myocardial infarction and stroke, compared to no use, while excessive, chronic use is clearly harmful. Among the general population, moderate alcohol use, defined as ≤2 drinks/day (men)/≤1 drink/day (women), when previously established and in the absence of alcohol or other addictive disorders, may be considered a component of a healthful "lifestyle." Persons coping with alcohol and other drug use disorders, however, can be unequivocally counseled toward abstinence as failure to control daily drinking promotes precursors, particularly hypertension, and eventual CVD and death.

Cocaine, Stimulants, Methylenedioxymethamphetamine, and Cardiovascular Disease

Cocaine is a clear cardiotoxin and proarrhythmic agent, and any level of use is associated with increased risk of CVD, sudden cardiac death, and stroke. Among persons 18 to 45 years of age in the United States, cocaine accounts for up to 25% of acute myocardial infarctions. Although all cocaine users are at risk, most patients with cocaine-associated myocardial infarction are young, nonwhite, male, cigarette smokers, without other risk factors for atherosclerosis, and with a history of repeated cocaine use. Only half of such patients have evidence of atherosclerotic coronary artery disease on subsequent angiography.

The most common medical symptom associated with cocaine use is chest pain, which may reflect myocardial ischemia or infarction. Cocaine use increases the risk of acute myocardial infarction by several mechanisms, including coronary vasoconstriction or vasospasm, increased adrenergic activity (which intensifies myocardial oxygen demand by increasing blood pressure, ventricular contractility, and heart rate), and increased platelet adhesion, aggregation, and intravascular thrombosis.

Opioids, Cannabis, and Cardiovascular Disease

Opioid- and cannabis-dependent populations are at higher risk for ischemic heart disease, largely reflecting comorbid tobacco and alcohol dependence. Injection use of opioids, and resulting embolic and infectious complications, including endocarditis, also poses obvious cardiac risks. Methadone, the opiate agonist used in the pharmacotherapy of opioid dependence, has been associated in some patients with prolongation of the QTc interval on the electrocardiogram and uncommonly with ventricular arrhythmia (torsade de pointes). Other data hint at a potential cardioprotective effect of long-term exposure to opiates. Isolated cannabis use and dependence have not been clearly linked to excess mortality or CVD, and most longitudinal cohort studies linking cannabis smoking to heart disease are confounded by tobacco use.

Management of Ischemic Heart Disease in Persons with Substance Abuse

In persons with substance abuse or dependence, care for hypertension, lipid disorders, diabetes, and heart disease is best addressed in concert with individuals' addiction treatment. Lack of engagement in substance abuse treatment should not, however, preclude careful attention to and care of these comorbid medical conditions.

Regarding modifiable risk factors, all adults should be screened for hypertension, high cholesterol (men aged ≥35, women aged ≥45 with no other risk factors), and excess weight, with diabetes screening recommended for adults with blood pressure of ≥135/80 mm Hg. A low-salt, high-fiber diet and regular exercise are beneficial both as primary and secondary CVD prevention. Men ≥40 years, postmenopausal women, and those with CVD risk factors including smoking should consider daily aspirin therapy. Smoking cessation, elimination of unhealthful alcohol use, and avoidance of cocaine and other stimulants are clearly of particular importance among patients with drug abuse or dependence.

Hypertension control should be focused on reaching and maintaining a "goal blood pressure" of below 140/90 mm Hg, or lower (<130/80 mm Hg) in the setting of diabetes, proteinuric chronic kidney disease, or known CVD. Treatment should follow national

guidelines. Of note, clonidine, a central α-2-agonist and oft-encountered antihypertensive medication among addicted persons, is not appropriate as monotherapy for hypertension due to lack of efficacy, the need for twice-daily dosing, reports of its abuse as a sedative, and the risk of potentially fatal rebound hypertension.

Cancer

Tobacco and Lung Cancer

Unlike CVD or other common cancers (e.g., breast or colon cancer), in which a constellation of modifiable factors such as weight, blood pressure, and diet combine with tobacco dependence to heighten disease and mortality risk, lung cancer has cigarette smoking as by far its most important cause. This is true of both non–small cell (85% of all lung cancers, includes squamous cell and adenocarcinoma) and small cell (15%) tumors.

Generally, lung and other cancers evolve as cumulative environmental exposures interact with genetic susceptibility. Over time, direct tissue injury from tobacco smoke promotes premalignant genetic mutations and tissue changes, including dysplasia, clonal patches, and angiogenesis, which progress to malignant cell invasion, early-stage cancer, and eventual metastasis. Returning to baseline levels of lung-cancer risk comparable to that of never-smokers occurs slowly following successful cessation. In women, while a significant (21%) reduction in risk appears within the first 5 years of quitting, excess risk compared to never-smokers may take up to 30 years to disappear. From a perspective of lung-cancer risk reduction, then, current smokers should be encouraged to quit as soon as possible and should be supported in abstinence for as long as possible.

Tobacco and Other Cancers

Smoking, smokeless-tobacco use, and secondhand smoke are causative factors in most nonlung malignancies, including leukemias, head and neck and esophageal cancers, and cancers of the pancreas, liver, stomach, cervix, kidney, large bowel, and bladder. In addition, chronic tobacco use mediates the majority of lung and nonlung cancers in persons dependent on other substances, including alcohol, stimulants, cannabis, and opioids.

Alcohol and Cancer

Alcohol consumption is a risk factor for the second and third most common causes of cancer mortality in 2006, colorectal cancer and breast cancer, though a dose-dependent association between alcohol intake and colorectal-cancer risk is not firmly established. Alcohol may increase estrogen and androgen levels in women, among other plausible mechanisms for alcohol's promotion of breast cancer. Alcohol is linked to most cancers of the digestive tract, particularly squamous cell carcinomas, including those of the oral cavity, head and neck, esophagus, and liver (hepatocellular carcinoma [HCC]), though it is not associated with stomach cancers. HCC arises in the setting of cirrhosis, the most common cause of which is heavy alcohol consumption, and the risk of alcohol-induced HCC is heightened in the setting of viral hepatitis. The effectiveness of screening for breast and colorectal cancers is well established in the general population, though guidelines do not vary by level of alcohol use. Colorectal cancer screening in all adults consists of fecal occult blood testing, sigmoidoscopy, or colonoscopy beginning at age 50 to age 75. Screening mammography every 1 to 2 years is recommended for women aged ≥40.

Viral Causes of Cancer among Drug Users

HIV, human papilloma virus (HPV), hepatitis B virus (HBV), and HCV are each prevalent among drug users and associated with increased risk of malignancy. Cervical cancer screening is recommended for all women who have been sexually active and have a cervix.

Alcoholic Pancreatitis, Liver Disease, and Viral Hepatitis

Addiction and Gastrointestinal Disease

Disorders of the intestinal tract and liver among addicted persons are primarily mediated by chronic heavy alcohol use and viral hepatitis. Alcohol and tobacco use are strongly associated with head and neck and esophageal cancers, particularly squamous cell carcinomas, and tobacco is a strong risk factor in gastric cancers. Excessive alcohol use in the setting of viral hepatitis (often contracted through high-risk sexual behavior or injection drug use) confers particularly high risk of hepatocellular injury, development of cirrhosis, and HCC.

Alcoholic Pancreatitis

Pancreatitis and alcoholic liver disease are well-known consequences of chronic alcohol misuse. The incidence of acute pancreatitis in developed countries correlates with rates of alcohol consumption as well as with gallbladder disease, the two chief causes of pancreatitis. Overconsumption of ethanol results in toxic levels of its metabolites, including acetaldehyde and fatty acid ethyl esters, which are thought to increase production of digestive and lysosomal enzymes by pancreatic acinar cells and thereby initiate the cascade of inflammatory and autodigestive pancreatic injury.

The management of acute pancreatitis consists largely of supportive measures, including pain control, intravenous fluids, fasting, electrolyte corrections, and insulin-based control of hyperglycemia. Alcohol abstinence is of course mandatory. Risk factors for disease severity include older age (>55 years), obesity, organ failure at admission, and pleural effusion or pulmonary infiltrates. Single or multiple episodes of acute pancreatitis may result in chronic pancreatitis, marked by fibrosis and mononuclear infiltrate (vs. neutrophilic in acute pancreatitis), chronic abdominal pain often following meals, and pancreatic insufficiency with fat malabsorption and glucose intolerance.

Alcoholic Liver Disease

Alcoholic liver disease ranges across a spectrum from asymptomatic fatty liver to alcoholic hepatitis, cirrhosis, and end-stage liver failure. Alcohol is primarily metabolized by the liver by way of the alcohol dehydrogenase pathway. Chronic, heavy alcohol use may also induce secondary microsomal enzyme oxidation pathways. Both pathways generate toxic metabolites including acetaldehyde and free-radical oxygen intermediates. Hypoxia associated with alcohol metabolism, increased levels of cytokines, neutrophil migration, and liver macrophagic Kupffer-cell activation all contribute to hepatocellular injury, chronic inflammation, and eventual fibrosis.

The incidence of alcoholic liver disease is quite variable, with cirrhosis developing in approximately 50% of persons who consume at least 1 pint of spirits (roughly 210 g of ethanol) daily for >20 years. Most persons consuming eight or more standard drinks per day, however, will develop precursor conditions such as alcoholic fatty liver. Physical signs that often accompany the presence of alcohol-related liver disease include right upper quadrant pain, enlarged or reduced liver edge, general muscular atrophy, bleeding disorders, and peripheral neuropathies. Elevated serum transaminase levels, particularly a ratio of elevated aspartate aminotransferase (AST) to alanine aminotransferase (ALT) of >2 in the setting of chronic heavy alcohol use, are highly suggestive of alcoholic liver disease. Imaging (including ultrasound, CT, or MRI) can

detect fatty changes, cirrhosis, or liver tumors. Liver biopsy is not required for the diagnosis of alcoholic liver disease, but is often used to exclude other causes of liver disease and to establish disease severity.

Alcoholic fatty liver is a direct, reversible effect of ethanol ingestion, and usually does not progress to alcoholic hepatitis or cirrhosis. It is often asymptomatic or characterized by mild abdominal pain; laboratory tests are often normal. Alcoholic fatty liver is characterized by macrovesicular steatosis and mitochondrial distortion, and is usually indistinguishable from other causes of fatty liver, including obesity, pregnancy, drug toxicity, or viral hepatitis. Alcoholic hepatitis is characterized by fever, hepatomegaly, jaundice and anorexia, and elevated serum transaminase levels, and can be accompanied by ascites in fulminant cases. Neutrophil infiltration and Mallory bodies on biopsy are highly suggestive of alcoholic injury as opposed to viral hepatitis. Cirrhosis may coexist with alcoholic hepatitis, and both usually begin in the pericentral liver with progression to panlobular regions. Cirrhotic fibrosis is the accumulation of scar or extracellular matrix. Progression of cirrhosis is marked by portal hypertension, varices, ascites, lower-body edema, jaundice, coagulopathies, and eventual fulminant hepatic failure with encephalopathy.

Viral Hepatitis

Hepatitis A

Hepatitis A virus (HAV) is the leading cause of acute viral hepatitis in the United States, and results in significant morbidity and health-care costs. Hepatitis A is a nonenveloped ribonucleic acid (RNA) virus that is excreted in stool and usually transmitted by fecal–oral contact, although transmission through blood is also possible. Most cases of HAV occur during community-wide outbreaks, but a high proportion of these cases occur in persons who report using drugs. The prevalence of anti-HAV antibodies is particularly high among drug users; in one study, the prevalence among IDUs was twice that in the general population.

Transmission between drug users is hypothesized to occur primarily by the fecal–oral route when people gather together to smoke, snort or swallow drugs, and secondarily by percutaneous transmission through sharing needles and other injection supplies.

Hepatitis B

As many as 1.4 million people in the United States are living with chronic hepatitis B infection, with new infections occurring at a rate of over 40,000 annually despite the availability of an effective vaccine. The prevalence of HBV infection among IDUs is particularly high (40% to 80%). Hepatitis B is a deoxyribonucleic acid (DNA) virus that is predominantly acquired through sexual contact (homosexual and heterosexual), but also by IDU and occupational exposure. Among drug users, HBV is transmitted parenterally through the sharing of needles and other contaminated injection equipment, or high-risk sexual behavior. HBV acquisition is a relatively early event for most IDUs, with 50% to 70% of injectors seroconverting within the first 5 years of initiating injection. Young IDUs thus manifest the highest incidence of new HBV infections in the United States, with transmission linked to injection practices (sharing needles and other injecting equipment) and high-risk sexual behavior (not using a condom and/or having multiple sexual partners). It is now recommended that IDUs be routinely screened for hepatitis B infection (serologic testing for HBsAg) if they are not known to be immune.

The hepatitis B vaccine is immunogenic, effective, and safe. Though vaccination has been recommended for IDUs by the CDC since 1982, uptake in this population has remained consistently low (less than 30%). Multiple barriers to successful vaccination among IDUs include generally poor access to health-care services, lack of awareness of the need for vaccination among drug users and health care workers alike, and the relative complexity of the vaccine schedule.

Hepatitis C

Approximately 4 million people have evidence of exposure to HCV in the United States, of whom 78% have chronic infection. HCV is the most common chronic liver disease in the United States, and accounts for the majority of liver transplants. Hepatitis C is a retrovirus with six major genotypes, genotype 1 being most common in the United States and Europe. It is very efficiently transmitted by contact with infected blood, and more rarely through sexual exposure. In the United States, up to 8% of HCV-infected persons are HIV coinfected.

IDU is the primary route of transmission of HCV infection. Among injectors, there is considerable geographic variation in HCV seroprevalence, but rates are consistently high, ranging from 14% to 51% in major U.S. cities. Acquisition of HCV infection is often rapid following initiation of drug injection, with greater than one in three IDUs becoming infected within the first 5 years after initiating injecting. Transmission risk increases with injection frequency and with injecting a mixture of cocaine and heroin ("speedball"). Sharing of drug-preparation equipment, including cookers and the filtration cotton, is also clearly associated with incident infection. Although sharing of intranasal cocaine-sniffing equipment (e.g., straws) has also been considered a possible route of HCV transmission, these data are inconclusive. Sexual transmission of HCV, although much less efficient than injection-related transmission, can also be a route of infection among drug users. Multiple sex partners and comorbid STDs increase the risk of sexual acquisition of HCV, and non-IDUs trading sex for money or drugs may be at particularly high risk.

Most patients do not seek medical attention during acute infection with hepatitis C because clinical manifestations are often mild. Following initial infection with HCV, approximately 15% to 20% of persons appear to permanently clear the virus, and 80% to 85% of persons develop chronic infection. HCV-induced cirrhosis develops in an estimated 15% to 20% of those with chronic infection, and HCV-related end-stage liver disease (ESLD) now constitutes the most common indication for liver transplantation in the United States.

Hepatitis D

Hepatitis delta virus (hepatitis D virus [HDV]), an incomplete RNA virus that requires coinfection with active HBV to become active, is transmitted in the same manner as HBV and is prevented by HBV vaccination. It is endemic in the Mediterranean region and in parts of Asia, Africa, and South America and appears to have been spread to nonendemic areas, such as the United States and northern Europe, by injection drug use. Outbreaks of severe and fulminant hepatitis, primarily as a result of coinfection with HDV and HBV, have been reported in IDUs and their sexual contacts.

Other Viral Causes of Hepatitis

Other viruses have the potential to cause hepatic disease among drug users as well, including Epstein–Barr virus, herpes simplex virus (HSV), and cytomegalovirus, each of which may bring about hepatitis-associated illnesses. Most often, these viruses are spread through direct contact, but they can be spread parentally as well. Although relatively rare in comparison to HAV, HBV, HCV, and HDV, it is important to consider these pathogens in the differential diagnosis of hepatitis among drug users.

Sexually Transmitted Diseases

STDs are common among substance users, often associated with sexual risk incurred in the setting of intoxication (particularly among users of stimulants such as cocaine and amphetamines) as well as with exchange of sex for money or drugs. Crack use is particularly strongly associated with sex in exchange for money or directly for drugs, and crack-smoking sex workers

report very-high-risk sexual practices, as well as low rates of condom use. STDs that present commonly among drug users include syphilis, gonorrhea, chlamydia, genital HSV, HPV, and trichomoniasis. In addition, HIV is transmitted among drug users both sexually and parentally; a full discussion of HIV infection is found elsewhere in this volume.

Syphilis

Syphilis is a readily curable, bacterial genital ulcer disease caused by *Treponema pallidum*. After declining throughout the 1990s, the number of reported cases of syphilis in the United States began increasing in 2001, with current rates of 3.8 cases per 100,000 being almost double those of a decade ago. This increase has been largely driven by outbreaks in some cities among MSM, with drug and alcohol use playing a significant role in transmission. Among drug users, rates of incident syphilis are very high. Risk behaviors consistently associated with syphilis incidence among drug users include crack cocaine use, multiple sex partners, and the exchange of sex for money or drugs.

Like all other patients, drug users with STDs should be treated with single-dose regimens, if possible. Benzathine penicillin (2.4 million units) is the preferred single-dose regimen for early syphilis (primary, secondary, or early latent), and has been used effectively for more than 50 years to achieve clinical resolution and to prevent sexual transmission and late sequelae. Treatment of late latent or tertiary syphilis, which requires a series of three weekly injections of benzathine penicillin (total of 7.2 million units), usually does not affect transmission and is intended to prevent occurrence or progression of late complications. All treatment requires follow-up quantitative nontreponemal tests to assess treatment response. High rates of compliance with screening and treatment for syphilis among drug users have been achieved when these services are offered on-site in substance abuse treatment programs.

Gonorrhea and Chlamydia

Gonorrhea (*Neisseria gonorrhoeae*) and chlamydia (*Chlamydia trachomatis*) are the most common bacterial STDs in the United States, with an estimated 600,000 cases of gonorrhea and close to 3 million cases of chlamydia each year. As with syphilis, rates of gonorrhea and chlamydia are much higher among drug users than among the general population. In cross-sectional studies of drug-using populations, close to half reported having had gonorrhea, and rates of current gonorrhea or chlamydia infection exceeded 5%.

These bacterial infections are a major cause of urethritis and proctitis in men, and cervicitis and pelvic inflammatory disease (PID) in women. However, because they are often asymptomatic, particularly in women, gonococcal and chlamydial infections are often detected only by screening tests. Screening is essential to prevent complications, including ascending infection, infertility, ectopic pregnancy, and chronic pelvic pain. In recent years, screening of women has been facilitated by highly sensitive new tests that do not require a pelvic exam or urethral swab, but instead amplify nucleic acid obtained from urine using a ligase chain reaction for *C. trachomatis* and *N. gonorrhoeae* (nucleic acid amplification test [NAAT]). Regular screening for gonorrhea and chlamydia is now recommended for sexually active women by the United States Preventive Services Task Force. Annual screening of substance-using women and of substance-using MSM should be performed.

Several antibiotics are effective in the single-dose treatment of gonorrhea, with cephalosporins, including cefixime (Suprax) and ceftriaxone (Cefizox), being preferred. With increasing rates of quinolone resistance, ciprofloxacin (Cipro), ofloxacin (Floxin), and levofloxacin (Levaquin) are not recommended for the treatment of gonorrhea among MSM or in areas with high rates of resistance. Treatment of gonorrhea and chlamydia is generally offered simultaneously, because of the frequency of dual infection. Efficacious regimens for the treatment of chlamydia include azithromycin (Zithromax) or doxycycline (Vibramycin), but azithromycin

is preferred because it can be given in a single, directly observed dose. As with other STDs, patients should be instructed to notify and refer their sex partners for testing and treatment.

Genital Herpes

Genital herpes simplex virus type 2 (HSV-2) infection is the most common infectious cause of genital ulcer disease, with at least 50 million persons infected in the United States. Although most cases of genital herpes are caused by HSV-2, genital infections with herpes simplex virus type 1 (HSV-1) are increasingly recognized. Serologic evidence of HSV-2 infection increases with age and number of sexual partners, and is more common among drug users. In recent studies, the prevalence of antibodies to HSV-2 among drug users has ranged from 44% to 58%.

The classic presentation of HSV-2 is with multiple vesicular or ulcerative genital lesions, but many infections may be asymptomatic. Shedding of virus occurs even in the absence of lesions, and HSV-2 transmission usually occurs at times of subclinical or asymptomatic shedding.

Optimal management of genital herpes includes antiviral therapy (with acyclovir [Zovirax], famciclovir [Famvir], or valacyclovir [Valtrex]), along with appropriate counseling on the natural history of infection, risk for sexual and perinatal transmission, and methods to prevent further transmission. Systemic antiviral drugs partially control symptoms when used to treat recurrent episodes, and may be used as daily suppressive therapy in those with frequent recurrences (≥6 per year). However, these drugs neither eradicate latent virus nor affect the risk for, frequency of, or severity of recurrences after the drug is discontinued. Recognizing the symptoms and signs of clinical episodes of HSV infection and promptly seeking treatment are key factors in reducing transmission rates.

Human Papilloma Virus

HPV infections are the causative agents for genital wart disease and cervical carcinoma, and are transmitted primarily through sexual contact. The prevalence of HPV is as high as 50% among sexually active adolescent and young adult women, and risk factors for HPV include number of sexual partners, early age of first sexual intercourse, drinking and drug use related to sexual behavior, and partner's number of sexual partners.

Trichomoniasis

Trichomonas vaginalis is a protozoan that causes vaginitis in women, and is highly prevalent among drug-using women. Recent availability of self-administered vaginal swab tests has obviated the need for pelvic exams followed by wet mount microscopy or vaginal culture in screening for trichomonas, making routine testing more feasible for a larger number of women. Because it is frequently asymptomatic, screening for trichomoniasis should be routine among drug-using women. Recommended treatment is with metronidazole or tinidazole, both of which can be given as a single dose. Patients should be counseled to abstain from alcohol during treatment and for 24 hours following completion of metronidazole and 72 hours after tinidazole. As with other STDs, sexual partners should also be treated.

Skin and Soft-Tissue Infections

Skin and soft-tissue infections are more common both among injection and non-IDUs compared to general populations. Methicillin-resistant *Staphylococcus aureus* (MRSA) has become the most common causative agent of community-acquired soft-tissue infections. Isolates

are usually not susceptible to β-lactam antibiotics previously used most widely, including first-generation cephalosporins (i.e., cephalexin) and extended-spectrum penicillins (i.e., amoxicillin-clavulanate).

Infective Endocarditis

In the pre-HIV era, endocarditis was the infection most classically associated with injection drug use, and it remains common among injectors today. An estimated 2% to 5% of active IDUs per year will develop infective endocarditis (IE), and the risk is even higher among those who are HIV-infected. IE remains a highly morbid condition among IDUs, with estimates of mortality ranging from 7% to 37%, although rates may be lower (approximately 10%) among those with right-sided endocarditis.

IE among drug users can affect any heart valve. Although native valve endocarditis in the general population is most often left-sided, IE is more commonly right-sided (tricuspid valve) when associated with injection drug use. This is thought to be due to a variety of factors, including direct valvular endothelial damage from impurities of the drug injected into the venous system (rendering right-sided valves most susceptible to bacterial infection), predilections of certain skin flora for right-sided valve surfaces, and direct effects on the valvular endothelium of specific drugs (which may present in higher concentrations to right-sided than to left-sided valves).

Many organisms are reported to cause endocarditis among injecting drug users. Although both the skin and the injected drug are implicated as the source of the pathogen causing endocarditis, the skin is thought to be the prime source in most cases. Overall, *Staphylococcus aureus* is most frequently reported, accounting for more than 50% of IE cases among IDUs, among whom methicillin-resistant infections are common. Other prevalent IE pathogens include streptococci and enterococci, and a variety of gram-negative and fungal infections can be seen as well. Polymicrobial presentations are more common among IDUs than among others with endocarditis.

Tuberculosis

Drug users are at increased risk for tuberculosis infection and disease. The prevalence of latent tuberculosis infection (LTBI) among drug users varies by locale and population studied, but rates of approximately 15% to 25% are typical. Drug users are heterogeneous with respect to their risk for LTBI, and research suggests that smokers of crack cocaine are at particularly high risk for tuberculosis infection.

It is uncertain whether drug use is associated with an increased risk of developing tuberculosis disease among persons with LTBI, though the presence of HIV infection clearly does increase this risk. Chemoprophylaxis is effective in reducing the likelihood of later developing active disease. Regular screening for and, when detected, treatment of LTBI should thus be offered to all drug users. The prevalence of tuberculin reactivity among HIV-seropositive drug users is generally lower than among HIV-uninfected persons, reflecting the diminished delayed-type hypersensitivity response associated with more advanced immunosuppression. Two-step ("booster") tuberculin skin testing may increase the sensitivity of this testing method. Interferon-γ release assays (QuantiFERON-TB Gold In-Tube and T-SPOT) are blood tests for TB that are now approved for use in place of the tuberculin skin test and may have increased sensitivity among substance-using populations, and also eliminates the need for patients to make a return visit to a health-care provider for interpretation of skin-test results.

Pneumonia and Chronic Lung Disease

Community-acquired pneumonia is common among drug users, particularly those with HIV infection. Recent studies have determined that the incidence of pneumonia ranges from 4.4 to 14.2 per 1,000 person-years among HIV-negative drug users, and from 47.8 to 90.5 per 1,000 person-years among HIV-positive drug users. Pneumonia is also the most common reason for hospitalizations among drug users, accounting for 27% of hospital admissions in one study.

Many factors contribute to drug users' increased susceptibility to pneumonia, including depression of the gag reflex by alcohol and drugs, leading to aspiration of oropharyngeal and gastric secretions; impaired pulmonary function as a consequence of cigarette smoking; and weakened immunity as a consequence of malnutrition and continuous antigenic stimulation. In addition, HIV infection is associated with a markedly increased risk of bacterial pneumonia, and recurrent bacterial pneumonia has been included as an AIDS-defining illness since 1993. The risk for pneumonia among HIV-infected drug users is approximately five times that of non–HIV-infected drug users.

Encapsulated bacteria, most commonly *Streptococcus pneumoniae*, followed by *Haemophilus influenzae*, are the most frequent causes of pneumonia in both HIV-positive and HIV-negative drug users, and are highly associated with classic symptoms of sputum production, chest pain, and fever. Atypical bacteria, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species are also common among drug users, and are more likely to cause dry cough and headache than classic pneumonia symptoms. *Pneumocystis carinii*, *Mycobacterium tuberculosis*, and *M. avium* are common among HIV-infected drug users, as discussed further elsewhere in this volume. Pulmonary tuberculosis should always be included in the differential diagnosis of drug users with pneumonia, and annual tuberculin skin testing of drug users is recommended. In addition, pneumococcal vaccine and annual influenza vaccines should be offered to all drug users.

Chronic lower respiratory tract diseases, including COPD, are the fourth leading cause of death in the United States. Tobacco smoking is by far the most important environmental risk factor for COPD. Cannabis use, while associated with COPD-like symptoms including airflow obstruction, chronic cough, bronchitis, and decreased exercise tolerance, is not a clear cause of COPD in studies that control for tobacco use.

Pulmonary Complications of Crack Cocaine Use

Crack cocaine and, to a lesser extent, intranasal cocaine use are associated with pulmonary complications. Intranasal cocaine may cause nonspecific bronchial irritation that results in wheezing in persons with a history of obstructive lung disease. Crack cocaine, on the other hand, can precipitate a broad spectrum of pulmonary complications, including asthma exacerbations (fatal and near-fatal asthma); barotrauma (pneumomediastinum and pneumothorax); non-cardiogenic pulmonary edema; diffuse alveolar hemorrhage; recurrent pulmonary infiltrates with eosinophilia; nonspecific interstitial pneumonitis; bronchiolitis obliterans with organizing pneumonia; pulmonary vascular abnormalities; and "crack lung" (acute pulmonary infiltrates associated with chest pain, hemoptysis, and a spectrum of clinical and histologic findings). Among crack smokers, the prevalence of respiratory symptoms (cough, black sputum production, wheezing, dyspnea, or hemoptysis) is greater than 50%.

Drug Use and Neurologic Disease

Tobacco, alcohol, and stimulant use are all clear risk factors for cerebrovascular events, including ischemic strokes and hemorrhage, which together comprise the third leading cause of mortality in the United States. As with CVD, smoking promotes atherosclerotic cerebrovascular disease progression and hypertension. Alcohol, as with cardiac events, relates to ischemic stroke risk in a J-shaped fashion, with moderate use being protective and heavy use increasing risk. Any alcohol use, however, appears associated with a greater risk of hemorrhagic stroke. Cerebral vasoconstriction has been implicated as the mechanism of acute cocaine-associated neurologic complications, including ischemic and hemorrhagic stroke, in several case reports and case-control studies. In addition, long-term cocaine and amphetamine use appears to predispose patients with incidental neurovascular anomalies, such as aneurysms and arteriovenous malformations, to present with intracranial or subarachnoid hemorrhages at an earlier point than in nonusers.

Focal CNS infections occur commonly among drug users, although most focal infections result from embolization of infected vegetations among patients with endocarditis. The most frequent focal infections are brain abscesses, which may also result from local spread of an ear or sinus infection, hematogenous dissemination from a distant focus, such as infection in the lung, skin, bone, or pelvis, or trauma with an open fracture or foreign-body injury. Spinal epidural abscesses are also common, and are caused by direct local extension of vertebral osteomyelitis, hematogenous spread from distant infection, or blunt spinal trauma.

Other Medical Complications

While other medical sequelae of drug use cannot be properly reviewed here because of space limitations, the reader is directed to recent reviews of pulmonary and renal complications.

Suggested Readings

Neaigus A, Gyarmathy VA, Miller M, et al. Injecting and sexual risk correlates of HBV and HCV seroprevalence among new drug injectors. *Drug Alcohol Depend*. 2007;89:234–243.

Ober A, Shoptaw S, Wang P, et al. Factors associated with event-level stimulant use during sex in a sample of older, low-income men who have sex with men in Los Angeles. *Drug Alcohol Depend*. 2009;102:123–129.

Reed C, Stuver SO, Tumilty S, et al. Predictors of treatment for hepatitis C virus (HCV) infection in drug users. *Subst Abuse*. 2008;29(1):5–15.

Tetrault JM, Crothers K, Moore BA, et al. Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. *Arch Intern Med*. 2007;167(3):221–228.

Yeo KK, Wijetunga M, Ito H, et al. The association of methamphetamine use and cardiomyopathy in young patients. *Am J Med*. 2007;120(2):165–171.

38 Psychiatric Complications of HIV-1 Infection and Drug Abuse

The human immunodeficiency virus type 1 (HIV-1) has infected 60 million individuals worldwide, of which 42 million are still living with the infection. The spread of the virus continues at a rate of 14,000 newly infected individuals per day. Progress has been made since the introduction of zidovudine (AZT) as the first antiretroviral agent, and the advent of highly active antiretroviral therapy (HAART) in 1996 decreased both the mortality and the incidence of AIDS. Unprotected sexual intercourse, injection drug use, and contaminated blood and blood-product transfusions are well-known mechanisms of HIV-1 transmission. Other risk factors include crack cocaine use in women and use of marijuana or volatile nitrites ("poppers") in the male homosexual population.

Scope of the Problem

The highest rates of HIV infection are in patients with dual diagnosis of severe mental illness and substance use disorder (SUD). In one study of HIV-positive participants with comorbid substance use and psychiatric problems (n = 1,848), HIV prevalence was 4.7% in patients having a diagnosis of both substance abuse and mental illness, whereas HIV prevalence was only 2.4% in patients diagnosed with a substance abuse disorder alone. Psychiatric illness appeared to almost double the risk of HIV—especially in those with concurrent poor psychosocial support. These findings were confirmed by a cross-sectional survey of 3,806 adults living with HIV across four major metropolitan areas in the United States, which showed that 72% of the respondents reported at least occasional use of various drugs and 40% of the respondents reported frequent use of various drugs—only 28% declared abstinence from all drugs. In the group reporting frequent use of drugs, more were likely to be identified as heterosexual, had public health insurance, and endorsed increased symptoms of depression, which illustrates the complexities of the relationship between the triple diagnosis of mental health, substance abuse, and HIV infection.

Drug Abuse Disorders

Alcohol use alone has been linked to multiple risk factors associated with HIV, including STD histories, condom nonuse, multiple sex partners, and lower HIV-related knowledge. These risks appear to increase substantially with increasing amounts of alcohol use, and those

demonstrating abstinence from alcohol appear to have the lowest risk profile. The impact of alcohol upon these risk factors remains present even in the absence of other drug abuse.

Intravenous drug use (IVDU) has long been associated with an increased prevalence of comorbid psychiatric diagnosis—especially dysthymia and depression. Depressive syndromes in IVDU populations have also been linked to increased willingness to share needles, syringes, and other paraphernalia, which further increases the risk of HIV transmission. Even after controlling for multiple confounding variables including age, race, gender, number of days on which injection drugs were used, and the average number of injections per injection day, a diagnosis of depression is significantly associated with injection risk behavior. Other data confirm that depressed patients are more likely to engage in sex with IVDU populations, heightening an already substantial risk of transmission. Being physically abused as an adult and Latino race appears to be a significant predictor of depression among HIV-seropositive intravenous drug users of both genders. However, data show that women appear to experience increased depressive symptoms as compared to men, and correlates of depression in both men and women include perceived functional limitation, greater negative feelings regarding condom use, lower social support, and a lower sense of empowerment/external locus of control.

Methamphetamine-dependent men who have sex with men (MSM) also demonstrate high lifetime rates of psychiatric disorders, including major depression and anxiety disorders. Generalized anxiety disorder, specific phobia, bipolar disorder, and major depressive disorder have all been linked to higher rates of sexually transmitted infections, including gonorrhea and HIV. Naturalistic interview studies have demonstrated the wide prevalence of a cycle of severe depression and anxiety in the context of methamphetamine use as well as persistent anhedonia. Almost all respondents in such studies reported that crystal methamphetamine was severely damaging to social relationships, with a resultant increase in self-isolation, random sexual encounters, and increased numbers of sexual partners with a decreased likelihood of condom use.

Psychiatric Disorders in HIV Infection

Common mental disorders among individuals with HIV and substance abuse include adjustment disorders, sleep disorders, depressive disorders, mania, dementia, delirium, pain, psychosis, and sleep disorders. A careful psychiatric assessment is necessary in order to engage in differential diagnostic considerations and differential therapeutics.

Mania and Bipolar Disease

Bipolar disease in the context of HIV is especially problematic in that it involves cyclical moods that predispose its sufferers not only to the risk factors of depression but also to the heightened risks of contracting HIV due to features of mania that include impulsivity, hypersexuality, and increased goal-directed behavior. Patients with comorbid HCV/HIV are at increased risk for comorbid psychiatric disorders, including bipolar type. Severity of bipolar illness has also been associated with HIV risk profile, including high rates of unprotected intercourse (69%), multiple partners (39%), sex with prostitutes (24%, men only), and sex trading (10%).

Schizophrenia

Patients with serious and persistent mental illness (SPMI) have been noted to have approximately twice the incidence of HIV as compared to patients without SPMI, and there is also a greater incidence of infection with HCV. However, the source of this increased risk has been

debated and some data suggest that in the absence of comorbid substance abuse, these patients do not share an elevated risk for acquiring HIV compared to other non-SPMI populations.

Depression

Depression is the most common co-occurring mood disorder with HIV, with rates increasing in the context of advancing age. Depression has been closely linked to apathy in HIV-seropositive populations, and both apathy and depression are linked to combination antiretroviral therapy (CART) nonadherence, and a greater frequency of injection drug–risk behavior among depressed injection drug users (IDUs).

HIV-seropositive women are a special risk group with regard to depression and IVDU, and they present with both increased severity of depression as well as an elevated incidence of depression. Women also report the poorest quality of life scores in the context of HIV infection, in spite of showing some protection against cognitive decline with respect to male counterparts. Drug use, violence, and depression have been deemed a "tripartite HIV risk" among African American women and are underexplored areas of research—again highlighting the need for effective psychiatric services in this at-risk group.

Psychosocial Issues

Sexual Abuse

Childhood sexual experiences have been linked as a strong predictor to psychological distress as well as risk of substance abuse and HIV transmission. Among MSM, those with a history of childhood sexual abuse were more likely to engage in high-risk sexual behavior, including unprotected receptive anal intercourse, engage in trading sex for money or drugs, report being HIV seropositive, and experience non–sexual-relationship violence. Individuals who experienced forced sexual contact as a child have a higher risk for showing increased rates of substance abuse and HIV-transmission risk as compared to a no-exposure-to-sexual-abuse group. An assessment of these groups should include a discussion of patterns of risk exposure and childhood sexual experience to better tailor interventions to the specific individual.

Risk-Taking Behavior

Previous cross-sectional data have illustrated a close relationship between substance abuse, depression, and behavior, but it is difficult to infer causal relationships from this data. Longitudinal data can better support causal associations, and one such study examining the relationship between depression and sexual risk behaviors in a community sample of 332 innercity drug abusers found that increasing severity of depression predicted sexual encounters with multiple partners as well as sexual encounters with known IDUs.

Adherence to CART

Previous studies examining the relationship between depression and HIV transmission have shown mixed results, but the role of depression upon adherence to CART has been confirmed in multiple studies on the subject. A recent longitudinal study on adherence rates of HIV-seropositive patients with concurrent mental illness and substance abuse demonstrated several concerning patterns. Almost 73% of participants met criteria for major depressive disorder, and depression was linked to nonadherence.

The presence of depression has also been linked as an independent risk factor in not only nonadherence but also HIV disease progression, viral load, and CD8 activation. This pattern has been documented in a study of CART-treated HIV-infected drug users. Clinical predictors of disease progression included nonadherence to CART as well as a higher score of depressive symptoms following CART initiation that remained significant even after controlling for nonadherence behavior.

Central Nervous System

When HIV was initially discovered, it was thought to affect only CD4 lymphocytes; however, it was recovered from brain, spinal fluid, and peripheral nerves in 1985, which showed its potential for direct CNS infection. Since that time, HIV-1 has been shown to penetrate the blood–brain barrier (BBB) early in the course of the infection, replicate in brain tissue using monocytes and multinucleated macrophages as hosts, and become an anatomic reservoir for the disease. The mechanisms whereby HIV-1 penetrates the nervous system remain inadequately understood, but the virus appears to enter the brain through endothelial gaps in brain capillaries, via the choroid plexus, or as a proviral form contained in a latently infected cell (monocyte), which differentiates into a macrophage once inside the CNS to become a productively infected cell. The virus is known to invade and destroy subcortical areas such as the basal ganglia and temporolimbic structures, as well as support cells such as astrocytes, which share similar CD4 receptors with their well-known lymphocyte host. This effect may be exaggerated in substance-abusing populations.

Peripheral Nervous System Pathology and Myopathy in HIV-1 Infection

Patients with HIV-1 infection may also present with a wide variety of symptoms involving the peripheral nervous system (PNS). Distal symmetric peripheral neuropathy (DSPN) is the most common presentation among patients with generalized neuropathies. Initial symptoms include trophic changes in the lower extremities, paresthesias, sensory loss, edema, and weakness. Medication-induced neuropathies have a clinical presentation that is similar to DSPN except that they present concurrent with the use of antiretrovirals. Inflammatory demyelinating polyradiculoneuropathy may be acute (AIDP), presenting at the time of seroconversion and the initial manifestation of HIV-1 infection, or chronic (CIDP), presenting as subacute or chronic weakness in upper and lower extremities, diminished deep tendon reflexes, and mild sensory abnormalities. Cranial nerves may also be involved, and mononeuritis multiplex can present as an abrupt-onset mononeuropathy with periodic additional abrupt mononeuropathies in other distributions and may involve the cranial nerves as well. Pain may accompany any of the neuropathies and may be both severe and incapacitating. Less-common presentations of PNS dysfunction include progressive polyneuroradiculopathy with early impairment of bladder and rectal sphincter control, and autonomic neuropathy with postural hypotension, diarrhea, and sudden arrhythmias with the risk of death.

Diagnosis and Management of HIV-1 Secondary Neurologic Complications

HIV-1 CNS involvement may occur at any time, but opportunistic infections and HIV-1–related malignancies affecting the nervous system are usually a late manifestation of the

HIV-1 infection, occurring most often in patients with a CD4 count less than 50 cells/mm^3. *Toxoplasma gondii* infection is a common cause of focal intracerebral lesions in patients with AIDS. However, primary infection is usually asymptomatic. Focal encephalitis with headache, fever, confusion, and motor weakness is the most common clinical presentation. Individuals with toxoplasmosis encephalitis are almost uniformly seropositive for antitoxoplasma immunoglobulin G antibodies. CT scan or MRI often shows multiple contrast enhancing lesions with associated edema. The majority of clinicians rely on empiric diagnosis, since definitive diagnosis requires a brain biopsy. Detection of *T. gondii* by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF), although highly specific, has low sensitivity and is usually negative once therapy has started. At times, individuals who are severely immune deficient may not mount an antibody response. Primary prophylaxis with daily DS TMP-SMX is recommended in toxoplasma-seropositive individuals with a CD4 count less than 100 cells/mm^3. This can be discontinued when the CD4 count is >200 for 3 or more months. The initial choice of therapy for toxoplasmosis encephalitis includes pyrimethamine, sulfadiazine, and leucovorin.

Cryptococcus neoformans is a common cause of meningitis and the prevalent CNS fungal infection in patients with AIDS. The typical clinical presentation includes subacute meningitis with fever, malaise, and headache in a patient with a CD4 count of less than 50 cells/mm^3. Cryptococcal antigen is invariably detected in CSF. Treatment usually includes amphotericin B deoxycholate combined with flucytosine for at least 2 weeks followed by fluconazole.

Other secondary neurologic infections associated with HIV-1 include progressive multifocal leukoencephalopathy (PML) secondary to polyomavirus JC virus, cytomegalovirus (CMV) infection encephalitis and polyradiculopathy, herpes simplex virus (HSV) encephalitis, neurosyphilis, mycobacterial infection, and other fungal infections. The incidence of PML after widespread use of HAART has significantly declined. There remains no established therapy for PML, and the main approach to care includes optimizing HIV therapy.

Non–Hodgkin lymphoma is a complication of advanced HIV-1 disease that may involve the CNS. A diagnosis can be made via neuroimaging, but a tissue diagnosis is typically required before initiation of treatment. Multiagent chemotherapeutic treatment is effective but may be short-lived. Incomplete responses and rapid progression have been noted historically in up to half of the patients.

Neurobehavioral Evaluation in HIV-1 Infection

Mental Status and Neuropsychological Assessment

The HIV-1–associated cognitive/motor complex consists of a combination of cognitive, motor, behavioral, and affective disturbances that may be severe and sufficient for the diagnosis of AIDS. It may be the presenting manifestation of HIV-1 infection or it may cause mild symptoms and may not be associated with significant impairment in the social or occupational functioning levels of these patients. Data support that asymptomatic HIV-1–positive patients have an elevated rate of cognitive dysfunction as compared to HIV-1–negative controls, but these are usually subtle impairments that are unrelated to the level of immunosuppression or to depression and are most evident in individuals with lower cognitive reserve. It is generally accepted by clinicians that HIV-1–related cognitive impairment can occur at any time during the course of the disease, but cognitive abnormalities in asymptomatic patients are associated with an increased risk of morbidity and mortality.

Although varying psychological tests have been used to determine or evaluate the earlier signs of HIV-1 effects on mental function, no definitive test can be used, either alone or in combination with others, to establish a diagnosis of HIV-1–associated cognitive/motor complex. A careful cognitive history can be an extremely useful adjunct in the differential

diagnosis of the etiologies of cognitive dysfunction in HIV-1–infected patients with cognitive complaints.

The most significant signs of cognitive impairment related to HIV-1 infection include early, mild problems with abstraction, learning, language, verbal memory, and psychomotor speed that progress to more serious difficulties with attention and concentration, slowing of information processing, slowed psychomotor speed, impaired cognitive flexibility, impairment in nonverbal abilities of problem solving, visuospatial integration and construction, and nonverbal memory in the late phases of the infection.

CSF Studies

CSF reflects changes consistent with HIV-1 infection, including the presence of HIV-1 virions, abnormally elevated IgG levels, HIV-1–specific antibodies, mononuclear cells, and oligoclonal bands. HIV-1 replicates in the brain with independent dynamics from other organs, making the CSF viral load more representative for the assessment of CNS infection. It correlates with the degree of neurocognitive dysfunction and has a role in monitoring the response to antiretroviral medications in the CNS. Although other CSF studies have been used in the assessment of CNS compromise in HIV-1 infection, their use is now limited because serum viral load measurements have replaced them in clinical practice. CSF β_2-microglobulin has shown a high correlation between its concentration and both the severity of the dementia and the level of systemic disease. Although elevation in the myelin basic protein and its degradation was found in patients with HIV-1–associated cognitive/motor complex and with PML, this was not seen in patients with other opportunistic infections. An abnormally low CSF CD4:CD8 ratio may have importance for treatment considerations and prognostic value for HIV dementia.

Neuroimaging

MRI and, to a lesser extent, CT are useful tools in the diagnosis of secondary infections and brain tumors. Primary CNS HIV-1 infection can be associated with characteristic imaging features, including cortical atrophy, ventricular enlargement, diffuse or patchy periventricular white-matter abnormalities, and, in children, calcification of the basal ganglia and delayed myelination. MRI is more sensitive than CT and is now considered the neuroimaging criterion standard. Both, however, are useful as diagnostic tools and have utility in assessing the prognosis of these patients.

Magnetic resonance spectroscopy (MRS) measures levels of metabolites in brain tissue. MRS in HIV disease, particularly HIV dementia, shows increases in choline and reductions in *N*-acetylaspartate, suggestive of neuroinflammation and neuronal injury. In some studies, these findings correlate with the severity of the HIV dementia along with CD4 counts and viral load.

Electrophysiology

There is currently relatively little role for electrophysiology in the diagnosis and management of uncomplicated HIV patients outside of that subset in whom one is assessing for the presence of epilepsy or other CNS lesions. However, research data using electrophysiologic techniques have provided some interesting findings. The percentage of patients with abnormal electroencephalograms appears to increase as the systemic disease progresses, and a low amplitude pattern may be found in advanced dementia and atrophy on neuroimaging. In asymptomatic patients, studies have found conflicting results, but the best available data support a very limited role, if any, of CNS dysfunction in nonimmunocompromised HIV patients. Evoked potential studies have also been useful in detecting preclinical abnormalities in neurologically and physically asymptomatic HIV-1–seropositive patients by showing significant delays in latency of response to the brainstem auditory-evoked potential, somatosensory-evoked potentials from

tibial nerve stimulation, and visual-evoked potentials. However, these are rarely used clinically at this point in time.

Treatment of Neuropsychiatric Disorders

Mental disorders secondary to medical conditions such as delirium, dementia, mood disorders, psychosis, and anxiety disorders are the most common neuropsychiatric conditions associated with HIV-1 infection. One of the most perplexing aspects of these presentations is that HIV-1–related neuropsychiatric manifestations very closely resemble other primary psychiatric (functional) disorders. Like syphilis, HIV-1 infection often confounds precise diagnostic criteria because of its characteristic as a "great imitator."

Delirium

It is estimated that as many as 30% of hospitalized medical/surgical patients may have an undetected delirium process. Delirium is a predictor of outcome in hospitalized AIDS patients, and delirious patients have higher mortality rates, longer lengths of inpatient hospitalizations, and a greater need for long-term care as compared to a group of nondelirious AIDS patients with similar demographics and markers of medical morbidity. Standardized and validated instruments exist for delirium screening and should be used routinely.

Prompt pharmacologic interventions may help remediate the various behavioral abnormalities associated with the delirium process. High-potency neuroleptics remain the standard of care for delirious patients, although their use in HIV-infected patients brings an increased risk of significant treatment-emergent side effects. At low doses, haloperidol and chlorpromazine (a low-potency neuroleptic) in both oral and intravenous formulations have been used effectively and with few adverse events in the treatment of delirium in hospitalized AIDS patients. Atypical antipsychotics are used now as first-line agents, and are both effective and better tolerated as compared to traditional neuroleptics. The experience, however, is still limited, especially in HIV-1–infected individuals, and they must be used with caution.

Lorazepam is useful in the management of severely agitated delirious HIV-1–infected patients when used in combination with a neuroleptic. Lorazepam alone, however, appears to be ineffective and is associated with worsening delirium. The notable exception to this is when treating delirium associated with GABAergic withdrawal, such as delirium tremens, benzodiazepine withdrawal, or barbiturate withdrawal. Benzodiazepines are the treatment of choice in these scenarios.

Dementia

It is beyond the scope of this chapter to review the different classes of antiretroviral drugs and their use in clinical practice in the context of HIV-cognitive impairment and dementia. The use of antiretroviral agents is generally recommended when CD4 count is below 350 cells/mm^3 or plasma HIV RNA is above 100,000 copies/mL. There are no established guidelines for HIV-associated cognitive and dementing illness. Like that of systemic therapy, the use of antiretroviral therapy (ART) in HIV-cognitive impairment and dementia is to produce complete virologic suppression in both plasma and the CNS.

Mood Disorders

While mood disorders associated with HIV-1 infection are most frequently depressive, manic and hypomanic disturbances have also been described. The diagnostic process for evaluating mood disorders is complex, requiring careful consideration of the interaction of medical

conditions, substances, and behavioral factors. Depressive spectrum disorders are commonly observed in patients with HIV-1–related disorders ranging from normal sadness to major affective disorders, as well as mood disorders that may be substance induced or a consequence of a general medical condition. Although it has been suggested that clinicians rely on psychological rather than somatic symptoms of depression to fulfill diagnostic criteria for depression in the medically ill, an all-inclusive approach is often the simplest and most clinically effective. Depression in medically ill patients is underdiagnosed and undertreated, and this is particularly true of HIV-1–infected persons who suffer an increased incidence of depression when compared with other medically ill patients or the general population.

Suicidal thoughts are frequently a symptom of depression, and patients need to be assessed carefully. Risk factors include social isolation, perceived lack of social support, adjustment disorder, personality disorder, alcohol abuse, HIV-1–related interpersonal or occupational problems, and a past history of depression. Other risk factors include current major depression, previous suicide attempt, and history of alcohol abuse. One should never blithely consider the notion of "rational suicide" as an understandable reaction to this devastating and socially stigmatized disease. Because of impaired decision-making capacities and cognitive inefficiencies associated with HIV-1 disease, it is vital that clinicians respond promptly to any and all reports of suicidal ideation. A thorough assessment of the patient includes a realistic appraisal of the psychosocial situation and of the motivation for completing the suicide, along with any appropriate neurodiagnostic assessment to rule out a potentially reversible organic mental disorder.

Antidepressants with greater affinity for the central muscarinic receptor should be avoided for symptomatic HIV-1–infected patients, which can mask or aggravate HIV-1–related cognitive impairment or precipitate delirium. Another adverse side effect of these agents is the possibility of excessive drying of the mucous membranes, which introduces the possibility of oral candidiasis that is often refractory to treatment in HIV-1–infected patients. Antidepressants that are preferable for HIV-1–infected individuals include selective serotonin reuptake inhibitors (SSRIs) and other second-generation antidepressants such as bupropion, venlafaxine, mirtazapine, and psychostimulants.

Fluoxetine has been shown to be safe in HIV populations, but inhibition of the CYP450 2D6 and 3A4 isozymes is problematic in patients with HIV. Similarly, paroxetine is not recommended in this population for the same reasons. Sertraline and citalopram have also been shown to be effective and well tolerated. Venlafaxine is also a reasonable choice because of its low interactions with other drugs.

Patients being treated with lithium carbonate or monoamine oxidase inhibitors before their diagnosis with HIV-1 disease should usually continue to take that medication. Increased vigilance in toxicity monitoring with a concomitant dosage alteration may be necessary as HIV-1 disease progresses, especially when infectious complications cause severe diarrhea or any other form of fluid loss due to the emergence of nephrotoxicity and neurotoxicity from lithium toxicity. Psychostimulants such as methylphenidate and dextroamphetamine may be tried in depressed patients who are symptomatic of HIV-1 infection, in those depressed patients in whom rapid improvement in symptoms is needed or who are cognitively impaired or who suffer from both depression and dementia. Methylphenidate is a safe and effective treatment for these syndromes. Response usually occurs within hours of the first administration and includes psychomotor activation, appetite stimulation, and qualitative as well as quantitative improvement in higher cortical functions. The initial administration of methylphenidate is usually 5 to 10 mg orally, and an adequate therapeutic response usually requires less than 30 mg daily. Methylphenidate can be continued safely for several months after the patient's symptoms remit. Special care should be taken in using dextroamphetamine, which has been noted to unmask or aggravate abnormal involuntary movements in AIDS dementia patients. The use of psychostimulants in managing depressive or cognitive symptomatology in drug-abusing patients is questionable, so they should be used cautiously if at all.

Sleep Disorders

Insomnia is one of the most prevalent neuropsychiatric disorders in HIV-seropositive populations. Estimates as high as 70% have been noted in some studies, if one looks at the incidence of insomnia across the HIV disease process. Insomnia has been linked to reduced quality of life as well as treatment nonadherence. However, there has been very limited research on the treatment of insomnia in this setting. Essentially, there appear to be four primary factors that impact the assessment and treatment of insomnia in individuals with HIV: (a) medications used to treat HIV, (b) antibiotics used to treat opportunistic infections, (c) the HIV infection itself, and (d) conditions frequently associated with HIV infection.

Insomnia is defined as persistent difficulty falling asleep, staying asleep, or nonrestorative sleep which is associated with impaired daytime function. Insomnia is common in the general population, but the prevalence of insomnia in HIV-positive individuals appears to be higher. It is easy to assume that HIV-associated insomnia is due to the stress of a highly stigmatized and potentially life-threatening physical illness, but this view is contradicted somewhat by a study of asymptomatic HIV-positive men, which showed that even prior to experiencing HIV/AIDS symptoms, there were more shifts to stage 1, increased awakenings, and lower sleep efficiency. The sleep changes that occur in HIV infection have been quantified in several studies employing polysomnography; however, the data are conflicting. There are reports of an increase in slow-wave sleep that occurs primarily during later sleep cycles, but this finding has failed to be replicated in other studies. Similarly, increased sleep latency, a reduction in the percentage of stage 2 sleep, and an increase in the number of nocturnal awakenings have been reported but have not been confirmed by subsequent studies. The pathophysiology of insomnia in HIV is equally unclear. It is agreed that insomnia becomes highly prevalent in the later stages of HIV infection, and this may be due to disruption of sleep centers via HIV-mediated neurotoxic effects, medication effects, opportunistic infections, HIV-associated dementia (HAD), and chronic depression.

A large number of different prescription medications are used to treat insomnia. These medications can be broadly categorized as benzodiazepines, nonbenzodiazepine hypnotics, antidepressants, and antipsychotics. The benzodiazepines are a relatively old group of compounds that exert a therapeutic effect on sleep via allosteric modulation of the γ-aminobutyric acid (GABA) receptor complex. Commonly used benzodiazepines include triazolam, temazepam, flurazepam, quazepam, lorazepam, oxazepam, and alprazolam. Major alterations in half-life and effect have been noted with the agents that require oxidation in the presence of protease inhibitors, so if a benzodiazepine is to be used, then we recommend that it be temazepam, lorazepam, or oxazepam in this patient population. Other alternatives include the typical benzodiazepine-like agents such as zolpidem, zaleplon, and eszopiclone.

Psychosis

Nearly 10% of patients with HIV infection have a diagnosed psychosis of one type or another. There are several potential causes for psychosis, and the initial evaluation for psychosis includes the same medical workup as that for delirium and dementia. Some are preexisting conditions unrelated to the HIV infection, whereas others are thought to result from delirium and CNS involvement of the HIV infection. Others may result from drug use inclusive of rare iatrogenic causes such as that which occurs with efavirenz. Many patients wiwth HIV-associated psychosis also manifest symptoms of cognitive decline, such as HIV-associated minor cognitive motor disorder (HMCMD) or HAD. In fact, psychotic symptoms may precede the onset of dementing illness. There is also a high association between psychosis and HIV-related mood disorders.

Treatment of psychosis in the context of HIV disease, whether or not there is concurrent CNS involvement, requires timely intervention. This is best accomplished with neuroleptics.

However, patients with HIV infection are more sensitive to side effects such as extrapyramidal reactions and neuroleptic malignant syndrome. This is particularly true with high-potency typical neuroleptics, whereas confusion and seizures are more frequent with low-potency neuroleptics. The atypical antipsychotics (risperidone, paliperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone) have also been shown to control HIV-related psychosis without having the same treatment emergent side effects. Quetiapine has been shown to have the least antiparkinsonian effects, and should be considered for patients with symptomatic HIV-related CNS disease, given the associated subcortical damage related to HIV infection. Risperidone is an effective alternative and has been reported to be well tolerated in low doses. Low doses should be used in any regimen involving protease inhibitors because of potentially heightened risk of extrapyramidal reactions and alterations in consciousness that have been reported with such combinations.

Anxiety

Anxiety disorders affect some 17% to 36% of patients with HIV infection with adjustment disorder with anxious mood, generalized anxiety disorder, and panic disorder. Persistent and chronic anxiety following notification of seropositive status affects about 20% of patients and, in time, may evolve into a fully developed posttraumatic stress disorder (PTSD). This may be problematic as avoidant behaviors secondary to untreated HIV-related anxiety may diminish treatment compliance and interfere with medical management of HIV disease.

In the differential diagnoses of anxiety, one should always be concerned about the common association with depression, and a careful assessment to rule out depressive illness is critical. Anxiety may also arise from multiple medical conditions, especially in patients with pain, respiratory compromise due to pneumonia, and delirium as well as substance-induced anxiety. As with other HIV-related psychiatric disorders, a comprehensive medical evaluation is essential, including an extensive review of medications. Antiretroviral medications, like efavirenz, have been associated with anxiety, irritability, restlessness, agitation, and insomnia.

Treatment with psychotherapy, self-hypnosis, and biofeedback is very effective in anxiety disorders. Moreover, all psychotherapies are useful for the development of adaptive behaviors that allow the individual to reduce anxiety while improving coping capacity. Combining pharmacotherapy with a benzodiazepine during psychotherapy may be necessary for acute reduction of symptoms. This is best accomplished with the use of intermediate-acting benzodiazepines without active metabolites such as oxazepam or lorazepam. Similarly, with chronic refractory anxiety, lorazepam is a better choice because of its ease of use and low neurotoxicity.

Pain in HIV Patients

HIV patients experience pain commonly, and prevalence of pain within 2 weeks has been estimated to be greater than 60% based on one outpatient survey. Patients answering this survey were noted to have multiple sources of pain and on average experienced 2.5 different pains in the preceding 2 weeks. Average pain scores were rated as 5.4 out of 10, and worst mean pain rated as 7.4 out of 10, indicative of moderately severe pain. The pain levels were noted to interfere with functional status across a variety of measures. Other factors influencing pain included the number of current HIV-related symptoms, treatment for HIV-related infections, and the absence of antiretroviral medications. Female gender, non-Caucasian race, and number of HIV-related physical symptoms were significantly associated with pain intensity, indicating perhaps a different pain experience in these vulnerable groups.

The most common source of HIV-linked pain is HIV-associated painful neuropathy, which appears to affect up to 30% of patients with HIV over the course of their disease. The causes of this painful neuropathy appear myriad and manyfold, but typically involves both

direct neurotoxic effects of HIV as well as potential effects from antiretroviral medications—especially the nucleoside reverse transcriptase inhibitors (NRTIs) (e.g., stavudine). In addition to these causes, patients may have additive neuropathy from such reasons as diabetes mellitus, nutritional deficiencies, or the late results of syphilis. Hyperalgesia and paresthesias are common manifestations of HIV-associated neuropathy, and diminished ankle-jerk reflexes are also frequently noted. Electromyographic data show abnormal sensory and motor conduction, supportive of a dying-back axonopathy. Neuropathy is virtually always progressive.

Tricyclic antidepressants have the most data with regard to non-HIV neuropathic pain management, but they must be used cautiously in HIV-seropositive patients due to anticholinergic effects and decreased tolerance. There is also data to suggest that tricyclics may be ineffective for HIV-related painful neuropathy. Alternative agents for treating HIV-related neuropathic pain include anticonvulsants (gabapentin or pregabalin), newer generation antidepressants (venlafaxine or duloxetine), or lidocaine topical applications (patches). Unfortunately, none of these agents has been subjected to rigorous testing in a double-blind, placebo-controlled trial in HIV-seropositive patients or in those whose pain is due to HIV-associated painful neuropathy.

Substance Use/Abuse and Treatment

IDUs are less likely to receive ART than are any other population. Factors associated with poor access to treatment include active drug use, younger age, and female gender, suboptimal health care, not being in a drug treatment program, recent incarceration, and lack of health-care provider expertise. Yet these individuals should be considered and can be treated effectively. Nursing-outreach interventions over 3 months, including home visits, have demonstrated improvements in making and keeping appointments; integration of care among HIV, substance abuse, and mental health providers; and access, adherence, and retention of patients in CART.

Other potential data-driven intervention models include brief peer-delivered educational interventions, which have demonstrated effectiveness in reducing crack cocaine use, injection drug use, and the number of sex partners who use injection drugs. Methadone maintenance treatment (MMT) programs remain an essential part of the treatment of dually diagnosed patients. Increased numbers of patients in MMT show IVDU abstinence. MMT has been demonstrated to dramatically reduce both illicit opiate use as well as criminal activity. More recent data support that MMT also reduces incarceration rates, which would likely diminish the risk factor of sharing needles while incarcerated and lower exposure to high-risk practices. In addition, opiate treatment–resistant dually diagnosed patients show better long-term survivability in MMT programs than their non–dually diagnosed counterparts.

Non-MMT programs centering around group activity and support also demonstrate significant roles for the treatment of this complex population, and involvement in either MMT or non-MMT programs is associated with improved ART adherence. Buprenorphine programs are likewise associated with improved CART adherence, although they are widely underused in HIV-seropositive populations in the United States. France appears to be most experienced with buprenorphine programs in HIV-positive populations, and data support their effectiveness in this population even though both methadone and buprenorphine have significant drug–drug interactions with HAART medications.

Conclusion

HIV-1 infection is a major health and social issue of our time, with drug abuse, unprotected sexual intercourse, and transfusion of contaminated products being well-determined risk factors.

As the prevalence of HIV-1 infection continues to increase, advances in treatments permit the prognosis to improve. Neuropsychiatric complications are now accurately diagnosed more often, and our understanding of their etiologies and effective treatment regimens continues to improve. Signs of neuropsychiatric disorders are now detected earlier, allowing prompt and aggressive management of these potentially devastating complications of the HIV-1 infection. The overall prognosis for these patients at the moment of seroconversion continues to improve, along with the quality of their lives. The contribution of neuropsychiatry is of great importance as we pay attention to the neurobehavioral aspects of HIV-1 disease in these individuals.

Suggested Readings

Arreola S, Neilands T, Pollack L, et al. Childhood sexual experiences and adult health sequelae among gay and bisexual men: defining childhood sexual abuse. *J Sex Res*. 2008;45:246–252.

Brew BJ, Letendre S. Biomarkers of HIV related central nervous system disease. *Int Rev Psychiatry*. 2008;20:73–88.

Himelhoch S, McCarthy J, Ganoczy D, et al. Understanding associations between serious mental illness and HIV among patients in the VA Health System. *Psychiatr Serv*. 2007;58:1165–1172.

Meade CS, Graff F, Griffin M, et al. HIV risk behavior among patients with co-occuring bipolar and substance use disorders: associations with mania and drug abuse. *Drug Alcohol Depend*. 2008;92:296–300.

Mimiaga MJ, Fair A, Mayer K, et al. Experiences and sexual behaviors of HIV infected MSM who acquired HIV in the context of crystal methamphetamine use. *AIDS Educ Prev*. 2008;20:30–41.

39 Acute and Chronic Pain

When acute, tolerable, and appropriate to injury, pain is biologically essential, signaling the need to identify the source of injury, seek help, and rest while healing occurs. When the severity of acute pain is high enough to initiate maladaptive stress responses, however, or its signaling imperatives have passed, treatment to relieve the pain or mitigate its effects is necessary to promote healing, well-being, and functional restoration.

When pain persists, it is never biologically adaptive. Indeed, chronic pain should be recognized as a heterogeneous and complex entity that should be considered a potentially serious illness in its own right. Chronic pain is associated with mood disturbance, sleep disorder, loss of function and impaired quality of life, and caregiver burden. It also is a public health problem of immense magnitude. In the United States, a recent evaluation by an expert committee noted that the estimated prevalence of chronic pain—at least 30% of adults and 20% of children in the United States—creates a societal burden that is greater than that of diabetes, heart disease, and cancer combined, including direct costs of at least $100 billion per year attributed to pain-related health-care utilization and lost productivity.

The assessment and management of acute and chronic pain are within the purview of all clinicians. The ability to apply basic principles of pain management, and to refer appropriately, should represent skills that are broadly acquired and kept up to date. Pain medicine also is a subspecialty, and although the numbers of specialists are relatively small—just a few thousand in the United States—patients with complex chronic pain problems should ideally have access to professionals with specialist competencies, if needed.

Principles of Pain Assessment

Assessment is the essential prerequisite to the safe and effective treatment of acute or chronic pain. Although it is often straightforward in the setting of an acute traumatic event, a comprehensive assessment should be entertained even in this setting to ensure that the plan of care is safe, likely to provide benefit, and capable of addressing the impact of the pain and comorbid conditions. When pain becomes chronic and the plan of care anticipates a longer, and perhaps indefinite, time frame, the need for a more detailed pain assessment is clear and all the elements of this assessment become more challenging.

The information obtained through pain assessment derives from an appropriate history, physical examination, review of records, and often confirmatory laboratory and radiographic procedures. The most important part of the history is to provide sufficient information to characterize the pain complaint and determine the impact of the pain on multiple functional domains.

The rest of the history also is important, particularly exploration of medical and psychiatric pathology. The chronic pain patient with a serious medical disorder may have pain attributable to the disease, related to its treatment, or unrelated to either. The patient should be asked about the severity and extent of disease, past and current treatments, and the goals of care going forward. Comorbid medical problems also must be recorded.

All chronic pain patients should be queried about other symptoms, including chronic fatigue, insomnia, and appetite changes. Psychological symptoms, such as anxiety or depressed mood, also should be ascertained.

Framework for Interpreting the Nature of the Pain

A useful framework that may assist in the interpretation of information obtained about the nature of the pain focuses on a set of key considerations. These include the distinction between acute and chronic pain and the utility of syndromic, etiologic, and pathophysiologic diagnosis.

Acute Pain versus Chronic Pain

Acute pain may be defined as pain that has been, or is anticipated to be, experienced for a relatively short period, typically no more than days to weeks. The most common types of acute pains are linked to recognizable tissue injury following trauma, including surgical trauma. Less common types are related to medical conditions or to primary pain diagnoses, such as headache. Acute pains can be monophasic (e.g., following surgery) or recurrent. They may be recognized as a syndrome even in the absence of tissue injury (e.g., migraine), or be expected as part of an underlying pathology producing cumulative damage (e.g., sickle cell disease).

Chronic pain (also called persistent pain) may be defined by a temporal criterion alone, which is conventionally either 3 months or 6 months. Alternatively, chronic pain may be defined using other clinical criteria, specifically *pain that persists beyond the healing of the inciting lesion, occurs in the context of a lesion that is not likely to heal, or is transitory but frequently recurrent*.

Etiology and Pathophysiology

One of the goals of the pain assessment is to identify the etiology of the pain—the lesion or the disorder that is responsible for activating or sustaining nociception. In many situations, such as acute postoperative pain, the etiology is obvious. In some chronic pain disorders, such as pain related to osteoarthritis or osteoporosis, the etiology also seems clear in relation to a specific site of chronic tissue injury. Etiology is uncertain in many other disorders, such as chronic headache, fibromyalgia, chronic back pain, and many types of neuropathic pain.

The potential value in an etiologic diagnosis lies in the ability to offer disease-modifying therapy to some patients. If an etiology can be identified and is treatable, and treatment has both a favorable therapeutic index and consistency with the goals of care, primary disease-modifying therapy should be entertained as a part of a pain management strategy. For example, joint replacement therapy, if feasible and appropriate, is a highly effective intervention for chronic pain related to advanced osteoarthritis. An etiologic diagnosis also may allow primary therapy for other aims (e.g., prevention of a complication, such as pathologic fracture) and may help clarify prognosis in some cases.

The term *pathophysiology* refers to the mechanisms that sustain the pain. These mechanisms cannot be determined in humans with clinical pain, and the information provided by the

pain assessment can only be used to infer the existence of a category of mechanisms. Although this is undoubtedly a gross simplification of extremely complex processes underlying pain perception, labeling by inferred pathophysiology has become clinically accepted for pain syndromes other than headache because it suggests assessment and treatment strategies that have proved clinically useful.

Pain Syndromes

Syndrome identification is extremely useful in pain assessment because it may provide information about underlying organic processes, suggest an efficient evaluation, guide the selection of treatments, and indicate prognosis.

Although the term *chronic pain syndrome* does not appear in the taxonomy of pain, the literature may apply it to patients with chronic pain associated with a high level of disability and psychiatric comorbidity. These associated manifestations have long suggested the potential value of a multidisciplinary approach to management that emphasizes both comfort and functional restoration. Indeed, the clinical challenge posed by the management of the patient with pain and disability was a prime driver of the development of pain medicine as a subspecialty. Although most patients with acute pain and, presumably, most with chronic pain do not have the type of overriding disability that is implied by the label, it is important to acknowledge the needs of this subgroup. Whereas most patients with pain can be managed adequately by a single clinician who expertly administers one or more treatments, patients with a complex chronic-pain illness may benefit most from the involvement of specialists in various disciplines, who together implement a multimodality approach intended to address pain and its consequences, and comorbid conditions. A specialist in addiction medicine may be an appropriate member of a multidisciplinary pain management team.

Pain and Substance Abuse

The clinical interface between pain and substance abuse can be best illuminated by a focus on the use of potentially abusable drugs used in the management of acute and chronic pain. The most important of these drugs are the opioids. Opioid therapy is the mainstay approach for the treatment of severe acute pain and chronic pain related to active cancer or another advanced medical illness. Although yet controversial, opioid therapy for the treatment of chronic non-cancer pain is well established in some countries and rapidly growing in the United States and others. The safe and effective use of opioid drugs requires competencies in pain assessment and management in all patient populations, and these skills must be most highly refined when these drugs are used to manage pain in populations with substance abuse histories.

Terminology and Characteristics of Relevant Phenomena

Many of the terms used to describe opioid-related phenomena, such as tolerance, are difficult to translate to the clinical setting. An understanding of terminology is a foundation to the development of clinical strategies that promote safe and appropriate prescribing. The effort to bring together the perspectives of specialists in pain management and addiction medicine to refine the meanings of key terms has been a notable advance.

Tolerance

Tolerance is a pharmacologic property of opioid drugs defined by the need for increasing doses to maintain effects. Tolerance can be induced reliably in animal models with little exposure to a drug and occurs to different opioid effects at varied rates and extents. Although there are subtypes based on the impact of learning and pharmacokinetic changes, it is the occurrence of the so-called analgesic pharmacodynamic tolerance—loss of analgesic effects associated with biologic processes induced in cells by the binding of the drug to its receptors—that characterizes opioid tolerance and raises clinical concerns.

If pharmacodynamic tolerance to analgesic effects were to occur regularly, it would be a major impediment to the clinical effectiveness. Alternatively, if the development of tolerance to the positive psychic effects of opioids, and the consequent need to increase doses to regain these effects, routinely drove aberrant use, this too would compromise the long-term utility of these drugs. The latter process has been perceived as a key step in the pathogenesis of addiction.

Physical Dependence

Like tolerance, *physical dependence* is a pharmacologic property of opioid drugs. It is defined solely by the occurrence of an abstinence syndrome (withdrawal) following abrupt dose reduction or administration of an antagonist. Because some degree of physical dependence can be produced with very little opioid exposure, and neither the dose nor duration of administration required to produce clinically significant physical dependence in humans is known, most practitioners assume that the potential for an abstinence syndrome exists after an opioid has been administered repeatedly for only a few days.

Physical dependence has been perceived as an impediment to the discontinuation of an ineffective or problematic therapy, suggesting to some clinicians that the decision to try an opioid for more than a short time means that therapy will be difficult or impossible to stop. The belief that a trial of long-term opioid therapy is something of a "life sentence" presumably leads some clinicians to consider an opioid trial as a last resort. Physical dependence also has been considered another key element in the pathogenesis of addiction. In this view, the need to reduce the adverse effects of withdrawal drives drug-seeking behavior. Like tolerance, physical dependence traditionally has been included in the definition of addiction.

Addiction

The development of a definition for addiction jointly endorsed by professional societies for pain and addiction in the United States represents an important piece of the effort to improve communication across disciplines. According to the statement endorsed by the American Pain Society (APS), American Academy of Pain Medicine (AAPM), and American Society of Addiction Medicine,

> [a]ddiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

This definition reinforces the conclusion that a diagnosis of addiction requires an assessment of drug-related behaviors to establish the existence of a seriously maladaptive pattern of drug use. Craving may involve rumination about the drug and an intense desire to secure its supply. Compulsive use may be indicated by escalating consumption of the drug without medical justification or sanction by a clinician. Continued use, despite harm, could involve outcomes that are problematic for physical or psychosocial well-being, work or other role

functioning, or relationships with health professionals. Although an addictive pattern of opioid use may involve phenomena recognized as likely tolerance or physical dependence, neither of these biologic processes is necessary for a diagnosis.

Abuse, Misuse, and Other Terms

Other terms commonly used in the setting of opioid treatment also have challenged precise definition. *Drug abuse* may be considered any type of drug use that is outside accepted societal and cultural norms. This definition is practical, but nonetheless implies that there is broad consensus about the nature of normative behavior. This is not always true, particularly during periods of changing perceptions (e.g., with respect to marijuana use) or when clinicians and patients do not share cultural backgrounds. Nonetheless, it is generally accepted that drug abuse includes any use of an illicit drug and any use of a legal drug in a manner that is contrary to clinician instructions, or to regulations or laws. Importantly, patients with the disease of addiction may or may not be actively abusing drugs, and most drug abuse is undertaken by individuals who do not otherwise meet criteria for a diagnosis of addiction.

Drug diversion should be considered apart from abuse or addiction. Diversion or the transfer of a licit drug into an illegal marketplace is considered a criminal act, and the individuals responsible may or may not be personally using the drug in question. Indeed, physicians in the United States who have been prosecuted for drug trafficking typically have not been accused of abusing the drugs they prescribed.

In the clinical setting, drug-related behaviors that are egregious enough to be labeled drug abuse may be positioned on a continuum of problematic *nonadherence behaviors*. Nonadherence behaviors, which also have been called *aberrant drug-related behaviors* and sometimes *red-flag behaviors*, are varied and may be difficult to interpret. Although it is widely agreed that a very serious nonadherence behavior, such as forging prescriptions, represents both drug abuse and a probable sign of addiction, a less severe behavior, such as repeated requests for early prescription refills, is more challenging to characterize. Many clinicians use the term *misuse* as a way to distinguish these less-egregious nonadherence behaviors.

Interpreting Nonadherence Behaviors in the Medical Context

All patients who are given an opioid or other controlled prescription drug for medical purposes must be routinely evaluated for drug-related behaviors throughout the course of treatment. In the ambulatory setting, nonadherence is particularly challenging. In some cases, it takes the form of undertreatment. This problem is seldom discussed but may be a significant issue, particularly when treating pain associated with a serious medical illness. The decision to take less medication than prescribed may be related to cost, fear of side effects or addiction, family concerns, or other factors. Education and support of the patient and family may require specific targeting of these concerns.

When nonadherence takes the form of excessive opioid use, the behaviors can be labeled as misuse or abuse, or perhaps addiction, depending on the nature of the problem. The type of assessment necessary to assess these drug-related behaviors is a core clinical competency for addiction specialists, essential for establishing a diagnosis and evaluating a treatment plan, but is relatively novel for pain specialists and other clinicians. This is an area of practice that must be improved. There is a broad consensus in the United States that clinicians who prescribe opioids or other controlled prescription drugs to manage medical disorders must possess basic skills in assessing drug-related behaviors in terms of the risks associated with abuse, addiction, and

diversion. Those who do not, or who encounter patients who pose a high level of challenge in assuring adherence, should not prescribe without help.

Principles of Opioid Therapy

The safe and effective prescribing of opioid drugs for acute or chronic pain requires skills in optimizing favorable pharmacologic outcomes (reducing pain and minimizing side effects) and reducing the risks associated with misuse, abuse, addiction, and diversion. These skills must be translated into a set of pragmatic decisions: Who should be selected for opioid therapy, how should the drug be selected and administered, and how should the treatment be structured to minimize the risks of abuse?

Selection of Patients for Opioid Therapy

There is a long-standing international consensus that opioid therapy is the mainstay treatment for patients with acute severe pain and patients with chronic pain related to active cancer or another type of advanced medical illness. Selection of an opioid to treat pain in these settings should be viewed as the "default" position; the decision to do otherwise should have a clear rationale.

In contrast to this view, there is no consensus about the role of opioid therapy to treat other types of chronic pain. The populations with chronic pain are very heterogeneous, represent many types of disorders and very diverse comorbidities, and largely encompass patients receiving care in community settings by clinicians who are not pain specialists. These populations include the increasing number of patients with pain caused by stable or indolent medical illness (including those who are cancer survivors with chronic pain) or a primary pain-related diagnosis (e.g., chronic headache and fibromyalgia).

The decision to select a patient with chronic noncancer pain cannot be based on the existing evidence of effectiveness. Although there have been many clinical trials of opioid therapy for noncancer pain, and these trials have been collated into systematic reviews, the existing evidence can provide little insight other than generally supporting the conclusion that opioids are efficacious for all types of pain and that some patients appear to benefit during long-term therapy (and a substantial minority stop treatment over time). There is no evidence of long-term effectiveness and no evaluation of comparative effectiveness, either comparing opioid regimens or comparing opioids with other treatment approaches for pain.

Optimizing the Outcomes of Opioid Pharmacotherapy

Based on receptor interactions, opioid analgesics can be classified as pure agonists or agonist–antagonists. The agonist–antagonist drugs include a mixed agonist–antagonist subclass (including butorphanol, nalbuphine, pentazocine, and dezocine) and a partial agonist subclass (including buprenorphine). The agonist–antagonists have a ceiling effect for analgesia and for respiratory depression, can reverse the effects of pure agonists in patients who are physically dependent, and are less preferred by individuals who abuse opioid drugs. Two other centrally acting analgesics, tramadol and tapentadol, have opioid activity mediated by the μ-receptor and often are categorized with the opioid agonists. These drugs have a mixed analgesic mechanism involving both μ-agonism and monoaminergic reuptake blockade.

Opioid Selection

The treatment of acute pain may be accomplished with any of the opioid drugs. In the ambulatory setting, the most common approach to the treatment of moderate or severe pain in

the patient with very limited or no prior opioid exposure involves the administration of a short-acting oral opioid, which may be combined with either acetaminophen or aspirin. In the United States, these drugs include hydrocodone, codeine, dihydrocodeine, oxycodone, tramadol, and tapentadol. Oral meperidine and propoxyphene also are used but are not preferred because of the potential for adverse effects. Although meperidine has lesser contractile effects on smooth muscle in preclinical models, this characteristic has no established benefits in the clinical setting; the drug is not preferred for either acute or chronic pain because of the potential for toxicity due to accumulation of an active metabolite, normeperidine, which may produce dysphoria, tremulousness, hyperreflexia, and seizures. Propoxyphene also has a toxic metabolite and produces a similar spectrum of potential toxicities, as well as serious cardiac toxicity with overdose.

In the inpatient setting, acute pain is usually managed with a pure μ-agonist such as morphine or hydromorphone, which is usually administered intravenously. The only certain advantage of this route is a faster onset of effect, the advantages of which often are worth pursuing as long as drug administration is in a monitored environment.

The agonist–antagonist opioids also can be used to treat acute pain. These drugs have less abuse potential than the pure agonist drugs, but the lack of oral formulations and the pharmacologic profile (e.g., ceiling effect) has limited their utility. Intranasal butorphanol has gained some acceptance in headache management, and the parenteral mix agonist–antagonists are sometimes used in monitored settings, such as emergency departments.

The partial agonist buprenorphine is available as a transdermal patch in some countries and has gained wide acceptance in the management of pain in the opioid-naive patient. In the United States, the sublingual tablets of buprenorphine that are approved for the treatment of addiction have been used off-label for pain, but experience is very limited. Some clinicians believe that buprenorphine may be especially useful for pain when the patient has a past or current history of drug abuse, but this potential advantage has yet to be established empirically.

The use of methadone in the treatment of pain has been growing steadily during the past decade, driven by its low cost, high efficacy in some clinical situations, and perceived value in reducing the risk of abuse in patients predisposed to addiction. This increasing use, which was initially welcomed by pain specialists as a means to improve access to effective pain therapy, has been associated with reports of negative outcomes—including mortality—in some populations. Recognition that the use of methadone may be associated with a relatively high level of risk has led to reexamination of its pharmacology in relation to analgesia and other effects.

Route of Opioid Administration

For chronic therapy, the oral and transdermal routes for opioid delivery are well accepted. The advent of oral modified release formulations allowed more convenient dosing, either once daily or twice daily, and the transdermal route offered 48- to 72-hour dosing interval. These formulations also may improve treatment adherence, with theoretical benefits on pain control. They are not preferred when rapid dose titration is needed for severe pain. The transdermal route may be favored by some patients to reduce the pill burden or gain from the potential for lesser constipatory effects; it is relatively contraindicated when the patient is likely to experience spikes of fever, which may alter the delivery characteristics of the patch and lead to periods of increased drug absorption. The use of the transdermal system also is limited by the difficulties involved in delivering high doses and the need for an alternative route to provide supplemental doses for breakthrough pain.

The rectal route occasionally is used for prolonged therapy, particularly at the end of life. Rectal administration of modified-release oral formulations has proved useful anecdotally.

The parenteral route typically is used for the treatment of acute severe pain in a monitored setting. The rationale for intravenous bolus therapy, including intravenous patient-controlled

analgesia, is the ability to provide pain relief quickly following a dose and titrate more effectively, unencumbered by the delay associated with oral absorption. Subcutaneous bolus injection also is widely used, particularly in the setting of pain related to advanced illness. In contrast, intramuscular injection is rarely appropriate, given the pain it causes, the risk of hematoma, and the occurrence of variable absorption from different muscles.

A variety of techniques for intraspinal opioid delivery (known as neuraxial analgesia) have been adapted to long-term treatment, and there is emerging evidence that properly selected patients can benefit greatly from this approach. The clearest indication is intolerable somnolence or confusion in a patient who is not experiencing adequate analgesia during systemic opioid treatment of a pain syndrome located below the level of mid chest. Continuous epidural infusion, which can be accomplished through either a percutaneous or implanted epidural catheter, is usually preferred if the patient has advanced medical illness and a life expectancy measured in just a few months. Otherwise, subarachnoid infusion using a totally implanted system should be considered. In a population with cancer pain, a controlled trial comparing neuraxial infusion and comprehensive medical management demonstrated that the spinal opioid treatment improved pain, side effects, quality of life, and even survival.

The potential for intraspinal infusion has increased further with the use of drug combinations. An opioid, such as morphine or hydromorphone, is usually combined with a local anesthetic, such as bupivacaine. Clonidine is often added, and other drugs may be considered for refractory pain, including other opioids, baclofen, midazolam, and ziconotide. Ziconotide is a unique calcium-channel blocker available only for neuraxial infusion and has been shown to be effective for cancer pain in controlled trials. As new drugs are tested for intraspinal therapy, the indications for the approach are likely to increase.

Dosing Guidelines

Treat Side Effects Treatment of opioid-induced side effects is an integral part of opioid therapy. Management of side effects enhances comfort and allows continued upward dose titration of the opioid drug, if necessary. Although respiratory depression fosters the greatest concern, tolerance to this adverse effect develops quickly and it is rarely a problem. The most common and persistent side effect during long-term treatment is constipation. Although less prevalent, persistent sedation or mental clouding also may occur and limit dose escalation.

Although the evidence is very limited, there is a large experience supporting the use of laxative therapy for opioid-induced constipation. Treatment is needed by a high proportion of those who receive opioids in the context of serious medical illness, most of whom have other factors contributing to constipation; a smaller proportion of patients without these factors require ongoing treatment. The conventional approach involves either the administration of a stool softener, docusate, in combination with a contact cathartic, such as bisacodyl or senna, or the administration of an osmotically active agent. The latter products include poorly absorbed sugars, specifically lactulose or sorbitol, or propylene glycol. The treatment of opioid-induced constipation that is refractory to these therapies may involve trials of drugs that have been used anecdotally, such as a prokinetic agent (metaclopramide), an acetylcholinesterase inhibitor (e.g., donepezil), lubiprostone, misoprostol, or colchicine. More specifically, refractory constipation can be treated with an opioid antagonist. Methylnaltrexone is now approved in the United States as a parenteral opioid antagonist specifically indicated for refractory constipation; the studies suggest that more than one half of treated patients respond with a bowel movement, most within an hour of dosing. There also is limited experience with oral naloxone for severe opioid-induced constipation.

Patients who experience persistent somnolence or mental clouding during opioid therapy may improve with elimination of nonessential centrally acting drugs or opioid rotation. Another strategy is to treat the symptom using a psychostimulant, such as methylphenidate or modafinil.

Monitoring Outcomes

Regardless of the pain syndrome or setting of care, opioid therapy must be monitored in terms of analgesic effects, side effects, impact on functioning, and drug-related behaviors. In the setting of chronic pain management, changes in therapy should be considered if an initial favorable balance between analgesia or side effects changes for the worse, physical or psychosocial functioning decline, or nonadherence behaviors occur. A simple framework for monitoring has been summarized using the mnemonic "the Four A's." Documentation of outcomes in the medical record should periodically describe the assessment of each element. This may be facilitated by use of a chart tool, such as the Pain Assessment and Documentation Tool.

Risk Assessment and Management

Monitoring for aberrant drug-related behavior should be considered a best practice during treatment with any potentially abusable drug in any clinical situation. Opioid therapy in all treatment contexts always carries a risk associated with its abuse liability. In some situations, such as acute pain management in monitored settings or the treatment of chronic pain in those with advanced medical illness, the risks may be very low or the management of these risks may be relatively simple. In other situations, such as the treatment of a chronic pain problem in the patient with a recent history of polysubstance abuse, the risks are very high. Irrespective of the level of risk, the most efficient and appropriate framework is a *universal precautions* approach. This approach, which has been emphasized in the setting of chronic pain management, should be broadly generalized. It empowers clinicians to act in patients' best interests by putting the emphasis on assessment and encouraging rational clinical decisions and appropriate documentation.

Patients in Methadone Maintenance Programs

Patients enrolled in methadone maintenance programs vary in the extent to which craving is controlled and drug-abuse behaviors are occurring. Chronic pain is highly prevalent in this population, but access to pain therapy is limited. Should a patient receiving methadone for addiction seek pain care, the assessment should clarify the nature and effectiveness of the program (the patient should specifically consent in writing to information sharing with the program, and the clinician who manages the pain should determine the results of recent urine drug screening and related information maintained by the program); this assessment should judge the strength of the recovery and the extent to which the patient has access to supports that may help to sustain it. Opioid therapy should be considered for long-term therapy only if there is evidence that the patient's recovery has been established sufficiently to justify a trial and other pain management strategies are unavailable or have proven to be ineffective.

Generally, patients who are considered for opioid therapy should be continued on their daily dose of methadone. This applies to all treatment settings. Occasionally, the patient undergoing methadone treatment for addiction responds so well to long-term opioid therapy for pain that the specific treatment for addiction can be withdrawn. This decision should be taken only if there is evidence over time to support it, and only after careful discussion with the patient and clinicians at the methadone treatment program.

Patients Receiving Opioid-Agonist Therapy with Buprenorphine

Buprenorphine offers another option for opioid-agonist therapy of addiction and is increasing in use. It is now being used as an analgesic in many countries. The assessment, assumption of high risk, careful selection of patients for consideration of opioid therapy, need to structure therapy in a manner to mitigate risk, and requirement for careful documentation during pain therapy all parallel the approach taken with methadone-maintained patients.

The pharmacology of buprenorphine is characterized by high-affinity binding to the μ-receptor, a half-life longer than a day, and partial agonism. The high affinity raises concern that the buprenorphine-treated patient may not respond to administration of a pure μ-agonist drug, at least at typical doses. There is very little experience with the coadministration of another pure μ-agonist drug to the buprenorphine-treated patient, either for acute pain or for chronic pain. Although it is possible that the patient who experiences severe pain during buprenorphine treatment for addiction could be managed by increasing and dividing the dose of buprenorphine, there also is very little experience with this approach. Based on anecdotal experience, acute pain should be treated initially with μ-agonist opioid doses that are conventional for the setting, but if the response is poor, the dose should be rapidly titrated. In most cases, the buprenorphine should be continued at the prior dose while this is carried out. For chronic pain, the same principles would apply, with the expectation that there is a dose of a pure μ-agonist that may provide added pain relief. Research is needed to clarify the outcomes associated with the management of acute and chronic pain in buprenorphine-treated patients.

Active Drug Abusers

Patients with active alcohol or drug abuse are presumed to be at high risk for nonadherence. In the monitored setting, acute pain can be managed using conventional means, such as intravenous patient-controlled analgesia, but staff must be prepared to manage the type of problems that may be associated with drug abuse, including the development of withdrawal phenomena, comorbid psychiatric disease, and responses to opioid drugs for pain that may be difficult to interpret.

In the ambulatory setting, the use of a controlled prescription drug in the context of current abuse is very challenging. Prescribing is not acceptable if diversion is expected, and even if it is not the case, the abusing patient may be perceived as incapable of honest reporting and this, too, would contraindicate therapy.

All cases deserve careful assessment, however, and there may be scenarios in which a trial of opioid treatment might be considered. For example, the patient who is actively abusing alcohol or marijuana and is entering a treatment program with close monitoring may be assessed as more likely to proceed into recovery if pain is controlled. Given the heterogeneity of the population abusing drugs, the question that must be addressed is whether the specifics of the situation warrant the risk of an appropriately structured treatment trial.

Conclusion

Although an exploration of the issues at the interface between pain and substance abuse focuses on the opioid drugs, decision-making in the clinical setting must be informed by a

broader knowledge of the varied modalities used to manage acute and chronic pain. Recent texts describe the breadth of therapies—pharmacologic and nonpharmacologic—that can be employed in the management of pain and the influence of a patient's substance-use history on the selection and implementation of these therapies. The optimal treatment of acute or chronic pain, irrespective of the pain diagnosis and the unique characteristics of the patient, always must consider the risks and benefits of an opioid-based treatment trial against the risks and benefits of other potential strategies. This analysis requires familiarity with other analgesic approaches, an understanding of conventional practice, and good judgment that takes into account the feasibility and goals that surround the plan of care.

Suggested Readings

Chou R, Ballantyne JC, Fanciullo GJ, et al. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain.* 2009;10(2):147–159.

Fine PG, Portenoy RK, and the Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation. Establishing "best practices" for opioid rotation: conclusions of an expert panel. *J Pain Symptom Manage.* 2009;38:418–425.

McNicol E, Boyce DB, Schumann R, et al. Efficacy and safety of mu-opioid antagonists in the treatment of opioid-induced bowel dysfunction: systematic review and meta-analysis of randomized controlled trials. *Pain Med.* 2008;9:634–659.

Ripamonti CI, Bareggi C. Pharmacology of opioid analgesia: clinical principles. In: Bruera EB, Portenoy RK, eds. *Cancer Pain: Assessment and Management.* New York, NY: Cambridge University Press 2010:195–229.

Rosenblum A, Marsch L, Joseph H, et al. Opioids and the treatment of chronic pain: controversies, current status and future directions. *Exp Clin Psychopharm.* 2008;16:405–416.

40 Psychiatric Comorbidity

Use of, and withdrawal from, alcohol and other substances of abuse can cause, mimic, or mask psychiatric symptoms. The overlap of signs and symptoms makes it difficult to accurately diagnose all conditions present. However, failing to diagnose any co-occurring disorders (COD) increases the likelihood that the individual's treatment needs will not be met, worsening the patient's prognosis.

For some time, individuals with both psychiatric and substance problems have been called "dually diagnosed." This term is now felt to be confusing, appearing to imply that only two conditions exist. Currently, individuals who concomitantly suffer from one or more psychiatric and one or more substance-related problems are said to have COD. The population of individuals with COD poses a particular challenge to the treating professional. A working understanding of psychiatric conditions and the motivation for substance use are important, as is the impact various substances of abuse have on psychiatric conditions. It is not enough for the treatment provider to deal with only one problem. If the treating professional is not proficient in the approach to one or the other problems, it is incumbent upon him to see to it that the COD patient gets the additional care he needs.

That psychiatric and substance use disorders (SUDs) commonly co-occur is now well recognized, as are the facts that such co-occurrence is predictive of high utilization of services and poor treatment adherence. Prior to this recognition, fractionation of care was the norm, with mental health providers refusing to treat substance abusers, substance abuse treatment providers refusing to work with those with mental illnesses, and both camps often missing the presence of one or the other disorders.

Once it became clear there was a population for whom addiction alone was not the case, the issue of cause and effect became a subject of debate. Arguments arose regarding which came first. Was the person depressed because he was drinking heavily, or did he drink heavily because he was depressed? Was she psychotic because she was a daily marijuana user, or did she choose to smoke the drug because, as she claimed, it calmed her nerves and helped her rest? Was he anxious because he chronically abused benzodiazepines (BZDs) and felt the rebound effect, or did he use the BZDs because of his chronic state of anxiety?

Traditional providers of addiction treatment saw the problem as substance abuse and any other unacceptable behaviors as simply excuses to justify continued drug use. The more psychologically minded developed the theory that the addicted individual used his drug(s) of choice as a means of treating uncomfortable or unacceptable impulses, the so-called self-medication hypothesis of addictive disorders.

Regardless of the cause(s) of ongoing substance use, many mental health treatment providers refused to treat any other psychopathology until the SUD had been addressed and the individual abstinent, sometimes for many months. Unfortunately, such an approach condemned

the individual with an untreated mental illness to a high likelihood of early relapse and an overall poorer outcome.

This fragmented approach to treatment left many, if not most, COD patients without treatment of any sort. For those who did seek treatment, early dropout was common. By the late 1980s, it was increasingly recognized that a new, coordinated approach to care was essential for meeting the needs of persons with COD. In response, the concept of "No Wrong Door" was introduced. No matter where the COD patient presented, providers were admonished to be ready to intervene on his or her behalf to make treatment immediately available. This approach meant that the alcohol-dependent client with depression must be given access to mental health care at the earliest possible time just as the bipolar client with cocaine dependence must receive immediate help for his stimulant habit.

The cost, morbidity, and mortality of COD prompted the U.S. government, in 2003, to create the Co-Occurring Center for Excellence (COCE) through the Substance Abuse and Mental Health Services Administration (SAMHSA). Its purpose was to function as a resource for the dissemination of information regarding evidence-based approaches to this population as well as to foster the adoption of such practices. Over its 5-year course, the COCE served as a clearinghouse for information, data collection, and grants for research on COD. Though its mission is over, this is still a valuable resource. COCE can be accessed at http://coce.samhsa.gov.

A consensus panel, also convened by SAMHSA, provided a definition of COD, a definition that will be used throughout this review. That is, that people with COD are

> . . . individuals who have at least one psychiatric disorder as well as an alcohol or drug disorder. While these disorders may interact differently in any person (e.g., an episode of depression may trigger a relapse into alcohol abuse, or cocaine use may exacerbate schizophrenic symptoms) at least one disorder of each type can be diagnosed independently of the other.

Epidemiology

Simply suffering from a mental illness greatly increases the likelihood that the individual will have a comorbid SUD. According to the SAMHSA, in 2002 there were over 17.5 million American adults with serious mental illnesses, of whom nearly a quarter had a comorbid SUD. Despite the numbers involved, more than half of those with COD received no treatment for either disorder and only 11.8% received treatment for both.

Further reports from SAMHSA suggest that the cost of treatment of mental health and substance abuse will top $239 billion in 2014. This is a fivefold increase over costs from 1986 ($42 billion) and double that of 2003 ($121 billion). Importantly, these data reflect only the direct costs of treatment, not the additional costs of substance-related illnesses, decreased productivity, police intervention, and incarceration.

Recognizing that preventing the emergence of COD is preferable to treating established illness, research has focused on the issue of which disorder came first. Unfortunately, the data are often contradictory. Some studies showed early onset of substance misuse in adolescence predicts the later development of some types of psychiatric disorders. Others found that childhood or other early psychiatric symptoms predict the later emergence of SUDs. Yet another suggested either could precede or follow the other depending on the exact psychiatric diagnosis and the specific substance of abuse, all of which make the development of prevention strategies very difficult.

Just as there may be a difference in the timing of onset of symptoms of substance use problems and of psychiatric symptoms, there is a difference in the frequency with which the various

psychiatric disorders are associated with substance use problems. For example, any affective disorder appears to be frequently associated with SUDs, with slightly more than 40% of cases of unipolar depression associated with alcohol problems. Bipolar disorder is associated with any SUD in more than 40% of cases and an additional 17% of unipolar respondents associated with a nonalcohol SUD. Further, the presence of an SUD increases the frequency of depressive episodes in individuals with either type of disorder as well as that of suicide in depressed individuals.

According to the Surgeon General's opinion, as many as 65% of persons with at least one mental disorder ". . . also have a lifetime history of a least one substance use disorder." A major source of data for that opinion comes from the Epidemiological Catchment Area study, considered one of the most comprehensive studies of COD and a rich source of information for nearly 20 years. A replication study is under way to update the information, and analysis of those data is now under way. It is likely that replication data will provide the same invaluable service as provided by its predecessor. However, for now the original study is the source of much of the data shown here. In this study, it was found that among individuals with schizophrenia, from 25% in community samples to 66% of individuals in specialized samples such as Veterans Affairs, community mental health, and inpatient samples are estimated to have comorbid SUDs. The anxiety disorders, on the other hand, have a much more variable rate of comorbidity, depending on the specific diagnosis. Nevertheless, SUDs co-occur at a much higher rate among individuals with anxiety disorders than among the general population, with the possible exception of social phobia.

The co-occurrence of psychiatric and SUDs has social, economic, and prognostic implications. When substance misuse and mental illness co-occur, the risk is great that, in general, the individual will not do as well as if he had not developed such a comorbid problem. Poverty and homelessness are more frequent, as are the risks of being both victim and perpetrator of violent assault. It is important to note that while most violent crimes are not committed by the mentally ill, those that are perpetrated by members of this population are more likely to be committed by those with COD. Furthermore, among the mentally ill, substance use also increases the risk of both accidental and homicide deaths. Yet another issue that has taken on extreme importance is that of greater risk taking among COD clients in terms of sexual behaviors and needle sharing. Such behaviors have resulted in an increased risk for HIV and similar medical conditions in this population.

Comorbidity, in short, is associated with a greater number of social and health consequences than either disorder alone. Thus, although substance misuse per se is a source of significant social and medical morbidity and mortality, in the case of the mentally ill, the problems become magnified many times over.

Evaluation of the Patient with Co-occurring Disorders

That it is extremely important to detect the presence of co-occurring conditions early in the evaluation process cannot be overstated. Identification of such conditions subsequent to initial hospitalization for psychiatric disorders results in more hospitalizations and poorer long-term outcome.

Having said this, it is also clear assessing the COD client is more complicated than assessing patients with either condition as, again, substance use and psychiatric disorders can mimic, mask, or exacerbate the symptoms of each other. It is obvious that a psychiatric workup is necessary if such has not already been done. Helpful information includes the patient's past diagnoses

if the patient is aware of what they may have been, past hospitalizations for psychiatric reasons, what prompted the psychiatric admission, response to treatment, family history of psychiatric problems, what medications he has had in the past, and how he reacted to each. Furthermore, the interviewer should ask about suicidal ideation, both current and past, as well as attempts.

It is also useful to determine if the psychiatric symptoms predated the onset of the individual's substance misuse. Note should be made as to whether or not the patient's psychiatric condition improves, disappears, or worsens when the patient is not using the substance(s). Unfortunately, it is often impossible to determine either of the above. If the patient uses substances daily and has no substantial periods of clean time, it will not be possible to know if his symptoms improve with abstinence. Likewise, if the patient has been using substances for many years, memory may not prove accurate as to whether the substance misuse or the psychiatric symptoms came first.

Although assuring the safety of the patient must always be a consideration in dealing with the chemically dependent, it is of paramount importance when dealing with the COD individual who poses a greater risk for dangerous behaviors. Patients in the immediate poststimulant dysphoric state or who are acutely under the influence of depressants such as alcohol are at an increased risk of self-harm, regardless of whether or not they have a comorbid psychiatric condition. Both acute and chronic use of substances of abuse, however, vastly magnify the risk of suicide in individuals with depression and other chronic, severe mental illnesses, including schizophrenia and bipolar illness. Thus, at intake and at frequent intervals throughout the treatment process, the patient's risk of suicide must be assessed.

The treatment provider must be prepared to make judgments about the safety of using medications in patients who may be acutely under the influence of a substance in order to adequately treat this complicated population.

Typical assessment questions must be asked of the COD patient—age at onset of use, what is used, quantity, and how the substance is administered, that is, orally, intranasally, intravenously, rectally, etc. The method called a time-line followback may be helpful to jog the patient's memory as to episodes of use. In this technique, the patient uses a calendar to remind himself of specific dates or events during which he was actively using. In addition, just as in a non-COD population, collateral information should be obtained if at all available. Oral screening tools used to assess for alcohol and other substance abuse may be less helpful in the COD population, though there is still a place for the Michigan Alcohol Screening Test (MAST) and Drug Abuse Screening Test (DAST) with this population. It must be borne in mind, though, that the COD population is more likely to experience social isolation and be unemployed and homeless, rendering some typical questions moot.

While the user may identify himself or herself as having a problem with a specific substance, it is important to ask about substances used with the drug of choice. For example, while readily admitting that he is addicted to cocaine, the same patient may neglect to mention, as feeling it is irrelevant, that he is also ingesting a fifth of hard liquor during cocaine binges. This knowledge is necessary in order to avoid missing such needs as safe withdrawal from alcohol and to screen for further physical damage that may result from such concomitant use.

Understanding the user's motivation for substance use can also be helpful in developing an overall treatment plan. The individual suffering from panic disorder and agoraphobia in middle school, for example, may find that alcohol, at least temporarily, will help relieve her anxiety symptoms. Fear of the return or worsening of anxiety symptoms in abstinence may impede her progress toward abstinence. Likewise, nicotine has been shown to lessen the cognitive problems associated with schizophrenia, a fact that the psychotic user may be exploiting, either consciously or unconsciously.

As noted previously, it has been postulated that the person with COD is self-medicating with his drug of choice, something argued for a couple of decades. Regardless of the motivation for use, the facts above citing the potential benefits of the substances abused make it important to ask the user what it is he wants to feel as a result of use of his drug(s) of choice. It is possible

that the only answer will be "to get high." However, it is also possible that there is truly a benefit that the user is seeking. Such information can be invaluable in establishing treatment goals.

Use and abuse of common substances, such as caffeine and tobacco, should be explored in any addicted population. However, it takes on even greater importance with COD clients. Caffeine may significantly worsen symptoms of anxiety and panic. Nicotine, on the other hand, may increase the metabolism of a variety of psychoactive medications, resulting in a need for even greater doses in order to treat psychiatric symptoms. The latter is particularly important in hospitals and other facilities that forbid smoking, as the abrupt withdrawal of nicotine can result in a rapid rise in psychiatric medications and the emergence of uncomfortable side effects.

Prescription and over-the-counter drug abuse should also be asked about. If the individual is getting early refills on any prescription, even those not typically thought of as intoxicants, efforts should be made to determine the reason. Clonidine, for example, may be abused to help mitigate the effects of opiate withdrawal. However, at high-enough doses, this α-adrenergic antihypertensive can result in a "drugstore high," a mild sedation in its own right. Likewise, highly anticholinergic agents such as benztropine, used, among other things, to counter the side effects of some antipsychotic medications, are well recognized for their significant abuse potential. Further, readily available over-the-counter medications containing dextromethorphan can induce a common, and potentially lethal, high, especially in alcohol abusers.

As with any substance-dependent individual, the COD patient should have intake and random drug screens performed. It is also essential, though, that the clinician be familiar with what the toxicologic tests available in his facility are actually testing for. For example, some emergency rooms and laboratories do not include phencyclidine (PCP) or lysergic acid diethylamide (LSD) in their routine screens, yet these substances are often around. Further, buprenorphine is surfacing as a recreational drug and also may not be on routine tests. Thus, it is helpful to be familiar with what one is really asking for in a "routine screen."

Medical screening is highly important in this population. As noted earlier, COD patients, especially those with psychotic disorders, are more likely to engage in high-risk behaviors than the non-COD population. Thus, the incidence of HIV, hepatitis C, and other health problems is quite high.

Treatment

Historically, three basic approaches to treatment of COD patients were used: sequential, parallel, and integrated models. In the sequential model, first one and then the other condition was treated. The idea was that one condition had to be under control before the second could be adequately addressed. Of course, determining which condition to treat first presented a significant problem. In addition, addiction-treatment programs have not typically been designed to meet the needs of the mentally ill, while mental health providers were reticent to treat intoxicated patients and ill-equipped to handle them.

In the parallel model, both conditions were addressed simultaneously, but in different programs with different staff. Poor communication between staff and the potential for the patient to receive mixed messages posed substantial risk, however. Further, treatment philosophies often clashed, and goals were often markedly different between addiction and mental health treatment programs.

Finally, in the integrated model, both conditions are treated simultaneously by providers knowledgeable about both conditions. This is the approach most strongly supported by providers and by evidence-based studies.

To address some of the deficiencies inherent in existing programs, there has been a major initiative at the national level to educate mental health and addiction-treatment providers in

each other's specialties. Cross-training is promoted at national, state, and local levels. Special certification programs have been developed to standardize and measure necessary levels of knowledge and skills, and to promote quality programming for treating individuals with COD. Where once treatment programs consisted, in many respects, of promoting the principles of Alcoholics Anonymous (AA) and other 12-step, self-help programs, it is now accepted that working with the dually disordered is a much more complex task than this. The treatment provider must help the patient gain an understanding of the patient's SUD, of the patient's mental illness, and of the impact one has on the other. Further, research suggests that family, legal, and vocational services be included in "integrated treatment."

A way of conceptualizing the severity of the needs of any given patient has been developed, the four quadrants of COD. Most states use this model for assessing which patients have the greatest needs. The practitioner working with patients with COD should be familiar with this concept. However, it is not as meaningful for the individual or small group of practitioners as it is for larger systems of care.

In the quadrant model, the mental illness and the SUD are viewed individually in terms of severity of symptoms, and then grouped together to determine the level of care the individual needs. Less-severe mental disorder and SUD are quadrant I, severe mental illness and less-severe SUD quadrant II, less-severe mental disorder with more-severe SUD quadrant III, and severe levels of both substance and psychiatric disorders quadrant IV. Clearly, the latter is viewed as requiring the highest level of care and may include housing, legal intervention, treatment for each disorder, and coordination among a number of entities in order to meet the individual's needs.

Comprehensive treatment for COD individuals demands that programming provide integrated mental health and addiction treatment and includes flexibility, repetition, long-term support, and medication where necessary. Increasing evidence suggests that individuals with COD are more likely to seek treatment in mental health programs with addiction-treatment components and less likely to receive the breadth of treatment recommended for treating COD clients in addiction treatment–based programs. Further, provision of on-site mental health care results in better psychological functioning and decreased substance use.

Medication(s) When Necessary

There is no question that some psychiatric conditions can be treated with psychotherapy, behavioral interventions, and other psychotherapeutic techniques. There has been considerable concern among addiction-treatment providers that jumping in quickly with a pill to treat a patient's discomfort sends a wrong message. That is, it signals that only a substance, not personal-learned strengths and skills, can help the individual through hard times. The problem with the latter reasoning, though, is that the addicted person with a co-occurring psychiatric condition who presents for treatment typically has not learned the alternate means of dealing with his hallucinations or depression, or he would not be there in the first place. Furthermore, psychotherapeutic interventions take time to be learned and rehearsed and, while effective for some psychiatric conditions, are not as beneficial for others. In addition, the dually disordered are at a high risk of dropout and relapse. Waiting for lengthy interventions to take effect may ensure the patient's early withdrawal from treatment long before a positive response can occur. Finally, at least for the severely mentally ill, medication is typically a first, not a last, choice. Early and vigorous intervention with medication, where indicated, using nonaddictive agents may help the patient stay in treatment and gain confidence that he can learn the techniques he needs for dealing with his substance use and psychiatric disorders.

That having been said, when dealing with the COD individual, as with any other person with an SUD, when medication is deemed necessary, every effort should be made to use medications that (a) do not induce euphoria, (b) do not cause dependence, (c) are effective in the individual who is actively using substance(s) of abuse, and (d) are safe when used by the active user.

Psychiatric Conditions, Medications, and Substances of Abuse

The following is not an exhaustive review of all possible medications to treat the various psychiatric conditions, but an effort to give the reader an overview of the types of information available regarding medications that have proven safe and effective in relieving psychiatric symptoms in patients with psychiatric disorders who continue to actively use substances of abuse. It cannot be overstated that the clinician must be vigilant about the possibility that a problem will arise with the medicated individual who is also abusing other substances. It is always possible the individual is using more substances than the treatment provider is aware of, increasing the possibility of a negative consequence.

Depression, Antidepressants, and Mood Stabilizers

Depression and mania can be improved by active treatment with medication even when the patient continues to abuse alcohol, opiates, nicotine, and perhaps marijuana. To date, no medication has been shown to be unequivocally superior in improving such symptoms among individuals abusing psychostimulants.

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) decrease depressive symptoms in unipolar depression in actively drinking alcoholics. The clinician is advised to make TCAs available in very limited supplies, however, to a member of this population, because of the potential for a lethal interaction with alcohol. Concomitant abuse of BZDs, alcohol, cocaine, and marijuana is common among opiate-dependent individuals. This fact, and that much of the research available regarding opiate addicts, comes from methadone maintenance patients, making it necessary to view data on this population with caution. Nevertheless, there is evidence that simply stabilizing opiate-dependent individuals on methadone improves depressive symptoms. Tricyclics and SSRIs also improve depression in individuals actively using opiates. It should be noted, however, that abuse of TCAs by methadone maintenance patients is a well-known phenomenon in clinics; thus, such drugs should be used only with close supervision and with only small quantities available. Sertraline may cause an initial rise in methadone levels, which will normalize after a brief interval. There is some evidence that SSRI medication may cause a slight improvement in depressive symptoms in individuals actively abusing marijuana. Thus, erring on the side of the patient and offering to treat these symptoms with medication may be reasonable.

Lithium is relatively ineffective in treating substance-dependent individuals with mania. Furthermore, there is an increased risk of toxicity with this medication if the individual is using alcohol or marijuana. Thus, this mood stabilizer should be avoided in COD clients with bipolar disorder or cyclothymia. Divalproex improves manic symptoms in actively drinking alcoholics with this disorder, although close observation of liver functions is essential. In one study, gabapentin decreased alcohol abuse in bipolar patients with alcohol problems. However, abuse of this medication is becoming increasingly recognized. Quetiapine appears to decrease both manic symptoms and cocaine cravings in dually disordered patients with bipolar disorder and substance use problems. It too appears to be abused by individuals in some populations, however. Carbamazepine must be introduced and used with caution among individuals on methadone, because it lowers this opiate's levels, leading to withdrawal. Tiagabine may decrease cocaine use in some individuals and has been effectively used for the treatment of bipolar disorder. Topiramate is sometimes used as a mood stabilizer and appears to decrease alcohol consumption in some alcohol-dependent individuals, producing interesting possibilities for the use of this agent in COD patients.

Psychoses and Antipsychotic Medications

Actively treating psychosis improves retention in both addiction and mental health treatment. Despite concern about the possible interaction between antipsychotics and alcohol, there is little in the literature to support this worry. This may, of course, reflect the long-held habit of withholding antipsychotic medications when individuals with psychoses began to imbibe. Thus, it

is reasonable to use this medication with caution in the COD patient. High doses of typical antipsychotic medications in conjunction with cocaine appear to increase the risk of dystonic reactions and, perhaps, neuroleptic malignant syndrome. Whether or not this applies to other psychostimulants is not known. Risperidone, olanzapine, and clozapine improve symptoms and retention among schizophrenic psychostimulant abusers. Clozaril also appears to decrease substance use in general in COD populations. Nicotine acts in competition with some antipsychotic medications (such drugs as haloperidol, fluphenazine, olanzapine, and clozapine), effectively lowering the levels of these agents. It is important for the treatment provider to keep this in mind in the event that a patient is abruptly forced to discontinue his routine dose of nicotine or to have it drastically reduced. The patient's level of neuroleptic medication may become suddenly far greater than it had been, resulting in greatly increased side effects and discomfort.

Anxiety Disorders

Treating anxiety symptoms in individuals actively using alcohol, psychostimulants, and opiates improves retention in treatment and provides some degree of symptom relief. BZDs are among the top three most-abused prescription drugs in the United States and may be abused by nearly half of individuals seeking treatment for substance misuse. These facts, and that there is some evidence of a disinhibiting effect of some BZDs when used by alcohol-dependent individuals, serve as relative, not absolute, contraindications to their use in this population. Alprazolam, in particular, has been suggested as having this effect. If this class of medication is used, it is advisable to use such agents with caution, in acute situation rather than as a maintenance strategy, under close supervision, and briefly, if at all possible. Furthermore, longer-acting agents should be used. TCAs, SSRIs, and venlafaxine are helpful in relieving anxiety symptoms in individuals with coexisting alcohol and anxiety problems. The existence of so many non–dependence-inducing, effective medications begs the question of necessity of using potentially addictive agents for the treatment of anxiety disorders for any but very short-term problems. Venlafaxine undergoes extensive hepatic metabolism, and close observation of liver functions is advised in individuals abusing alcohol. Many cases of fatal reactions have been reported of opiate dependent individuals using and abusing BZDs. Consequently, use of this class of agents for individuals with this problem is not advised. Rather, a trial of an SSRI, as in depression, is preferable. Buspirone appears to be effective in reducing symptoms of generalized anxiety disorders in actively drinking alcoholics. However, it is also extensively metabolized in the liver, making close monitoring essential.

Use of Disulfiram and Anticraving Medications in COD Populations

The use of disulfiram in any population is sometimes controversial, but among those with severe mental illnesses, much more so. Manufacturers themselves warn about the possible emergence of psychosis as a result of the use of this drug. However, with close monitoring for a worsening of psychiatric symptoms, this medication has proven beneficial in reducing alcohol consumption in some populations. It appears that acamprosate may be safe and effective for helping reduce alcohol consumption in individuals with mental illnesses, though definitive studies are lacking. Naltrexone may also be safe and effective in reducing alcohol consumption in this population. If there is any suspicion of covert use of opiates, however, this medication should be avoided.

Special Considerations: Tobacco Use in Co-occurring Disorders

That ongoing tobacco use is associated with increased risk of relapse in substance abusers has become increasingly accepted over the last two decades. However, it also appears that ongoing tobacco use is associated with increased likelihood of early dropout from treatment. Historically,

individuals with COD, especially those with psychotic disorders, were not expected, or even encouraged, to stop smoking. Infamously, cigarettes were used to bribe inpatients for good behaviors. For example, compliance with rules could result in the individual being rewarded with a cigarette at hourly intervals. There was a popularly held, and fully discredited, belief that there was something about schizophrenia that somehow protected against the development of cancer, so there was no need to treat nicotine dependence.

It is now quite clear that smoking cessation in COD patients is something that should be strongly promoted. However, it must be borne in mind that nicotine has some very positive effects on symptoms of psychiatric disorders, making it an even more attractive drug than it would otherwise be. The COD patient may require a great deal more support, repetition, and help with motivation than might otherwise be the case. Treatment of individuals with COD should include nicotine cessation training as an integral part of any programming, both to aid in retention and to improve overall patient health.

Conclusion

Individuals with both substance use and psychiatric disorders constitute a substantial and difficult-to-treat subsection of the addiction population. Addressing only the substance use predicts a lack of improvement in the psychiatric condition and early relapse to alcohol and other drug use. Addressing only the psychiatric condition likewise is unlikely to result in a decrease in substance use. Early and vigorous treatment for each condition should be initiated, including use of medications where indicated. In the latter case, care must be taken that medications used should be proved safe in the individual actively abusing alcohol and other substances, effective in treating the psychiatric condition when the individual is actively using, and nonaddictive where at all possible.

Much remains to be done to demonstrate that one therapeutic modality is clearly superior to another for the treatment-specific comorbid conditions, though studies are under way. It is clear, however, that concomitant treatment of all conditions present—medical, psychiatric, and substance related—must occur if there is any likelihood of improvement in any condition. It is also clear that this complicated and diverse population will present challenges for the treatment community for some time to come.

Suggested Readings

Center for Substance Abuse Treatment, Division of Systems Improvement. *Co-occurring Center for Excellence (COCE)*. Rockville, MD:Substance Abuse and Mental Health Services Administration 2009.

Elbogen EB, Johnson SC. The intricate link between violence and mental disorder: results from the National Epidemiological Survey on Alcohol and Related Conditions . *Arch Gen Psychiatry*. 2009;66(2):152–161.

Jaffee WB, Griffin ML, Gallop R, et al. Does alcohol use precipitate depression among patients with co-occurring bipolar and substance use disorders. *J Clin Psychiatry*. 2009;70(2):171–176.

Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2007;64(5):543–552.

Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *Drug Abuse Warning Network, 2006: National Estimates of Drug-Related Emergency Department Visits*, SAaMHS Administration, ed. Rockville, MD:Department of Health and Human Services 2008.

41 Medication Interactions

Drug interactions can occur through several mechanisms, and one or more of these mechanisms may be responsible for observed clinical manifestations. The mechanisms for drug interactions include effects of drugs on hepatic metabolism by cytochrome P450 (CYP) enzymes; on glucuronidation; on the function of the efflux transporter, P-glycoprotein (P-gp); and on absorption of drugs. Pharmacodynamic interactions are also important. Some drugs, when taken in combination, can exhibit synergism that might increase drug effects, resulting in toxicity.

Drugs can exert effects on hepatic metabolism by the alteration of CYP enzyme functioning. For example, the U.S. Food and Drug Administration (FDA) has classified CYP 3A4 inhibitors as strong, moderate, or weak, based on their effects on CYP 3A4 substrate metabolism. Increased systemic exposure to buprenorphine, a CYP 3A4 substrate, is noted following concomitant administration with ketoconazole, a strong CYP 3A4 inhibitor. While in vitro assays can demonstrate inhibition of CYP 450 enzymes, we often learn of inducing properties of a drug through clinical observation. For instance, the HIV antiretroviral (ARV) medication, nelfinavir, is known to inhibit CYP 3A4; however, it has been associated with reductions in the plasma concentrations of methadone, possibly due to induction of other CYP 450 enzymes involved in its clearance.

Glucuronidation is a mechanism by which many drugs are eliminated by rendering metabolites water soluble so that they can then be excreted. For example, methadone can inhibit zidovudine (AZT) glucuronidation, resulting in increased concentrations of that drug, which may, in turn, be associated with AZT toxicity. Drug interactions can also be associated with specific drug effects on the P-gp efflux transporter. For example, cocaine has been shown to induce the efflux pump, P-gp, which could potentially result in lower concentrations of drugs that are substrates of P-gp.

Other mechanisms of drug interactions include production of active metabolites resulting from coconsumed drugs and degradation of drugs in the gastrointestinal (GI) tract as a result of decreased GI mobility induced by another drug taken concomitantly. It has been shown that simultaneous cocaine and alcohol consumption results in the formation of cocaethylene, a cocaine-like compound that can contribute to toxicities associated with the abuse of these substances. Altered absorption can also be associated with clinically significant drug interactions, as in the case of methadone slowing GI mobility, which in turn can expose pH-sensitive drugs to an environment that can result in their degradation.

Pharmacodynamic interactions can result when two or more drugs with similar pharmacologic effects are coadministered. For example, when buprenorphine and benzodiazepines (BZDs) (e.g., alprazolam) have been injected together, deaths have resulted that are thought to be related to depression of the CNS with a resulting decrease in respiration. When given alone,

buprenorphine has been shown to have a ceiling effect at which higher doses do not produce further opioid-agonist effects; however, its injection with BZDs may result in a potentially life-threatening drug interaction.

It can be difficult to determine what mechanism(s) are responsible for adverse drug interactions. Controlled studies in humans that include simultaneous administration of medications and measurement of plasma drug concentrations are important for understanding pharmacokinetic (PK) and pharmacodynamic drug interactions; these interactions are important in the treatment of medical and mental disorders.

Drug Interactions between Opioids Used for Treatment of Opioid Dependence and Other Medications

Currently approved medications for the treatment of opioid dependence include methadone, buprenorphine, and L-acetyl-methadol (LAAM). However, LAAM is not currently available, and methadone is the most widely used medication for the treatment of opioid addiction. Buprenorphine is increasingly being used to treat opioid dependence, and its availability by prescription should result in more widespread use for treatment of opioid addiction.

The potential for adverse drug interactions in methadone-maintained patients has been recognized for many years when opiate withdrawal symptoms were observed in those who were prescribed rifampin for the treatment of tuberculosis, and similarly, phenytoin and/or carbamazepine were prescribed for the treatment of seizure disorders. This interaction of carbamazepine and methadone was noted when carbamazepine was studied as a pharmacotherapy for the treatment of cocaine dependence in methadone-maintained individuals and was found to be associated with opiate withdrawal and decreased the methadone trough. In the ensuing years, other adverse drug interactions, mainly between opioid therapies and medications prescribed for illnesses that occur at high frequency in opioid-dependent patients, have been observed (e.g., ARV therapies such as AZT, whose metabolism may be inhibited by methadone inhibition of glucuronidation, leading to AZT toxicity; or induction of methadone metabolism by efavirenz, leading to opiate withdrawal; or increased buprenorphine and norbuprenorphine concentrations in those receiving the protease inhibitor [PI] combination of atazanavir/ritonavir, which has been associated with cognitive dysfunction in some; or opioid toxicity observed in methadone-treated patients receiving the antibiotic ciprofloxacin). However, the availability of other medications to treat opioid dependence, albeit with little known of potential drug interactions with those therapeutics, led to a question of whether it might be possible to "match" patients with opioid dependence to medication regimens that would be associated with fewer drug interactions, thus improving clinical outcomes in those with co-occurring conditions.

Drug Interactions between Opioids and Antiretroviral Medications

Opioid-dependent patients frequently engage in high-risk behaviors that make them more susceptible to some infectious diseases. This possibility is conferred through engaging in high-risk behaviors such as sharing of injection equipment (syringes, needles, cotton, etc.) that may be contaminated with infectious agents and/or by high-risk sexual behaviors.

The treatment of choice for opioid dependence in the individual who is opioid addicted and who also has HIV disease is opioid therapy; methadone has been the most frequently utilized medication for the treatment of opioid addiction in this population. To a far lesser extent, LAAM was utilized in this population until it became unavailable, and more recently, buprenorphine is being utilized in opioid-dependence treatment in those with HIV/AIDS.

The first medication to be FDA-approved as a treatment for HIV/AIDS was AZT. This nucleoside reverse transcriptase inhibitor (NRTI) was used as a single agent to treat HIV disease prior to the use of multidrug therapy (highly active antiretroviral therapy [HAART] in those with HIV/AIDS). When methadone-maintained patients with HIV were prescribed AZT, some developed symptoms that appeared to be consistent with opioid withdrawal, including muscle/joint pain, insomnia, anxiety, and depression. Examination of the methadone trough in these patients showed therapeutic concentrations. This led to a PK study in which both methadone and AZT concentrations were examined in those with heroin addiction and AIDS. Methadone treatment was associated with a 41% increase in AZT exposure. In some patients, this was sufficient to result in AZT toxicity, which can resemble opiate withdrawal. The possible explanations for these findings included that of slowed GI transit associated with methadone treatment resulting in increased absorption of AZT and/or the possibility that methadone inhibited glucuronidation (the principal means of AZT metabolism). A second study examined the effect of other opioid-dependence pharmacotherapies on AZT metabolism. This study showed that, unlike methadone, both LAAM and buprenorphine nonsignificantly lowered AZT concentrations over an 8-hour dosing interval, while naltrexone, an opioid-antagonist medication, had no effect on AZT concentrations. The results from this study indicated that methadone interactions with specific medications might not be reflective of interactions that could occur with other opioids. This led to further investigations to determine the presence of drug interactions between HIV medications and opioids used in opioid-dependence treatment (methadone, LAAM, and buprenorphine).

Current pharmacotherapy treatment of HIV disease includes a combination of medications from at least two classes. The backbone of HAART consists of either a PI, often boosted by low-dose ritonavir—a PI that inhibits CYP 3A4 enzyme activity and therefore can delay metabolism of PIs that are substrates of CYP 3A4—or a nonnucleoside reverse transcriptase inhibitor (NNRTI). In addition, two NNRTIs are added to complete the regimen. Some of these medications have significant effects on CYP 3A4, including induction by some drugs and inhibition by others.

Further investigation of drug interactions between methadone and ARV medications revealed that other medications with CYP 3A4-inducing properties were also associated with opiate withdrawal when administered concomitantly with methadone.

Should medications used to treat HIV alter methadone metabolism, there are two principal adverse events of concern. The first is that of the onset of opiate withdrawal symptoms. If opioid-maintained individuals with HIV disease experience opiate withdrawal with HAART, they may not adhere to the prescribed HIV treatment regimen. Poor adherence to HIV therapeutics has been linked to ongoing drug abuse. Poor adherence can also result in development of viral resistance and failure of the HIV therapeutic regimen, underscoring the need for those providing methadone-maintenance therapies to be aware of the potential for adverse drug interactions in their patients with HIV/AIDS who are receiving HAART. Another possibility is that of opioid toxicity, which can potentially result in cognitive impairment or respiratory depression. While there have been clinical episodes of opioid toxicity thought to be precipitated by the use of methadone with an ARV medication that inhibits methadone metabolism, to date, only one drug-interaction study has been conducted in human volunteers that shows significant increases in methadone concentrations and LAAM concentrations when administered with an ARV (again, an NNRTI drug) known to inhibit CYP 3A4, delavirdine. No significant opioid toxicity was observed in this study, but delavirdine was dosed only for 7 days in this

drug-interaction study. With ongoing treatment as in clinical care, the potential for developing opioid toxicity should be considered. Results from drug-interaction studies in humans showing significant interactions with methadone have resulted in the U.S. FDA decision that full approval of any HIV medication would require a drug-interaction study to be conducted between methadone and the drug under FDA consideration.

Drug Interactions between Opioids and Medications Used to Treat Other Infectious Diseases

Hepatitis C Medications: Interferon

Hepatitis C virus (HCV) infection is a common co-occurring infection in opioid-dependent individuals; at particularly high risk are those who are injection drug users (IDUs) and who have engaged in high-risk injection practices. Many of those with co-occurring HCV will require treatment for this infection. The current standard of care for treatment of HCV is a combination of interferon and ribavirin. Thus far, two drug-interaction studies have been conducted exploring the potential for adverse drug interactions between opioid therapies and HCV medications.

Methadone has been studied in combination with interferon and no significant drug interaction was identified. The impetus for this study was complaints of adverse symptoms in methadone-maintained patients receiving treatment for HCV. However, the administration of interferon and ribavirin is itself known to be associated with a variety of adverse events (e.g., nausea, anorexia, myalgias, depression, and insomnia), some of which may be mistaken for opiate withdrawal symptoms. There is no additional contribution to the medication side effects that can occur with medications used in the treatment of HCV due to drug interactions with methadone. Buprenorphine has yet to be studied in this population.

Tuberculosis Medications: Rifampin

The adverse drug interaction between methadone and rifampin, a mainstay of tuberculosis treatment, has long been known. Rifampin is an inducer of CYP 3A4, which has been associated with opiate withdrawal in methadone-maintained patients. Rifabutin appears not to produce this adverse drug interaction to the same degree as rifampin and is recommended as a substitute for rifampin in this population. The interaction between buprenorphine and rifampin is currently under study. Several study participants to date have experienced opiate withdrawal requiring early study termination underscoring the potency of rifampin as a CYP 3A4 inducer. A second study to determine whether the alternative medication, rifabutin, is associated with adverse drug interactions in buprenorphine-treated patients is currently under way. Isoniazid is an inhibitor of CYP 3A4 and has not been reported to produce significant adverse drug interactions in combination with methadone.

Antibiotics

Opioid dependence, particularly that associated with injection drug use, is associated with a variety of infectious processes that often require antibiotic treatment. Frequent complications of injection drug use include skin infections such as abscesses, cellulitis, endocarditis, and sepsis. There are limited reports of adverse drug interactions between methadone and antibiotic medications. However, ciprofloxacin, a widely used antibiotic effective for a large number of infections, has been associated with opioid toxicity when administered to methadone-maintained

patients. Some antifungal medications, including fluconazole and voriconazole, are potent inhibitors of CYP 3A4 and may also be associated with increases in opioid exposure. Increases in opioid exposure may be better tolerated in those receiving treatment with buprenorphine as compared to methadone or LAAM. The reason for this is that buprenorphine is a partial agonist associated with a ceiling effect in terms of its opioid-agonist effects. Increasing doses of buprenorphine do not produce proportional opioid-agonist effects, meaning that respiratory depression, a common cause of morbidity and mortality with toxic doses of full μ-opioid agonists, is less likely to occur in those treated with buprenorphine.

Drug Interactions between Opioids and Benzodiazepines

BZD use is prevalent in the population of those with substance use disorders (SUDs) and, specifically, in those with opioid dependence. Epidemiologic studies have suggested that co-occurring psychiatric disorders, such as depression, anxiety, sleep disorders, and polysubstance abuse, contribute to the high rate of BZD use among opioid-dependent individuals.

Methadone and buprenorphine could have PK interactions with BZDs, since they share CYP enzyme metabolic pathways. Many BZDs are weak competitors for CYP 3A4; methadone is metabolized by a variety of CYP isoforms. Buprenorphine is metabolized by CYP 3A4, but is also a weak inhibitor of this enzyme. There are few clinical studies that have investigated PK interactions between BZDs administered concomitantly with methadone, but none have directly studied PK interactions between BZDs and buprenorphine. Human clinical studies are needed to investigate the simultaneous use of opioids and BZDs at therapeutic doses in order to determine the possible clinical consequences resulting from PK interactions between these medications.

Currently, pharmacodynamic interactions are the major concern in those who ingest both methadone or buprenorphine and BZDs. It is of clinical importance to note that methadone and BZDs are administered orally when used therapeutically, while buprenorphine tablets are administered sublingually. Buprenorphine, an opioid partial agonist, has been shown to have a ceiling effect at which higher doses do not produce further opioid-agonist effects; however, when abused in combination with BZDs intravenously, significant morbidity and mortality has been reported. A synergism between opioids and BZDs to produce respiratory depression may result from common intracellular transduction pathways between opioids and the $GABA_A$ receptor system, resulting in increased chloride ion conduction and decreased membrane excitability. Methadone alone has been shown to produce respiratory depression in humans; this effect may be potentiated by coadministration of BZDs. The degree of respiratory depression observed with methadone and BZD administration has been reported to be greater than that observed when BZDs are simultaneously administered with buprenorphine. In contrast, buprenorphine and BZDs, when administered by the injected route, may produce severe adverse events as a result of rapid attainment of high (toxic) plasma concentrations of the drugs. This may result in a synergism between the two medications and consequent depression of the CNS as well as a potentially lethal decrease in respiration.

Adverse Effects Related to Drug Interactions

Adverse effects related to drug interactions can be quite harmful to patients requiring opioid therapy for treatment of opioid dependence. For those who experience opiate withdrawal symptoms related to induction of opioid metabolism, it is quite possible that nonadherence to

prescribed regimens will occur, which could result in poor clinical outcomes, worsening of disease, and increased substance abuse. In situations in which a drug interaction results in inhibition of opioid metabolism, it is possible that adverse events could include cognitive impairment, decreased respiration, and possible adverse effects on cardiac conduction.

In recent years, increasing attention has focused on the effect of LAAM and methadone on cardiac QTc interval. LAAM was removed from the market in Europe and was black-box-labeled in the United States following a series of deaths linked to the occurrence of cardiac dysrhythmias including Torsades de Pointes. Both LAAM and methadone have been shown to block hERG (human ether-à-go-go) potassium channels, which can be associated with slowed electrical conduction in the heart, in some cases producing arrhythmia. In some, this has been observed to be correlated with the use of higher doses of methadone (>100 mg daily).

Drug Interactions between Prescription Opioid Analgesics and Other Medications

Morphine exerts its analgesic effects through agonism at μ-opioid receptors. It is metabolized chiefly through glucuronidation by two enzymes: UDP-glucuronosyltransferase (UGT) 2B7, which produces the 6-conjugate (M6G); and UGT 1A3, which produces the 3-conjugate (M3G). The M3G metabolite possesses neuroexcitatory effects, while M6G is responsible for the analgesic effects. Both genetic variability of the UGT enzymes 2B7 and 1A3 and drugs that inhibit or induce UGT enzymes could affect the M3G–M6G ratio. However, patient response to morphine analgesia is not well understood because the UGT enzyme system is not as well studied as the CYP 450 enzyme system. Inhibitors of UGT enzymes that might decrease the formation of both metabolites include tricyclic antidepressants, such as amitriptyline, nortriptyline, and clomipramine. Morphine's glucuronidation may be competitively inhibited by morphine itself as well as by the coadministration of chloramphenicol or diazepam. Some in vitro studies have shown that morphine might be a P-gp substrate. Therefore, the inhibition of P-gp would be permissive of morphine entrance through the blood–brain barrier, potentially enhancing its CNS effects, including analgesia. Whether this potentiation occurs is still unclear; however, drugs that are P-gp inhibitors that could theoretically enhance CNS morphine effects would include the immunosuppressant, cyclosporine; the calcium channel blocker, diltiazem; and the antifungal medication, itraconazole.

Hydromorphone and oxymorphone are morphine analogues that are both metabolized by UGT enzymes. Hydromorphone is the CYP 2D6–produced metabolite of hydrocodone, and like morphine, it is minimally metabolized by CYP enzymes. To date, there is no published literature regarding PK alteration and changes in clinical efficacy of hydromorphone when UGT enzymes are inhibited or induced.

Opioid analgesics such as methadone, oxycodone, and hydrocodone share the same CYP 2D6 pathway for metabolism with numerous other drugs. When multiple substrates of CYP 2D6 are ingested concurrently, altered drug levels may occur, but are difficult to predict. In one known example, methadone has been reported to inhibit CYP 2D6 and may alter the PK of the antidepressant desipramine, a substrate of CYP 2D6. Methadone has been reported to be associated with increased desipramine levels. Other tricyclic antidepressants (imipramine), antipsychotics (risperidone and other phenothiazines), analgesics (codeine), antiarrhythmics (flecainide), and some β-blockers are also substrates of CYP 2D6 and may have the potential for adverse drug interactions based on increased plasma concentrations if given with methadone. Dextromethorphan, a substrate of CYP 2D6, has been associated with delirium in a patient receiving methadone. This adverse event abated with cessation of dextromethorphan and was attributed to the effect of methadone on dextromethorphan clearance.

Buprenorphine is chiefly metabolized by CYP 3A4. Opioid toxicity or opioid withdrawal is expected as a consequence of drug–drug interactions with 3A4 inhibitors (azole antifungals, macrolide antibiotics, and nefazodone) and inducers (rifampin and some antiepileptics). However, the ability to predict those interactions is difficult, and thus far, few drug–drug PK interactions have been associated with adverse events in those receiving buprenorphine and other medications concurrently.

Drug Interactions between Stimulants and Other Medications

Psychostimulants produce euphoria, mood elevation, sharpened sensory perception, increased energy, and, in some, extraversion. Adverse effects typically predominate when high doses are ingested or as a result of drug interactions when stimulants are ingested with other medications. As sympathomimetic agents, psychostimulants produce cardiovascular effects, including hypertension and increased cardiac output. Interactions may occur with the coadministration of psychotropic and cardiovascular medications. The increase in CNS and cardiovascular stimulation that might occur could be related to serotonergic syndrome, which is a constellation of symptoms that includes neuromuscular hyperactivity, autonomic hyperactivity, and altered mental status. Psychostimulants might interact adversely with antidepressants as a result of excess serotonin activity, particularly monoamine oxidase inhibitors (MAOI) or selective serotonin reuptake inhibitors (SSRI), and produce symptoms of serotonin toxicity. Fatal case reports have confirmed evidence of the relationship between serotonin syndrome and coadministration of MAOIs, SSRIs, and illegal stimulants.

Amphetamines and MDMA (3,4-methylenedioxymethamphetamine, also known by the street name, ecstasy) are metabolized primarily by CYP 2D6, showing nonlinear kinetics with unpredictable effects. Drugs that inhibit CYP 2D6 may increase the serum concentration of amphetamine and MDMA, leading to risk of toxicity. Inhibitors of CYP 2D6 include several SSRIs (e.g., paroxetine and fluoxetine), ARV medications (e.g., ritonavir), and antiarrhythmics (e.g., quinidine).

Cocaine- and methamphetamine-addicted individuals are usually multidrug users, and their conditions are often complicated by co-occurring mental disorders. The opioid-dependent population has been shown to use cocaine at high rates. Among opioid-dependent individuals, up to 50% use cocaine while being treated for opioid dependence. Those patients may require multidrug therapy and close monitoring for drug interactions, since opioid–cocaine dependence has been associated with poor clinical outcomes in opioid-dependence treatment.

Cocaine has recently been shown to diminish buprenorphine concentrations. The underlying PK interaction between those drugs is not obvious since each had been reported to be metabolized by different pathways. Lower buprenorphine plasma concentrations may result from induction of buprenorphine metabolism through an effect of cocaine on CYP 3A4 or through an ability of cocaine to induce the efflux pump, P-gp. Another possible explanation is that cocaine metabolites are known to be vasoconstrictors, which might reduce buprenorphine absorption sublingually. Cocaine use appears to have a similar, but less severe, effect on methadone concentrations. This reduced effect may be related to the fact that methadone is metabolized by several CYP 450 enzymes; therefore, the effect of cocaine on CYP 3A4 function regarding methadone metabolism is diminished in the presence of otherwise normal metabolic processing by the liver relative to effects observed for buprenorphine, which is primarily metabolized by CYP 3A4. Methamphetamine has not been associated with adverse drug interactions in combination with either methadone or buprenorphine to date.

Disulfiram (also known by the trade name Antabuse) is an FDA-approved treatment for alcohol dependence and has shown promise as a treatment for cocaine dependence as well. Initially, disulfiram was evaluated in patients with co-occurring cocaine and alcohol dependence. Study participants in the disulfiram arm of the study used less cocaine; however, it was not clear if the reduction of stimulant use was due to the reduction in alcohol intake or a direct action of disulfiram to reduce cocaine use. A more recent study evaluated disulfiram as treatment for cocaine dependence in a population of primary cocaine users without alcohol dependence. This randomized, placebo-controlled study that included cognitive–behavioral therapy (CBT) or interpersonal psychotherapy showed that disulfiram exerted a direct effect in reducing cocaine use rather than a secondary effect in reducing concurrent alcohol use. The observed effect of disulfiram was postulated to be associated with reduced cocaine consumption resulting from its ability to inhibit the function of aldehyde dehydrogenases. Aldehyde dehydrogenase inhibition is responsible for the disulfiram–alcohol interaction as well as the inhibition of dopamine (DA) β-hydroxylase and of the aldehyde dehydrogenase–mediated metabolism of serotonin to 5-hydroxyindoleacetic acid; the latter two may be associated with reduction in positive effects of cocaine use. When receiving disulfiram treatment, study participants have reported reduction in cocaine-associated subjective effects such as "high" and "rush"; cardiovascular toxicity was not observed. Furthermore, the safety of disulfiram for the treatment of alcohol and cocaine dependence was studied in randomized clinical trials that showed that disulfiram generally has an acceptable side-effect and drug-interaction profile.

Drug Interactions between Alcohol and Other Medications

Alcohol is a potent CNS depressant that may interact with many drugs; it affects multiple systems within the brain, but mainly it acts as an agonist at γ-aminobutyric acid (GABA) receptors. When used concurrently with other depressants such as BZDs and opioids, increased sedation and serious depression of respiratory and/or cardiac function can result.

Alcohol is primarily absorbed through the stomach and the small intestine and largely metabolized by the liver. Hepatic alcohol metabolism occurs via alcohol dehydrogenase, catalase, and the microsomal CYP 450 pathway, which leads to the oxidation of alcohol to acetaldehyde. Drugs that share the same CYP P450 metabolic pathway as alcohol may interact in several ways, including reduction in hepatic metabolism of other drugs resulting from acute alcohol ingestion, increased drug clearance in the presence of chronic alcohol intake, and reduced elimination of drugs resulting from alcoholic liver disease.

Benzodiazepines

Alcohol may have significant interactions with BZDs, medications that are commonly prescribed for anxiety and insomnia. BZDs (e.g., diazepam, lorazepam, alprazolam, clonazepam, and temazepam) are generally considered safe when used alone; however, they can be dangerous if taken with alcohol. BZDs and alcohol can act synergistically in that these drugs facilitate inhibition at GABA receptors and alcohol decreases the excitatory effect of glutamate at *N*-methyl *D*-aspartate (NMDA) receptors. This mechanism may help to explain fatal overdose in the presence of opioids and/or BZD and alcohol. BZDs may enhance the adverse psychomotor effect of ethanol since it has been reported that BZD concentrations are elevated following a single dose of alcohol and BZD. PK changes are expected with both acute and chronic drinkers; however, clinical studies have shown that following a 10-mg (intravenous) dose of diazepam or

1-mg (oral) dose of alprazolam, chronic alcoholics had significantly lower concentrations of the BZDs than healthy nonalcoholics, suggesting that PK alterations may be more prominent in alcoholics with chronic consumption of large amounts of alcohol and who may be more likely to have impaired liver function.

Bupropion

The antidepressant and smoking-cessation medication bupropion is metabolized to hydroxybupropion, which is an inhibitor of and substrate for CYP 2D6. Patients with a history of alcohol use metabolize bupropion faster with consequent production of active metabolites; therefore, the use of bupropion and alcohol may increase the risk of lowering the seizure threshold (especially during alcohol withdrawal), which is a known adverse event associated with bupropion use in persons with alcohol dependence. Bupropion treatment of depression or nicotine dependence should be carefully considered in a patient with an alcohol use disorder or known misuse of alcohol.

Methadone

A pharmacodynamic interaction has been reported to occur between alcohol and methadone. Although a direct effect on PK of methadone has not been found, severe adverse events including deaths have occurred in patients who coingest these substances. Interestingly, no drug interaction of clinical significance has been detected between methadone and disulfiram. These findings underline the need to treat co-occurring alcohol disorders in opioid-addicted patients receiving opioid-agonist therapy. Clinical reports of adverse events related to alcohol ingestion in buprenorphine-treated patients have not been published to date.

Cocaine

Cocaine metabolism is mainly accomplished through hydrolysis by esterases in the serum and liver. In the presence of alcohol, cocaine undergoes transesterification, resulting in production of cocaethylene, an active metabolite that is structurally similar to cocaine. Cocaethylene is less potent than an equivalent cocaine dose with respect to neurochemical, pharmacologic, and behavioral properties; however, when cocaine and alcohol are used together, some studies have suggested that cocaethylene may have the potential to increase cocaine-associated toxicities. A placebo-controlled, double-blinded study reported that the behavioral and physiologic effects of intranasal cocaethylene in humans are similar to those of cocaine. Like cocaine, cocaethylene produces euphoria and increases both heart rate and systolic blood pressure; the slower elimination of cocaethylene could result in its accumulation, with increased potential for toxicity with binge use of cocaine and alcohol. Data from some human studies have shown much higher concentrations of cocaethylene, even exceeding those of cocaine following fatal overdose.

Methylphenidate

Methylphenidate (MPH) is normally metabolized to an inactive substance, ritalinic acid. Coadministration with ethanol produces an active metabolite, ethylphenidate, obtained via metabolism by carboxylesterases in the liver. Coadministration of MPH with ethanol is also believed to elevate MPH plasma concentrations, decrease clearance, and increase half-life of the drug, underscoring a potential for toxicity with coabuse of these drugs.

Drug Interactions between Cigarette Smoke or Nicotine and Other Medications

Cigarette smoke is known to contain, in addition to nicotine, thousands of different ingredients (e.g., polycyclic aromatic hydrocarbons, *N*-nitrosamines, and aromatic amines). Those compounds, especially aromatic hydrocarbons, through tobacco combustion may induce CYP 1A1, 1A2, and 2E1 with consequent change of metabolism and elimination of other drugs that are taken at the same time.

Induction of CYP 1A2 by cigarette smoking is responsible for many clinically relevant drug interactions, making therapeutic outcomes unpredictable and possibly leading to toxicities. Several classes of drugs that are metabolized by CYP 1A2 include atypical antipsychotics, SSRIs, BZDs, and β-blockers. In addition to toxicity related to PK interactions, smoking may also be associated with other adverse events, such as increased risk of cardiovascular and cerebrovascular disease. Some of these risks could potentially be exacerbated by drug interactions.

A major concern with cigarette smoking with regard to drug interactions is that those affected by other comorbid conditions, for example, schizophrenia and/or alcohol use disorders, have higher rates of cigarette smoking than the general population. Smoking is the most prevalent of the SUDs in patients suffering from schizophrenia. Between 72% and 90% of those with schizophrenia are smokers compared with 24% of the general population. In the alcohol-dependent population, over 80% are tobacco smokers, and an epidemiologic study has revealed that smokers have a 4% to 10% increased risk of developing an alcohol use disorder. As a result of cigarette smoking with its associated induction of CYP 1A2, increased metabolism and/or decreased plasma concentrations may be observed for many antipsychotics (olanzapine, clozapine, fluphenazine, haloperidol, and chlorpromazine) and other adjunctive therapies for schizophrenia, including antidepressants (imipramine, clomipramine, and fluvoxamine) and BZDs (alprazolam, lorazepam, oxazepam, and diazepam). The possibility of alcohol abuse in those with co-occurring mental illness and those who smoke cigarettes may place these individuals at risk for adverse drug–drug interactions as their clinical condition is likely to require that they be treated with several medications.

Conclusion

Drug interactions between presently ingested substances, both licit and/or illicit, are a leading cause of morbidity and mortality. This chapter gives a broad overview of drug interactions among illicit substances (i.e., cocaine), legal drugs (i.e., alcohol and tobacco), prescription medications (i.e., ARV and analgesics), and other pharmacotherapies to treat SUDs (e.g., methadone, buprenorphine, and disulfiram). Patients requiring medications to treat SUDs often have co-occurring medical (e.g., HIV/AIDS) and mental (e.g., schizophrenia) illnesses that will require additional medication treatment. These clinical realities place patients with SUDs at greater risk for potentially toxic drug interactions. Furthermore, the clinical management of patients with polysubstance (i.e., opioid/cocaine/alcohol) abuse is common and complex, and can have unpredictable outcomes.

Suggested Readings

Berk SI, Litwin AH, Arnsten JH, et al. Effects of pegylated interferon alfa-2b on the pharmacokinetic and pharmacodynamic properties of methadone: a prospective, nonrandomized, crossover study in patients coinfected with hepatitis C and HIV receiving methadone maintenance treatment. *Clin Ther.* 2007;29:131–138.

Kharasch ED, Walker A, Whittington D, et al. Methadone metabolism and clearance are induced by nelfinavir despite inhibition of cytochrome P4503A (CYP3A) activity. *Drug Alcohol Depend.* 2009;101:158–168.

McCance-Katz EF, Moody DE, Morse GD, et al. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. *Drug Alcohol Depend.* 2007;91:269–278.

McCance-Katz EF, Rainey PM, Moody DE. Effect of cocaine use on buprenorphine pharmacokinetics in humans. *Am J Addict.* 2010;19:38–46.

McCance-Katz EF, Rainey PM, Smith P, et al. Drug interactions between opioids and antiretroviral medications: interaction between methadone, LAAM, and delavirdine. *Am J Addict.* 2006;15:23–34.

42 Models of Prevention

School-Based Programs

Preventive interventions and related initiatives to reduce substance abuse have been the focus of a great deal of research. A wide variety of activities have been used to achieve the goal of reduced drug abuse, particularly among adolescents. These prevention activities range from educational and skills training activities that take place within schools, families, and communities to mass media public service announcements (PSAs); policy initiatives, such as requiring health-warning labels on cigarettes and alcohol; changes in school rules (i.e., "zero-tolerance" policies); and laws and regulations, including increased cigarette taxes and minimum purchasing-age requirements. However, the bulk of the drug-abuse prevention research in the United States in the past 25 to 30 years has concentrated on school-based prevention programs. Because the general pattern of substance use initiation and escalation is well documented, many prevention programs aim to prevent early-stage substance use or delay the onset of use among adolescents. Typically, these programs are provided to middle school or junior high school students and target the use of tobacco, alcohol, and marijuana because these are the most widely used substances in the United States and because preventing them may reduce the risk for the abuse of other illicit drugs and their associated negative outcomes. Research shows that the most effective approaches to the prevention of adolescent drug abuse are derived from psychosocial theories and focus primarily on the psychosocial risk and protective factors that promote the initiation and early stages of substance use.

The Importance of Prevention

Prevention is important because it offers a logical alternative to treatment. Many experts believe it is easier and less expensive to prevent substance abuse than it is to treat such an insidious disorder once it has developed. However, from a historical perspective, most initial efforts to develop effective substance abuse prevention programs achieved only a limited degree of success. Many failed completely because they were based on erroneous assumptions about the causes of drug abuse. The first major breakthrough came at the end of the 1970s in the area of school-based smoking prevention. That work stimulated a great deal of prevention research and led to the development of several promising prevention approaches.

The School as the Site of Prevention Efforts

The development and testing of approaches for preventing adolescent substance abuse have largely focused on middle/junior high school students. Schools have served as the primary setting for prevention efforts in large part because they offer the most efficient access to large numbers of adolescents. Furthermore, in addition to their traditional educational mission, schools often take steps to address a variety of social and health problems among students, particularly those that present a significant barrier to the achievement of educational objectives.

Etiology and Implications for Prevention

To provide a context for understanding existing substance abuse prevention efforts and for developing a prescription for the most effective preventive interventions possible, it is necessary to be familiar with the factors associated with the initiation and maintenance of tobacco, alcohol, and drug abuse.

Etiologic Determinants

A variety of risk factors for early-stage substance use, as well as several protective factors that offset the effects of risk, have been identified. Furthermore, a number of theoretical models have been developed or applied to the phenomenon of alcohol and drug use among youth. A large body of literature demonstrates that substance abuse results from the complex interaction of a number of different factors, including cognitive, attitudinal, social, personality, pharmacologic, biologic, and developmental factors.

Social Factors

Social factors are the most powerful influences promoting the initiation of tobacco, alcohol, and drug abuse. These include the behavior and attitudes regarding substance use among significant others, such as parents, elder siblings, and friends. Studies reveal that parents' use of alcohol, tobacco, marijuana, and other illicit drugs, and parental attitudes that are not explicitly against use, often translate into higher levels of use among children and adolescents. Poor family relationships and inadequate parenting practices (i.e., lack of parental monitoring) have been identified as risk factors for youth substance use.

Cognitive and Attitudinal Factors

Individuals who are unaware of the adverse consequences of tobacco, alcohol, and drug use, as well as those who have positive attitudes toward substance use, are more likely to become substance users than those with either more knowledge or more negative attitudes toward substance use. Positive expectations about the effects of substance use are also predictive of substance use behavior.

Personality Factors

Substance use is associated with a number of psychological characteristics. Substance users have lower mood, self-esteem, assertiveness, personal control, and self-efficacy than nonusers, and are more anxious, impulsive, and rebellious than nonusers. The clinical literature also suggests that individuals with a specific psychiatric condition or symptoms (e.g., anxiety and depression) may use particular substances as a way of alleviating these feelings.

Pharmacologic Factors

The pharmacology of commonly abused substances varies, although animal research has shown that several drugs of abuse (cocaine, amphetamine, morphine, nicotine, and alcohol), each

with different molecular mechanisms of action, affect the brain in the same way by increasing strength at excitatory synapses on midbrain dopamine (DA) neurons. Furthermore, virtually all of these substances produce effects that are highly reinforcing and dependency producing. For tobacco, alcohol, and most illicit drugs, tolerance develops quickly, leading to increased dosages and an increased frequency of use. Once a pattern of dependent use has been established, termination of use produces dysphoric feelings and physical withdrawal symptoms.

Behavioral Factors

Substance use is highly associated with a variety of health-compromising or problem behaviors. Individuals who use one substance are more likely to use others. Indeed, substance abuse among young people is often considered to be part of a general syndrome reflecting a particular value orientation. Youth who smoke, drink, or use drugs tend to get lower grades in school; are not generally involved in adult-sanctioned activities, such as sports and clubs; and are more likely than nonusers to become involved in antisocial or delinquent behavior, aggressiveness, and premature sexual activity.

Initiation and Developmental Course

Since the 1960s, some degree of experimentation with substance use has become commonplace in contemporary American society. This is particularly true with respect to alcohol, tobacco, and marijuana, which are the most widely used and abused substances in society. For most individuals, experimentation with tobacco, alcohol, and marijuana typically takes place during the adolescent years. First use and intermittent experimentation generally occur almost exclusively within the context of social situations. After a period of experimentation and regular use, some individuals develop patterns of use characterized by both psychological and physiologic dependence.

Substance Use Progression

Research indicates that experimentation with one substance frequently leads to experimentation with others in a logical and generally predictable progression. Most individuals begin by using alcohol and tobacco, progressing later to the use of marijuana. This developmental progression corresponds closely to the prevalence of these substances in our society, with alcohol being the most widely used, followed by tobacco and then marijuana. Some individuals may also use inhalants early in this sequence because of the wide availability. For some individuals, this progression may eventuate in the use of depressants, stimulants, hallucinogens, and other drugs. However, many individuals either may discontinue use after a short period of experimentation or may not progress from the use of one substance to the use of others.

Adolescence and Substance Abuse Risk

Adolescence is frequently characterized as a period of great physical and psychological change. During adolescence, individuals typically experiment with a wide range of behaviors and lifestyle patterns. This occurs as part of the natural process of separating from parents, developing a sense of autonomy and independence, establishing a personal identity, and acquiring the skills necessary for functioning effectively in an adult world. However, many of the developmental changes that are necessary prerequisites for becoming healthy adults increase an adolescent's risk of smoking, drinking, or using drugs. Adolescents who are impatient to assume adult roles may smoke, drink, or use drugs as a way of appearing more grown-up and laying claim to adult status. Adolescents may also engage in substance use because it provides them with a means of establishing solidarity with a particular peer group, rebelling against parental authority, or establishing their own individual identity.

Prevention Strategies

Prevention has been conceptualized in terms of supply- and demand-reduction models and as primary, secondary, and tertiary prevention. Each encompasses a different aspect of prevention, and has substantially different operational implications.

Supply- and Demand Reduction

Supply-reduction efforts are based on the fundamental assumption that substance use can be controlled by simply controlling the supply or availability of drugs. This has been the driving force behind the activities of law-enforcement agencies, particularly with respect to the interdiction of drugs by governmental agencies, such as the Drug Enforcement Administration (DEA), the Federal Bureau of Investigation (FBI), and local police departments. Demand-reduction efforts, on the other hand, are conceptualized as those that attempt to dissuade, discourage, or deter individuals from using drugs or reducing the desire to use drugs. Demand reduction includes prevention, education, and treatment programs.

Types of Prevention

Consistent with usage in the field of public health, primary prevention interventions are designed to reach individuals before they have developed a specific disorder or disease. As such, they target a general population of individuals who, for the most part, have not yet begun using tobacco, alcohol, or other drugs. The goal of these approaches is to prevent substance use and abuse by intervening upon individual and/or environmental factors viewed as promoting or supporting this type of health-compromising behavior. Secondary prevention involves screening and early intervention. Tertiary prevention involves preventing the progression of a well-established disorder to the point of disability. However, one criticism of this classification system is that it is difficult to distinguish between tertiary prevention and treatment in that both involve care for persons with an established disorder.

Information Dissemination

Information dissemination programs have taken the form of public information campaigns and school-based tobacco-, alcohol-, and drug-education programs. Public information campaigns have involved the use of pamphlets, leaflets, posters, and PSAs to increase public awareness of the problem of tobacco, alcohol, or drug abuse and alter societal norms concerning use. School programs have involved classroom curricula, assembly programs featuring guest speakers (frequently policemen or health professionals), and educational films.

Many informational approaches have been designed to deter substance use by emphasizing, even dramatizing, the risks associated with substance use. The underlying assumption of fear-arousal approaches is that evoking fear is more effective than a simple exposition of the facts. These approaches go beyond a dispassionate presentation of information by providing a clear and unambiguous message that substance use is dangerous. In addition, traditional prevention programs have sometimes focused on the immorality of substance use. Program providers not only teach the objective facts but also "preach" to students about the evils of smoking, drinking, or using drugs, and exhort them not to engage in those behaviors.

Affective Education

The results of evaluation studies testing the effectiveness of affective education approaches have been as discouraging as evaluations of informational approaches. Although affective education approaches have, in some instances, been able to demonstrate an impact on one or more of the

correlates of substance use, they have not produced an impact on substance use behavior. While some of the components of affective education that focus on personal skills (e.g., communication and assertiveness) may be helpful as part of a larger prevention strategy, they are not effective in changing drug-use behavior when emphasized on their own.

Alternatives

One method of preventing substance abuse has been to restructure part of the adolescents' environment to provide them with alternatives to substance use and activities associated with substance use. Several different alternative approaches have been developed. The original model for alternatives typically involved the establishment of youth centers providing a particular activity or set of activities in the community (e.g., hobbies, team sports, and community service). It was assumed that if adolescents could be provided with real-life experiences that would be as appealing as substance use, their involvement in these activities would actually take the place of involvement with substance use.

While these approaches may seem worthwhile, few alternative approaches have been evaluated properly, and those that have been evaluated are ineffective in preventing substance-use behavior.

Toward Theory-Based Interventions: Psychological Inoculation

The pioneering prevention research at the University of Houston toward the end of the 1970s triggered a major departure from traditional approaches to tobacco, alcohol, and drug abuse prevention. Unlike previous approaches that focused on information dissemination and/or fear arousal, the strategy focused on the social and psychological factors believed to be involved in the initiation of cigarette smoking.

The application of the concept of psychological inoculation as a smoking-prevention strategy is fairly straightforward. Smoking is conceptualized as being the result of social influences (persuasive messages) to smoke from peers and the media that are either direct (offers to smoke from other adolescents or cigarette advertising) or indirect (exposure to high-status role models who smoke). If adolescents are faced with peer pressure to try cigarettes, for example, they can be forewarned and prepared by providing them with the necessary skills for countering such pressure. They can be trained on what to say in specific situations to diffuse or negate attempts at peer pressure, and they can be taught to form counterarguments in situations when they see older youth posturing and acting "tough" by smoking.

Resistance Skills Training

There are several variations in the prevention model. These interventions were designed to increase students' awareness of the various social influences to engage in substance use. A distinctive feature of these prevention models is that they place more emphasis on teaching students specific skills for effectively resisting both peer and media pressures to smoke, drink, or use drugs. These resistance skills–training programs (also referred to as "social influence" or "refusal skills–training" approaches) are based on a conceptual model stressing the fundamental importance of social factors in promoting the initiation of substance use among adolescents. These influences come from the family (parents and older siblings), peers, and the mass media. Adolescents may be predisposed toward substance use because substance-use behavior is modeled by parents or older siblings, or because of the transmission of positive messages and attitudes concerning substance use.

In general, results from long-term follow-up studies of school-based social-influence approaches indicate that these prevention effects are typically not maintained. While this has

led some to conclude that school-based prevention approaches may not be powerful enough to produce lasting prevention effects, others have argued that the apparent failure of studies testing resistance skills–training approaches to produce long-term prevention effects may have to do with factors related to either the type of intervention tested in these studies or the way these interventions were implemented.

Competence Enhancement

Since the end of the 1970s and up to the present, considerable research has also been conducted with a prevention approach that teaches general personal and social skills either alone or in combination with components of the social resistance–skills model. These competence-enhancement approaches are more comprehensive than either traditional cognitive–affective approaches or the more recent resistance-skills model. In addition to recognizing the importance of social learning processes, such as modeling, imitation, and reinforcement, competence-enhancement approaches posit that youth with poor personal and social skills are not only more susceptible to influences that promote drug use but also motivated to use drugs as an alternative to more adaptive coping strategies. They are based on social learning theory and problem behavior theory. Substance abuse is conceptualized as a socially learned and functional behavior, resulting from the interplay of social and personal factors. Substance-use behavior is learned through modeling and reinforcement and is influenced by cognition, attitudes, and beliefs.

Conclusion

A number of substance-abuse prevention approaches have been developed and tested over the years. The most common approaches to tobacco-, alcohol-, and drug-abuse prevention are those that focus on providing factual information about the adverse consequences of using these substances, with some approaches including a mix of scare tactics and moral messages. Other commonly used approaches to substance-abuse prevention have used affective education and alternatives approaches. The existing evaluation literature shows rather conclusively that these are not effective prevention strategies when the standard of effectiveness concerns the ability to influence substance-use behavior. On the other hand, research shows that the most effective prevention approaches are based on an understanding of the etiology of substance abuse supported by a sound theoretical model. Contemporary school-based substance-abuse prevention programs that focus on social-resistance and competence-enhancement skills are effective in large part because their assumptions about the causes of substance use are consistent with more recently conducted etiologic research.

Harm Reduction

The harm reduction (HR) model grows from the clinical- and preventive-medicine framework of public health, whose goals include reducing morbidity and mortality in populations by using the tools of primary, secondary, and tertiary prevention. In HR, rather than focusing on the reduction of drug use per se, primary prevention seeks to reduce the harms of drugs and drug-control policies and the risks of illicit drug markets. Secondary prevention aims to limit the prevalence and severity of these individual psychologic harms and medical disorders associated with continued drug use and addiction (i.e., effective treatment and rehabilitation, HIV programs). Tertiary prevention involves limiting collateral medical and social consequences of drug

use, drug markets, and addiction for individuals, families, and communities—once drug use has become a prevalent and chronic condition.

Harm Reduction in the United States

While there are exceptions, most American politicians and public officials have publicly rejected many HR premises and ignored the evidence supporting HR, even as drug policy in the United States remains officially blind to abundant evidence of its own failures. While Europeans and Australians established and expanded such programs in the 1980s (often in response to the all-too-apparent American catastrophe of HIV among injection drug users [IDUs]), the United States resisted needle and syringe programs (NSPs), arguing that syringe distribution encourages illicit drug use and "sends the wrong message."

In 1988, Congressional amendments first banned the use of federal funds for NSPs (because they could "promote drug use"). Until 2008, the very term "harm reduction" was banned from government vocabulary and from federal grant applications. HR policies (e.g., medical marijuana) have been attacked by U.S. government officials as "surrender in the War on Drugs" and stepping stones to "drug legalization." President Barack Obama's campaign pledged support for needle exchange, and in 2009, officials agreed to rein in federal officers threatening California's medical marijuana program (with over 250,000 registrants).

New Models and Services for Active Drug Users

Syringe Exchange Programs

Early in the HIV/AIDS epidemic, the sharing of syringes was clearly linked to HIV transmission. By 1995, about half of the new HIV infections in the United States (now estimated by the Centers for Disease Control and Prevention [CDC] as 55,000 per year) were attributed directly or indirectly to drug use. The institution of NSPs was the first well-organized and explicit HR program in the United States and in many European and Asian countries and had a marked impact—by 2007, less than one-third of newly reported AIDS cases in the United States and Western Europe were among IDUs or their sexual partners. However, in many countries, NSPs still meet with strong opposition and are not implemented at levels adequate to affect the spread of blood-borne pathogens.

The positive effects of NSPs on syringe sharing and a wide range of other behaviors linked to HIV/AIDS risk were well documented in the United States, Great Britain, the Netherlands, and Australia by the early 1990s.

Needle and Syringe Programs in the United States

Despite very favorable early reports on the public health impact of NSPs worldwide and endorsements by national commissions (i.e., *the National Commission on Acquired Immune Deficiency Syndrome, the CDC, the General Accounting Office, the National Academy of Sciences, Institute of Medicine, and the Office of Technology Assessment*), implementation of NSPs faced daunting challenges throughout their American history: funding shortages, continued police harassment, and, in some cities, criminal prosecution for activists caught distributing syringes. Many American NSPs operate without the legal sanction of local authorities, and all sanctioned syringe exchange programs (SEPs) operate under strict rules—which may include limits on the number of syringes that can be dispensed to individual clients, restrictions on where NSPs can be located and what hours they are open—requirements hindering their ability to achieve maximum effectiveness. U.S. federal support for even the evaluation of NSPs did not occur until 1992, the 11th year of the AIDS epidemic. And (until 2009) the United States prohibited the use of federal funds to pay for NSPs either in America or overseas. It is the

private sector, charitable foundations, and community volunteers and activists, along with state and local officials, which provide the funds and personnel for many NSPs in the United States.

In 2000, New York State began a pilot program under which 2,500 community pharmacists could sell syringes under a waiver of paraphernalia laws; this program has been evaluated and found to produce positive outcomes.

Needle and Syringe Programs Outside the United States

Unlike the United States, most countries in Western Europe, and many elsewhere, never enacted prescription or paraphernalia laws, and two that did—France and Austria—revoked them during the mid-1980s when HIV/AIDS came on the scene. By the late 1980s, virtually all developed countries allowed legal access to sterile injection equipment through syringe exchanges, over-the-counter sales, or both. Most NSPs abroad are strongly supported by government officials at the national and local levels, most law enforcement officials, and a substantial majority of public opinion. Most public health authorities agree on the importance of reaching as many drug injectors as possible and minimizing the circulation of used syringes through aggressive syringe exchange and distribution efforts.

Peer Outreach and Education

Most needle and syringe exchange programs rely on active drug users such as outreach workers and volunteers. Their HIV prevention efforts engage the highest risk groups for overdose and new-onset HIV infection—active drug users not in treatment—through street outreach in local drug scenes, drop-in centers, and social service settings. Rather than aiming solely to direct people who use drugs into treatment, they focus most of their energies on minimizing drug-related harms outside formal treatment settings.

Overdose Prevention

In many areas of the world, where HIV has been controlled by HR programs, drug overdose is the leading cause of death among IDUs. Since the 1990s, a series of overdose prevention programs have evolved: educational programs using both popular media and underground publications, better emergency medical services and police response systems, new models for the distribution of injectable narcotic antagonists that reverse overdose symptoms (naloxone [Narcan]) as well as cardiopulmonary resuscitation (CPR) training for users' networks, and formation of groups of victims' families who work with local authorities to improve response to overdose emergencies. These programs are now being piloted and studied in the United Kingdom, Australia, and parts of Europe as well as in U.S. cities, including Chicago, Boston, San Francisco, and New York. Naloxone distribution has also been initiated, although on a limited basis, in countries including Tajikistan, China, Kyrgyzstan, Kazakhstan, and Russia. Such programs and many others described below are facilitated by the development of drug user eductational organizations and the community involvement of drug users and their advocacy organizations in overdose prevention.

Other Initiatives Supporting Safer Drug Use

HR efforts also seek to reduce the damage resulting from drugs of unknown purity or potency, which is especially important as new drugs (e.g., ecstasy and other club drugs) arrive in a country that has little history of experience with their effects. Some syringe exchanges have taken the initiative and distributed information gained from users about which street drugs are particularly potent or have dangerous adulterants. This information, however, tends to be erratic, comes only after a hazardous batch of drugs hits the street, and reaches only a small fraction of users.

Drug Consumer Groups

Organized and subsidized self-help groups of people who use drugs have played a modest but important role in the formulation and implementation of drug-control policies in the Netherlands, Germany, and Australia and have begun to exercise some influence in Switzerland and the United States. The Rotterdam "Junkie Union" began the first Dutch syringe exchange in response to the hepatitis B epidemic.

"Safe Spaces" for People Who Use Drugs

Low-threshold facilities known as "contact centers," "street rooms," "health rooms," "harm reduction centers," "supervised consumption facilities," and "safe injecting rooms," where active users congregate, are now officially tolerated (and sometimes even government-sponsored) in many European cities. Another innovation worth noting is the "apartment dealer" arrangement, adopted informally in Rotterdam, whereby police and prosecutors refrain from arresting and prosecuting apartment dealers—including sellers of heroin and cocaine—as long as they do not cause problems for their neighbors.

Addiction Treatment as Harm Reduction

In the HR model, the pathologies of addiction and challenges of drug treatment are seen as inseparable from prohibitionist drug policies, and these policies' collateral damages must be addressed in all treatment and HR programs. The recent advent of HR-oriented drug treatment also acknowledges a different set of goals than those of conventional treatment (i.e., total abstinence) and may even include the wishes of the clients to continue some forms of safer drug use at lower levels (i.e., "controlled drug use") and certainly not to make continued drug use a basis of termination of treatment. "Low-threshold" treatment models may also address users other real and perceived needs (e.g., for health care, housing, and legal assistance) as pathways to engaging clients, placing only minimal demands regarding cessation of all drugs. A pillar of HR approaches to drug treatment for many years has been for the medical prescriptions of "substitution" medications, especially of opiates, on a long-term basis as "maintenance treatment," which has now become an integral part of HR policy and practice worldwide.

Drug Substitution and Maintenance Treatment

Drug substitution, drug replacement therapies, and maintenance treatment are an essential part of HR strategies in many countries. But substitution treatments have a long and complex history. Despite strong medical and public health evidence for their effectiveness, these approaches still encounter opposition in many societies that consider them to violate the goal of a "drug-free society." A crucial factor is the right of physicians to prescribe maintenance drugs for their addicted patients.

It was not until the early 1960s, with the pioneering work of Drs. Vincent Dole and Marie Nyswander, that the concept of addiction treatment using the prescription of maintenance drugs was reintroduced in the United States.

Methadone

There are hundreds of studies on the effects and outcomes of methadone-maintenance treatment (MMT). Positive outcomes include the complete elimination of or large reductions in daily heroin use and injecting, reductions in criminal behavior and arrests, reductions in death rates, and increased employment. The public health significance of MMT soon became

apparent as the rate of HIV infection among those in MMT was found to be inversely proportional to the time in treatment.

Buprenorphine's safety and efficacy are well established, but it remains underutilized due to slow uptake of prescribing among office-based physicians. While current buprenorphine treatment guidelines advance a treatment model substantially less intense than that of conventional methadone maintenance, they still go far beyond the level of care and monitoring standard in treating other chronic conditions, such as diabetes, depression, or HIV/AIDS. As of 2008, 13,000 physicians had been certified (following completion of the federally required training) to prescribe buprenorphine, yet only an estimated 67% were actually treating patients.

Low-Threshold Maintenance

Low-threshold maintenance treatment does not "require" ancillary services (such as counseling), nor does it make retention in treatment contingent upon total abstinence from heroin and/or other drugs. Accordingly, it can accommodate a far broader segment of addicts in the community for a longer period of time. These programs frequently provide fewer ancillary services, although referrals are usually offered to relevant sources available to the general population. Many do not demand regular attendance, urine tests, or regular counseling contacts, all of which are standard requirements in U.S. methadone clinics. Support for low-threshold programs is based on their relatively low cost; the relative ease of establishment on a large scale; their proven success in establishing contact with people who use illicit drugs but are put off by programs with more rigorous requirements; and the fact that, as expected, their patients have been shown to fare better than drug users not enrolled in any programs.

Other Drug Substitution Initiatives

In the United States from 1919 to 1923, several morphine- and heroin-assisted therapy clinics were in operation until their termination by the government. British physicians prescribed injectable opiates early in the 20th century and in a controlled trial in the 1970s; a small morphine-maintenance program was initiated in 1983 in the Netherlands and was deemed modestly successful in improving the health and functioning of most of the addicts and in reducing their involvement in criminal activities. Another program, operated by the Municipal Health Department in Amsterdam, prescribed injectable methadone and dextromoramide tartrate (Palfium)—an opioid that can be taken orally—to a group of long-term heavy opioid users; the latter medication did not gain user acceptance and was difficult to administer. In Italy during the late 1970s, a number of physicians dissatisfied with the quality of care for heroin addicts began providing addicts with injectable morphine on an outpatient basis. The Italian government legalized this prescribing experiment in 1980, but approval was abruptly withdrawn a few years later.

Prescription of Nonopioid Drugs

Methadone is not a treatment for primary addiction to cocaine, amphetamine, alcohol, and other nonopioid drugs, although use of these drugs by heroin addicts in MMT will often decline over time. But opioid-maintenance programs do not directly address the consumption of nonopioid drugs, such as amphetamines and cocaine. This is an increasingly important limitation, given the dramatic growth since the late 1970s in cocaine and multidrug consumption, notably the use of "crack" cocaine and "cocktail" combinations of cocaine and heroin known as "speedballs," and the recent rise in use of amphetamine-type substances worldwide.

Drug Policy Reform as Harm Reduction

Although addiction treatment innovations and expanded access, preventive interventions such as SEPs, environmental changes to make drug use safer, and overdose prevention programs play a crucial role in reducing the harms associated with drug use under prohibition, it is changes in drug control policy that offer the best chance for minimizing drug-related harm. By reducing the association of drug use with criminal prosecution, a system that drives drug use and people who use drugs to the most dangerous margins of society, the reform of punitive legal policies can produce clear benefits in the realm of public health and social order. Marijuana, the most widely used illicit drug, has been a special target for such law reform.

Marijuana Policies

In the United States in the 1970s, the movement to decriminalize marijuana was driven by the realization that criminal sanctions created greater harm than marijuana use itself. During the 1970s, 11 states decriminalized marijuana, effectively reducing the punishment for possession of small amounts to sanctions other than imprisonment. The impact on marijuana consumption and related problems was negligible, but decriminalization did reduce the number of marijuana arrests and prosecutions.

Medical Marijuana

Many patients have found marijuana to be a relatively safe, well-tolerated, and rapidly effective way to deal with some medical conditions: reducing nausea in chemotherapy, intraocular pressure in glaucoma, muscle spasms and chronic pain; stimulating appetite; relieving the symptoms of HIV/AIDS, cancer and chemotherapy, multiple sclerosis, and epilepsy. The hostility to this use of marijuana, especially by federal officials in the United States, where the campaign for medical marijuana has been most vigorous, has made it almost impossible to gain support for rigorous research to confirm (or disprove) these widespread beliefs. Polls indicate that a majority of Americans believe marijuana should be medically available, and numerous organizations, including the American Public Health Association and the American Federation of Scientists, have issued resolutions in support of medical marijuana. In 1988, a DEA administrative law judge ruled that marijuana should be moved to Schedule II, making it available for medical purposes, but the agency refused to comply. Thus, marijuana remains a Schedule I drug, meaning that in the eyes of the U.S. government, it has no legitimate medical use, and further research on its medical properties has been stifled. Hundreds of individuals received marijuana for medical purposes in the 1980s, but this federal program was discontinued, and all but eight of the original recipients have either died or been cut from the program.

Medical Marijuana in Canada

Although Canada's Controlled Drugs and Substances Act (CDSA), the central law on illegal drugs, prohibits possession, cultivation, trafficking, and importing and exporting of marijuana, the Minister of Health is authorized to grant exemptions from the Act for a medical or scientific purpose, or if it would be otherwise in the public interest. In 1997, a small group of Ottawa lawyers and physicians applied unsuccessfully on behalf of an AIDS patient for medical access to cannabis. However, the minister introduced a narrow exemption from the Act for medical cannabis in 1999, and by May 2002, 658 exemptions had been granted under this program. Access to medical marijuana was initially permitted to a small number of applicants in the late 1990s through such a ministerial exemption, and formal regulations followed in 2001, driven by a successful constitutional challenge to the marijuana laws. As of June 2009, 4,029 individuals

were authorized to possess marijuana under the regulations. The Canadian government is now exploring ways to permit both the cultivation and possession of cannabis for therapeutic reasons.

Conclusion

The HR paradigm has made great progress during the last decade. A public health conception of drug use, the foundation of HR, is now generally far better understood than previously, although often still willfully misinterpreted by its opponents. Nonetheless, in an increasing number of countries and regions of the world, HR is now regarded as mainstream drug policy (e.g., virtually throughout all countries of Western Europe), while zero-tolerance supporters are growing ever more isolated and marginalized as their failure and its high cost become evident. This sea change is driven by genuine national concerns, including a new interest in the implications of drug addiction, AIDS, and the huge illicit drug markets for human rights and the potent effects of HIV epidemics on regional and global security, fueled by high levels of opium production in Afghanistan (destined for European markets), a growing drug trade in China, and a vicious power struggle over the U.S. drug markets now occurring in Mexico.

Although HR programs continue to spread, their availability and scale are still well below levels required to achieve the public health goals that we should be setting in the drugs area. Thus, zero tolerance and the basic premises of the "War on Drugs" remains the stated drug policy in the United States. And while the United States is the most important and most influential opponent to HR, it is not the only country to bitterly oppose these policies. Other countries that oppose HR policies are Russia, Japan, and Sweden, which play vocal roles in setting UN drug policies.

Work Setting

While not denying the equally important role that love plays, this chapter focuses on the role that work plays in the recovery process. Though the entry or return to employment can have many benefits, recovering substance abusers may face many problems when returning to the workplace, and therefore, there is a need for a coordinated range of services for facilitating their success.

There are two basic groups of recovering substance abusers in the treatment setting: those who, as a consequence of their abuse or other environmental or family factors, have never worked and those who have worked and been suspended from their jobs or fired as a consequence of substance abuse. The first group is looking to enter the workforce for the first time and the second group is looking to return. Although there are similarities between the two, care must be taken to fully understand the unique dynamics influencing each group's movement toward work.

Recovering substance abusers entering the labor force for the first time may be confronted with poor, inadequate, or unrealistic concepts of what work is and who they are and can be as workers. Individuals who grew up in disadvantaged or unstable homes because of poverty, generational substance abuse, or family conflict may never have worked formally or been raised with close "worker" role models. Employment may be seen by recovering substance abusers as foreign and unknown, creating feelings of inadequacy and fear. Many of their lifestyle patterns and habits are maladaptive and not conducive to work. Adolescents and young adults whose lives have focused on drug or alcohol addiction have not experienced many of the stresses and fears that most people gradually confront in high school educational programs or their first part-time or summer jobs.

These individuals arrive at the job market overwhelmed by the enormity of the task of entering the "straight" world and meeting employers' expectations that they have already completed the more basic vocational development tasks. Still, a position in the labor force is attractive, because it offers to place them into a recognized position in society for the first time in their lives.

Vocational Rehabilitation

Rehabilitation can be simply defined as the series of steps taken by a disabled person to achieve fulfillment in life. The process that specifically addresses an individual's work fulfillment and remuneration is referred to as vocational rehabilitation. A further distinction in terms is important because of the specific needs of recovering substance abusers. The process for many who are characterized by a late onset of substance abuse, or who have worked before and are returning to competitive employment, may appropriately be termed vocational "rehabilitation." These individuals are being restored to a former level of functioning. However, for those recovering people who have lived on the fringe of society, never having worked before, vocational "habilitation" provides a more accurate understanding of their need to learn what work is about and to establish for the first time effective work behaviors.

There are three basic vocational rehabilitation strategies. The first and most desirable strategy is to remedy the cause of the person's disability by restoring or developing functional ability. The second strategy is to enhance the individual's other vocational/educational attributes so that the person can compensate for the disability. The third strategy is to adapt the work environment so that the person's disability is not a functional impairment. This tactic is least feasible because the provision of specialized tools or techniques or making physical changes in a workstation usually does not effectively rectify the consequences of a recovering substance abuser's disability. However, an example of this strategy might be the alteration of a regular work schedule to allow a recovering person to keep ongoing counseling support appointments.

The ultimate guideline for all rehabilitation and vocational rehabilitation is to provide help so that the recovering individual becomes less dependent on external resources and more independent by making changes in himself or herself.

Assessment

The first and most crucial component of vocational rehabilitation for any disabled group is assessment. The fourth step of the Alcoholics Anonymous (AA) recovery program is a "searching and fearless moral inventory." A similar vocational inventory needs to be undertaken by recovering individuals to develop their vocational plans.

Motivation is a crucial ingredient and, unless properly assessed and addressed, will lead to resistance from the client and frustration for the counselor later in the process. If the client is not able to progress to a point where the client is keeping appointments on time and demonstrating initiative and choice in selecting from available vocational options, then the client's motivation is questionable. Certainly, a criterion for evaluating motivation, as well as overall work readiness, is the client's chemical abuse status. If the individual is neither drug- and alcohol-free nor stabilized on a prescribed medication like methadone, then the client is unable to be endorsed for employment. Moreover, a vocational/educational assessment battery would have little value if the client was abusing drugs or alcohol when involved in the testing.

Counseling and Referral

The basic goal of counseling is accelerated learning. As a result of a proper assessment, a counselor should be able to depict what a client needs to know and clues for helping the client learn

what he or she needs to know. A basic epistemological principle applies, helping a client understand the unknown by examining what the client already knows.

Vocational counseling has four classic elements: developing a positive self-concept, obtaining occupational information, expressing the self in occupational terms, and learning job-seeking skills.

Placement and Follow-Up

The National Association on Drug Abuse Problems (NADAP) is a private nonprofit organization based in New York City that provides placement assistance to recovering substance abusers. NADAP has found that for many recovering persons it is necessary to augment the individual vocational rehabilitation counseling with specialized group workshops. These workshops have been designed as "groups" because work is public and requires socialization. As members of these groups, clients can be further assessed in terms of their ability to interact appropriately. The workshops also provide clients with opportunities to learn and practice job-related social skills.

Impediments to Vocational Rehabilitation Service Delivery

The federal government has joined with state and local governments in endorsing the connection between work and recovery. This is evident in their policy developments and antidiscrimination legislation. This extends to funding provisions for training and job opportunities for recovering substance abusers. Certainly the Rehabilitation Act of 1973 serves as a cornerstone for the legal rights and public opportunities available to individuals with disabilities.

However, it is naive to believe that this support alone guarantees vocational rehabilitation services to those who need and desire it. There are three major categories of hindrances to effective provision and use of these services by recovering substance abusers: the clients themselves, the programs that treat them, and the society to which they return.

Improving Vocational Rehabilitation Services

The past four decades of providing vocational rehabilitation services to men and women recovering from drug and alcohol abuse point to three guidelines for improving these services: understanding, expansion, and coordination.

Regretfully, there will probably always be new drugs surfacing that carry with them certain unique vocational impairments. These impairments will need to be examined as they become evident and new rehabilitation strategies and resources will need to be developed to address them. However, we now have an understanding of the depth and scope of the effect that substance abuse has on an individual's vocational development and of the basic rehabilitation principles to apply. Most recovering substance abusers can make progress if they are allowed to do so in a slow, gradual manner with a full complement of support services. Although it may be too strong to say that relapse is frequently part of the recovery process, we know that it is a reality for many clients. This is true in terms of a client's vocational development as well. It is not necessarily a neat progression but one that may be characterized by false starts and occasional steps backward. For some, because of the chronic nature of their substance abuse histories and the multiple handicaps they have, competitive or full-time employment may not be a realistic goal. For others, it will be appropriate only as a very long-term goal.

In keeping with these characteristics, we must adopt more of a mental health model of rehabilitation as opposed to a medical one. We must acknowledge this understanding in the design of vocational programs and in the expectations about working that we communicate to clients.

Finally, for there to be effective vocational rehabilitation of recovering substance abusers, there needs to be increased coordination of relevant services. Drug and alcohol prevention programs need to include career exploration, educational remediation, occupational skills training, and work-adjustment experiences into their services. Treatment programs must integrate comprehensive educational/vocational services into the early, middle, and late stages of their clinical treatment.

In addition to the expected increases in employment, it appears from recent research that vocational rehabilitation programs are one of the psychosocial support services that can be effective in reducing drug use. Moreover, employment, specifically, can be an effective reinforcement for abstinence. Clearly, such an outcome justifies the costs associated with integrating these components into substance abuse treatment programs. Both because of what it demands from an individual in recovery and because what it provides for that individual, sustained employment is a significant component of successful treatment.

Work dignifies us as human beings. Unless we provide men and women recovering from substance abuse with support and opportunities to achieve this dignity, to earn a place in society, we should not fault them for taxing our welfare system, straining our criminal justice system, and perpetuating a destructive subculture.

Suggested Readings

Andrews J, Hops H. The role of peers and family as predictors of drug etiology. In: Scheier LM, ed. *Handbook of Drug Use Etiology*. Washington, DC: American Psychological Association; 2010.

Drucker E. Drug prohibition and public health: 25 years of evidence. *Public Health Rep.* 1999;114:14–29.

Drucker E. *A Plague of Prisons: The Epidemiology of Mass Incarceration in America*. New York, NY: The New Press, 2010.

Faggiano F, Vigna-Taglianti FD, Versino E, et al. School-based prevention for illicit drugs use: a systematic review. *Prev Med*. 2008;46:385–396.

Snyder LB. Substance use and the media. In: Scheier LM, ed. *Handbook of Drug Use Etiology*. Washington, DC: American Psychological Association; 2010.

Sullivan SG, Wu Z. Rapid scale up of harm reduction in China. *Int J Drug Policy*. 2007;18:118–128.

43 Substance Abuse among Adolescents and the Elderly

Substance Abuse among Adolescents

Substance use (alcohol and illicit drugs) among adolescents in general, across all grade levels 8, 10, and 12, has shown a steady and considerable decline over a decade or more, though with some exceptions. Rates appear to have stabilized in recent years. Marijuana, in contrast, has shown an increased trend in use over the last 2 to 3 years, affecting the rate of illicit drug use, whereas illicit drug use other than marijuana has more or less held steady or declined. This recent rise in marijuana use has been associated with an even longer decline in adolescents' perceived risk of regular marijuana use. It is almost without exception that substance use increases with the next higher grade level or age in adolescents. Inhalant use, on the other hand, shows the reverse prevalence, being most common in eighth graders, and heroin use is equally distributed across the grades, though annual prevalence rates remain nominal at less than 1% in any of the three grades. However, narcotic use other than heroin has remained elevated at 9% in grade 12 students for many years. By far, the two most common substances used by adolescents are alcohol and marijuana, with annual rates for senior high school (grade 12) students of 66% and 33%, respectively, in 2009. However, marijuana has been the most common substance of daily use among adolescents for more than a decade, with rates over 50% higher than for alcohol. Prescription-drug misuse among high school seniors remains a concern at approximately 15% per annum. Included in this group are narcotic analgesics (Vicodin and Oxycontin), stimulants used for treatment of attention-deficit hyperactivity disorder (ADHD) (Adderall and Ritalin), and sedatives/tranquilizers.

Community samples of adolescents have found lifetime rates of substance use disorder (SUD) to range from approximately 10% to 30%, with rates of alcohol use disorders and drug use disorders (predominantly cannabis) similar, apart from one study. This wide range in SUD rates may be attributed to differences in methodology and categorization of SUD. Several common themes are identified in these studies in that SUD rates increase with age, appear to be greater in males, and are quite infrequent for ages 13 and younger.

In summary, despite the overall decline in substance use and SUD in adolescents, the prevalence remains high and is the greatest with older adolescents. As well, it is important to recognize the historical cyclic pattern of substance use and abuse rates. One can also surmise that cannabis would appear to be the most significant and the most common substance of dependence in adolescents, with alcohol being the predominant substance of abuse.

Development and Course of Disorder

Adolescence is a time of major risk for the onset of substance abuse. The peak age of onset for both alcohol and drug use disorders is in late adolescence/early adulthood, between the ages 18 and 20. Adolescence, as seen from a developmental perspective, represents a time of convergence of significant neurobiologic, 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.

An abundance of risk factors have been, and continue to be, identified in the prediction of substance abuse in adolescence/young adulthood. These various 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 psychophysiologic vulnerability to the effects of substances).

Protective factors are those that reduce the likelihood and level of substance use. Multiple protective factors have been identified, which include 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.

Substance abuse in adolescence is clearly associated with significant negative consequences in the developmental tasks' multiple life areas, including behavioral, emotional, social, and academic/vocational problems.

In summary, the onset of substance abuse in adolescence with its biopsychosocial determinants is a serious problem, with a direct impact on development and a strong link to future SUD.

Comorbidity of SUD

The association of SUD and mental health disorders is well established. In clinical and treatment studies of adolescent SUD, elevated rates of comorbid mental health disorders have been found across settings from hospitalized/residential to outpatient status with prevalence rates ranging from 55% to 80%. 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.

The most common comorbid psychiatric disorders seen in community studies of adolescent SUD are the disruptive behavior disorder (DBD), in particular CD, with these disorders showing a prevalence range of 25% to 50% and a median of four times greater likelihood of co-occurrence with SUD than without. This is followed by depression with a prevalence range of 20% to 30% and a median of over twice the likelihood of co-occurrence. These findings are relatively consistent with clinical studies, though there is a fair degree of variability in prevalence rates between studies, depending on the clinical population sample. SUD, on the other hand, is a common comorbid disorder in clinical studies of youth that present with serious emotional disturbances or mental health disorders.

Conduct Disorder

CD and SUD are strongly associated, with CD typically preceding the onset of SUD. This relationship, however, appears to be reciprocal with each condition heightening the expression of the other. In such a manner, CD may influence the early adolescent development of SUD, and the severity of CD has been found to predict the severity of SUD. Early-onset substance use has been associated with later criminality. Furthermore, if substance use or drug dealing is reduced, there is

a subsequent decrease in criminality. Juvenile offenders with comorbid SUD have shown greater additional psychopathology than juvenile offenders without SUD. It is also important to recognize that no relationship with early conduct problems has been found for the onset of SUD in adulthood.

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% to 38%; however, similar findings have not been found in community samples.

The significance of comorbid ADHD appears to lie with its association with CD in adolescents. The clustering of ADHD, CD, and SUD has been found in several studies of adolescents. Together, longitudinal prospective studies of ADHD into adolescence, in comparison to normal controls, and a large population-based study examining the relationship of ADHD, CD, and SUD in adolescents provide consensus that ADHD as a risk factor for SUD is strongly mediated by its association with CD and/or externalizing disorders of oppositional defiant disorder (ODD)/CD. In essence, ADHD when not associated with another DBD is not generally seen as a significant independent risk factor for the development of SUD in adolescence. The severity of ADHD may have an impact on the risk for development of SUD in adolescence.

Adolescents with ADHD have shown an earlier age of onset of SUD and a more rapid progression of SUD from abuse to dependence than normal controls; as well, adolescents with SUD and comorbid ADHD have exhibited more severe substance abuse than those without ADHD. No significant gender differences have been found in the effects of ADHD on SUD in adolescents. The persistence of ADHD into young adulthood has been shown to be an independent risk factor for the development of SUD.

Depressive Disorders

In adolescents with depression, comorbid SUDs are associated with earlier onset of and more severe 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. Recently, it has also been shown that simply a greater severity of substance use in adolescents with treatment-resistant major depressive disorder (MDD) and without comorbid SUD is associated with increased severity of depression and comorbid ODD and CD. Adolescents with low substance-related impairment at the end of treatment for depression demonstrated the best response.

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. A history of recent interpersonal separations and family dysfunction has been found to be more common in adolescents who attempt suicide with depression and comorbid SUD than without. Alcohol abuse has been most often associated with increased risk, though the number of substances used may be a more important predictive factor.

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, carrying a significant morbidity and mortality.

Psychotic and Bipolar Disorders

There is a paucity of studies that report the incidence of comorbid primary psychotic disorders (PPD)/schizophrenia-related disorders and bipolar disorders (BD) in the adolescent SUD

population. This absence of reporting may be 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 PPD and BD are not commonly or reliably reported in the adolescent SUD population, a detailed discussion of their association is beyond the scope of this chapter.

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. From these studies, social anxiety disorders (SADs) and PTSD have been identified as the most clinically significant of the anxiety disorders. SAD precedes 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.

Treatment

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. 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.

As of date, there has been a proposed shift away from large-scale outcomes–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.

Psychosocial Treatments

Waldron and Turner undertook a comprehensive review and meta-analysis of specific 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. Waldron and Turner 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 taken within a short-term (28 days/admission to a specialized) inpatient hospital or residential care setting. However, an intensive outpatient program employing the Minnesota model was included as part of Winters and colleagues' study, which showed treatment outcomes similar to those from the short-term residential care.

Pharmacotherapy

The role of psychopharmacology in the treatment of adolescent substance abuse has not been adequately investigated. Barriers include the lack of safety and efficacy information for the use of psychotropic medications in younger populations and a general reluctance in the consideration of psychopharmacology to treat adolescent SUD. A review of the literature investigating psychopharmacologic treatment of adolescent SUD, with or without comorbid psychiatric disorders, revealed a paucity of studies. However, clinical studies have reported high rates of medication use by adolescents receiving SUD treatment, though on the other hand many treatment studies will omit altogether the reporting of medication use in this population. When pharmacotherapy is used in the treatment of adolescent SUD, it is typically for comorbid psychiatric symptoms or disorders and not directly for the SUD.

Pharmacotherapy for SUD Open-label studies of buprenorphine treatment for adolescents with opioid addiction, naltrexone treatment for adolescents with alcohol dependence, and ondansetron treatment for youth with alcohol dependence have shown a reduced frequency of substance use.

Randomized clinical trials of 28 days of buprenorphine treatment and 12 weeks of buprenorphine–naloxone treatment in youth with opioid dependence reported significantly greater treatment retention and greater abstinence than did comparison treatments of clonidine for detoxification and short-term detoxification with buprenorphine–naloxone, respectively.

A randomized controlled trial (RCT) ($n = 26$) of acamprosate treatment for 90 days in adolescents with alcohol dependence reported that the number of youth continuously abstinent and the number of continuous days abstinent were greater in the acamprosate group than in the placebo group.

Pharmacotherapy for Comorbid Disorders A randomized, controlled pilot study of sertraline in a small number of 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.

Conclusion

SUD is a complex and serious problem in the adolescent population, with a significant impact on normal development, and thereby on society in general. Adolescent SUD must be viewed through a developmental lens with adolescence being a period of major risk for the development of SUD. It is closely interrelated with other mental health disorders and social problems requiring comprehensive assessment and an integrated developmentally appropriate treatment approach in working with the adolescent and their family. Significant advances have occurred in determining evidence-based treatments for adolescent SUD. There is a strong case that can be made for the need to provide psychiatric care for adolescents in SUD treatment with psychiatric comorbidity being more the rule rather the exception. The intervention needs of comorbid youth may best be served by an integrated treatment approach focusing both on SUD and comorbid psychiatric disorders in order to enhance treatment for these conditions. The implementation of treatment specific for adolescent SUD is paramount to an integrated approach. One must consider both the chronicity of SUD in some adolescent populations and

the self-limited nature of substance use and related problems in others. Defining the adolescent SUD population better, such as in terms of substance dependence and substance abuse versus the general category of SUD, or employing a standard measure of substance use severity may assist in the development of more specific evidence-based treatment approaches.

The Older Drug Abuser

Older adults in the United States have experienced a period of rapid cultural change unlike any other in history. The 2008 National Survey on Drug Use and Health (NSDUH) estimated that 40% to 60% of those between the ages 45 and 64 had used illicit drugs at some point in their lives.

Some older adults who began drug use in their earlier years became addicted and continued use over time. Drug abuse in early years affects health and well-being later in life. The chronic misuse of certain drugs, particularly stimulants, is associated with neurodevelopmental abnormalities that can impair cognitive function during early to middle age, and that may interact with aging to speed the onset and progression of degenerative brain processes such as dementia and Alzheimer disease.

The U.S. Census Bureau estimates that in 2010 about 32% of the U.S. population, or 98.6 million residents, will be 50 years of age or older. The proportion will grow to nearly 37%, or about 161.1 million, by 2050. The misuse and abuse of psychotropic drugs by older adults is a matter of great concern, both for the health of the individual patient and for public health. The prevalence of illicit drug abuse by those 50 and older is projected to increase in the coming years, and this will create problems for those individuals, for their families, and for a health-care system that is not presently oriented toward screening, assessing, or providing care for the older drug abuser.

Epidemiology of Drug Abuse and Addiction in Older Adults

Increasing Prevalence of Illicit Drug Use

Rates of illicit drug use peak in the general population around ages 18 to 25 and decline with increasing age. Rates of illicit drug use among adults aged 65 or older have historically been quite low. However, as the baby-boom generation has aged, the prevalence of illicit drug use among older adults has increased. In the 2008, NSDUH, a national household survey conducted annually by the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA), reported that 40% to 60% of those between the ages 45 and 64 had used illicit drugs at some point in their lives.

Projected Need for Drug Abuse Treatment by Older Adults

Across all ages, substance abuse treatment admissions have increased over time. Total admissions to treatment reported to Treatment Episodes Data System (TEDS) for a drug problem or a combined drug and alcohol problem (excluding admissions for alcohol alone) increased from 932,300 in 1992 to 1,356,802 in 2007. Individuals aged 50 or older have grown from 20,383 (2.2%) admissions in 1992 to 114,561 (8.4%) in 2007. There has also been a shift away from admissions for alcohol alone toward illicit drugs alone or in combination with alcohol. In 1992, admissions for problems with alcohol made up only about 77% of all admissions for people aged 50 and higher. By 2007, over half (55%) of all older admissions were for drugs alone or in combination with alcohol, reflecting the increasing upward trend in older admissions for problems with multiple substances.

Effects of Drug Use on Health

Increased Risk of Physical Problems

Aging can be considered a set of progressive degenerative changes that cumulatively affect an individual's neurologic and physiologic capacities. The normal aging process involves loss of brain cells, reductions in muscular volume and strength, reduced cardiovascular function, reduced function in body organs, increased vulnerability to infection and chronic illnesses, and increased risk of mental health disorders. How a given individual ages depends on genetic and environmental factors.

Drug abuse and addiction can interact with the aging brain and body to increase the apparent rate of aging by speeding the decline in cognitive and functional capacity and by increasing the vulnerability to both chronic and acute illnesses. Individuals in their 50s who have a SUD may be more similar in their medical morbidity profile to non–drug-using individuals in their 60s in terms of general health, physical and social functioning, bodily pain, and mortality risk. Chronic misuse of addictive drugs can have serious clinical effects.

Neurotoxicity and Neuroprotective Effects

Normal aging processes interact with the neurobiologic systems implicated in drug abuse. Drugs of abuse act on the dopaminergic, serotonergic, and glutamatergic systems of the brain. It has been demonstrated that both heroin and cocaine reduce the number of dopaminergic receptors in the brain and that these changes persist for significant periods of time after cessation of drug use. The dopaminergic, serotonergic, and glutamatergic systems also change as part of normal brain aging. Changes associated with aging include decreases in dopamine (DA) receptor binding in the striatum and in extrastriatal regions (including the frontal cortex, anterior cingulate gyrus, temporal insula, and thalamus) that can affect motor and cognitive functions. The nature of the interactions between aging and drug misuse is an important area for further research.

Interaction of Drug Neurotoxicity and Neurology of Aging Specific drugs may interact with normal aging to increase health risks. Drug pharmacokinetics (PK) (the relationship between the drug dose and its concentration in the body) and pharmacodynamics (the relationship between the concentration of a drug in the body and the pharmacologic response to it) change as the body ages. Individuals older than 65 react differently to a number of drugs (and to alcohol); of particular note are drugs affecting the CNS, particularly benzodiazepines (BZDs) and opioids. Although the mechanisms for these functional changes are not well understood, it is known that some CNS drugs may penetrate the blood–brain barrier more readily with advancing age, neurotransmitters and receptors change with age, glucose metabolism slows as cerebrovascular function declines, and hormone levels change with age.

Increased Risk of Mortality

Illicit drug use increases several premature-death risk factors, and these risk factors tend to increase as an individual ages. Direct risks include the immediate consequences of drug use, including poisoning (overdose) and increased risk of an accident while intoxicated, such as falling or having a traffic accident. Indirect risks include those associated with the illicit nature of drug abuse, including criminal activity, physical trauma, arrest, and incarceration. Indirect risks also include contracting substance abuse–related illnesses, including chronic infectious diseases such as the HIV and hepatitis C, through sharing of unsanitary injection equipment. Smoking is prevalent among those who use illicit drugs and is associated with higher rates of many chronic illnesses (such as cardiovascular disease [CVD]) as well as cancer.

Chronic Illnesses and Use of Medications: Iatrogenic Addiction or Abusive Misuse

Use of Psychotropic Medications by Older Population

Psychotropic medications are commonly prescribed for older adults. It has been estimated that one-third of all such psychotropic medications are prescribed for those aged 65 or older. Epidemiologic surveys show that increased age is associated with a higher likelihood of prescriptions for antipsychotics, antidepressants, and/or hypnotics. Women are more likely to be prescribed medications than men. These prescriptions are often for multiple indications and for long periods of time. Older adults are at risk for unintentional or "inadvertent" nonmedical use, which can result in adverse health consequences, toxicity, cognitive impairment, falls, and motor vehicle accidents. Prescription medications may also be misused. The inappropriate use of prescription drugs includes sharing medications, using higher doses for longer durations than prescribed, recreational use, and of course, persistent abuse and dependence.

Many psychotropic medications prescribed for older adults, including tricyclic antidepressants and BZD sedatives, can lead to a variety of cognitive impairments, including effects on attention, executive function, language, memory, and perception. Cognitive impairment may be reversible once the drug is discontinued. BZDs, either used by prescription or misused without a prescription, may cause drowsiness or cognitive impairment, increasing the possibility of falling (causing hip and thigh fractures) and of vehicle accidents.

Use of Pain Medications

Opioid analgesics are increasingly prescribed for chronic pain, and there is ongoing concern that opioids prescribed for pain management may evolve into misuse or addiction. Persistent pain is common among older patients, including among patients who are dependent on opioids. Even patients with a history of SUDs are more likely to be prescribed opioid medications for pain than in past years.

Patients prescribed opioid medications are at higher risk for opioid-misuse problems, especially patients with co-occurring depressive and anxiety disorders. Pain can be treated successfully using opioid medications, but physicians must balance the risks and benefits of pain medication.

Pain-medicine physicians would benefit from better screening methods, better ways to recognize and intervene if opioid treatment for pain shifts from benefit to harm, and better ways to screen for co-occurring mental disorders such as depression.

Medications and Interactions with Illicit Substances

Aging results in a progressive decline in the functional reserve of body organs and physiologic systems. Drug effects, both medical and nonmedical, can be altered by the effects of aging, including delayed renal excretion, delayed gastrointestinal (GI) absorption, increased body fat and decreased proportion of body water, and reduced basal metabolic rate. There is a decline in the functionality of the circulatory, GI, and hepatic systems. Older adults are also much more likely to suffer from chronic illnesses, such as diabetes, CVDs, and hypertension. These diseases may have a greater impact than age per se on the level of impairment in body system functionality.

Physiologic changes associated with aging can alter drug metabolism and drug PK. With aging, the metabolism of many drugs is slowed, increasing their bioavailability compared to physiologically younger individuals. This reduced drug tolerance can contribute to accidental drug overdose or adverse drug interactions in older adults. Older adults may also reduce their level of use since the effects of illicit drug and alcohol use persist for longer periods.

Older adults are more likely to suffer from a variety of chronic physical and mental disorders than younger adults, and this likelihood increases with age. A study of a national random sample of 1.2 million Medicare beneficiaries found that 65% had multiple chronic conditions. It is estimated that prescription medications are used by 60% to 78% of older adults. Individuals 65 and older consume about 30% of all prescription medications. Although it has been suggested that the most common type of drug misuse is underuse, polypharmacy—prescribing multiple medications—is also common for older patients. Since the likelihood of adverse drug interactions increases with the number of medications prescribed, older adults are more susceptible to adverse drug effects simply because they are prescribed more medications than younger adults.

Symptoms of substance abuse in the older patient may include confusion, fatigue, irritability, insomnia, forgetfulness, or emotional instability. These symptoms may be mistaken for conditions common in old age, presenting the potential for misdiagnosis and inappropriate prescribing. Patients may play an active role in medication misuse. The prescription medications that are most likely to be intentionally misused or abused by older adults include sedative-hypnotics (BZDs and barbiturates), anxiolytics, and opioid analgesics. These medications are often prescribed for insomnia, anxiety, and chronic pain, which are conditions common in older patients. In turn, older patients may seek to take these because of their psychoactive effects (that is, reinforcement and reward). Prescribing clinicians should closely monitor the patient for adverse side effects, inappropriate use, or use of medications for longer periods or in higher dosages than planned.

HIV, Aging, and Drug Abuse

HIV, the virus that causes AIDS, is most commonly contracted through sexual contact with an infected individual or through sharing contaminated syringes or other injection drug use components. Until about 1995, adults over the age of 50 comprised about 10% of the cumulative number of AIDS cases, but the number of newly diagnosed HIV infections among older adults has increased in recent years. In 2005, about 19% of newly diagnosed AIDS cases were 50 or older. Given the relatively long latency period of AIDS, it is likely that many individuals live with undetected HIV infection for a number of years, and HIV infection is diagnosed only when symptoms begin to appear in later years. It is also likely that some of the increase in new cases results from higher HIV testing rates, following the revised recommendations of the U.S. Centers for Disease Control and Prevention (CDC). The CDC estimated that in 2006, about 10% individuals with HIV were age 50 or older when they were infected.

Treating Substance Abuse in Older Adults

The number of individuals 50 and older admitted to drug abuse treatment in 2007 (208,910, or 11.5%) was more than double the number admitted in 1992 (102,705, or 6.6%). Alcohol, long the primary problem at treatment admission among older adults, has been supplanted as the primary problem by drugs alone and by combined drugs and alcohol for those aged 50 and older.

Screening and Assessment

Screening for SUDs is an important first step in identifying the need for preventive interventions or drug treatment in older adults. Many symptoms of substance abuse and withdrawal (such as mild cognitive impairment, irregular heartbeat, and tremor) are seen in many aging individuals. It is important for medical providers to have a high "index of suspicion" and to

understand the symptoms of substance abuse and dependence in order to be able to properly diagnose, treat, and refer the older patient.

Current standardized criteria for diagnosing SUDs were developed and validated using young and middle-aged populations. They may not be appropriate for older or elderly populations because the diagnostic criteria are oriented toward adverse consequences in a younger population. Diagnostic criteria based on failure to meet role obligations or adverse social, legal, or interpersonal consequences may miss older adults with SUDs. Older and elderly adults are more likely to be socially isolated and are less likely to be employed, married, have minor children, or have legal involvement. The criteria for increased tolerance leading to increased levels of consumption do not consider the pharmacodynamic changes that lower drug tolerance in the elderly. Tolerance or withdrawal symptoms may not create problems for individuals who do not have major role obligations and whose performance is therefore not closely observed. Drug and alcohol abuse and dependence rates are often very low in the older population.

Prevention of Illness

Drug abuse treatment can be considered primary prevention because it reduces the incidence of chronic illnesses associated with misuse of drugs. For example, for those 50 years and above, smoking-cessation interventions are primary prevention: they can increase longevity and, by avoiding the cost of treating chronic illness associated with smoking, can also reduce healthcare costs over the life of the individual. Models of smoking cessation suggest that it could add over 3 years to life depending on the effectiveness of the smoking-cessation intervention.

Access to Medical Care

Because of illnesses associated with aging, the older drug abuser often has a connection with a primary-care provider. This medical provider can play an important role in screening, diagnosing, and assessing SUDs, and in recommending and referring the patient to appropriate treatment. It is also important for physicians to recognize the risk of prescription drug abuse in their elderly patients.

Older Offenders

It has been estimated that about 70% of older offenders—those aged 50 or older—have a SUD. Alcohol-only disorders are more common among older inmates. Relatively few older inmates have received drug abuse treatment. Although some correctional administrators suggest that incarceration speeds the aging process and the general deterioration of health, others suggest that the prevalence of health problems among older inmates is similar to or only somewhat higher than those of the aging adult in the general population. These problems include dementia, cancer, stroke, incontinence, arthritis, ulcers, hypertension, chronic respiratory ailments, chronic GI problems, prostate problems, heart disease, and deteriorating kidney functions. Higher rates of offender health problems may, in part, be attributed to the long-term consequences of smoking, drug and alcohol use, and other risky and unhealthy behaviors.

Treatment Outcomes

Despite earlier concerns that elderly substance abuse patients might not fare well in treatment, many recent studies have found that older patients in treatment for SUDs have outcomes that are similar to or better than those of younger patients. Patients aged 55 or older do have more medical problems than younger patients, but they may have better substance abuse outcomes and comparable or better levels of functioning in mental health, family, and legal domains.

Conclusion

An increasing overall population of older Americans, combined with an increasing prevalence of drug abuse and addiction in this population, suggests the need for greater clinical attention to the drug abuse–related problems of aging. Specific concerns are especially rooted in the interaction of drugs of abuse with an aging body. The normal complexities and consequences of aging are accentuated in the face of drug abuse and addiction. Clinicians will need to increase their vigilance about drug abuse and addiction in their older patients.

Suggested Readings

Christensen K, Doblhammer G, Rau R, et al. Ageing populations: the challenges ahead. *Lancet.* 2009; 374(9696):1196–1208.

Copeland WE, Shanahan L, Costello EJ, et al. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch Gen Psychiatry.* 2009;66(7):764–772.

Han B, Gfroerer JC, Colliver JD, et al. Substance use disorder among older adults in the United States in 2020. *Addiction.* 2009;104(1):88–96.

Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology.* 2010;35(1):217–238.

Schepis TS, Adinoff B, Rao U. Neurobiological processes in adolescent addictive disorders. *Am J Addict.* 2008;7:6–23.

44 Women and Addiction

Recent epidemiologic surveys demonstrate that the gender difference in prevalence of alcohol use disorders has narrowed in recent decades. Findings from two cross-sectional analyses of drinking across birth cohorts demonstrated little variation in lifetime drinking histories between men from different birth cohorts and those in similar age groups. By contrast, women born between 1954 and 1963 had significantly more lifetime drinking than those born in the previous cohort of women born between 1944 and 1953. Increases were particularly significant among White and Hispanic women—beginning with those born in the United States after World War II.

Telescoping

The phenomenon of "telescoping" has been consistently observed in investigations of gender and substance use disorders (SUDs). *Telescoping* is a term used to describe an accelerated progression found in women from the initiation of substance use to the onset of dependence and first admission to treatment. In particular, women are more likely than men to show an accelerated progression between regular use and treatment seeking for opioids, cannabis, and alcohol. Thus, when women enter treatment for SUDs, they typically present with more severe clinical profiles (e.g., more medical, behavioral, psychological, and social problems characteristic of SUDs), despite having used the substance for a shorter period of time.

Biologic Issues

Sex differences in the neurobiological correlates of SUDs have been elucidated in a growing number of studies over the past decade. In particular, sex differences related to responsivity to drugs of abuse and to relapse have been demonstrated in animal models and human studies in three areas: (a) neuroactive gonadal steroid hormones, as well as fluctuations of these hormone levels across the menstrual cycle; (b) sex differences in stress reactivity and relapse to substance abuse; and (c) sex differences in neurobiologic correlates evident from neuroimaging studies.

Neuroactive Gonadal Steroid Hormones

Animal models have demonstrated that neuroactive gonadal steroid (e.g., estradiol, testosterone, and progesterone) affect the reinforcing properties of drugs under numerous conditions. Neuroactive steroid hormones can have excitatory and inhibitory effects on the brain and may influence the saliency of drug effects. These gonadal steroid hormones are linked in mediating neurobehavioral processes related to the reward system and can mediate reinforcing effects of abused drugs. Ovarian steroid hormones (e.g., estrogen and progesterone), metabolites of progesterone, and negative allosteric modulators of the $GABA_A$ receptor, such as dehydroepiandrostenedione (DHEA), are neuroactive and can influence the behavioral effects of drugs. In animal models, for example, DHEA reduces self-administration and cocaine seeking in rats. Changes are also evident in brain function and neurochemistry across the phases of the menstrual cycle that are likely correlated with fluctuating levels of estrogen and progesterone, and these fluctuations have been correlated with the reinforcing properties of drugs of abuse in women.

In human studies, the follicular phase of the menstrual cycle is associated with greatest responsivity to stimulants such as cocaine. A number of studies indicate that during the follicular phase, when estradiol levels are high and progesterone low, the effects of stimulants are increased compared to the luteal phase when both estradiol and progesterone levels are elevated. It is unclear whether these effects are attributable to estradiol or progesterone.

Overall, accumulating evidence from animal and human studies demonstrate sex differences in the role of neuroactive steroid hormones on drug abuse, but the findings vary depending on the drug studied, the species, and the specific outcome measured.

Sex Differences in Stress Reactivity and Relapse to Substance Abuse

In a related area of investigation regarding sex differences in the neurobiologic correlates of SUDs, the hypothalamic–pituitary–adrenal (HPA) axis controls gonadotropin and gonadal steroid hormone release through a complex feedback mechanism. The HPA axis is also the neuroendocrine pathway for the stress response. Sex differences in neuroendocrine adaptations to stress and reward systems can function as a mediator for susceptibility to drug abuse and relapse in women.

Human laboratory studies have examined sex differences in stress response and relapse to substance abuse, including sex differences in emotional and autonomic differences in response to stress and cues. Human studies among cocaine-dependent subjects demonstrate greater stress response in men than in women, with higher adrenocorticotropic hormone (ACTH) and cortisol levels following exposure to stress and drug cues. This HPA dysregulation in women may be associated with greater emotional intensity at lower levels of HPA arousal than in men and may be one key to enhanced vulnerability to use substances in response to negative affect among women. Similar results have been found in alcohol and nicotine dependence.

Neuroimaging and Neurobiologic Correlates

Neurobiological correlates of SUDs can be assessed with neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), which can measure information processing in discrete brain circuits that may not be behaviorally observed but may be connected with

manifestations of alcohol or drug use disorders. Sex differences in neural activity have been demonstrated using fMRI techniques, including the response of medial prefrontal cortex for drug reward anticipation and receipt, and stress- and cue-induced craving. Another line of work indicates the possibility of neural correlates of sex differences in treatment outcome.

Role of Co-occurring Disorders

Mood and Anxiety Disorders

Mood and anxiety disorders are some of the most common co-occurring psychiatric conditions among women with SUDs. Epidemiologic studies utilizing the National Comorbidity Survey (NCS) and the National Survey on Alcohol and Related Conditions (NESARC) data show that lifetime rates of mood and anxiety disorders among individuals with SUDs are significantly higher among women than among men.

The order in which co-occurring psychiatric conditions develop may help elucidate the etiology as well as help determine the best treatment approach. Some individuals manifest depression prior to the development of an SUD (i.e., primary depression), while others manifest depression following the development of an SUD (i.e., secondary depression). A third group of individuals develop depression and the SUD simultaneously. Of these three potential orders of onset pathways, the most common is secondary depression. Furthermore, women are more likely than men to present with secondary depression, and therefore may be more likely to respond to depressive symptoms by "self-medicating" with alcohol and drugs. In fact, one study found that the risk of developing heavy drinking was 2.6 times greater for women with, as compared to without, a history of depression.

To date, few investigations have examined gender differences in response to psychotherapeutic or pharmacotherapeutic treatments for mood and anxiety disorders among individuals with co-occurring SUDs. The use of agents targeting substance use, such as naltrexone or disulfiram, as add-on treatment for individuals with co-occurring mood or anxiety disorders is underexplored.

Eating Disorders

Eating disorders (EDs) occur more frequently among women than among men, with a lifetime prevalence in women estimated to be 2 to 3 times higher than in men. The majority (90%) of the cases of anorexia nervosa (AN) and bulimia nervosa (BN) are found in women. In contemporary Western cultures, thinness in women has come to signify attractiveness, competence, success, and self-control and may negatively affect the development and perception of women's body image.

Women with SUDs demonstrate higher rates of EDs, in particular the purging subtypes of bulimia, than women in the general population. Rates of co-occurring lifetime drug use disorders up to 26% among individuals with EDs have been reported. Among women with BN, in particular, and co-occurring SUDs, there is also a high reported rate of severe childhood sexual abuse. Similarly, among women with BN or binge-eating disorder (BED), rates of substance abuse are greater among those with, compared to those without, a history of sexual or physical abuse. Evidence-based behavioral treatments for EDs include cognitive–behavioral therapy (CBT) and interpersonal therapy. Psychopharmacotherapy for EDs has focused on antidepressant medications. Given the biological, psychological, and social factors involved in the development of EDs, treatment is complex and requires a multidisciplinary approach.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a syndrome marked by symptoms of intense horror, helplessness, or fear following exposure to a distressing event that involves real or perceived threat to physical integrity. PTSD typically results from an extreme, catastrophic, or overwhelming experience (e.g., sexual assault, natural disaster, combat exposure) and is characterized by the following three symptom clusters: (a) reexperiencing the event through flashbacks, nightmares, and intrusive memories; (b) avoidance of stimuli (e.g., people, places, thoughts, feelings) associated with the event; and (c) increased arousal, such as hypervigilance, trouble sleeping and concentrating, and increased irritability. Among victims of sexual assault, prevalence estimates of PTSD range from 14% to 80% and, among victims of physical assault, from 13% to 23%. Notably, interpersonal victimization is more likely than noninterpersonal traumas, such as serious accidents and natural disasters, to lead to the development of PTSD.

Although selective serotonin reuptake inhibitors (SSRIs) are the pharmacological treatments of choice for PTSD, only three published studies have examined their use among patients with co-occurring alcohol or drug use disorders, and all of those studies tested sertraline. There was a trend for the sertraline group to show less severe PTSD symptoms, particularly in intrusion and hyperarousal symptoms. Follow-up cluster analyses identified that the medication-responsive group tended to have earlier PTSD (i.e., primary PTSD).

Personality Disorders

Personality disorders (PDs) are serious mental disorders characterized by inflexible patterns of thoughts and actions that are pervasive across situations and that begin during adolescence or early adulthood. Individuals with PDs demonstrate impaired functioning in at least two major areas, such as interpersonal functioning and affectivity. Prevalence rate across genders for any PD is approximately 14.8%.

Individuals with co-occurring personality and SUDs are more likely to have greater severity and, earlier age of onset of their SUDs, as well as higher rates of polydrug use, and more use of illicit drugs. High rates of self-harm and suicidal behaviors are common in women with co-occurring personality and alcohol and drug use disorders, requiring careful assessment and close monitoring. Finally, women with co-occurring personality and SUDs present with many complex problems and urgent needs. A specialized CBT intervention, dialectical behavior therapy (DBT) includes a variety of treatment modalities (e.g., individual therapy, skills group, telephone coaching, therapist consultation team) and was originally designed for suicidal patients with borderline personality disorder (BPD). Over the past decade, DBT has been adapted to address problems associated with co-occurring substance use and BPD. The four core DBT skills include (a) mindfulness, (b) distress tolerance, (c) emotion regulation, and (d) interpersonal effectiveness. These core skills are relevant to both substance abuse and other problem behaviors. Several randomized controlled trials indicate that DBT is associated with superior substance use outcomes, maintenance of treatment gains, and good retention among women with BPD and SUDs.

Specific Substances

Alcohol

Gender and Epidemiology

In general, men consume and misuse alcohol at significantly higher rates than do women. However, this gender gap has decreased over time due to women's increased use of alcohol. Similarly, examination of changes in the age of initiation of alcohol use over the past 50 years shows

significant narrowing of the gender gap. Some researchers propose that women's increase in alcohol consumption can be explained by sociocultural factors, such as society's increased acceptance of women's use of alcohol.

Telescoping Effect

Compared to men, women experience shorter time intervals between the initiation of alcohol use and the onset of significant alcohol-related problems (e.g., medical, social) and entrance into addiction treatment. This accelerated course of alcohol dependence, or "telescoping," may be attributed to a variety of biologic, socioeconomic, psychologic, and cultural factors. Women may be more adversely affected than men by alcohol due to the lower percentage of total body water, decreased first-pass metabolism because of lower levels of alcohol dehydrogenase in the gastric mucosa, and slower rates of alcohol metabolism. Sociocultural factors, such as the negative stigma associated with women and heavy drinking, economic barriers such as lack of insurance and lack of childcare, may cause women to wait until symptoms are more severe before entering treatment.

Triggers for Alcohol Use

Gender differences in triggers for alcohol use have been observed. In general, women are more likely than men to consume alcohol in response to stress and negative emotions, whereas men are more likely than women to consume alcohol to enhance positive emotions or to conform to a group. These differences in drinking motives should be considered when designing prevention and treatment plans for men and women with alcohol use disorders. Compared to men, women with alcohol use disorders are significantly more likely to have co-occurring psychiatric disorders, including EDs (specifically BN), BPD, depression, and anxiety disorders, such as PTSD. It is important to address co-occurring psychiatric conditions among women with alcohol use disorders, as these conditions may serve to impede substance use treatment efforts.

Treatment

Women are less likely than men to seek treatment, and some data indicate that once in treatment women are more likely to drop out or attend fewer sessions. These differences may be affected by gender differences in factors such as childcare responsibilities, transportation, financial status, and social stigma. Offering childcare, prenatal care, women-only admission, and services specific for women's issues may be particularly effective in getting women to initiate and continue treatment. To enhance women's treatment-retention rates, researchers have developed and implemented interventions specifically designed for women-only groups. Early results are promising, indicating that women not only experience fewer relapses in women-only treatment groups, but also gave higher satisfaction ratings for the treatment.

Stimulants

Gender and Epidemiology

In contrast to alcohol, rates of stimulant use are similar among men and women. However, both preclinical and clinical studies suggest that women may be particularly vulnerable to the reinforcing effects of stimulant drugs. In the past, women may have evidenced lower prevalence rates of stimulant drug use; however, societal changes are altering the "protective factors" (e.g., social stigma) that once lowered the rates of drug use. Because women may be more susceptible to the reinforcing effects of stimulants and "protective factors" are diminishing, women may be particularly at risk for using stimulants.

Hormones

Hormones may play an important role in the reinforcing effects of stimulant drugs for women. Both basic and clinical studies indicate that estrogen increases the reinforcing effects of stimulants for women, whereas progesterone decreases the reinforcing effects. In response to cocaine administration, women have been found to report increased subjecting feelings of "high" and increased heart rate during the follicular phase, when levels of estrogen are elevated and progesterone levels are low, as compared to the luteal phase, when levels of progesterone and estrogen are low. Furthermore, exogenous administration of progesterone has also been shown to result in attenuated subjective responses to cocaine administration among women.

Treatment

Preclinical studies suggest that women may have a harder time quitting stimulants than do men. Research suggests that CBT is as effective in treating stimulant use disorders among women as in men. One study focusing on 359 women methamphetamine-using offenders who were treated in a modified therapeutic community program ($n = 234$) or standard outpatient treatment ($n = 125$) found that both treatment groups improved on psychosocial measures with a greater effect size seen in the modified therapeutic community.

Currently, there are no approved pharmacotherapy treatments for cocaine dependence. However, preclinical studies suggest that baclofen, a GABAergic drug, may be more effective in reducing cocaine use for women than for men. In one study, female rats injected with baclofen self-administered cocaine significantly fewer times than did male rats injected with baclofen. Clinical studies using naltrexone to reduce cocaine use and bupropion to decrease methamphetamine use indicate that these pharmacotherapies may be more effective in treating men than women.

Opioids

Prescription Opioids

Gender and Epidemiology In 2006, 5.2 million Americans reported using prescription opioids for nonmedical purposes. A 141% increase in prescription opioid abuse was reported from 1992 to 2003. There are a number of potential explanations for this increase: prescription opioids are relatively easy to obtain from a variety of sources (e.g., primary care physicians, the Internet), less social stigma is attached to prescription drug use as opposed to the use of "harder" drugs like cocaine or heroin, and prescription opioids are less closely monitored by law enforcement than other illicit drugs.

Comorbidity Compared to nonopioid users, individuals who have used prescription opioids nonmedically and/or are dependent on opioids are more likely to suffer from anxiety disorders, affective disorders, or other SUDs. Men are more likely to be diagnosed with co-occurring SUDs and antisocial personality disorder (ASPD), whereas women are more likely to be diagnosed with an affective disorder (e.g., major depressive disorder [MDD]) and suffer from more severe occupational, economic, or medical problems.

Heroin and Intravenous Drug Abuse

Gender and Epidemiology

Data from the 2008 National Survey on Drug Use and Health (NSDUH) indicates that 0.2% of the U.S. population aged 12 and older has used heroin. Using data collected from a community sample, one study ($n = 408$) found that in comparison to men, women use smaller amounts of the heroin, use heroin for a shorter period of time, and are less likely to inject heroin (59% of women heroin users endorsed a history of injecting vs. 76% of the men). Among injection drug

users (IUDs), no sex differences in the duration or amount of use were revealed. In general, intravenous (IV) users report more instability in employment, more problematic use, and more health problems (e.g., hepatitis C, HIV, cirrhosis) than do non-IV users.

Triggers for Heroin and Intravenous Drug Abuse

Women's injection of drugs may be more influenced by the injection risk behavior of their sexual partner. For example, it has been found that women who injected heroin were significantly more likely than men to have a sexual partner who also injected heroin (96% vs. 82%). Female users are also more likely than male users to be introduced to injection by their sexual partners. In another study of older individuals with heroin dependence, women were more likely to describe the adverse consequences of their addiction on their families, but both men and women expressed concerns about hepatitis C and mental health issues.

Adverse Consequences of Needle Sharing

Individuals with intravenous drug abuse (IVDA) who share needles or preparation equipment are at increased risk for numerous physical diseases, including hepatitis B and C, as well as HIV. Research to date is inconsistent as to whether sex differences in injection risk behaviors occur. Other results suggest that although women are more likely to share needles, they are also more likely to engage in protective behaviors such as carrying clean syringes.

Treatment

Less than one fourth of individuals with opioid use disorders receive treatment. Potential reasons for low rates of treatment include the belief that using opioids is not as serious as using other illicit drugs, since they are prescribed by physicians. For individuals with co-occurring chronic pain, they may fear that the pain will return or be exacerbated if opioid use ceases. To date, little research has investigated gender differences in the treatment of opioid use disorders. Preliminary findings for a manual-based, 12-session group treatment specifically designed for women using methadone suggests this may be an effective way to treat opioid dependence in women.

With regard to opioid-agonist therapies, methadone-maintenance therapy has been associated with reduced heroin use and improvements in psychiatric, medical, and legal problems. It has been found that both men and women remained in treatment for a significantly longer period of time when given methadone as opposed to L-acetyl-methadol and that women given methadone remained in treatment longer than women given buprenorphine (115 vs. 105 days), although this finding did not reach statistical significance.

Cannabis

Gender and Epidemiology

According to the 2004 NSDUH, approximately 96.6 million Americans (40.2%) have tried marijuana, with 25.4 million (10.6%) having used within the last year, making it the most commonly used illegal drug in the United States. Among individuals who used marijuana within the past year, approximately 35.6% abused or were dependent on marijuana.

In comparison to women, men are more likely to use marijuana daily (2.0% vs. 0.7%), have more initial opportunities to use marijuana, and initiate marijuana use at a younger age (16.4 years vs. 17.6 years). Men and women may also differ in their risk of becoming dependent on marijuana. For women, there is approximately a 1% chance of becoming dependent during the first 5 years after initial use. For men, during the first year there is a 1% chance of becoming dependent, but for the following 2 years, there is a 4% chance per year that men will become dependent on marijuana. Research suggests that women enter treatment for marijuana use disorder after significantly fewer years of use than men do (i.e., telescoping effects).

Hormones

Unlike other substances (e.g., stimulants), no relationship between the menstrual phase and women's use of, or response to, marijuana (e.g., mood and pulse rate) has been observed. However, marijuana use may be related to the menstrual cycle for women who have severe premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD).

Negative Effects of Marijuana Use

Marijuana use may affect attention processes and memory up to 7 days after use and the effects of marijuana use on neuropsychological processes may differ for men and women. When comparing heavy marijuana users to light users, it has been noted that visual–spatial memory was impaired in women who smoked heavily. In men, however, no such difference was observed.

Comorbidity

When compared to individuals without marijuana dependence, those with dependence are significantly more likely to have co-occurring psychiatric disorders (90% vs. 55%). In particular, marijuana dependence has been found to be associated with conduct disorder, ASPD, alcohol dependence, mood disorders, anxiety disorders, depression, PTSD, and social phobia. Although gender differences in rates of comorbidity have not been thoroughly explored, there is some evidence that differences may exist. For example, one study found that social anxiety disorder (SAD) was correlated with marijuana use in women but not in men.

Treatment

Due to low numbers of women in treatment, no studies have been published regarding gender differences in the effectiveness of treatment for marijuana use disorders. However, research (with predominately male participants) suggests that CBT, contingency management treatments, motivational enhancement therapies, and oral administration of δ-9-tetrahydrocannabinol (THC) and nefazodone are effective treatments for marijuana dependence.

Nicotine

Gender and Epidemiology

In 2008, approximately 70.9 million Americans (28.4%) reported currently using nicotine. This includes people who smoke cigarettes and cigars, use smokeless tobacco, and use pipes to smoke tobacco. Males use nicotine at higher rates than do females (34.5% vs. 22.5%).

While most people understand the serious consequences of nicotine use, few are aware that women may be at an increased risk for health problems caused by smoking. Compared to men, women who smoke are twice as likely to have a heart attack, experience faster lung deterioration, and are at increased risk for chronic obstructive pulmonary disease (COPD) and lung cancer. Furthermore, smoking may cause women to commence menopause earlier, experience increased menstrual bleeding, have difficulty becoming pregnant, or experience spontaneous abortion. The children born to women who smoke while pregnant are at increased risk for sudden infant death syndrome (SIDS), death or severe complications caused by lung impairment, or low birth weight.

Triggers for Nicotine Use

Both pharmacological and nonpharmacological factors influence nicotine use and dependence. Nicotine is the main pharmacological factor in tobacco that plays a key role in the acquisition

and maintenance of use. Nonpharmacological factors are stimuli that are often paired with nicotine, which can be both proximal (e.g., the smell of a cigarette) and distal (e.g., people associated with smoking). Compared to men, women may be influenced less by nicotine factors and more influenced by proximal cues. These gender differences in underlying motivations or triggers for use may help inform gender-sensitive treatment approaches.

Treatment

Women may have more difficulty quitting smoking than do men. Data from the Centers for Disease Control and Prevention (CDC), which surveys over 10,000 U.S. citizens, indicate that over a million fewer women than men over the age of 35 are able to quit smoking. Menstrual cycle phase may be associated with women's success at smoking cessation. Women who attempt to quit during the first 14 days of their menstrual cycle (e.g., the follicular phase) may be more likely to be successful in their attempt than women who attempt to quit in the second half of the cycle (e.g., the luteal phase) and that women have greater nicotine withdrawal symptoms and craving if they quit smoking in the luteal versus follicular phase.

Nicotine Replacement and Nonnicotine Medication Research is inconclusive as to whether there are sex differences in the efficacy of nicotine replacement therapy (NRT). In 2004, a meta-analysis of 11 placebo-controlled NRT patch trials indicated that NRT is equally effective for men and women. More recently, however, three additional placebo-controlled trials to this meta-analysis and the results indicated that NRT is significantly more effective for men than women. Nonnicotine medication (bupropion and varenicline) is equally effective in men and women up to 12 weeks after treatment. However, no research has examined the abstinence rates following longer periods of time after treatment.

Behavioral Treatments Although medications are the standard approach to help individuals quit smoking, therapy and counseling generally enhance the efficacy of medication treatment and appear to be more effective in women than in men. There are a number of approaches to counseling that may specifically help women address obstacles to quitting. For example, interventions that teach women how to cope with cues (e.g., distracting oneself from cues), since research suggests women respond more to nonnicotine factors, may be particularly helpful.

Smoking during pregnancy is another issue of concern for women. This is a complicated issue because of the social stigma attached to smoking during pregnancy. Often, women report abstinence when they are still smoking. Behavioral treatment approaches are particularly important for smoking cessation during pregnancy, because many medications are contraindicated in pregnancy. Therapy should be modified specifically for pregnant women (e.g., incentives for cessation, such as vouchers that can be exchanged for baby supplies) both while women are pregnant and after delivery, since approximately 65% of women who quit while pregnant relapse within 6 months of delivery.

Treatment Outcome for Women with SUDs

Treatment Seeking and Utilization

The Treatment Episodes Data System (TEDS) captures data on national treatment admission rates and provides information on the extent to which women participate in substance abuse treatment. Based on the TEDS data, the overall proportion of men to women within the treatment system has remained fairly constant (e.g., from 1995 to 2005) at 2:1.

A recent review of the literature between 1975 and 2005 examining characteristics associated with treatment outcome in women with SUDs concluded that over their lifetime, women are less likely to enter treatment compared with men. However, once women enter treatment, gender itself is not a predictor of treatment retention, completion, or outcome. While gender itself does not necessarily predict outcome, there are a number of gender-specific predictors of outcome, and patient characteristics and treatment approaches can affect outcomes differentially by gender.

Gender-Specific Treatment for Women with SUDs

Historically, the majority of substance abuse treatment models have been designed for men and based predominantly on male norms. More recently, however, gender-specific interventions are beginning to emerge. Gender-specific interventions and services for women are designed specifically to provide information and services that are tailored for women. Gender-specific and gender-sensitive treatments have emerged in response to mixed-gender programs, which often fail to address women's specific needs, such as childcare assistance, pregnancy, parenting, domestic violence, sexual trauma and victimization, housing, income support, and social services.

Behavioral Couples Treatment

Dyadic conflict and relationship stress appears to affect the substance use of men and women differently. For example, studies show that women are more vulnerable than men to consuming alcohol subsequent to marital discord, divorce, negative emotional states, and interpersonal conflict. Furthermore, having a partner that abuses alcohol or drugs is more strongly related to relapse for women than for men.

Because relationships and family discord play a critical role in women's substance use problems, treatment interventions designed specifically to address these issues may be particularly beneficial. One such treatment approach is behavioral couples therapy (BCT), which has been shown in numerous studies to lead to reduced drinking and positive dyadic adjustment among men with substance abuse problems, decreased intimate partner violence (IPV). BCT is founded upon two fundamental assumptions: (1) family members (specifically spouses or other intimate partners) can reward abstinence and (2) a reduction of relationship distress and conflict leads to improved substance use outcomes by reducing possible antecedents to relapse and heavy use. Compared to traditional individual-based treatments (IBTs), participation in BCT results in significantly less partner violence, lower substance use severity, higher rates of marital satisfaction, greater improvements in psychosocial functioning of children living with parents, and better cost-benefit and cost-effectiveness.

Additional Issues

Pregnancy and Substance Abuse

Alcohol Use in Pregnancy

Data from the 2008 NSDUH indicates that approximately 10.6% of pregnant women use alcohol, while 4.5% report binge drinking. Alcohol use during pregnancy may cause pregnancy-related complications (e.g., preterm labor, spontaneous abortions) and negatively affect the fetus.

Approximately 1 in 300 to 1 in 1,000 children born per year in the United States are diagnosed with a fetal alcohol spectrum disorder (FASD). Children with FASD experience physical abnormalities (e.g., malformed ears, flattened midface), cognitive and behavioral changes (e.g., impulse control problems, attention-deficit hyperactivity disorder [ADHD]), and psychiatric disorders (e.g., mood disorders, conduct and behavior disorders).

Four main treatment interventions are used to treat/prevent alcohol use in pregnant women: (a) primary care treatment of women of childbearing age who meet criteria for alcohol use disorders, (b) detoxification, (c) follow-up programs for women who used alcohol while pregnant, and (d) brief interventions. Research suggests that brief motivational interventions may be particularly effective in reducing the use of alcohol during pregnancy.

Nicotine Use in Pregnancy

Past month prevalence rates indicate that 16.4% of pregnant women report using nicotine. Research indicates that using nicotine during pregnancy may cause maternal complications (e.g., vitamin and mineral deficiencies, pregnancy-induced hypertension), neonatal complications (e.g., low birth weight, congenital malformations, and intrauterine growth restriction), and long-term consequences for the children (e.g., cognitive deficits). Although research suggests that bupropion and behavioral interventions are effective treatments for smoking cessation in women, NRT may increase negative birth outcomes, but studies indicate that it is unclear whether associated low birth weight is a direct effect of the NRT or rather the associated heavy smoking among women referred for NRT.

Marijuana Use in Pregnancy

Data from the 2001 Maternal Lifestyle Study indicates that 11.1% of pregnant women use marijuana (3, 287). The use of marijuana during pregnancy can lead to maternal complications (e.g., negative effects on duration of pregnancy, implantation), complications for the neonate (e.g., intrauterine growth retardation, acute myeloblastic leukemia), and long-term effects on the children (e.g., slower motor development, increased depressive symptoms). To date, no research has investigated specific treatment interventions for pregnant women using marijuana.

Opioid Use in Pregnancy

Approximately 7,000 children born each year in the United States are exposed to opioids prenatally. Both the mother and fetus are at risk for overdosing, which can lead to complications such as, coma, hypothermia, and circulatory collapse. The use of opioids during pregnancy can also cause the fetus to develop neonatal abstinence syndrome, which includes symptoms such as irritability, temperature disregulation, and seizures. Treatment options for pregnant women using opioids include methadone maintenance and detoxification. Studies suggest that treatment of pregnant opioid-dependent women and their children in specialized treatment programs can help enhance maternal and child outcomes.

Cocaine Use in Pregnancy

A multisite study of university hospitals found a 10% rate of cocaine use among pregnant women using illicit drugs. Cocaine use during pregnancy can cause significant maternal complications (e.g., pneumonitis and placental abruption) and put the fetus at risk for adverse outcomes (e.g., HIV and harm fetal–placental circulation). Since withdrawal is not life-threatening for the mother or fetus, treatment to support cessation of use and ongoing relapse prevention and abstinence are indicated for cocaine use in pregnant women. Anticraving medications,

for which effectiveness studies are inconclusive, are typically avoided, since the FDA has not approved the medications for pregnant women.

Cultural Issues

Epidemiology

Approximately 98 million minorities live in the United States (33% of the U.S. population). Rates of illicit drug use vary by race/ethnicity, with rates being estimated as follows (from smallest to largest): Asian Americans (3.6%), Hispanics (6.2%), Native Hawaiians or other Pacific Islanders (7.3%), European Americans (8.2%), Native Americans or Alaska Natives (9.5%), African Americans (10.1%), and individuals reporting more than one race (14.7%). Rates of substance abuse or dependence also vary by race/ethnicity, with rates being estimated as follows (from smallest to largest): Asian Americans (4.2%), African Americans (8.8%), European Americans (9.0%), Hispanics (9.5%), individuals reporting more than one race (9.8%), and Native Americans or Alaska Natives (11.1%).

Risk Factors for Diverse Women

In order to effectively counsel diverse women with SUDs, it is imperative that clinicians are knowledgeable about cultural histories, norms, practices, and environments. Common correlates of SUDs are found among women from diverse ethnic/racial groups. Many women with SUDs may also experience other at-risk behaviors and conditions, such as high-risk sexual behaviors, co-occurring psychiatric disorders, physical and medical problems (e.g., HIV/AIDS), traumatic histories and victimization (e.g., rape, loss of children), functional problems (e.g., unemployment), incarceration histories, and experiences of racism.

Treatment

There is limited research available that addresses the treatment of SUDs among specific ethnic groups, due mainly in part to the strict criteria and guidelines in clinical research. Therefore, it is best practice at this time to use evidence-based treatment modalities and programs (e.g., CBT) modified to address common correlates found among diverse women with SUDs. For example, treatment programs should address co-occurring disorders (e.g., PTSD caused by trauma histories) or other functional problems in diverse women's lives.

Sexual-Minority Issues

Epidemiology

Limited research has been conducted to date on sexual-minority women and SUDs. Within these studies, definitions of sexual-minority women have varied, making the interpretation and generalizability of the results difficult.

Compared to heterosexual women who report having sex only with men, sexual-minority women (including lesbians, bisexual women, and women who have sex with women [WSW]) use alcohol at higher rates and have more alcohol-related problems. Lesbians and bisexual women were also found to be more likely to meet criteria for alcohol dependence and/or participate in treatment than heterosexual women. Sexual-minority women are also more likely than heterosexual women who reported having sex only with men to use marijuana, analgesics, nicotine, and to meet criteria for substance dependence.

Risk Factors

Compared to heterosexual women, sexual-minority women report significantly higher rates of traumatic events, such as discrimination, and verbal and physical attacks from peers, parents,

and partners. Sexual-minority women also report higher rates of mood and anxiety disorders, suicidality, and psychological distress. Discrimination, traumatic events, and psychological problems may put sexual-minority women at increased risk for SUDs. Furthermore, social structures within the United States may also place sexual-minority women at risk for developing SUDs. Bars are one of the few social outlets that exist in the United States where sexual minorities feel free from ostracism or scrutiny, which may lead to higher rates of alcohol use among lesbian and bisexual women.

Treatment

Although homosexuality has not been considered a clinical disorder in the DSM for more than 25 years, some clinicians still support conversion therapy, designed to convert homosexuals to heterosexuals. Early research on SUD treatment of sexual minorities indicates that many programs refused treatment to sexual minorities or focused on "converting" the patients to heterosexuals or had limited experience and training in treating SUDs among sexual minorities. A more current study also found that many counselors are not trained to work with sexual minorities and are unaware of legal and family issues for sexual minorities.

Legal Issues

Drug Use and Civil Law

Over the last 20 years, states have criminally prosecuted pregnant women using illicit drugs in an attempt to protect fetuses, which has led to women's incarceration and the loss of custody of children. Limitations to the punitive approach include the fact that it may cause pregnant women using illicit drugs to choose an abortion or avoid medical care altogether.

Research shows that mothers who abuse substances are more likely to have their children placed in out-of-home care. Mothers using substances who lost the custody of their children experienced more psychological and functional impairments, homelessness, victimization experiences, higher frequencies of drug use, and engaged in more risky sex practices, as compared to mothers using substances who did not lose custody of their children. However, custodial mothers are less likely to start treatment for SUDs, and if started they are more likely to drop out of treatment, possibly due to childcare responsibilities. One line of research offering promise for effective treatment for pregnant and parenting women with SUDs reported that 61% percent of women who attended a residential substance abuse program for pregnant and parenting women were completely drug- and alcohol-free throughout the 6-month follow-up period.

Drug Use and the Criminal Justice System

Nearly 1.9 million individuals are arrested each year for drug abuse violations. Approximately 17% of crimes are committed for drug money, and between 25% and 33% of crimes are committed under the influence of drugs. Within state prison facilities, 60% of the women (vs. 40% of men) were committed for property or drug crimes. It is estimated that 80% of incarcerated women used substances in the past and that approximately 60% of women met criteria for drug dependence.

Conclusion and Future Directions

Over the last decade, there has been an increasing number of studies focusing on gender differences in SUDs, as well as gender-specific treatments and outcomes for women with SUDs. Current research supports that there are important gender differences in biologic, psychological, cultural, and socioeconomic factors that affect the initiation, use patterns, disease acceleration,

and help-seeking patterns in women, as well as gender-specific predictors of substance abuse treatment entry, retention, and outcomes for women. Further research will enhance our understanding of basic biological mechanisms that underlie these gender differences in substance use vulnerability, responsiveness, and neurobiologic correlates of addiction.

Suggested Readings

Back SE, Waldrop AE, Saladin ME, et al. Effects of gender and cigarette smoking on reactivity to psychological and pharmacological stress provocation. *Psychoneuroendocrinology*. 2008;33(5):560–568.

Fox H, Sinha R. Stress, neuro-endocrine response and addiction in women. In: Brady KT, Back SE, Greenfield S, eds. *Women and Addiction: A Comprehensive Handbook*. New York City: Guildford Press; 2009:65–83.

Grucza RA, Norberg K, Bucholz KK, et al. Correspondence between secular changes in alcohol dependence and age of drinking onset among women in the United States. *Alcohol Clin Exp Res*. 2008;32(8):1493–1501.

Newman JL, Mello NK. Neuroactive gonadal steroid hormones and drug addiction in women. In: Brady KT, Back SE, Greenfield SF, eds. *Women and Addiction: A Comprehensive Handbook*. New York City: Guildford Press; 2009:35–64.

Tetrault JM, Desai RA, Becker WC, et al. Gender and non-medical use of prescription opioids: results from a National US survey. *Addiction*. 2008;103:258–268.

45 Special Populations

African Americans

Clearly, socioeconomic factors interact with sociocultural and political issues to greatly increase the burden of substance abuse on communities that often have to struggle with the effects of poverty and limited resources. African Americans are often stigmatized as being at greater risk of becoming substance abusers. The evidence, however, paints a more complex picture. Prevalence of overall substance abuse disorders is indeed greater. However, these global statistics often hide findings that show the opposite, depending on age of use, gender, residence, and type of drug. The household survey of youth consistently shows that African American youth are less likely to abuse many types of drugs and alcohol. Among teenagers, Caucasians are more likely to drink or use some drugs than African American youth. African Americans tended to begin drinking and to use marijuana at an older age than did other ethnic groups and are less likely to smoke. As a consequence, African Americans are less likely to suffer from alcohol-related problems. Use of designer drugs is rare among African American youth.

Preventive and Risk Factors

Multiple factors contribute to the ethnic differences in use patterns. As noted above, socioeconomic factors are important. They are important not only because the cost of a drug may determine its use but also because income can determine where one resides. Drugs of abuse may be more easily accessible in inner city and marginalized areas. Place of residence also adds to economic and cultural determinants. African Americans who live in the same locations as Caucasians consequently have the same use pattern. Regardless of race, the same access to drugs tends to show the same abuse pattern both in the type of drug used and in the prevalence of abuse. Academic achievement and peer drug use have been consistently shown to have protective effects. In a recent study, they were shown to be significant predictors of alcohol and marijuana use among high-risk African American youth. Religiosity and spirituality have been proposed as protective factors. One way in which these factors may work in inner-city youth may be through preventing posttraumatic stress disease (PTSD) or other complications of trauma exposure. Understanding the mechanisms by which religion might influence substance use and the reasons why these mechanisms may vary by race and ethnicity may provide clues to implementing effective prevention programs.

Medical Comorbidity

Alcohol- or substance-abusing African Americans compared to other ethnic groups have worse outcomes in mental health, physical health, and social outcomes when socioeconomic factors are controlled. These agents adversely affect health outcome irrespective of race. African Americans, however, seem to have a worse morbidity and mortality.

African American alcohol-, heroin-, or cocaine-dependent persons are less likely to have primary medical care, but more likely to have a chronic illness, prior medical hospitalizations, and more emergency room visits.

One of the most important comorbid conditions is AIDS. African Americans experience striking disparities in HIV infection rates compared with other populations, and they are at particularly high risk for developing AIDS. African Americans make up just 13% of the U.S. population, but more than half of the total AIDS cases diagnosed in 2004.

Mental Illness Comorbidity

Substance abuse is often comorbid with mental disorders as well. Persons diagnosed with mood or anxiety disorders were about twice as likely to suffer also from a drug use disorder (abuse or dependence) as respondents in general. Similarly, persons diagnosed with drug disorders were roughly twice as likely to suffer also from mood and anxiety disorders. This observation has important implications for African Americans.

Prevention

The paradigms of primary and secondary prevention are applicable, but they must be tailored to specific minority groups. Further exploration in this area is critical. The problem of awaiting the availability of treatment programs continues the devastating rates of HIV, violence, and incarceration for the African American population. As noted previously, spirituality can have a protective effect. Spirituality has been found to be especially influential in substance abuse prevention and treatment for African Americans. Spirituality is often found to be incorporated into activities with the African American community, and most of these events are centered around the Black Church. In fact, spirituality and perceived social support were found to serve as protective factors for smoking and alcohol use among African American college students. Given these findings, involvement in the church may be especially salient for African Americans at risk for abuse.

Treatment

There is now little doubt that treatment can work, and it works for a variety of substances, across ethnicity, and in a variety of settings. Treatment programs, especially if they address cultural needs, are effective and have strong participation by ethnic minorities. Moreover, effective treatment also can mean reductions in behaviors that increase the risk of HIV. Racial disparities in treatment participation and access are well documented. African Americans have more unmet needs than other ethnic groups.

Conclusion

Alcohol and substance abuse disorders greatly impact the African American community. While the prevalence of substance use is not substantially different from other ethnic groups, the burden to individuals and the community is greater. Drug abuse is clearly a problem that exacerbates the consequences of discrimination and poverty. Most importantly, substance

abuse contributes to the disparities in morbidity and mortality seen in the general health in African Americans and accounts for some of the excessive disease burden seen with mental disorders.

Hispanic Americans

Despite the recent advances in the biopsychosocial treatment of addictive disorders, addiction to drugs and alcohol continues to be a major challenge among the different Hispanic American groups who reside in the United States. Additionally, disparities within the field of addiction are a major factor insofar as the lack of substantial progress among Hispanic American addicts who reside in this country is concerned. Racial and ethnic discrimination, excessive poverty, lack of parity between medical and addiction care, excessive emphasis on criminalization-oriented policies, lack of universal access to health care, insufficient preventive efforts, and the like all contribute to the current crisis faced in the United States insofar as access to care, full rehabilitation, and the biopsychosocial aspects of prevention of the Hispanic American addicts is concerned. As a result of this failure within the addiction system of care that currently prevails in the United States, a very large number of Hispanic American addicts do not receive appropriate treatment, and a very large number of Hispanic American addicts drop out from treatment prematurely. Among these previously eluded barriers to appropriate care for the Hispanic American addicts, the lack of medical insurance stands as a formidable one.

Lack of culturally-oriented manpower, insufficient cross-cultural expertise, lack of sensitivity toward ethnic, racial, and other minority groups, lack of appropriate educational levels, and excessive poverty levels all contribute to the lack of preventive programs, quality of care, lack of access, insufficient psychosocial treatments, and inadequate research efforts vis-à-vis the Hispanic American addicts who reside in this country.

Definition of the Population

The number of Hispanics continues to grow in the United States, whether it is internal growth within the U.S. territory or via migration from Central America and the Caribbean, South America, or the Iberian Peninsula. The Hispanic population in the United States grew from 29.3 million (9%) in 1990 to 35.3 million (12.5%) in 2000. This number does not include the Hispanic illegal aliens who are currently estimated to be about 11 million.

The growth of the Hispanic population during the decade of 1990 to 2000 surpassed any other ethnic group living in the United States. Hispanics grew during this decade at a rate of 58%. In contrast, Asians grew 50%, Native Americans grew 17%, Blacks grew 16%, and the Whites grew only 3%.

Another factor that needs to be taken into consideration with respect to the multiple ethnic and minority groups that reside in the United States is the U.S. median family income levels. The median family income level for Hispanics who reside in the United States, in accordance with the U.S. Census Bureau report, 2000, was $30,735, in comparison to $51,205 for Asian families, $44,366 for White families, $30,784 for Native American families, and $27,910 for Black families.

From a different although important perspective, when defining the Hispanic population who reside in the United States, we should also address the uninsured population. In accordance with the U.S. Census Bureau report, 2000, 43.6% of illegal aliens in the United States were uninsured from a medical point of view; also, 34.2% of the foreign-born aliens were also medically uninsured; additionally, 18.2% of the naturalized U.S. population was medically uninsured, and, finally, 14.2% of the U.S. native-born population was medically uninsured.

Current Substance Abuse Trends among Hispanics

Hispanics are currently the highest growing segment of the U.S. population. Similarly, 13% of the admissions in the Treatment Episode Data Set (TEDS) in 1999 were Hispanics. Likewise, in 1999, among Hispanic admissions to TEDS, 42% were Mexicans, 35% Puerto Ricans, 2% Cubans, and 21% other Hispanics. TEDS in this context represents those admitted for substance abuse treatment. TEDS also represents admissions for substance abuse treatment in facilities that receive some public funding. In 1999, in accordance with TEDS, the Hispanic gender distribution of substance abuse admissions was 69.6% Hispanic men and 31% Hispanic women. Also in 1999, the most common substances of abuse among Hispanics were alcohol (36%), opiates (32%), and marijuana (14%); other substances used by Hispanics were cocaine (11%) and stimulants (4%).

Cannabis is the most widely used illicit drug; that is, it is being used by 3.8% of the global population older than 15 years. Cannabis use accounts for about 80% of the illicit drug used worldwide. Along these lines, dependent heroin users have an increased risk of premature death from drug overdoses, violence, suicide, and causes related to alcohol. Additionally, 5% to 10% of new HIV infections worldwide are attributable to use of drugs intravenously or as a result of sharing contaminated equipment.

Sociocultural Considerations

In recent years, a major emphasis and priority have been accorded to investigational and clinical efforts focusing on the basic social and cultural structures and processes that influence directly or indirectly health in general, and mental health in particular, including addictive behavior. In general, social and cultural factors influence health and mental health outcomes, affecting exposure and vulnerability to illnesses, risk-taking behaviors, the efficacy of health promotion efforts, as well as access to, and availability of, health and mental health care, including addiction services, and the quality of such services. The factors that link the sociocultural environment to health or mental health outcomes is of utmost importance. In this context, socioeconomic status, social class, gender-related issues, and ethnic and racial factors all relate to potential disparities in the health and mental health–care systems. Undoubtedly, social policies and cultural norms have unique linkages to human behavior and personal health.

Ethnic identity and spirituality have both been evaluated with respect to their potential influences vis-à-vis treatment outcomes among Hispanic American addicts in treatment with methadone. This study showed that while spirituality has no influence vis-à-vis the increase of drug use and abuse at follow-up with methadone maintenance, ethnic identity definitely demonstrated to be related to a greater number of drugs used at follow-up with methadone maintenance treatment programs. No significant effects were found for spirituality.

Public Policy Considerations

In discussing the subject of substance abuse among the different Hispanic populations residing in the United States, one must also address issues related to public policy development and implementation. To begin with, we recommend and expect that Hispanics be directly involved and fully participate in the design and implementation of such policies. This type of involvement will ensure identification with these policies and, more importantly, compliance with them. Hispanic consumers must also be involved at all levels of this process because they will be the recipients of the impact of these policies. Hispanics based on their clinical skills and cultural knowledge can better plan and design culturally sensitive program models geared to the treatment of Hispanic patients. In doing so, they can also serve as ideal role models for future generations of Hispanic mental health professionals.

Conclusion

For decades, the substance abuse problem has been devastating for the Hispanic population residing in the United States. However, not enough attention has been given to this problem, particularly with respect to preventive approaches, epidemiologic research, culturally sensitive clinical interventions, treatment outcome studies, and public policy formulations. Additionally, program development and fiscal allocations have not been commensurate with the size of these problems. Recently, however, the substance abuse and HIV epidemics have extended into the white population of this country. As a result of this shift, the government, particularly at the federal level, has been forced to pay more attention to the substance abuse problem. Generally, traditional agencies and government bureaucracy have overlooked the need for basic awareness of the characteristics, conditions, and circumstances surrounding the Hispanic substance abuser.

Asian Americans and Pacific Islanders

Recent research findings have shown that biologic, psychological, and social/cultural factors affect the onset and course of substance abuse. Coinciding with the increasing numbers of Asian Americans and Pacific Islanders in the United States, there are increasing efforts to evaluate substance use issues among them. However, factors that influence substance abuse among Asian Americans/Pacific Islanders remain multifaceted.

Epidemiology

The estimated number of U.S. residents in July 2007 who said they were Asian or Asian in combination with one or more other ethnic group was 15.2 million. This group comprised about 5% of the total U.S. population. Between 2006 and 2007, the percentage growth of the Asian population was 2.9%, the highest of any ethnic group during that time period. The increase in the Asian population during the period totaled 434,000. In 2007, there were 5 million self-identified Asians in California, the state with the largest Asian population. California also had the largest numerical increase from 2006 to 2007 at 106,000. New York (1.4 million) and Texas (915,000) followed in population. Texas (44,000) and New York (33,000) followed in numerical increase. In Hawaii, Asians made up the highest proportion of the total population (55%), with California (14%) and New Jersey and Washington (8% each) next. Asians were the largest minority group in Hawaii and Vermont. The estimated number of U.S. residents in July 2007 who said they were Native Hawaiian and Other Pacific Islander, either alone or in combination with one or more other ethnic groups, was 1 million. This group comprised 0.3% of the total population. In 2007, Hawaii had the largest population (269,000) of Native Hawaiians and Other Pacific Islanders (either alone or in combination with one or more other races), followed by California (262,000) and Washington (50,000). California had the largest numerical increase (2,900) of people of this group, with Texas (2,500) and Florida (1,100) next. In Hawaii, Native Hawaiians and Other Pacific Islanders comprised the largest proportion (21%) of the total population, followed by Utah (1%) and Alaska (0.9%). Between 2006 and 2007, the percentage growth of the Native Hawaiian and Other Pacific Islander population was 1.6%. The increase in the Native Hawaiian and Other Pacific Islander population during the period totaled 16,000.

In 2007, the major Asian groups in the United States were Chinese (3.54 million), followed by Filipinos (3.05 million), Asian Indians (2.77 million), Vietnamese (1.64 million), Koreans (1.56 million), and Japanese (1.22 million). Other Asian groups (13%) include Burmese,

Cambodian, Hmong, Laotian, Thai, and Tongan. These estimates represented the number of people who were either of only a particular Asian group or of that group in combination with one or more other Asian groups or races.

Prevention

Various people have written about prevention strategies against substance abuse for Asian Americans/Pacific Islanders, but the effectiveness of these measures has not been studied. Most authors agree with the thought that culturally responsive prevention strategies should be linked into the natural support systems of that particular Asian Pacific community, for example, in the Filipino community, using the church as a forum for prevention work. Prevention should provide Asian parents with the skills they need to help their children assimilate into American culture, such as helping them with their roles in the educational and recreational processes. Programs should develop strategies to minimize shame and loss of face in Asian Americans/Pacific Islanders. One example of how this can be done is by using a community intermediary to manage interpersonal conflicts between parents and youth. Finally, community education programs might use more personalized contacts for prevention, such as a door-to-door education campaign in the high-risk community.

A family-oriented approach in which an extended family is included in issues of prevention, intervention, and treatment will have the best chance of success in the Asian community. One needs to address issues of denial, underreporting, and the need for getting outside help. It is very important to preserve the family unit as a hedge against substance use.

Treatment

Despite the growing body of evidence that shows that addictive disorders in Asian Americans/Pacific Islanders are significant, there remain many barriers to treatment. These barriers include cultural, individual, and practical issues. Studies have shown that Asian Americans/Pacific Islanders have poor access to medical and psychiatric health care as well as to addiction treatment. This occurs despite the fact that Asian Americans/Pacific Islander and non–Asian Americans/Pacific Islander substance abusers do not differ in terms of treatment retention and outcome once they have received treatment. As seen from the TEDS data, an increasing number of Asian Americans/Pacific Islanders are entering substance abuse treatment; however, they are still greatly underrepresented in various addiction treatment settings. This underrepresentation of Asian Americans/Pacific Islanders in treatment may result from many factors. As for the cultural factors, the traditional way to "handle" an Asian addict is to either deny the problem or attempt to handle the issue within the family structure.

Factors Influencing Substance Use in This Population

Genetic/Biologic Factors

Although multiple factors, including genetics, have been proposed to affect the addiction process, there is a striking lack of information between genetics and drugs of abuse in the Asian Americans/Pacific Islander population. Yet the best genetic data came from the twin studies of alcohol abuse, so we use this as a model for much of the discussion that follows. Most recently, new findings have come out of China linking genetics to opioid addiction among Han Chinese. This exciting new discovery will be discussed at the end of this section.

The best-studied area is still the genetic contribution to the development of alcoholism. Family and adoption studies have found a significant hereditary contribution in alcoholism, although these data were not derived from the Asian Americans/Pacific Islander population. For Asians, the transmission of alcohol genes and the mechanism for impaired alcohol metabolism are areas of special interests.

Nonbiologic Factors

The genetic studies have made a major impact on our understanding of the inheritance of alcoholism. Even with this biologic predisposition, however, the expression of alcoholism can be affected by environmental, social, and psychological factors. It is difficult to disentangle the specific environmental factors that affect drinking, but for the purpose of discussion, we separate them into family/cultural, acculturation, and psychological factors.

Family/Cultural Factors Family unity and other cultural factors play a significant role in the development of substance abuse issues. It was suggested that the relatively late age of onset of alcohol use for Asian American youth compared with that for non–Asian American youth might be a result of parental modeling or cultural influences. Asian American students, who had a more abstinence-promoting environment than their European American counterparts, were less likely to drink alcohol. Asian students were less likely to have "adult and peer influences to use alcohol or cigarettes" and had "less offers of alcohol" and "increased likelihood of having an intact family." It was concluded that a strong family connection and the lower prevalence of parents and peer use might reduce Asians' alcohol use. The importance of norms and values in Asian cultures may moderate drinking by Asian Americans/Pacific Islanders.

Acculturation Factors The degree of acculturation into mainstream America has correlated significantly with the development of addictive disorders. This is the case not only for Asian Americans/Pacific Islanders but also for Hispanics and some African Americans. The definition of the acculturation process varies, but some have based it on a number of generations residing in the United States and the ability to speak English and/or their ethnic languages.

Conclusion

With the rapid growth of the Asian Americans/Pacific Islander populations in the United States, there is an increased need to address substance abuse issues among these populations. The limited epidemiologic data suggests that, in general, Asian Americans/Pacific Islanders are at a relatively lower risk for substance use than other ethnic groups. However, it also suggests that rates of alcohol use, smoking, and use of some illicit drugs may not be as low as generally assumed. Recent finding of a strong genetic contribution to the development of opioid addiction among Han Chinese supports the biologically mediated process in addiction but also the severity of the problem in China. We also know that environmental influences can also play a role in contributing to substance use patterns. Past findings of Asian Americans/Pacific Islanders infrequently use substance treatment services, which have led to a misperception as a lack of need for services by them. In fact, Asian Americans/Pacific Islanders who entered treatment are younger and appeared in treatment for the first time, suggesting an increased need and acceptance for treatment. At present, there is a paucity of empirical information on the effectiveness of treatment and prevention programs targeting Asian Americans/Pacific Islanders.

American Indians and Alaska Natives

Living in balance and harmony has been highly valued traditional belief constructs among American Indians/Alaska Natives for many centuries. However, the introduction of the recreational use of alcohol to American Indians by English colonists hallmarked a deleterious change in the harmony and overall well-being of indigenous groups residing in North America.

Alaska Natives were introduced to alcohol in 1741 by Russian fur traders, in a similar fashion to American Indians. Fur traders relied upon rum and whiskey in their negotiations with Alaska Natives. Insofar as that, even the shrewdest traders or those who sought maximum profit refused to trade with a sober native. The demand for alcohol by Alaska Natives became significant and most likely contributed to the development of a concoction called *hoochinoo*, a fermented alcoholic beverage made from dried fruit, berries, flour, and yeast. This drink was made by Alaska Natives when alcohol usually supplied by Russians was not available. Alcohol use during the 1700s and 1800s throughout Alaska Native villages was significant, resulting in the prohibition of alcohol in the territory of Alaska, which was under the jurisdiction of the U.S. War Department during this period. The majority of American Indians/Alaska Natives do not experience significant substance abuse problems. However, continuing challenges exist today with regard to substance abuse in American Indian/Alaska Native communities.

Epidemiology

The study of epidemiology among American Indians/Alaska Natives with substance abuse is inherently challenging. Since the American Indian/Alaska Native population comprises 562 federally recognized tribes, characterizing substance abuse in this population as one distinct category is not possible because each tribe has its own unique history, culture, language, and traditions. In addition, there may be differences biologically as different tribal groups may have historical origins from various regions of the continent. In fact, from an anthropologic sense, American Indians/Alaska Natives are a part of a worldwide population of *indigenous peoples.*

Sociocultural Considerations

Studies analyzing how childhood characteristics are associated with the stage of substance use in adulthood have also been limited. In a sample consisting of two closely related Northern Plains tribes (NP) and a Southwestern tribe (SW), four correlates of substance abuse based on hierarchical stages were used, including lifetime abstinence, use of alcohol alone, use of marijuana/inhalants with or without alcohol, and use of other illicit drugs with or without the previously listed substances.

Participation in cultural and traditional activities and traditional ceremonies has been an important area of research as it relates to American Indians/Alaska Natives with substance abuse problems. Culturally based treatments are utilized in numerous substance abuse programs serving American Indians/Alaska Natives. However, formalized studies analyzing the potential effects of traditional activity participations on substance abuse behavior are relatively limited. To date, studies conducted have found both positive and negative associations with cultural identity and traditional activity participation among American Indians/Alaska Natives with substance abuse problems.

Prevention

Preventing the initiation of alcohol, drugs, and tobacco has been known to assist in decreasing overall substance abuse rates in various populations. Implementing effective prevention protocols for American Indians/Alaska Natives is critical, since they are known to have earlier onset of illicit drug and alcohol use and more negative consequences compared to other racial/ethnic groups. Identification of potential protective factors is important in implementing effective prevention programs.

Cultural Considerations in Evidence-Based Substance Abuse Treatments for American Indians/Alaska Natives

Currently available psychotherapeutic interventions include motivational interviewing, cognitive–behavioral therapy (CBT), 12-step facilitation, psychodynamics, contingency management, network therapy, group therapy, and family therapy, which have been shown to be effective in various studies. However, their effectiveness and cultural relevancy among American Indians/Alaska Natives are relatively unknown. Currently available evidence-based treatments have not been thoroughly tested among various ethnic/minority groups; thus, the assumption that these substance abuse treatments are effective among all patients is not valid. Although consisting of various distinct tribes, American Indians/Alaska Natives share many cultural characteristics, including similarities in behavior patterns, lifestyle, values, beliefs, views, and attitudes. Thus, adequate attention to these factors is critical when providing evidence-based treatments to American Indians/Alaska Natives.

Utilization of Traditional Healing Methods for American Indians/Alaska Natives with Substance Abuse Disorders

Traditional healing continues to be a highly valued form of treatment for urban and reservation-based American Indians/Alaska Natives with a variety of health problems, including addiction. Although a variety of definitions and opinions exist with regard to what constitutes Native American traditional healing, traditional healing can be thought of as a spectrum of activities from participation in traditional activities, including drumming, bead making, and attendance of powwows, to participation in specific traditional ceremonies. Common traditional treatments used in substance abuse facilities servicing American Indians/Alaska Natives include smudging ceremonies, sweat-lodge participation, and talking circles, a traditionally founded form of group therapy. Participation in these ceremonies may contribute to a renewed elevated sense of self- and cultural pride, thus serving as a potential protective factor for substance abuse problems.

Genetics

It has been a widely held popular belief that "the reason" for high rates of alcoholism and substance abuse among American Indians/Alaska Natives is a genetic predisposition. However, to date, limited data exist that posit that genetic characteristics are significant risk factors for a wide variety of substance use disorders (SUDs) among American Indians/Alaska Natives.

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

HIV/AIDS has become an emergent health problem among American Indians/Alaska Natives. Native Americans have the third highest rates compared to other racial/ethnic groups in the United States, behind African Americans and Hispanics. Furthermore, urban American Indians may be at greater risk for HIV infection than American Indians residing on reservations due to significant risk factors known to exist in urban areas. These risk factors include the tendency to trade sex for money or drugs, and unsafe sexual practices. In addition, various health-related disparities known to exist among American Indians/Alaska Natives may contribute to an increased risk of HIV/AIDS, including limited access to culturally appropriate HIV/AIDS prevention and treatment programs, limited access to adequate health care, and decreased access to proper medical management.

Methamphetamine

The effects associated with methamphetamine abuse have exacerbated many significant psychosocial problems known to exist among American Indians/Alaska Natives. For example, methamphetamine has been associated with increased domestic violence crimes, burglary, assault and battery, and child neglect/abuse among American Indians/Alaska Natives. In a 2006 Bureau of Indian Affairs survey of 96 tribal law enforcement agencies, 74% ranked methamphetamine as the drug that poses the greatest threat to their community, 64% indicated increases in domestic violence and assault/battery, and 48% reported an increase in child neglect/abuse cases due to recent increases in methamphetamine use. Methamphetamine abuse has also been reported as a significant substance abuse problem among American Indian/Alaska Native groups residing in urban areas.

Nicotine

While alcohol was introduced to American Indians/Alaska Natives by Europeans, tobacco was introduced to colonists by American Indians. Tobacco has been used by American Indians and other indigenous groups throughout North and South America for religious and ceremonial purposes for at least 2,000 years and possibly up to 7,000 years. However, American Indians/Alaska Natives have the highest smoking rates compared to any other racial or ethnic group in the United States and are at higher risk for many tobacco-related health problems. Various risk factors for smoking among American Indians/Alaska Natives include lower socioeconomic status and high rates of unemployment and poverty.

Urban American Indians/Alaska Natives

A significant number of American Indians/Alaska Natives currently reside in urban areas (two-thirds). However, unique challenges exist with regard to providing the much needed culturally relevant treatment services. A significant shortage of comprehensive substance abuse services exists in the urban setting. In addition, many individuals who reside in urban areas may be unaware that clinics providing substance abuse services specifically for American Indians/Alaska Natives exist. In addition, challenging dilemmas exist with regard to understanding the "community of urban American Indians/Alaska Natives." More aggressive outreach efforts are needed in order to increase American Indians/Alaska Natives who may require substance abuse treatments.

Conclusion

Substance abuse has significantly impacted the American Indian/Alaska Native population. Due to a variety of complicating factors, including historically based traumas and various health-related disparities, a comprehensive approach to prevention and treatment programs should be considered. In addition, recognizing the need for blending currently available evidence-based treatment approaches with the incorporation of culturally relevant approaches is essential for optimizing potentially useful prevention and treatment programs.

New Immigrants and Refugees

Since its inception as a nation more than 200 years ago, the U.S. population has often consisted of 10% to 20% foreign-born people. In the 2000 census, 31,107,889 people were foreign-born, and an additional 3,527,551 people were born in various territories outside of the United States (e.g., Puerto Rico, Virgin Islands).

Refugees

Unlike other immigrants, most refugees would have preferred to remain in their country of origin. Refugees have fled their homeland to avoid prejudice, incarceration, or even death for their political or religious beliefs, or their ethnic affiliation. Although people have fled war and social tumult throughout human history, the number of people involved in such flight has dramatically increased. A United Nations report estimated that 45 million people had left their homelands between 1945 and 1967—a trend that continues annually. This recent trend has greatly increased the number of people coming from underdeveloped countries, from which many arrive poorly prepared for life in the United States.

Clinical Assessment

Working with Translators

In the 2000 census, 9.5 million inhabitants of the United States reported that they spoke English either "not well" (6.3 million) or "not at all" (3.2 million). The greatest proportion was Spanish-speaking, accounting for 4.1 million. The second largest group was Asian–Pacific Islanders, with 1.6 million. Indo-Europeans comprised 1.3 million, with the remainder coming largely from Africa. Patients with inadequate skills in English will need a translator for an adequate assessment, unless the clinician speaks the patient's language.

Obtaining a Substance Use History

Substance use and abuse manifest many similarities across cultures. Through a supportive, informed, and empathetic approach, the clinician can usually obtain a complete picture of the patient's substance-related problem. At times, the clinician may have to seek help from the literature if the substance, route of administration, or pattern of use is unfamiliar. PubMed and other Internet-based sources can assist in bringing a broad published literature to the service of the patient abusing unfamiliar drugs, and consuming them in an unfamiliar way.

Culturally Competent Evaluation

In most respects, the evaluation continues largely as it would for other patients from indigenous ethnic groups. Review of systems should emphasize specific queries regarding psychological symptoms (e.g., anorexia, weight or sleep changes, fatigue, crying spells, fears, chronic pain, headache, bowel changes, anhedonia, hearing or seeing things not perceived by others), since foreign-born patients might not spontaneously report such symptoms to a nonkin person. While taking a family history, the clinician should be alert to patriarchal or matriarchal kin systems, because patients may not consider nonkin to be relatives in the biogenetic sense. A social history should reflect the patient's former life in the country of origin, as well as the past and present life in the country of immigration.

Mental status should be culturally informed because orientation in time and space can be affected by culture (e.g., Buddhist and Islamic calendars, differences in counting floors of a building). Education can affect the ability to do arithmetic or replicate figures with paper and pencil. English fluency and literacy can affect naming, reading, writing, and enunciating. To interpret proverbs, the patient needs to consider a proverb familiar to the patient's culture. Ability to discern similarities in unlike objects depends upon education and familiarity with the objects.

The final step consists of putting the entire story together into a coherent, integrated whole. This process should provide information regarding the patient's cultural identity, his or her explanation or understanding of the disorder, and sociocultural factors that favor recovery or chronicity. The clinician should consider the cultural aspects of the doctor–patient relationship. Finally, cultural factors that might support or impede the diagnosis and care plan should be considered.

Acquiring the Migration History

Immigrants and refugees come from every corner of the world, from the largest and most sophisticated cities to the most remote and undeveloped of rural villages. Inquiry into this premigration phase of the patient's life can enhance the clinician's understanding of the patient and the presenting clinical problem. This dialogue also enables the patient to inform the clinician regarding that unknown portions of the patient's past life.

Special Comorbidity Risks

Refugees are at special risk to diverse posttraumatic psychiatric disorders, which can accompany SUD. The latter include PTSD, major depressive disorder (MDD), phobic disorder, generalized anxiety disorder, and panic disorder. Somatization and somatic presentations are also highly prevalent among migrants. These disorders may predate SUD, occur around the same time, or appear after SUD has been successfully treated.

Interpretation of Findings

Acculturation

The "melting pot" in the United States has introduced new models and methods of substance use. European Americans not schooled in the ceremonial use of tobacco developed tobacco dependence along with its myriad biomedical disorders. Some young Somali refugees, with no exposure to alcohol use in their Islamic families, have chosen weekend drunkenness as an "American" recreational form. Cultural changes can include changes in traditional substance use.

Other changes also modify the drinking or drug use context following relocation to a new society. For example, the nature of work, transportation, and other technology can increase the risk associated with even mild intoxication or morning-after hangovers. Increased access to high-speed vehicles, complex machinery, and the smooth interaction and coordination of many workers can render intoxication newly risky for the immigrant. In addition to the individual, society at large bears the cost of vehicular and industrial accidents.

As a consequence of these changes, alcohol and/or other drugs can become a virtual scourge for certain subgroups in the United States. For them, substance abuse is a major cause of child neglect, family disruption, divorce, vehicular accidents, injury, and death.

Cultural Diversity within Groups

Groups of immigrants to the United States differ greatly. The same is true of individuals within these groups, for whom the new country presents many choices and alternatives. Some immigrants remain staunchly traditional to their country of origin. Others assimilate to a considerable extent with the "mainstream" American culture. Years following relocation, immigrant groups often manifest greater differences among themselves than were previously manifested in the country of origin.

Failure to acculturate successfully to the new country can increase the risk of substance abuse. Successful acculturation can be identified by the immigrant's ability to speak English, hold a job, use the social institutions of the receiving society (e.g., banks, libraries, health care), access the mass media, and establish relationships outside of the immigrant's own group.

Migratory History and Onset of Substance Abuse

Some cases of substance abuse begin after migration. However, most cases among adult migrants involve continuation of premigration substance abuse or dependence, rather than new cases.

High-Risk Immigrant Groups

As a nation composed largely of immigrants and refugees, we tend to idealize these groups as harking back to our own origins. However, idealization should not render us blind to subgroups at high risk to substance abuse. The propensity of foreign countries to "dump" their problematic citizens in the United States (and other immigrant countries) was first recognized more than 150 years ago, when several European countries sent prisoners and debtors to the United States at public expense as a means of being rid of them.

Treatment and Recovery

"Mainstream" Treatment Modalities

Addicted persons of virtually any ethnic background accept care in detoxification centers, emergency rooms, and inpatient hospital units. The challenge to continued treatment begins beyond this acute phase. Once beyond the pain of withdrawal or other health emergency, the addicted person may become more selective about continued care.

The "three A's" integral to successful rehabilitation following early acute care are as follows:

- Availability: The treatment must be reasonably close at hand so that the person can participate in the recovery-centered endeavors. Telemedicine services can greatly facilitate services to rural areas or ethnic neighborhoods.
- Access: The patient must have access to the program; lack of insurance or language barriers can prevent entry.
- Acceptance: The patient and the program must accept each other.

An analysis of barriers in one health-care system revealed four categorical sources of cultural barriers to mental health care. Two of these general barriers lay on the health-care side, that is, the clinicians and the health-care system. The other two categories consisted of the patient barriers (e.g., antitherapeutic attitudes, ignorance, lack of resources) and the patient's family and community (e.g., not supportive, not understanding).

Self-Help in Recovery

Some self-help activities can occur regardless of ethnic affiliation, such as avoiding people and places associated with use. However, other forms of self-help may differ across cultures. These differences can be due to cultural values, customs, or institutions.

Alcoholics Anonymous can change form and content considerably when translated across culture and language. Entire communities can engage in self-help, through eliminating substance abuse and associated problems.

Religious Conversion and Recovery

Conversion to abstinence-oriented religion has alleviated addictive disorders for many around the world. For example, Hispanics throughout the Americas have joined abstinence-oriented fundamentalist Christian religions as a means of achieving sobriety and resisting invitations to drink. Buddhist monasteries have served as places of recovery, especially when a charismatic abbot leads the way.

Previous Exposure to Treatment

We sometimes assume that treatment for addiction is available only in a few industrialized societies. However, treatment exists virtually wherever addiction occurs. Inquiry into previous

treatments in the country of origin can provide important information. Treatment can include community sings, herbal medications, and sweat lodges. Often these modalities possess a ritual or ceremonial dimension. Ceremonies can be useful in engendering social support for the recovering person, establishing a new social persona, and fostering new attitudes toward a sober lifestyle.

Psychotherapies

English literacy or advanced education is not necessary for successful psychotherapy. Supportive counseling can be applied in any setting; it can be especially efficacious if the immigrant patient is seeking an advisor for successful adjustment to the new society. CBT and behavioral modification can apply to members of any group. Examples include desensitization for phobic disorder or PTSD.

Family therapy may involve special considerations, depending on the family structure and traditions in the patient's culture and family. In family therapy, the explicit family hierarchy will often hold sway so that family members do not typically confront a matriarch or patriarch in front a therapist. This special challenge is not a rationale for circumventing the family, however. Whenever possible, the family should be involved in the patient's assessment and care, as well as other members of the patient's social network who are committed to the patient's recovery. Elements of interpersonal psychotherapy and psychodynamically oriented psychotherapy can also have their place in cross-cultural care.

Pharmacotherapy and Culture

Medications are often thought of as mechanistic modalities that affect neurotransmitter systems, but have no cultural relevance. To some extent, this may be true. For example, one does not have to understand the pharmacotherapy of diazepam (Valium) to obtain relief in the midst of alcohol withdrawal.

Medications can also play important social and cultural roles. For example, disulfiram (Antabuse) and naltrexone (ReVia) have provided an excuse for recovering alcoholics to refuse friendly invitations by peers to go out drinking or drug using.

Prevention

Religious affiliation with groups that forbid any use of alcohol or other recreational drugs has been effective as prevention, as well as a treatment. Abstinence-oriented religion also provides easier access to leadership as compared to religions that require clergy to study for many years before becoming leaders; immigrants themselves have become the leaders and clergy in fundamentalist sects. Community consensus against alcohol abuse or use of illicit drugs may evolve from these church enclaves. A danger is that the abstinence-oriented sect may ultimately turn against addicted people, lumping the persona with the drug.

Armed Forces

Substance use and abuse, including heavy alcohol use, illicit drug use, and tobacco use, have long been associated with military life. The armed services have experienced problems with alcohol abuse from the earliest days of military service, in part because heavy drinking has been an accepted custom and tradition that continues today. In the past, alcohol was thought to be necessary for subsistence and morale and as such was provided as a daily ration to sailors and soldiers. There are numerous early documented accounts of alcohol abuse among military personnel. Within the predominantly male U.S. military population, heavy drinking and being able

to "hold one's liquor" have served as tests "of suitability for the demanding masculine military role." A common stereotype has been to characterize hard-fighting soldiers as hard-drinking soldiers. Alcoholic beverages have been available to military personnel at reduced prices at military outlets and, until recently, during "happy hours" on base. In addition, alcohol has become part of the military work culture and has been used to reward hard work, to ease interpersonal tensions, and to promote unit cohesion and camaraderie.

Similar to alcohol, illicit drugs (including illegal drugs as well as prescription drugs used nonmedically) have been used by soldiers since they discovered that certain herbs reduced pain, lessened fatigue or increased alertness, or helped them cope with times of boredom or panic that accompany battle.

Development of Military Substance Use Policy

The Vietnam War and the resulting reports of substance abuse from returning servicemen led to the development of Department of Defense (DoD) policy on substance use and abuse. In 1967, DoD convened a task force to investigate drug and alcohol abuse in the military and in 1970 formulated a drug and alcohol abuse policy based on task force recommendations. The policy emphasized the prevention of drug and alcohol abuse through education and law enforcement procedures focusing on detection and early intervention. However, treatment was provided for problem users with an emphasis on returning them to service.

U.S. military substance use policy continues to be updated periodically and has focused mainly on illicit drug use and alcohol abuse. Current DoD policy requires the following with regard to drug and alcohol abuse programs and resources:

- Education and training on DoD policies for drug and alcohol abuse and/or dependency, and on effective measures to alleviate problems associated with drug and alcohol abuse and/or dependency
- Prevention programs designed to deter substance abuse to include drug demand reduction (DDR), a urinalysis testing program, mandated across the services supported by a program manager at the installation level to oversee urinalysis testing and outreach programs
- Treatment and/or rehabilitation for military personnel who abuse alcohol
- Periodic assessment of the nature and extent of drug and alcohol abuse in DoD

Military and Civilian Comparisons

To help gauge the progress of substance use policies and programs, military leaders often use the civilian population as a comparison benchmark. To make this comparison, military data were drawn from the 2008 health behavior survey and civilian data from the 2007 National Survey on Drug Use and Health (NSDUH), a nationwide survey of substance use.

The findings indicate that substance use patterns in the military do not simply mirror similar use among civilians. The lower rates of drug use (excluding prescription misuse) among military personnel compared with civilians suggest either that military policies and practices deter drug use in the military or that military personnel hold attitudes and values that discourage substance use. Because of the military's stringent policy prohibiting drug use and the urinalysis testing program to enforce it, it seems likely that the difference in drug use prevalence between military personnel and civilians results from military policies and practices. In contrast, the higher rates of heavy drinking among younger military personnel suggest that certain aspects of military life may foster heavy drinking or that those military policies and programs directed toward reducing these substances have not been as effective as similar efforts among civilians.

Prevention

All services include drug abuse prevention information as part of general military training, ranging from the earliest days of recruit training to other times during their career. Education includes information on the hazards of drug use, administrative and punitive consequences, responsible decision-making, and healthy alternatives to drug use. Many commands use drug-detection dogs to periodically search barracks and vehicles at installation gates. Selected high-risk target groups, such as units preparing to deploy to areas where drug use is prevalent, often receive tailored drug abuse prevention information and education.

The military also has a drug-testing program, commonly referred to as urinalysis, that plays a key role in drug use prevention. The purpose of drug testing is to deter service members from using drugs and to permit commanders to detect drug abuse and assess the security, readiness, and discipline of their commands. Drug testing is conducted under a number of different situations, including random testing at least once per year, probable cause searches, during inspections, and during any valid medical examination, including emergency room treatment.

Intervention and Treatment

Through the years, DoD and the services have developed and implemented intervention and treatment programs that address alcohol, tobacco, and illicit drug abuse issues. These programs have changed over time to adapt to the changing social and military environment.

Factors Influencing Substance Use in the Military

There are a number of complex factors that contribute to substance use and misuse in the armed forces, including individual, social, cultural, and environmental influences. Individual factors include demographic, genetic, and psychological components. Individual factors such as age and genetic makeup are also possible risk factors for substance use.

Conclusion

Heavy alcohol use, illicit drug use, and cigarette smoking constitute significant detriments to the health, productivity, and welfare of military personnel. Substance abuse is a major contributor to mortality and morbidity and also adversely affects work performance. To address these issues, DoD has set forth a series of policies designed to decrease the impact of substance abuse on military personnel. Alcohol abuse, drug abuse, and smoking policies are now included in a broader health promotion framework that encourages healthy lifestyles to promote high-level military performance and readiness. Current policies include prevention, intervention, and treatment components and have been the genesis for a wide range of programs to address substance abuse issues. Although the programs appear to have face validity, more research is needed to demonstrate their efficacy and effectiveness.

Suggested Readings

Fong TW, Tsuang JW. Asian-Americans, addictions, and barriers to treatment. *Psychiatry.* 2007; 4(11):51–59.

McCabe SE, Hughes TL, Bostwick WB, et al. Sexual orientation, substance use behaviors and substance dependence in the United States. *Addiction.* 2009;104(8):1333–1345.

Primm BJ, Hewitt WW, Primm AB, et al. Addicted populations. In: Ruiz P, Primm A, eds. *Disparities in Psychiatric Care*. Baltimore, MD: Lippincott Williams & Wilkins; 2010.

Ruiz P, Langrod JG. Hispanic Americans. In: Lowinson JH, Ruiz P, Millman RB, et al., eds. *Substance Abuse: A Comprehensive Textbook*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:1103–1112.

Stiffman AR, Alexander-Eitzman B, Silmere H, et al. From early to late adolescence: American Indian youth's behavior trajectories and their major influences. *J Am Acad Child Adolesc Psychiatry.* 2007;46:849–858.

46 Incarcerated Populations

Substance abuse is a significant problem among individuals incarcerated in jails and prisons throughout the world. Substantial research evidence from many countries has indicated that jail and prison inmates have a higher prevalence of preincarceration substance abuse compared to the general population. This is particularly evident with regard to illicit opioids (primarily heroin), cocaine, and the abuse of multiple substances—patterns of substance abuse that are most closely associated with adverse health and criminogenic consequences. Some inmates continue to use substances during incarceration, and most such individuals do not receive substance abuse treatment while incarcerated or upon release. As a consequence, substance abuse either continues or resumes quickly after release into the community, placing such individuals at increased risk for death from drug overdose, HIV, and hepatitis B and C infections, increased criminal activity, and reincarceration. Correctional health officials, treatment providers, and policy makers need innovative, effective, and cost-beneficial approaches to help inmates with substance abuse histories successfully transition to the community following release from incarceration.

The impact of substance abuse among inmates, both during incarceration and upon release to the community, is exacerbated by the large numbers of individuals imprisoned throughout the world. According to the latest available estimate of the number of persons incarcerated and the rate of incarceration in 218 countries, there were 9.8 million individuals incarcerated in prisons throughout the world, with the United States having the highest number of prisoners and the highest rate of incarceration. Furthermore, in 71% of these countries, prison populations have been increasing, and this trend is expected to continue. Because of these circumstances, it is crucial that effective interventions designed to address substance abuse be developed, implemented, and evaluated.

To understand the context in which the above topics are discussed, it is important to understand the distinction between jails and prisons, which is most pronounced in the United States. Jails typically hold individuals who are awaiting trial or sentencing or are serving shorter sentences for less serious offenses (typically less than 1 year). Prisons typically confine individuals who have been convicted of more serious crimes and thus are serving longer sentences.

Epidemiology

Epidemiologic studies have consistently found a higher prevalence of substance use, abuse and/or dependence among jail and prison inmates than the general population. This has been the case independent of nationality, gender, the measure(s) used to assess an individual's consumption of

substances (e.g., use, abuse, and/or dependence), and the criteria used to assess substance abuse and/or dependence. A recent nationwide study in the United States reported that only 2% of the general U.S. population met standardized diagnostic criteria of drug abuse or dependence in the last 12 months compared with 52% of state inmates and 44% of federal prisoners in the year prior to incarceration.

Regarding the regular use of heroin, in the United States, recent studies have reported inmates' lifetime prevalences ranging from 12% to 15%. In each of these studies, regular use of heroin was defined as having used heroin once a week or more frequently for at least a month. Moreover, most epidemiologic studies of substance abuse among jail and prison inmates report on preincarceration behavior, either lifetime or the year prior to incarceration. Relatively few studies examine the prevalence of substance abuse during incarceration.

Finally, as emphasized below, most jail and prison inmates do not receive treatment for substance abuse, and without such treatment, jail and prison inmates are likely to return to drug abuse and crime shortly after return to the community, and rates of postrelease criminal activity among such individuals are very high. Among incarcerated individuals, those with preincarceration heroin addiction typically become readdicted within a month of release from incarceration. Because of these circumstances, as well as the increased threat of HIV and hepatitis infection and overdose death, treatment interventions that begin during incarceration and continue in the community are urgently needed for such individuals.

Prevention

Prevention strategies can be classified in three different ways. Primary prevention involves prevention of new onset drug use, secondary prevention intends to prevent the progression from drug use to symptomatic drug abuse or dependence, and tertiary prevention is concerned with reducing the adverse consequences for those with drug abuse or dependence. Ideally, given that substance abuse is a major contributor to suicide, criminal behavior, injuries, overdose death, and many types of infectious disease, perhaps the most promising approach would involve preventing the onset of use in childhood or early adolescence through a combination of interventions, including those that enhance protective factors and reduce risk factors, as well as regulatory approaches. Examples of the former type of intervention would involve collaboration among parents, educators, physicians, and community leaders, whereas the latter strategy would include laws, policies, and enforcement to reduce supply and demand. These interventions have also been shown to prevent or at least delay the onset of delinquent and criminal activity as well, thus substantially reducing the risk for incarceration. However, many such interventions involving enhancement of protective factors and reduction of risk factors have not been evaluated in real-world settings. Moreover, a recent nationwide survey conducted in the United States indicated that teachers often do not have adequate time to provide such interventions, and parents' priorities have focused on economic concerns and survival, limiting their ability to devote sufficient time and energy to substance abuse prevention initiatives. Furthermore, given that over 80% of incarcerated individuals in both Great Britain and the United States and well over half of such individuals overall in the European Union have been estimated to have a history of illicit drug *use*, in addition to the high prevalence of substance *abuse* reported above, perhaps the most feasible prevention strategy would involve harm reduction (HR)—decreasing the risk for life-threatening consequences—more in line with tertiary prevention approaches defined above.

Among the most frequent and severe consequences resulting from drug abuse, specifically drug injection, in prison, are HIV and viral hepatitis infections. Increased risk of these diseases among prisoners has been documented in 16 countries, with injecting drugs and sharing

injection equipment being major contributors to such circumstances. Unfortunately, most nations do not have adequate prevention services for incarcerated persons despite the fact that the Council of Europe and the WHO have developed guidelines emphasizing that inmates have the right to the same prevention and treatment services as those available in the community. Furthermore, corrections officials at times have denied that substance use and drug injection occur in their facilities, and this circumstance, together with budgetary constraints and overcrowding, can contribute to the lack of services for infection prevention.

HR services include the provision of information and education with regard to drug-related disease, voluntary testing and counseling concerning HIV and hepatitis, and interventions designed to reduce risky sexual and injection-related behaviors. Such procedures have been implemented in several European nations, Canada, and Australia. A major HR intervention targeted toward reducing HIV and hepatitis infections in prison is needle-exchange programs (NEPs). Only a small number of countries have implemented these programs, starting with Switzerland in 1992. A review of the literature on the effectiveness of prison-based NEPs reported that they have substantially reduced the sharing of injection equipment, with no increases in injecting or drug use.

Treatment

Challenges to Implementation and Evaluation

Prisons and jails provide a significant opportunity to enlist individuals with histories of substance dependence into treatment. The provision of effective treatment in correctional settings not only has the opportunity to reduce the health- and crime-related impact of substance abuse postrelease but also has the potential of decreasing the frequency and severity of facility management problems as more inmates become enrolled in treatment. However, in many countries, scarce resources are devoted to substance abuse treatment in correctional facilities, where security is the primary concern. Security concerns are increased when inmates need to be moved to different areas of the facility for treatment, and some corrections personnel may be opposed to certain types of treatment, particularly opioid agonist therapy, particularly in the United States. As a consequence, many incarcerated individuals with histories of substance abuse do not receive treatment, and the range of modalities offered is often quite limited. For example, in the United States, less than 20% of inmates with substance abuse histories receive treatment during incarceration, with drug education being the most common service provided. Furthermore, while the results of a recent survey of correctional programs and organizations in the United States indicated that most correctional agencies provide some type of substance abuse treatment, the median proportion of offenders with access to such treatment at any given time is under 10%.

Another challenge to the development, implementation, and evaluation of new correctional substance abuse treatment programs involves the different priorities, agendas, and beliefs about inmates on the part of treatment personnel and correctional employees. Treatment staff tends to view inmates with substance abuse histories as persons with some type of illness who are in need of help. In contrast, correctional personnel may view such inmates as individuals in need of punishment and control. Thus, establishing and maintaining new programs resulting from recent justice system/treatment collaborations has been challenging. Progress in this regard has been slow and gradual over the past several decades in creating novel initiatives that combine criminal sanctions with rehabilitation, such as residential drug-abuse treatment programs for incarcerated individuals and corrections-based therapy, including opioid agonist therapy, for inmates with opioid addiction histories. Ongoing cooperation among diverse correctional, treatment, and research organizations is crucial for such new programs to operate

continuously. Sufficient jurisdictional and/or correctional funding is also needed for the continuous operation of new substance abuse treatment programs.

It also needs to be emphasized that, given the diversity among incarcerated individuals with substance abuse histories with regard to severity of addiction, criminality, psychological functioning, and other relevant dimensions, a single approach is not likely to be effective for all individuals. Therefore, a persistent challenge to treatment providers, corrections officials, and researchers has been to determine what types of treatment work best for what types of individuals. While this question has dominated the substance abuse treatment field for many years, achieving progress has been slow.

Furthermore, many correctional substance abuse treatment programs have never been rigorously evaluated, and most published reports on the effectiveness of substance abuse treatment for incarcerated populations are anecdotal and descriptive. Meta-analyses of correctional substance abuse treatment have consistently reported that most studies have major methodologic problems. Caution is advised in interpreting the results of a number of evaluations of substance abuse interventions because of limitations such as short postrelease follow-up periods, low postrelease assessment rates, infrequent use of comparison groups, multivariate methods, standardized assessment instruments, and appropriate control variables. Nevertheless, there have been some well-controlled studies of corrections-based substance abuse treatment, which are discussed below.

Modalities

Therapeutic Community

The therapeutic community (TC) modality in a correctional setting operates on the premise that inmates with long histories of severe substance abuse must change their attitudes and thinking patterns to reduce the influences of lifestyles condoning violence, manipulation, and irresponsibility found in the prison environment. Because of these circumstances, inmates in TC treatment reside apart from other inmates in order to minimize such negative influences and to develop a sense of community in which the community members themselves serve as therapeutic agents. Inmates residing in the TC rely on their group leader, typically a recovering person, and peers to provide rewards and sanctions. TC members support and reward abstinence from substance abuse and crime, and the adoption and maintenance of prosocial attitudes and values. Confrontation and sanctions are employed as a response to negative behaviors, and positive feedback is employed as a response to positive behaviors.

There are challenges to the implementation and operation of TCs in the correctional setting. Similar to other substance abuse treatment programs conducted within prisons and jails, TCs require strong, consistent commitment to the program on the part of correctional administrators and staff. Furthermore, a considerable amount of space within the facility needs to be devoted to provide TC members with housing, food service, and rooms to conduct group treatment sessions. As a result, TCs can be expensive to operate.

There is evidence that offenders who receive a three-stage TC approach administered in a U.S. prison, in work release during the transition from the institution to the community, and in combination with aftercare involving outpatient individual counseling, group therapy, and reinforcement sessions had lower rates of postrelease relapse to drug use and criminal recidivism at 5 years postrelease than did offenders who receive little or no treatment. Other long-term, methodologically rigorous follow-up studies conducted in the United States using comparison or control groups have reported similar results for incarceration-based TC treatment followed by community-based aftercare.

Another of the most rigorously conducted evaluations of TC treatment involved a 5-year postrelease follow-up of 715 male prison inmates who were randomly assigned to either

TC treatment or a control (no treatment) condition. Results of this study, found that while over 75% of the sample had been reincarcerated, inmates assigned to the TC group had significantly lower reincarceration rates than controls, with no group differences reported for relapse to heavy drug use.

Cognitive–Behavioral Interventions

Because of the influence of substance-abusing peers and the multiple demands of housing, legitimate employment, and family are significantly diminished during incarceration, greater opportunity exists for focused, comprehensive treatment that intends to change patterns of behavior, thinking, and feeling that contribute to substance abuse and criminality. Some clinicians and researchers have contended that cognitive–behavioral treatment programs are among the most promising for reducing relapse to substance abuse and criminal recidivism because they focus on internal client factors and predispositions contributing to deviant behavior. Furthermore, cognitive–behavioral interventions are less expensive than TCs to operate as they place fewer demands on correctional staff and require less space. Although cognitive–behavioral programs have been widely used throughout the world for over two decades, they have been subject to relatively few controlled evaluations. Among the few more methodologically rigorous evaluations of prison-based cognitive–behavioral treatment was a multisite evaluation involving over 2,000 inmates. Three-year postrelease outcomes, analyzed separately for men and women, indicated that while both male and female program participants had lower rates of rearrest and drug use than their counterparts in the comparison group, the findings were only significant for males. Subsequently, a 1-year postrelease analysis of a cognitive–behavioral treatment program for women prisoners found that treated women had significantly less drug use and arrests than a comparison group.

Boot Camps

Boot camp programs, which primarily operate in the United States, are highly structured and are patterned after military basic training. They involve vigorous exercise (including obstacle courses), military drill, ceremony, and discipline. Inmates are required to wear uniforms and are subject to confrontation and sanctions on the part of drill instructors for rule violations. Proponents of boot camps claim that such interventions instill self-discipline needed to avoid relapse to substance abuse and criminal recidivism.

Opioid Agonist Maintenance

The use of opioid agonists such as methadone and buprenorphine for the treatment of opioid dependence in the community is among the most rigorously and frequently studied of all the drug-abuse treatment modalities. These medications have been found effective in numerous randomized controlled trials and are on the WHO's list of essential medications because of their extensively documented ability to reduce heroin use and HIV-risk behaviors. These medications act by occupying the opioid receptor and blocking the euphoric effects of self-administered heroin or other opioids. Forty years of research evidence in community-based settings throughout the world has found that opioid agonist therapy, primarily involving the provision of methadone maintenance, is highly effective in reducing heroin addiction, criminal activity, and HIV-related risk behavior. In addition, methadone maintenance treatment has been found superior to other types of substance abuse treatment in retaining patients in treatment. Treatment retention is crucial to successful treatment outcome; research results have consistently reported that regardless of modality, greater treatment duration is related to reduced substance abuse and crime.

However, despite its effectiveness, opioid agonist maintenance treatment is underutilized in jail and prison settings, particularly in the United States. In contrast to the United States,

a number of other countries have routinely offered it to incarcerated populations, including nearly all nations in the European Union, Canada, and Australia.

Sociocultural Considerations

It is strongly recommended that interventions for incarcerated individuals be tailored to the inmates' specific sociocultural needs. Individual characteristics of inmates may influence drug-use behavior and therefore the types of interventions that may be most promising for reducing drug use and its disastrous public health and public safety consequences. Ideally, all services to be provided to incarcerated populations need to be based on an assessment of individual inmate needs. The greater prevalence of substance abuse among women than among men, both overall and compared to their counterparts in the general population, suggests that the gender of the inmate be one dimension that needs to be strongly considered in the development of appropriate interventions for inmates with histories of drug abuse. In addition to gender, nationality, ethnicity, and rural/urban status are likely to be factors that have a bearing on one's pattern of drug use and thus the type(s) of treatment that may be most appropriate.

In addition, many individuals enter jails and prisons with poor health in addition to drug abuse, often brought on by socioeconomic conditions such as unsanitary living conditions and lack of access to affordable health care. These circumstances are typically exacerbated by the prison environment, where overcrowding, poor nutrition, and poor ventilation are commonplace along with violence, unprotected sex, and drug use and injection. These circumstances, in turn, can lead to the development of many infectious diseases, including HIV and hepatitis.

Following Release to the Community

It has been well documented that upon release from incarceration, individuals with histories of substance abuse typically experience multiple stressors that substantially increase their risk of relapse. Prominent among these factors are the need for stable housing and legitimate employment, the stigma of being labeled an ex-offender, poor or conflictual relationships with family members, and meeting multiple requirements regarding criminal justice supervision. In the United States, the escalation of parole and probation caseloads has made it increasingly difficult for parole and probation agents to effectively monitor and supervise their clients' behavior. Finally, as indicated previously, most newly released inmates do not receive drug-abuse treatment upon reentry to the community.

Furthermore, many newly released inmates return to neighborhoods where drug abuse is rampant. Such individuals frequently encounter friends, neighbors, former drug business associates, and/or family members who are drug dependent and often pressure or otherwise encourage the former inmate to relapse. Such areas generally lack opportunities for legitimate employment as well.

Special Considerations

Given the multiple stressors facing newly released inmates with substance abuse histories upon return to the community, as well as the high rates of relapse involved, it is crucial that jail- and prison-based treatment programs provide a continuum of care in the community.

As emphasized above, the benefits of incarceration-based treatment are greatly enhanced by the provision of community-based aftercare. Perhaps the most promising programs for reducing relapse and recidivism may be corrections-treatment partnerships in which a single treatment team or primary counselor takes primary responsibility for provision of services, both during incarceration and in the community.

However, successfully developing and implementing such programs, independent of the modality involved, is a very challenging task because it involves frequent collaboration between various agencies (corrections and substance abuse treatment) with different, and often conflicting, priorities and agenda. It is helpful in this regard to first conduct a pilot, or exploratory study to alleviate interagency tensions and develop feasible procedures. It is strongly recommended that both treatment and corrections staff be equally involved in planning the intervention, with responsibilities of various agency personnel specified in advance. In addition, differences with respect to logistics and space need to be reconciled so that treatment procedures do not interfere with routine security and other procedures in jail or prison.

Conclusion

From the above, there is considerable research evidence to indicate that jail and prison inmates have substantially higher rates of substance abuse than the general population. This is particularly evident with regard to patterns of use found to be most closely associated with adverse health- and crime-related consequences, such as addiction to opioids (primarily heroin), cocaine, and/or multiple substances, as well as drug injection. While substance abuse tends to be more frequent prior to incarceration than during incarceration, substance use, including injection, is not uncommon in jails and prisons. Unfortunately, most inmates with substance abuse histories do not receive treatment while incarcerated, and either relapse or continue substance abuse upon release, greatly increasing the likelihood of HIV and hepatitis infections, overdose death, criminal activity, and reincarceration.

As documented previously, there are a number of treatment interventions that can be effective in reducing substance use and its attendant health and criminogenic effects for incarcerated individuals. However, it is important to recognize that the benefits of incarceration-based substance abuse treatment may diminish following release to the community. Therefore, it is advised that a continuum of treatment spanning incarceration and the community be implemented to further help interrupt the pernicious cycle of relapse, recidivism, and reincarceration.

Furthermore, one of the effective treatment interventions reviewed herein, opioid agonist maintenance, is underutilized in jail and prison settings. Consistent with the recommendations of others, expanding the availability of such treatment in prisons and jails has several potential benefits, including reduction of heroin use and injection in facilities where such behaviors are common, alleviating withdrawal symptoms among newly arrived, opioid-dependent inmates, and reducing readdiction, transmission of blood-borne viruses, and overdose death following release. Therefore, in keeping with the longstanding positions of the WHO and the National Institutes of Health (NIH), we recommend that opioid agonist treatment be expanded in correctional settings.

Another challenge to the successful development and implementation of effective and innovative incarceration-based substance abuse treatment programs is that agencies with different and sometimes conflicting priorities and agenda need to be in constant collaboration. It is crucial that both treatment and corrections staff establish and maintain an equal partnership with regard to planning the intervention, with responsibilities of various agency staff defined in advance. Furthermore, potential conflicts concerning logistics and the allocation of space for treatment-related activities need to be reconciled so that intervention procedures do not interfere with routine security and other procedures in jail or prison.

Moreover, both correctional and treatment personnel need to recognize individual diversity among jail and prison inmates with histories of substance abuse. It needs to be emphasized to practitioners, administrators, and policy makers that no single intervention is effective for all clients. In view of the observation that failure to adequately match inmates to interventions may lead to increased substance abuse and its attendant health- and crime-related consequences, funding appropriate services and assessment needs to be emphasized.

Finally, the urgency of the need to provide effective substance abuse treatment to jail and prison inmates with histories of substance abuse needs to be emphasized. As documented earlier, without such treatment, not only the lives of the newly released inmates themselves but also those of others are threatened, given the increased likelihood of relapse, primarily to heroin and/or cocaine addiction and drug injection, patterns of use associated with overdose death, and exposure to HIV and hepatitis infections. In addition to adverse health consequences, there are also public safety consequences, in that relapse to the above-mentioned substance abuse patterns are related to an increase in the frequency of criminal behavior. These circumstances are exacerbated by the observation that increases in the worldwide prison population are expected to continue.

Suggested Readings

Chandler RK, Fletcher BW, Volkow N. Treating drug abuse and addiction in the criminal justice system: improving public health and safety. *J Am Med Assoc*. 2009;301:183–190.

Fazel S, Bains P, Doll H. Substance abuse and dependence in prisoners: a systematic review. *Addiction*. 2008;101:181–191.

Stewart D. Drug use and perceived treatment need among newly sentenced prisoners in England and Wales. *Addiction*. 2008;104:243–247.

Toumborou JW, Stockwell T, Neighbors C, et al. Interventions to reduce harm associated with adolescent substance use. *Lancet*. 2007;369:1391–1401.

Taxman FS, Perdoni ML, Harrison LD. Drug treatment services for adult offenders: the state of the state. *J Subst Abuse Treat*. 2007;32:239–254.

47 Substance Use Disorders among Health-Care Professionals

Physicians who abuse substances often self-prescribe them and choose different substances than the general population. Nurses, who are often on the front lines of health-care delivery, can easily divert medications from patients for their own use. Pharmacists, having perhaps the greatest direct access to psychoactive drugs of all health-care professionals, are also prone to self-medication. Finally, dentists who are prone to addiction often turn to nitrous oxide, given its easy access for them.

Epidemiology

Lifetime rates of substance use disorders (SUDs) among health-care providers are in the 11% to 14% range. The 1992 Physician Substance Use Survey (PSUS), which polled 9,600 physicians about their own use of alcohol and other drugs, is the most extensive survey of physician substance use performed in the United States to date. The PSUS reported a lower rate of SUDs than did other surveys: 8% lifetime rate for physicians. However, it relied on physician self-report and may have underestimated actual prevalence. Like physicians, the prevalence of substance abuse among nurses is comparable to that in the general public.

Health-care professionals are more likely to abuse benzodiazepines (BZDs) and opiates other than heroin, more likely to abuse alcohol, and less likely to abuse recreational street drugs such as marijuana and cocaine than the general public. One older study found that pharmacy students were abusing drugs at alarmingly high rates: up to 62% abused drugs at some point in the past and 19% were using a substance regularly. As recently as 2006, the American Nurses Association estimated that 6% to 8% of nurses practiced while impaired by alcohol or other drugs.

Among physicians, psychiatrists, emergency physicians, and anesthesiologists are at the highest risk of abusing substances. Conversely, pediatricians, pathologists, radiologists, and obstetrician-gynecologists have the lowest reported rates of substance abuse. Among physicians who misuse drugs, emergency medicine physicians tend to use more illicit drugs, anesthesiologists tend to misuse narcotic analgesics, and psychiatrists are more likely to misuse BZDs. It is likely that availability and familiarity are contributing risk factors for medical specialists.

Risk Factors

A substantial number of health-care professionals with SUDs report a family history of substance abuse, significant stress at both work and home, emotional problems, and sensation-seeking behaviors. When health-care professionals do misuse substances—whether alcohol, tranquilizers, or other substances of abuse—they often do so for reasons of "self-treatment." Physicians often work long hours, beyond any standard job description, and may find self-treatment an expedient alternative to taking the time to make and keep appointments with physician colleagues.

Being a female health-care professional may also increase risk. Compared to their male counterparts, female physicians who have an identified SUD are younger, more likely to have coexisting psychiatric or medical illness, and more likely to have suicidal ideation and/or to have attempted suicide while intoxicated. Furthermore, compared to men, once they had achieved initial sobriety, women physicians had significantly shorter time to first relapse.

Younger age may also increase risk. One study found that older health-care professionals are significantly less likely to suffer from an SUD than their younger colleagues.

Prevention

Education on physician health and the risks of self-treatment should be a standard component of physician education at all levels, from medical school to residency and fellowship, and throughout continuing medical education. Similar educational interventions are appropriate for nurses, pharmacists, dentists, and veterinarians. Every state in the United States except one has a physician health program, which may be an ideal agency to provide continuing education through presentations at hospital grand rounds.

Hospital chiefs, practice managers, administrators, and other health-care leaders should consider substance abuse, among other health problems, when staff exhibit performance problems. Also, since health-care workers may begin misusing substances in an attempt to treat their own physical or emotional discomfort, we recommend that all medical professionals have a primary care physician, resist the temptation to self-diagnose, and never self-prescribe. Seeking medications from colleagues—even a few painkillers here or there—is a bad practice that jeopardizes the career of the prescriber and the well-being of the person obtaining such medications. Physicians prescribing medications for another health-care professional should do so only in the course of their usual medical practice, and always generate a note into an appropriate medical record indicating the reason for the medication and the dosing details.

With the possible exception of true emergencies, we recommend that health-care professionals not prescribe for family or friends or bring drugs home from office supplies or samples. Many states limit or prohibit prescribing for self and family.

Health-care professionals should attend to their own health and wellness. Studies have shown that physicians who exercise, do not smoke, eat well, drink in moderation, and are otherwise attuned to their own health are better caregivers across all measures. This may also be true for other health-care professionals.

Signs and Symptoms

Initial signs of substance misuse among health-care professionals almost always appear outside of the workplace. By the time problems arise at work, the SUD may be quite advanced. One study concluded that physicians received treatment for substance abuse an average of 6 to 7 years after problem onset.

Initial warning signs of SUDs include difficulties at home, loss of interest in activities previously enjoyed, disrupted family relationships, vehicle crashes, accidents, and injuries. Behavioral symptoms are nonspecific, but include apathy, anxiety, lack of self-discipline, strained communications with others, personality changes, and abrupt mood swings.

Physical signs include change in eating habits and weight, poor self-care, a generalized deterioration in appearance, dilated pupils, watery eyes, smelling of alcohol, slurred speech, conjunctival injection, dilated or constricted pupils, falling asleep at odd times, and, rarely, needle marks, bruises, or bandages. Health-care providers who abuse intravenous (IV) drugs often inject themselves in areas of their body that are not exposed to view, such as lower extremity veins or those in the genital area.

Sometimes, health-care professionals with SUDs will make direct statements of distress. These may include expressing constant sadness or tearfulness, excessive anxiety or irritability, unprovoked anger or hostility, expressions of hopelessness or worthlessness, and feeling or acting isolated.

When signs of substance misuse become manifest in the workplace, symptoms may include deterioration in the quality of work, repeatedly showing up late for meetings and appointments, recurring absences, continually seeking special accommodations, repeatedly having trouble in getting along with staff and patients, or not responding to pages when on call. While none of these warning signs alone confirm a diagnosis, taken together with other symptoms they may indicate the need for an evaluation.

The level of impairment by health-care professionals varies according to pattern of use (e.g., morning vs. evening, weekday vs. weekend), onset and duration of action of the specific substance, the amount consumed, and the degree of tolerance. Some individuals with tolerance will tend to show symptoms when they are in withdrawal, whereas others will show more prominent signs when intoxicated.

Intervention

The first step in helping a colleague who may have a problem is having him evaluated. One approach to a directive intervention is summarized by the acronym "FRAMER." The first step is to gather the *facts*. These facts should include written documentation of any oral complaints about the colleague. The second step is ascertaining one's own *responsibility* for reporting a colleague who is suspected of having a problem. Are there mandatory reporting requirements by the state licensing board? Hospital rules and regulations, medical staff bylaws, and other regulations might also mandate a certain course of action. Regardless of law, health-care providers may also have an ethical obligation to intervene with a colleague before he or she can harm patients, a family member, or self.

The third principle is to have *another person* present at the initial meeting with the colleague. This person can serve as a witness to what you discuss and also might act as a buffer if things begin to heat up. Ideally, this other person should be a member of the hospital's wellness program, the department chief, or an addiction specialist. If you do not have administrative authority over the target physician, bring someone else who does. The meeting should begin with a *monologue*, during which you list the observations that have led to your concern. The purpose of this monologue is to state facts, which are not open to debate. Avoid drawing conclusions, which may lead to arguing about details or having the individual spend all his time refuting each and every point of concern. If the individual admits to having a substance abuse problem, then the colleague should be thanked for his or her honesty and referred to treatment immediately. If the individual denies any problems, insist on an independent *evaluation*. If the evaluation concludes that an SUD is present, then the evaluation should be followed by appropriate treatment. The individual should be placed on immediate leave from all professional

responsibilities and not allowed to return until the evaluation and any needed treatments are completed. Finally, tell the individual that you will expect a *report* back from the evaluating or treating entity. This report should specify requirements for aftercare, a plan for reintegration into practice, any workplace restrictions, and any recommendations for continuous monitoring.

Evaluation

The initial evaluation of any health-care worker with a possible SUD should begin with a discussion about any limits of confidentiality. In certain situations, licensing boards of other authorities may require evaluation records or treatment discharge summaries as a condition of return to practice. Ideally, a full history and physical examination should occur. When assessing the health-care professional's substance use, evaluators should gather as much detail as possible about what drugs were abused and how the drugs were procured (were they self-prescribed, diverted from patients, samples stolen from an office), whether tolerance and withdrawal symptoms are present, whether they were used during working hours or in other dangerous situations (i.e., before driving, while tending to children, etc.), when use began, and what the peak amount ever used was. Evaluators must, however, exercise discretion in how much of this information to include in reports that may ultimately go to others.

Collateral history from family members can be helpful. However, family members may downplay problems in an effort to protect the professional. Also, asking family members for collateral information can potentially strain family relationships. It should be done only when essential and then as delicately as possible. Information should also be obtained from a small number of professional colleagues. Care should be taken to protect the health-care professional's confidentiality to the greatest extent possible. An inadvertent misstep by the evaluator might result in significant harm to the individual once she or he is ready to return to work.

When the individual denies using substances, we recommend obtaining laboratory testing immediately. Some substances of abuse (e.g., cannabis) may be detectable for weeks after cessation of chronic use. However, alcohol and many pharmaceuticals have a fairly narrow detection window in a blood or urine sample (12 to 72 hours). Hair samples can provide detection windows of up to 3 months and may be useful in certain circumstances. However, they are controversial for detecting smoked drugs, because passive exposure can contaminate the hair and cause a false positive result.

We recommend consultation with a toxicologist before collecting the specimen for testing. Every specimen should be collected under the federally mandated protocol. Given the significant legal and professional sanctions that health-care professionals face, specimens must be handled properly and laboratories should use chain-of-custody procedures.

Treatment

If the evaluation of the health-care professional confirms an SUD, we recommend entry into a structured treatment program. This may be inpatient or outpatient; typical programs last between 2 weeks and 4 months. The American Society on Addiction Medicine has treatment placement guidelines, which may be helpful. Individuals who remain in treatment do better than those who drop out, but we could find no studies supporting a specific length of treatment for health-care professionals. Residential facilities often provide medical stabilization of

drug-dependent individuals, followed by an intensive psychosocial treatment program that includes group therapy, individual therapy, family meetings, psychopharmacologic evaluation, psychological evaluation, and 12-step fellowship meetings. Some programs offer aftercare plans, which can include reunion gatherings for successful graduates.

Residential treatment can be quite costly ($8,000 to over $50,000 per month), and insurance usually covers only a fraction, if any, of this cost. This expense may be prohibitive for younger professionals, especially those in training. Outpatient programs, or partial hospitalization, may be available closer to home, allow for greater family participation, may accept insurance benefits, and can be much more affordable.

Monitoring

Every hospital is mandated by the Joint Commission (formerly the Joint Commission on Accreditation of Health Care Organizations, or JCAHCO) to have a process apart from discipline by which physicians and other professionals can seek confidential help for health-related matters. However, not every hospital has such a committee, and those that exist have varying degrees of experience and expertise. Some situations regarding health-care professional substance use may warrant immediate attention from a state's physician health program, nursing wellness committee, or some other nondisciplinary agency. The goals of these entities are to identify, assess, refer for treatment, and monitor health-care providers with SUDs (and other impairing conditions). They can also provide guidance to individual health-care professionals, hospital administrators, and department chiefs about treatment resources and licensing regulations. Given that these entities also monitor health-care professionals, they can also provide advocacy for health-care practitioners with documented recovery to licensing boards, insurance companies, and hospitals.

Comparing efficacy of various monitoring entities is often difficult because of differences in the criteria they assess and monitor. Variables include length of follow-up, total abstinence versus relative abstinence, ability to resume work, and others. Despite their differences, most professional monitoring programs report success rates in the 75% to 85% range, far better than those reported for the general population.

Sociocultural Considerations

Because health-care professionals are often among the socioeconomic elite, those outside of the profession may see them as immune from problems—including substance abuse. Within the professions, a culture of denial has sometimes turned a blind eye to SUDs. This blindness might stem from the fact that many health-care providers do not see addiction as a treatable brain disease. Fortunately, this seems to be changing.

Some who fail to intervene with professional colleagues might do so for fear of triggering a disciplinary action, thereby preventing their colleague from being able to practice again. A few have advocated that, because patients' lives are at stake and the risk of relapse is too great, any health-care professional who has had an SUD should never be allowed to return to practice. However, the actual risk to patients by impaired physicians is quite low, and the likelihood of recovery is very high. We therefore recommend that health-care professionals who are recovering from SUDs continue to practice, provided they accept close supervision, random drug screens, and are fully compliant with monitoring by the appropriate professional entity.

Legal Considerations

Many states mandate health-care professionals to report professional colleagues who they suspect of being impaired because of substance abuse. Given the extensive professional scrutiny that can result, such a report should only occur after careful consideration of the facts, discussion with colleagues, and consultation with an attorney familiar with state licensing regulations. Individuals and health-care entities that fail to report a colleague in these circumstances risk disciplinary action themselves.

These reporting regulations may include a waiver of the reporting requirement when referral is made to a professional health program for treatment and monitoring, provided the health-care professional complies with all treatment and monitoring recommendations. This avenue is commonly referred to as a "diversion program," because the report is diverted away from the licensing agency and made instead to a professional health program. Our experience is that physicians almost never refuse a referral to the state physician health program when they understand the alternative is a board report.

To support their addiction, some health-care professionals may engage in illegal acts, such as self-prescribing, diverting medications, stealing medications, or prescribing for family members or fictional patients. These individuals should obtain legal counsel from an attorney who is experienced in dealing with health-care professionals, hospitals, and licensing entities.

A final legal consideration is whether to self-report information to the licensing board about a possible infraction of their rules and, if so, how much information to disclose. Health-care providers must honestly answer all questions on license renewal and other credentialing forms. Failure to answer questions honestly can result in sanctions that are more severe than those that might have occurred if the health-care professional had disclosed the information initially. However, health-care professionals should be cautious about providing unnecessary detail, which could lead to unwelcome scrutiny or disciplinary procedures. We recommend consultation with an attorney prior to disclosing any information about substance use treatment or monitoring.

Ethical Considerations

Ethical dilemmas arise when basic principles are in conflict with one another, which may occur when dealing with a colleague who has an SUD. For example, we have a basic duty to respect the *autonomy* of others. However, when a health-care professional is actively misusing psychoactive substances, this duty often directly competes with other guiding principles such as *justice*, *beneficence* (defined as "doing good"), and *nonmaleficence* (alternately defined as "preventing harm" and/or "not inflicting harm on others").

These conflicts and tensions may be most pronounced when we are not certain about the cause of a colleague's unusual behavior, when we might have suspicions about substance use but little confirmatory evidence. The peril here is failure to act, which may result in harm to the health-care professional or others, versus false accusations that could result in the health-care professional being forced out of work and numerous patients being left without their physician.

Ethical issues also arise because state physician health programs by their very structure are often coercive. Physicians are not free to refuse evaluation, treatment, or monitoring when the alternative is a report to the state licensing agency. Coerced treatment is effective, but should be applied cautiously and with ethical oversight. Furthermore, many centers that specialize

in evaluating health-care professionals also provide treatment at the same site. If a health-care professional is sent to one of these sites for a 1- to 5-day evaluation and the recommendation is made for a 4- to 12-week stay (at even greater expense), can we be sure that financial incentives did not play a role in the recommendation? Once such a recommendation is made, it is often hard if not impossible for the state program to overrule it.

Further ethical questions arise because our testing for substances of abuse has become exceedingly sensitive, but serious questions remain regarding specificity of those same laboratory tests and the positive predictive value of their results. The Substance Abuse and Mental Health Services Administration (SAMHSA) has issued an advisory cautioning that ethyl glucuronide (EtG) testing be used for clinical purposes only, and not used solely as the basis of reports in forensic programs.

Given that reporting a positive EtG result can have significant deleterious ramifications for the health-care provider, it may be that monitoring agencies should not use this test at all or, if ordered for clinical purposes, not report all positive results to licensing agencies and employers. Reporting all positive EtG results to the licensing board is ethically indefensible. Even if the board does not impose a sanction, the process of investigation has substantial economic and emotional costs for the monitored physician.

Special Considerations

How should a health-care professional inform a potential employer about a history of substance use treatment? We generally counsel professionals to wait to make a disclosure until they know that they are interested in the position, and to make the disclosure in a face-to-face interview. We also advise them to have a short, factual statement prepared and practice it several times before friends or a sponsor. The statement should briefly state that they had a problem with a substance, that they completed a treatment program and entered a continuing care program that includes laboratory monitoring, what they have learned from this experience, and how it has changed them for the better.

How should professional health programs respond when professionals who are being monitored suffer from conditions such as attention-deficit hyperactivity disorder (ADHD), anxiety, or chronic pain that warrant treatment with psychostimulants, BZDs, or narcotic analgesics? Most monitoring programs insist on abstinence from all intoxicating substances, including alcohol, illicit drugs, and psychoactive prescription drugs. However, many will allow health-care professionals to receive appropriate treatment as long as it is provided by a usual treatment provider who is knowledgeable about the history of substance abuse. This course of action is appropriate. Those with co-occurring SUDs and ADHD can be treated safely with stimulant medications, and that those with co-occurring SUDs and chronic pain can safely be treated with narcotic analgesics.

And finally, medications such as naltrexone, methadone, and buprenorphine may have an important role in managing addictions in health-care professionals. Some health-care professionals who have had histories of opioid use have been allowed back to practice contingent upon taking daily naltrexone. We are also aware of health-care professionals who lost their licenses because of opiate abuse and were eventually allowed to return to practice on buprenorphine maintenance therapy, with the full knowledge of the licensing board. In addition, we are aware of a small number of opioid-dependent physicians who are on methadone maintenance therapy, but as of this writing we are not aware of any who have returned to practice on this medication. We believe that there is merit in allowing health-care professionals to return to work either while taking or contingent upon taking medications such as these.

Conclusion

Health-care professionals are neither immune from SUDs nor at higher risk for them. However, professionals' patterns of use often reflect both the availability and knowledge of psychoactive prescription medications. Everyone in the healing profession can facilitate early detection and treatment by helping to educate staff members about these matters, knowing how to refer a colleague for assistance without fear of hurting his or her career, and by ensuring that the colleague receives appropriate workplace support and accommodation.

Health-care professionals whose lives have been affected by substance use can and do recover, and they usually can return to work safely and effectively. Early intervention is best, but intervention needs to occur whenever possible. Most states offer treatment and monitoring programs for physicians, nurses, and other health-care professionals. Health-care professionals in recovery from substance abuse have high success rates. Great care must be taken to ensure that these professional health programs operate under the highest ethical standards.

Suggested Readings

Berge KH, Seppala MD, Lanier WL. The anesthesiology community's approach to opioid- and anesthetic-abusing personnel: time to change course. *Anesthesiology*. 2008;109(5):762–764.

DuPont RL, McLellan AT, Carr G, et al. How are addicted physicians treated? A national survey of physician health programs. *J Subst Abuse Treat*. 2009;37(1):1–7.

McLellan AT, Skipper GS, Campbell M, et al. Five year outcomes in a cohort study of physicians treated for substance use disorders in the United States. *Br Med J*. 2008;337:a2038.

Knight JR, Sanchez LT, Sherritt L, et al. Outcomes of a monitoring program for physicians with mental and behavioral health problems. *J Psychiatr Pract*. 2007;13(1):25–32.

Wunsch MJ, Knisely JS, Cropsey KL, et al. Women physicians and addiction. *J Addict Dis*. 2007;26(2):35–43.

48 The Homeless

To understand the interaction between homelessness and substance abuse requires unraveling multiple strands of a very tangled condition. Statistically defining homelessness can offer some insight into the risk factors for problems with alcohol and drugs, but further elaboration of the myriad stressors of being homeless begins to shed light on the condition, treatment, and barriers to abstinence. There is agreement that people who are homeless are at an increased risk for substance abuse and dependence. One condition does not automatically cause the other, but each can complicate problems associated with the other. Those who use or abuse substances are more likely to become chronically homeless and have difficulty accessing and receiving treatment for their multitude of problems, including addiction, and difficulty establishing and sustaining sobriety. Ethnicity, gender, and age influence drug of choice and treatment acceptance and success. Interestingly, homeless women substance abusers seem to respond in a more positive fashion to treatment; homeless youth are particularly difficult to treat. Philosophy regarding treatment has evolved from putting supports in place to minimizing the impact of a system that contributes to homelessness, to a focus on and assumption of individual pathology. The literature is replete with multiple treatment modalities that have been developed, although research reflects a gap between research and practice, and their limited success on the homeless substance-abusing population. Recognition and amelioration of the challenges in life, as well as collaboration among community providers to provide support, are imperative to prevent and minimize the disruption and devastation wrought by substance abuse and dependence in this vulnerable population.

Epidemiology

Homelessness and substance abuse problems can be intertwined. Defining and discussing the prevalence of both situations will allow a better understanding of the interaction between the two. There are approximately 2.5 to 3.5 million homeless people in the United States. Of these, 23% were reported to be chronically homeless. Temporary homelessness caused by disasters or evictions is different from episodic homelessness, and it is thought that *chronic* homelessness poses the most significant burden on those who experience it. Fifteen percent to 57% of those homeless in urban areas are considered chronically homeless. In a 2006 U.S. Conference of Major 23 City survey on hunger and homelessness, the population demographics of homeless were reported: Whites (39%), Hispanics (13%), Asians (2%), African Americans (42%), and Native Americans (4%). Twenty-six percent of them were reported to have substance abuse problems, 16% mental health problems. Thirty percent were family with children, 51% single men, and

17% single women. Causes of homelessness reported from this survey included poverty, unemployment, lack of affordable housing, lack of needed services for substance abuse and mental illness, job loss, domestic violence, and prisoner reentry.

Prevalence of substance abuse problems in those who are homeless has been notoriously difficult to establish because of different definitions, methodologies, and tools for assessment. However, it is generally agreed that about 20% to 35% of those who are chronically homeless have alcohol or drug problems (although some claim it is as high as 50%, with 23% reporting problems with alcohol and 27% with drugs). An additional 10% to 20% have dual diagnoses (mental illness and substance use disorders [SUDs]), which may exacerbate their life difficulties. The prevalence of seeking and/or receiving treatment by those who are homeless with substance abuse problems has been poorly studied, although it is suggested they have significantly limited success in accessing services.

Men are two times more likely than women to receive treatment. Those aged 18 to 25 are thought to have the highest rate of treatment need, *but* the lowest rate of treatment receipt. About 18% of those homeless who have substance abuse problems receive substance abuse treatment from a specialty facility. Of those who are admitted for inpatient substance abuse treatment, those there for first admission report marijuana as their drug of choice and those with more than four admissions report their drug of choice is opioids, and are more likely (24% vs. 8%) to be homeless. Thirteen percent of those in substance abuse treatment were homeless at the time of admission (this translates into >120,000 admissions for substance abuse treatment by persons who were homeless). It is reported that one-fourth of the homeless admitted for substance abuse treatment had co-occurring disorders (mental health and substance abuse), and that one-third to one-half of homeless vets have co-occurring disorders. Among jail detainees with mental illness, 72% had co-occurring disorders. Homeless addicts also impact on other systems of care. A recent study reviewed over 5,000 acute hospitalizations of those who were admitted because of suicide and substance abuse (substance-induced suicide syndrome). These folks were more likely to be homeless, unemployed, uncooperative, have shorter lengths of stay, and have more rapid improvement in their symptoms. This study concluded there is a need for intensive addition component to outpatient care and additional outpatient services to care for suicidal substance-abusing patients.

Those who are homeless are at risk for being substance abusers. Risk for substance abuse as predicted by gender, length of time afflicted with substance dependence, and ethnicity can be powerful reflections of the need for services. Co-occurring disorders are common. It is readily apparent from the extant literature that these people are living disrupted lives and are in desperate need of support and treatment.

Sociocultural Considerations

There are numerous sociocultural risk factors to consider in understanding the development of substance use/abuse in the homeless population. SAMHSA (Substance Abuse Mental Health Service Administration, a federal oversight organization that coordinates setting of federal standards, monitoring, and research funding) notes other challenges for those with substance abuse and homelessness that can complicate their lives:

1. Inadequate access to appropriate screening
2. Fragmented services
3. Lack of appropriate discharge planning
4. Poor integration of care
5. Insurance coverage limitations
6. Stigma and discrimination

Individual characteristics can also interfere in treatment considerations and delay engagement by the consumer into treatment: these include disaffiliation/social isolation, distrust of caregivers and authority, mobility, and multiplicity of needs. Although society and governmental and funding agencies may be distressed by homeless people with substance abuse problems, some of these homeless people do *not* view substance abuse treatment as a high priority, or even important. A recent survey asked homeless persons what they needed urgently. They responded finding a job (42%), help finding permanent housing (30%), and assistance paying expenses. The *13th* most frequent response was treatment for use of alcohol or drugs; only 5% mentioned detoxification.

Other social/cultural considerations are extant as well. Men are more likely to report alcohol- and drug-related problems, while homeless women are more likely to report higher rates of mental illness. Women need child care; once offered, this enhances positive outcomes for women in treatment. Research reflects that there are more positive results in treatment of homeless women with substance abuse, perhaps because programs take into account physical and sexual abuse and motherhood. In a group of adolescents studied for several years, it was noted that ultimately about 5% become homeless. Risk factors associated with this included poor family functioning, few financial supports, and separation from parents or caregiver. These observations might have an impact on decisions for early intervention.

And finally, conceptualization of substance use and abuse as in issue of individual responsibility has influenced the development of treatment protocols. In lieu of addressing individual needs for housing, stable funding, work, and social skills development, substance abuse often is considered, by policy makers and funders, to be a disease of choice, and treatment philosophy embraces addressing individual pathology instead. System-level features (how and which services are provided, how access to services is structured) affect how homeless people with substance abuse problems access the care they need.

Factors Influencing Substance Use in People Who Are Homeless

Numerous factors contribute to the development and maintenance of substance abuse in the homeless population. *Access to care* remains a huge obstacle for those who are homeless and have substance abuse. But access must be more broadly drawn; a wide variety of services are necessary to keep people supported once they are housed, and access to these services is critical: "health care, mental health care, money management, benefits assistance, job training, transportation, parenting skills."

Funding of mental health and substance abuse services is often along separate funding streams, with discrete lines for monitoring, reporting, standards, and accountability. As such, patients needing access to both kinds of treatment may find themselves treated by two sets of clinicians who often have opposed therapeutic skills sets and different established goals and expectations of outcomes.

Funding for housing must always be a salient consideration. While Section 8 housing is often refused for consumers with a known history of substance abuse, other federal resources have been made available: Community Development Block Grants (CDBG) and the McKinney-Vento Act in 2000 have authorized federal homeless assistance programs to provide transitional and permanent house to the homeless; access to stable housing is paramount in the battle for sobriety.

The concept of *treatment matching* (matching patient needs and characteristics) with specific treatments has been studied, but not supported by research. Exploration of what types of clinician "treater styles" work most effectively with what kind of patients is an intriguing research paradigm, but one that is as yet unexplored.

Treatment

Before turning to an explicit discussion of models of care, it is important to consider defining successful outcomes: these can include complete sobriety, graduation from treatment programs, attainment of life skills objectives (employment, school, money management, housing), change in psychological realms, improvement in interpersonal relationships, ability to cope with problems and stress, and a global improvement in one's life. Which goals are pursued and achieved will depend on a variety of factors, including the system of care and personal attributes of the individual. For now, present research seems to focus mainly on treatment program completion.

Different models of care have been proffered for the treatment of homeless persons with substance abuse problems. A survey has reported that the *most frequent* inpatient treatment for homeless persons with substance abuse is hospital detoxification, and the most likely outpatient treatment is a 12-step recovery program. Interestingly, however, most research has been done on day treatment and therapeutic communities (TCs). Models of care include the medical model, the social model, 12-step recovery, harm reduction (HR), intensive outpatient, day treatment, case management, and contingency management interventions.

The *medical model* (particularly medical detoxification) was an early focus in the treatment of addiction; however, only about 5% of people with alcohol dependence need acute medical intervention. A consistent finding in research effectiveness treatment is the connection between length of time spent in treatment and positive treatment outcomes; unfortunately, dropout rates can be as high as two-thirds. Brief interventions have not been found to be useful in the homeless substance abuse population. As such, an acute care model like the medical model is typically insufficient for someone with chronic homelessness.

The rise of the *social model* reflected the different needs of a chronically ill population; its key characteristics include

1. *Use of nonprofessional staff* often in the midst of their own recovery, who do not make diagnoses, but instead act as role models
2. *Open admissions* with less record-keeping and no standardized assessment
3. A *reliance on natural recovery* (vs. therapeutic treatment)
4. A *focus on experiential knowledge* and spiritual understanding (compared to formal diagnoses and professionally driven treatment plans)

While both models are typically noninstitutional, and view alcoholism as a treatable disease that requires personal responsibility for recovery, the social model is considered more cost-effective, and as such, primarily serves indigent populations. Unfortunately, there are no reports of randomized clinical trials for efficacy of social model patients followed longitudinally.

12-step recovery programs, which include self-help and peer support, are the dominant approach to treatment of alcoholism in the United States. There is some support for the effectiveness of this treatment, but little research on the efficacy of this approach with homeless substance abusers per se, although there is speculation that it might be helpful in addressing the need to connect with a supportive community. The focus on sobriety may not meet the total needs of the homeless individual (which include affordable housing and stable employment), which would leave them at risk for relapse.

Another model of substance abuse treatment is known as *harm reduction*, which is designed to provide a variety of services to meet the individual needs of *each* drug abuser; instead of demanding users conform to rigid program requirements, treatment is designed to meet the individualized needs of persons with substance abuse problems.

Results of treatment may differ depending on client makeup (solely substance abuse vs. dual diagnoses), model of delivery, and availability to and intensity of additional services. Treatment for this challenging population must include addressing *both* the homelessness *and* the substance abuse. As noted above, multiple programs exist to address housing. Once established

in housing, many individuals, with supports, are able to remain housed and are less likely to use crisis services or hospitals, or end up detained by law enforcement. *Housing first models* (see discussion below) seem to enhance users' acceptance of treatment, as well as retention, particularly if wrap-around high-intensity services are proffered.

It is apparent that those who are homeless have an increased need for treatment but will probably face more difficulty in accessing it. Multiple models of care have been developed and efficacy research performed. Unfortunately, considerable flaws in design and execution, as well as small sample size and ethical concerns, have conspired to limit interpretation of results as well as replicability. Issues regarding dropout rates must be addressed; dropout rates as high as two-third are common, so the occurrence of relapse (and the offer of relapse prevention) must be expected, and hopefully used as opportunities for growth and change via *nonjudgmental* intervention. Predictors of poor housing stability include assaultiveness, self-destructiveness, and medication noncompliance.

A variety of housing modalities have been offered and studied:

1. *Supportive housing* (either scattered site or congregate).
2. *Housing ready* (compliant contingency, stay if sober, ready to occupy housing, psychiatric stability, sobriety, willingness to comply).
3. *Housing first* (placement in housing regardless of clinical status or receipt of mental health or substance abuse services).
4. *Wet housing*: where substance use is discouraged but allowed without consequence on site; abstinence may be an unrealistic standard for most dually diagnosed residents during the engagement and pretreatment stages.
5. *Damp housing*: where substance use is discouraged, not allowed on site, but tolerated off-site.
6. *Dry housing*: where substance abuse is not allowed; any use results in dismissal from the program.
7. *Transitional housing*: location in housing that is stable, but temporary; occupancy changes as one advances through program.
8. *Permanent housing*: stable housing considered an end point (no further moves necessary); typically associated with wrap-around services (learning social skills, activities of daily living, help with transportation to appointments, accessing medication) that help the patient remain in independent living. Of note, the strongest predictor of program completion is the existence of social supports.
9. *Therapeutic communities*: where substance abuse is conceptualized as a disorder of the whole person, with problems not just with drugs or alcohol but also in conduct, attitudes, moods, emotional management, and values. TCs promote sobriety, and set goals of eliminating antisocial behavior and facilitate a change in lifestyle, including attitudes and values.

Stabilization of housing should always be part of the consideration in the overall treatment plan. As noted above, numerous housing models have been attempted with mixed results. A recent meta-analysis of 30 studies on housing models for persons with mental illness examined 44 different housing situations; the results reflect that more stable housing results if the patient participates in a program that assumes a model of care (vs. nonmodel housing). Permanent supported housing (where a consumer is established permanently and offered considerable support to remain in independent living) has the largest effect on stabilizing housing, but there was no statistical difference between the housing models (permanent supported housing, residential).

Linkage to services necessary to survive being homeless also plays a huge role in the recovery of homeless people with substance abuse problems. The need for an integrated, comprehensive, community-based system of care has been shown numerous times. These services can lead to employment, permanent housing, decrease in legal problems, decreases in substance abuse, and improved mental health. To meet the challenges for this population, multiple supports

should be offered: aggressive outreach, permanent housing, treatment environment, strategies to increase motivation, family-based therapy, and peer leadership.

Engagement

This is the first step in treatment. A working relationship is established, typically via outreach to the patient in his or her own environment, or in a safe, nonthreatening environment. Practical assistance is offered, including crisis intervention, support, stabilizing medical and mental health problems, reducing legal issues, and encouraging family involvement. A study of homeless dually diagnosed men and women reflected that men say themselves as forced into treatment; as such, it has been suggested that motivational interviewing might enhance the men's need for control and as such might be particularly effective for this subset of the population.

Persuasion

The patient slowly becomes aware that substance abuse is creating problems in his life. The individual and family begin to meet, and group meetings discuss the pros and cons of substance abuse. Non–substance abuse social skills are encouraged (how to get together in non–substance abuse venues). Structured activities are offered, including social and recreational outlets. Damp housing is considered, and a focus on psychiatric stabilization ensues. The patient is approaching a time when they understand the consequences of their substance use, and are sufficiently engaged and supported to move into active treatment.

Active Treatment

Active treatment is comprehensive. It includes outreach and case management. Hopefully, substance use begins to abate, and the consumer is offered strategies to reduce substance abuse, like social skills to resist peer pressure. Self-help groups like AA (Alcoholics Anonymous), NA (Narcotics Anonymous), and Recovery Anonymous are encouraged. Individual therapy is offered, and patients learn to substitute healthy activities for substance-using activities. Medications (disulfiram [an alcohol antagonist], naltrexone [an opioid antagonist]) are considered to help maintain sobriety. Dry housing can be offered, as well as techniques for coping with stress.

Maintenance/Relapse Prevention

Maintenance and extended recovery are the focus. Interpersonal social skills are honed, as are problem-solving skills. Lifestyle improvement can be tackled (smoking cessation, improved diet, and exercise). Independent housing can be attempted and the consumer can offer himself or herself as a role model for those in earlier stages of recovery.

Efficacy of integrated treatment has been a focus of research. The following results have been reported (integrated treatment vs. usual care): increased retention (55%), decreased substance use (40%), employment (40%), stable housing (60% vs. 50%), money for basic needs (70% vs. 45%), $6000 per individual in criminal justice savings from fewer arrests, and fewer hospitalizations.

Beyond integrated treatment, other forms of treatment reported include

1. *Intensive outpatient treatment* to homeless people should include linkages to shelter and/or public housing; provision of food, medical care and social services, case management, long-term rehab, and strategies to engage chronically homeless.
2. *Day treatment* found to be useful in homeless cocaine abusers. This includes active programming each day (6 to 8 hours), including community meetings, psycho education (relapse prevention, assertiveness, medical awareness, relaxation, 12 steps, and job training), and individual and group counseling, with eventual transition to aftercare programs for relapse prevention.

3. *Assertive outreach*: case managers diligently and robustly reach out to potential consumers with the hope of engaging them in treatment.
4. *Modified TCs* seek to incorporate additional services to address the needs of those who are homeless (education, jobs, legal, housing); they are somewhat more flexible than traditional TCs and often last 18 to 24 months. Research reflects they are a viable treatment option for homeless mentally ill consumers.
5. *Contingency management interventions*: where housing/work placement is contingent on provable sobriety. There is little research to support the concept's usefulness.
6. *Intensive case management* includes "outreach, assessment, treatment planning, linkages, monitoring and evaluation, client advocacy, crisis advocacy, system advocacy, supporting counseling, practical support, and program linkage." This form of support seems particularly challenging with a homeless population who suffers with issues of control and trust (as they may have a fear of being watched or monitored and dislike intrusiveness and drug testing). While its general efficacy has not been established by research, it definitely decreases hospitalization and emergency department visits.
7. *Residential programming*: where the intent is to stabilize housing so that access to the patient is gained to begin engagement in treatment.
8. *Lottery*: for allotted time periods of sobriety or completing therapeutic tasks, patients earn "lottery" tickets that offer them a chance to win prizes.
9. *Payeeships*: where a person besides the recipient of a disability check is named to supervise the use of the check. Research shows those involved have fewer days of homelessness, but there were no positive substance abuse outcomes.

A wide variety of treatment models have been tried and proved effective with some individuals, but overall, no statistical significance between treatment modalities has been reported in the literature. One key issue does resonate: treatment must be long-term. Brief interventions have been reliably demonstrated to have no long-lasting effects when utilized with those who are homeless and have substance abuse problems.

Experience has demonstrated that interagency collaboration is imperative. People who are homeless and have substance abuse problems have complex multiple needs that require responses from a wide variety of agencies. Linkage to said agencies is imperative. Unfortunately, there are funding limits, limits in information technology, lack of available services, lack of political will, and legislative/political opposition.

A focus on tangible needs of the homeless (housing, money, employment) is certainly necessary, but to date, in the research literature specific *treatment* modality does not appear to differentially affect outcomes. Certainly, "global" treatment has positive effects, but even these diminish over time if treatment is not sustained.

Suggested Readings

Leff HS, Chow CM, Pepin R, et al. Does one size fit all? What we can and can't learn from a meta-analysis of housing models for persons with mental illness. *Psychiatr Serv*. 2009;60:478–482.

National Alliance to End Homelessness. Homelessness counts report 2007. http://www.naeh.org. Accessed June 4, 2010.

SAMHSA Office of Applied Studies. Results of 2008 National Survey on drug use and health: national findings (Office of Applied Studies NSDUH Series H-3, HHS Publication No. SMA 09-4434). Rockville, MD: SAMHSA Office of Applied Studies 2008.

Shelton KH, Taylor PH, Bonner A, et al. Risk factors for homelessness—evidence from a population based study. *Psychiatr Serv*. 2009:465–472.

The U.S. Conference of Mayors. Hunger and Homelessness Survey: a status report on hunger and homelessness in America's cities. U.S. Conference of Mayors; 2006. www.usmayors.org/uscm/hungersurvey/2006/report06.pdf. Accessed June 4, 2010.

49 Training and Education

Medical Education on Addiction

The need for physicians and other health professionals to have competence in detecting and treating alcohol dependence and other addictions is clear from the magnitude of their negative impact on human health and well-being. In the United States, tobacco, alcohol, and illicit drug use represent 3 of the top 10 actual causes of death, accounting for 537,000 deaths in 2000 (22.3% of all deaths). In 1995, the total cost of alcohol and drug abuse to society in the United States was estimated to be $276.4 billion (or 3.7% of total gross domestic product).

Screening and brief intervention in health-care settings reduce smoking, hazardous drinking, and medical consequences of alcohol and tobacco use. Reduction in drinking is associated with improved health and quality of life. Behavioral interventions and medications are effective for treating substance use disorders (SUDs).

Despite the significant effect of alcohol and drug use on public health and the availability of effective prevention and treatment strategies for health-care professionals, physicians have been slow in implementing evidence-based screening, brief intervention, and treatment.

Current Medical Education Requirements

There currently are requirements for education regarding substance use and addiction at each level of medical education in the United States. The Liaison Committee on Medical Education (LCME), a collaboration between the Association of American Medical Colleges (AAMC) and the American Medical Association (AMA), accredits U.S. medical schools. The LCME refrains from proscribing a specific curriculum or minimum time spent on any given topic; however, its accreditation standards include requirements for training in six clinical disciplines, including psychiatry and "behavioral and socioeconomic subjects, in addition to basic science and clinical disciplines." "Substance abuse" is included as one of 33 "behavioral and socioeconomic subjects." In 2005, the AAMC reported that of the 131 accredited MD-granting U.S. medical schools, 122 included "substance abuse" in a required course and 62 offered elective training in this area.

In order to practice medicine in any U.S. state or territory, physicians must pass the United States Medical Licensing Examination (USMLE). This examination consists of three parts: step 1 assesses knowledge of sciences basic to the practice of medicine, step 2 assesses clinical knowledge essential to the supervised practice of medicine, and step 3, taken after one year of postgraduate training, assesses clinical skills necessary for the independent practice of medicine. All three steps include content related to substance use and addiction, including content

on prevention, detection, and diagnosis. However, specific requirements regarding treatment, including screening and brief intervention or medications (e.g., naltrexone, bupropion, nicotine, varenicline, buprenorphine) for treatment of SUDs, are not mentioned.

The Accreditation Council for Graduate Medical Education (ACGME) is responsible for accrediting postmedical school medical training programs in the United States. Residency training program requirements are developed by Residency Review Committees (RRC) for each medical specialty. Requirements for postgraduate training in emergency medicine, family medicine, pediatrics, psychiatry, and obstetrics and gynecology specifically include recognition of substance abuse or addiction. Requirements for anesthesiology, internal medicine, neurology, and pain medicine refer to recognition of co-occurring psychiatric conditions or behavioral aspects of care, but not specifically substance abuse or addiction. Preventive medicine, physical medicine, and rehabilitation and surgery have no references to required knowledge of SUD detection, prevention, or treatment. Psychiatry is the only medical specialty with a minimum length of time devoted to a clinical rotation in addictions treatment—1 month (or 2% of clinical rotation time).

In order to be eligible for the program, candidates must have "satisfactorily completed an ACGME accredited general psychiatry residency prior to entering the program." The duration of clinical addiction psychiatry training must be 12 months. The curriculum must contain 17 specific aspects of addiction psychiatry. Clinical experiences must include evaluation, consultation, and management of patients with substance-related disorders related to the following substances: alcohol; opioids; cocaine and other stimulants; cannabis and hallucinogens; benzodiazepines (BZDs); other substances of abuse, including sedatives, hypnotics, or anxiolytics; and miscellaneous/unusual drugs (e.g., nutmeg, designer drugs, and organic solvents/inhalants).

The American Board of Psychiatry and Neurology (ABPN) is an American Board of Medical Specialties (ABMS) member whose mission is "to serve the public interest and the professions of psychiatry and neurology by promoting excellence in practice through certification and maintenance of certification processes." The ABPN provides certification and maintenance of certification examinations in addiction psychiatry.

The Accreditation Council for Continuing Medical Education (ACCME) accredits Continuing Medical Education (CME) for activities by U.S. physicians in independent practice. All states require continuing education for renewal of licensure to practice medicine. The ACCME does not prescribe specific content for CME; rather, it emphasizes that CME content addresses important "practice gaps"—differences between current medical practice and evidence-based best practices particularly those that have a major impact on public health. In 2008, the Office of the National Drug Control Policy (ONDCP) partnered with ACCME to address important practice gaps in physician management of patients with high-risk substance use and addiction as a prototype for bridging gaps in health-care quality that would apply to physicians in all medical specialties.

Graduate Medical Education

Educational interventions on the diagnosis and treatment of SUDs are associated with increased knowledge and skills among house staff and more positive attitudes toward patients with SUDs. Family medicine residents indicated a high level of satisfaction with a new 20-hour course on alcoholism that included didactics, supervised intake assessments, and participation in group sessions. Implementation of a longitudinal didactic series over a 3-year internal medicine residency mitigated the usual negative effect of graduate medical education on attitudes toward patients with high-risk alcohol use and alcoholism. Pediatric residents receiving an alcohol and other drug curriculum that included interactive didactics, participation in a community-based adolescent alcohol and other drug program, role-playing practice, and interview skill sessions performed significantly better than untrained controls on tests of knowledge, skills, and abilities

in assessing and managing alcohol and other drug disorders. Participants in a Chief Resident Immersion Training Program demonstrated significantly improved knowledge, skills, and confidence related to addiction treatment than nonparticipating peers at 6- and 11-month follow-up.

Continuing Medical Education

CME interventions for addictions have been associated with mixed results.

Brief experiential training aimed at improving optimism and attitudes toward patients with addiction has had mixed results. Brief training on alcoholism and the implementation of a brief questionnaire to assess drinking resulted in modest improvement in alcohol histories and no change in smoking histories based on inpatient chart review. A learner-centered, experiential training program increased the confidence of faculty (80% internal medicine) in diagnosing and managing patients with SUDs and increased their optimism about patient outcome. Primary-care multidisciplinary teams demonstrated a significant change in attitude after a 2-day experiential training on alcohol use disorders, whereas trained emergency medicine teams and control teams demonstrated no change in attitudes. General practitioners and nurses in a primary-care clinic received training and supervision for a 3-month period in alcohol screening (CAGE and Michigan Alcoholism Screening Test [MAST]) and referral. Both reported increased optimism about alcoholism treatment and improvement in the frequency of asking about alcohol problems. Interactive training sessions teaching general practitioners to use the drink-less brief intervention package significantly increased practitioners' confidence in implementing the elements of screening (49% to 90%) and brief intervention (40% to 92%) for high-risk alcohol use.

Conclusion

Tobacco, alcohol, and other substance use continue to take a tremendous toll on health. Physicians have the potential for significant positive impact in preventing and treating high-risk substance use and SUDs. Medical education has not kept pace with advances in prevention and treatment of SUDs such that many physicians are unprepared to effectively manage patients with high-risk substance use and addiction. Ongoing efforts to address this significant practice gap include training of addiction specialist champions for medical school faculty, development of model curricula, and updating requirements at every stage of medical training to include appropriate training for physicians in every patient-care specialty. Empirical data support novel educational approaches to improve physician competency in screening, brief intervention, and treatment of at-risk substance use and SUDs. Continued efforts to refine educational approaches and reduce institutional barriers such as lack of reimbursement or other institutional support are needed to further improve medical education in addiction prevention and treatment.

Psychologists: Training and Education

Psychologists are uniquely trained to assess and treat disorders that frequently co-occur with substance abuse and substance dependence, and the treatment of the co-occurring disorders enhances an individual's chances of recovery. Despite these unique skills, few psychologists themselves are adequately trained in the assessment and treatment of SUDs, thus limiting their effectiveness within this population.

In the general U.S. population, approximately 1 in 10 individuals has an SUD. In psychiatric inpatient facilities, the prevalence rate climbs as high as 1 in 2, and 90% of offenders entering prison meet diagnostic criteria for an SUD. With prevalence rates this high, adequate training and education of psychologists in the assessment and treatment of SUDs can no longer be elective or absent entirely from training curricula.

Each year, drug and alcohol abuse contributes to the deaths of more than 120,000 Americans. SUDs cost taxpayers in excess of $360 billion annually in preventable health-care costs, extra law enforcement, auto accidents, crime, and lost productivity. A sizable portion of the general population uses psychoactive substances in response to anxiety or depressive disorders, both areas in which evidence-based practices (EBPs) have excelled. Adding a core SUD education and training component to skills already inherent in quality psychology programs would place psychologists in a uniquely qualified position to effectively treat SUDs.

The existing literature that examines the training in substance abuse for doctoral-level psychologists is scarce. A survey of rehabilitation psychologists found that while most treated patients with alcohol and drug abuse issues, few felt adequately trained to intervene with such patients, with a majority rating their training as poor. Twenty percent reported receiving no formal training in substance abuse. Of those having received some training in this area, most had either completed a graduate course where substance abuse was discussed (42%) or participated in a continuing education or postgraduate workshop on substance abuse (40%). Only one in five reported having completed a graduate course fully devoted to substance abuse.

Given this data and the high prevalence of SUDs across patient populations, it is imperative that psychologists be proficient in the assessment and appropriate referral of individuals with SUDs through knowledge obtained about the disease of addiction, the use and interpretation of assessment materials, and clinical training as a requirement to graduate from any institution conferring a degree of doctorate of philosophy or psychology preparing students to practice in the field of psychology.

Conclusion

The overarching goal of every graduate training program is to provide students with the requisite knowledge, attitudes, and skills to be successful in their professional careers. For the behavioral sciences, as in many other fields of study, this task is complicated by the ever-growing body of knowledge in the discipline. Advances in neuroscience, particularly neuroimaging and neurogenetics, have created new challenges for educators responsible for keeping an up-to-date, relevant curriculum. Given the finite period of time available to train students, difficult decisions must be made on what to teach and what to leave out of the didactic and clinical course of study.

Nursing Education in Addictions and Substance Abuse

Nurses are educated in a variety of programs in the United States. Registered nurses may complete their initial nursing education in a 2-year community college for an associate degree in nursing, or a 4-year university program for a Bachelor of Science degree in nursing. Three-year hospital-based nursing diploma programs have become rare in the United States. Advanced practice nurses (APNs) are educated in university settings at the graduate level and receive

either a master of science degree or a master of science in nursing degree. Typically, these programs are 2 years in length and prepare nurses to be nurse practitioners, nurse midwives, clinical nurse specialists, or nurse anesthetists. APNs have advanced education in pharmacology, pathophysiology, and physical assessment, as well as courses that are related to their specialty area. Many APNs also have prescriptive authority; requirements for collaboration with medical physicians for prescriptive authority vary from state to state; however, some APNs are able to practice independently. Additionally, many schools have recently begun to educate people with a college degree in another field, allowing them to become nurse practitioners after completing a 3-year intensive program.

In each of these programs, students study the care of adults, children, pregnant women, medical and surgical illnesses, and psychiatric/mental health. Addiction issues are often addressed as part of the mental health course; many schools have integrated mental health concepts throughout the nursing curriculum instead of having a separate course dealing with mental health concepts. Addiction issues may be encountered in any health-care setting, and therefore, this approach may make sense; however, the danger is that the topic may not be discussed in full detail and therefore may not be given the importance needed to prepare nurses to deal with this complicated disease. All nurses use a problem-solving approach to assess patients and identify problems, and plan, implement, and evaluate interventions. Knowledge of generalized nursing care as well as specialized knowledge of addictions is essential to provide effective care for people with addictive disorders.

"Addictions nursing is a distinct specialty practice that integrates the biological, behavioral, environmental, psychological, social, and spiritual aspects of human responses to the illness of addiction into the nursing care provided to those affected by this disorder/disease, regardless of the clinical setting." Addictions nurses provide direct care, consult with other health-care providers, shape policy, and advocate for patients. Nurses provide care to individuals, families, communities, or special populations and use evidence-based, holistic strategies to formulate this care. With a point of care that may exist anywhere in the wellness–illness continuum, addictions nurses focus care on specific phenomena of concern as identified in the *Scope and Standards of Addictions Nursing Practice* (2004).

Nursing Education

Addiction nursing education is currently focused on patients with addiction and their treatment; it is important that all undergraduates have some clinical experiences in caring for patients who have problems related to their addictive disorder. Model curricula have been developed and include content related to neuroanatomy and neurochemistry as it relates to addiction, assessment for early signs of risk behaviors, brief intervention skills, assessment and treatment of withdrawal symptoms, harm reduction (HR), and trauma informed care. All of these topic areas should be included in nursing education about addictive disorders. Pharmacology of addictive substances, etiology of abuse and dependence on substances, care of affected family, and mobilization of community resources should also be included in educational programs. Nursing education should also include information about the risk for addiction among nursing and other health-care professionals. Ideally, addictions content should be included throughout the nursing curricula since addictions issues occur in all stages of health and disease and throughout all of the different specialties in nursing.

Graduate education for practice in the specialty of addictions nursing needs to include theory and research, evidence-based content on addictions, as well as development of clinical skills such as assessment, differential diagnosis, and interventions or treatment of individuals and families dealing with addictive disorders. All APNs need basic skills in assessment of addictive disorders and the need for referral for specialty care.

Addictions Nursing Specialty Organizations

The first U.S. specialty gathering in addictions nursing took place at the 1975 National Council on Alcoholism (NCA). This group was initially known as the National Nurses Society on Alcoholism. In 1978, the Drug and Alcohol Nursing Association (DANA) was formed by a group of nurses who objected to the National Nurses Society on Alcoholism sole focus on alcohol. The National Nurses Society on Alcoholism separated from the NCA in 1981 and became the National Nurses Society on Addictions (NNSA) to reflect the broader scope of the practice of its members. In 1985, this group expanded to become the International Nurses Society on Addictions (IntNSA). IntNSA sponsors an annual conference and has published an addiction nursing journal since 1989 and other publications on addictions nursing. It has published a core curriculum on addiction nursing and has worked with the American Nurses Association (ANA) to develop *Scope and Standards for Addictions Nursing Practice*. Impaired nursing practice and approaches to caring for the impaired nurse have been a major focus of this organization. Development of certification exams on a generalist and specialist level has been undertaken with other nursing organizations.

The Role of the Certified Professional Addictions Nurse

In 1989, the NNSA sought to create a separate specialty of nursing that reflected a specific body of knowledge and related skill sets and competencies. In addition, another organization, the National Consortium of Chemical Dependency Nurses (NCCDN), also was developing a similar goal. These organizations shared a common goal recognizing the need to develop a theoretical body of knowledge and promote research in the work of addictions nursing.

Currently, the organizations that have the ability to credential a nurse in the field of addictions nursing are the IntNSA and the Consortium of Behavioral Health Nurses and Associates (CBHNA). IntNSA offers the Certified Addictions Registered Nurse (CARN) at the generalist level and the CARN-APN for the APN. The CBHNA offers the chemical dependency (CD) credential. Both certifications assure that the nurse is certified as knowledgeable in the field of addictions nursing, and this credential serves as a benchmark of expertise.

The role of the professional nurse providing treatment to individuals who suffer from addictive disorders requires a specialized knowledge base, skill set, and core competencies. Completion of the certification process validates that a nurse has expertise in specific domains of practice and provides a standard that the nurse adheres to as a part of his/her professional ethical mandates in health care.

The Role of the Nurse in Addiction Treatment

Nurses have an important role in providing addiction treatment to patients in both acute care setting and outpatient setting. Patients present in all treatment settings with diagnosed and undiagnosed disease and fear of disclosure due to concerns of being "labeled," undertreated, or poorly treated. Nurses have a critical role in engaging the patient in treatment and acknowledging their disease with compassion and empathy. The nurse can obtain a good substance abuse history both with thorough physical exam and with nonjudgmental, thoughtful interviewing. Often the diagnosis of addiction is missed because no one asks the questions, the questions are asked in a judgmental manner, or toxicology testing does not occur. Toxicology testing should be utilized as a tool to assist the nurse and the patient in identifying and addressing substance use. Toxicology screening allows for a dialogue if it is presented in a nonthreatening, nonaccusatory manner.

Conclusion

Nurses can play an important role in treatment for addiction to cocaine, alcohol, nicotine, opioids, and other drugs. Screening is a natural fit as nurses are often the providers who spend the most direct, hands-on time with the patient—triaging, screening, assessing, educating, supporting, and assisting with specific service needs. Caring for patients with opioid dependence involves a great deal of hands-on care by the nurse, and treating patients with opioid dependence can have good outcomes with the support of an educated nurse. The nurse can assist the patient in looking at his/her disease, agreeing to an intervention and assisting in this process. Interventions could range from brief motivational interviews to assistance with detoxification, aftercare, or medication-assisted options.

Social Worker Education and Training in the Care of Persons with Substance Use Disorders

Substance misuse is a common occurrence in the United States and throughout much of the rest of the world. According to the 2008 National Survey on Drug Use and Health (NSDUH), an estimated 20.8% of U.S. residents aged 18 and above met criteria for substance abuse or dependence. Competent assessment and treatment of SUDs is paramount in the helping professions. Social workers provide services across a range of agencies, populations, and geographic locales; as such, they routinely assess, treat, and refer patients affected by SUDs. According to the Bureau of Labor Statistics, 21% of social workers were employed in mental health and substance abuse positions in 2006. The prevalence and wide-reaching effects of substance misuse underscore the importance of specialized education and ongoing training among social workers in the treatment of this vulnerable population.

U.S. History of Alcohol and Drug Use Treatment by Social Workers

Social workers have played a role in the treatment of SUDs since the days of Charity Organization Societies (COS) and the settlement house movement of the late 1800s. At the time, the prevailing attitude toward addictions was that such disorders represented a moral deficit in the individual. A notable social work figure and prominent COS leader, Mary Richmond, however, rejected the moral model, and promoted the notion that "inebriety" was a disease in need of early identification and treatment. In the early days of the social work profession, assistance was generally offered through educational activities associated with the growing temperance movement; however, few direct services were offered to individuals with SUDs. In fact, many individuals with SUDs were confined to institutions or incarcerated because of the prevailing moral model and the lack of knowledge regarding SUDs on the part of helping professionals, including social workers.

Licensure and Certification of Social Workers

All states have licensing, certification, or registration requirements for the practice of social work. Typically, there are four categories of practice that jurisdictions may legally regulate: (a) *bachelor's*: the baccalaureate social work degree, which is granted upon completion of a 4-year degree; (b) I: the MSW degree in social work without post-MSW experience; (c) *advanced*

generalist: the MSW degree with 2 years of supervised post-master's work experience; and (d) *clinical*: MSW with 2 years of post-master's clinical social work practice. State Boards of Social Work require that social work degrees are granted by programs accredited by the Council on Social Work Education (CSWE) (from the Association of Social Work Boards [ASWB]).

General Education and Training

A bachelor's degree in social work (BSW) is typically the minimum requirement for entry-level social work positions; however, the MSW degree has become the standard for many positions and is required for independent clinical practice. As of 2006, the CSWE accredited 458 bachelor's programs and 181 master's programs. Doctoral education in the United States has grown considerably in recent years. In 1957 there were only 10 social work doctoral programs, in 1990 there were 47, and in 2003 there were 72. The growth in doctoral programs is largely the result of a growing emphasis on research, publication, and grant funding.

Substance Abuse Treatment Services Provided by Social Workers

According to a 2000 survey of National Association of Social Workers (NASW) members, 71% of respondents reported activities related to the diagnosis or treatment of patients with SUDs in the past 12 months; however, only 2% of the sample identified substance abuse as their primary area of practice. The sample reported a mean of 35.4 hours spent in professional development training during the past year; however, the number of hours spent in substance abuse–related training was only 4.4 hours for the same 12-month period. Although the majority of the respondents (81%) reported lifetime training in substance abuse (primarily through continuing education courses), only 1% of the sample had completed a substance abuse certification program. The findings from the NASW survey seem to suggest that although social workers routinely assess and treat SUDs, only a few treatment agencies and/or practitioners have embraced SUDs as a specialty area of primary practice. There also appears to be disproportionate availability and/or interest in training related to substance abuse disorders. Given the high prevalence of SUDs among patients treated by social workers, the survey highlights the need for increased coursework focused on substance abuse in social work programs, as well as increased continuing education opportunities related to substance abuse.

Education and Training in Substance Use Disorders

It has been long agreed that social work programs are primarily responsible for training social workers to effectively treat SUDs. However, there is a large gap between science and practice in the addiction field. This gap may be the result of values and models gained through professional training. However, despite the prevalence of SUDs among patients being treated by social workers, substance abuse specialties and coursework are limited in schools of social work. Consequently, social workers enter the field with little or no training in the area of substance use and related issues. Bina et al. conducted a survey of a random sample of social work programs (30% of the 187 accredited programs in 2007 to 2008) and found that none of the programs surveyed offered a substance abuse specialization. Furthermore, 52% did not offer a single substance abuse– specific course. Not surprisingly, the majority of social workers (54%) report the need for more training in the area of substance abuse assessment and treatment. The paucity of training provided to social workers is associated with a lack of practitioner knowledge of SUDs, more negative attitudes toward patients with substance use problems, and decreased effectiveness and quality of treatment provided.

Evidence-Based Practice in Addictions

There is growing emphasis on the use of EBP in the field of social work, as researchers and practitioners alike advocate for the highest quality care for patients. This increased momentum is underscored by the growing number of publications on EBP across social work disciplines, including mental health services, health, and social welfare. There also has been an increase in the number of social work textbooks dedicated to the topic of EBP, as well as meta-analyses and systematic reviews of EBPs—all of which make EBPs more accessible to academicians and practitioners. Although EBPs are becoming more widely advertised and disseminated, practitioners remain ambivalent about embracing EBPs. There remains a large gap between processes that are supported by science and the processes used by social work practitioners. The translation time from the scientific world to the "real world" of practice, in fact, is estimated at between 15 and 20 years, and some empirically supported practices never translate into community practice. Given the large body of literature in substance abuse treatment, including the growth of several evidence-based interventions, social workers need to remain abreast of the current treatments to ethically and most effectively treat their patients.

Conclusion

Historically, social workers have played key roles in the assessment, treatment, and understanding of SUDs. Given the large numbers of individuals impacted by SUDs, and the growth of programs to treat them, social workers will continue to be among frontline staff in addictions treatment. As such, social workers have considerable influence on the prevailing attitudes toward individuals with SUDs and the type and quality of treatments available to them. There is promising momentum for an increased emphasis in the field of social work on the use of evidence-based and best practices to more effectively treat patients. To the extent that social workers embrace this movement, the field as a whole serves to gain tremendous credibility as an equal partner in the helping professions. Social work programs can facilitate the adoption of an EBP framework by teaching future practitioners, academicians, and administrators about how to critically analyze research literature, how to implement EBPs, and how to disseminate practices in community agencies.

Counselor Training and Education

The majority of substance abuse treatment in the United States is provided in addiction specialty care centers. Counselors comprise the greater part of the work force in these centers and they provide most of the behavioral treatments. In the broader context of behavioral health care, counselors are a distinct professional group with a defined academic and training curriculum, competency, and licensure standards. In the addiction treatment field, the term counselor is used as a job title for individuals with a wide range of backgrounds who provide counseling services. These counseling positions are occupied by individuals with a variety of backgrounds including professional counselors, social workers, or individuals who enter the addiction workforce due to life experiences rather than academic and professional training. Historically, many of the counselors working in addictions are themselves recovering from alcohol and/or drug dependence. Proponents of a recovering addiction treatment workforce suggest that recovering persons may possess a special empathy for drug-dependent patients that makes them

particularly effective in working with this population. Critics of this view claim that many of these "recovering" professionals may hold strong bias as a result of their own experience, insisting that their approach is the only or the best, which may limit their effectiveness. Just as the patients presenting for addiction treatment are a diverse population so are the environments in which treatment is provided and so also is the counseling workforce that provides a great deal of that treatment.

Licensure and Certification Issues

While legal requirements and standards for credentialing of substance abuse and mental health counselors in the United States are established at the individual state government level, there are national and international efforts to support the adoption of ACC and to standardize certification testing for substance abuse counselors. The International Certification and Reciprocity Consortium (IC&RC) was formed in 1981, with a mission to advance reciprocal competency standards for substance abuse professionals and to support the member certification/licensure boards. The IC&RC currently reports that over 37,000 alcohol and drug abuse counselors are certified by over 73 member certification boards. In 2007, the IC&RC board voted to stop using the oral case presentation method (CPM) and instead revised the written examination to cover questions of competency in the core functions, which were previously addressed in the CPM.

The National Association for Addiction Professionals was founded in 1972, as the National Association of Alcoholism Counselors and Trainers (NAACT), and later became the National Association for Alcoholism and Drug Abuse Counselors (NAADAC) in 1982. The primary objective of NAADAC is to develop a field of counselors with professional qualifications and backgrounds. In 1990, concerned with the lack of national standards and the confusion caused by numerous acronyms used by state certification boards, NAADAC developed a national certification that required applicants to be certified at the state level, pass a national examination, and have an academic degree. This was the first time in the addiction counselor credentialing process that academic degrees were paired with competencies as a basis for certification. They now offer three levels of national certification for addiction counselors, which are commensurate with education, hours of work experience, contact hours, and length of supervised experience. They also offer a Tobacco Addiction Specialist (TAS) certification.

Role of the Specialty in Addiction Treatment and Training within and Across Specialties

As the addiction treatment delivery system changes, the roles, skills, and knowledge required by counselors will also change. There are current efforts focused on broadening the availability of addiction treatment services beyond the specialty-care settings. Primary-care physicians have a unique opportunity to identify substance abuse in individuals who are seeking care for other medical problems. Traditionally, physicians have been reluctant to address these issues due in part to the lack of resources to treat substance abuse problems once they are identified. Increasingly substance abuse services such as identification, referral, and monitoring are being addressed in primary care settings by having counselors available in the primary care setting or by developing close collaborative relationships to provide linkage to those services off-site. These settings require new knowledge and skills to address early detection and motivating non–treatment-seeking individuals. These practices are significant because they show considerable promise for extending the benefits of substance abuse treatment to populations that currently do not access treatment.

Conclusion

Counselors play a critical role in the delivery of addiction care. The distinction *counselor* has developed more as a job than as a profession within the substance abuse field and the training and certification standards reflect this vocational emphasis. Much of the required training for substance abuse counselors is based on a job analysis of the functions performed by individuals in these positions, and historically less emphasis has been placed on specialized knowledge. While the Substance Abuse Mental Health Service Administration's Treatment Improvement Protocol 21 (SAMHSA TIP) provides a comprehensive guide to the development of training for addiction counselors, it also documents the substantial gap between these standards and the actual and needed competences of addictions professionals in the field. State, national, and international efforts to develop and evaluate uniform minimum competency standards have helped the addiction counselor job progress into a profession. However, the gap between science and practice in addiction care highlights a critical challenge presented by the lingering apprentice model of addiction counselor development. Academic preparation and professional training activities for addiction counselors will need to become more comprehensive and provide greater continuity to develop the capacity to integrate science-based improvements into the treatment of addiction.

Other Mental Health Professionals

In general when we think of treatment of individuals with SUDs, the primary focus is on the role of physicians. However, the treatment of individuals with SUDs requires a complex coordinated team, a multidisciplinary group. In order to maximize the professional team's efficiency and efficacy, it is vital that the role of each member of the group is structured and understood.

There is minimal research literature on the role of nonphysician professionals in the substance abuse treatment team. Addressing their role requires an in-depth understanding of the type of standardized training that exists for these professionals. Only then is it possible to suggest modalities for improving the contribution of individual professional groups and that of the overall team. The range of settings in which treatment is provided further complicates the professional roles. These range from the emergency room, acute inpatient detoxification, to 2-year treatment facilities in therapeutic communities. Furthermore, the role of these nonphysician health professionals may vary with setting. They probably play a major role in community settings. This is likely due to the difficulty of recruiting physicians in community clinics. It is important that all members of these professional groups are provided with the right balance of mental health and substance abuse training for their level and range of practice. Therefore, the field must provide high-quality appropriate training within each profession. The role of these professionals is not limited to treatment and a number of them. There is no standard homogeneous education/training available to educate and train other addiction health professionals. However, there are limited fellowship, workshops, and training available for the other professionals in the field of addiction. Some of this training or certification are recommended or approved by specific state or professional organizations. Some institutes offer fellowship or other training for all other professionals, occupational therapists, nurses, and chaplains.

Physician Assistants

Definition

A physician assistant (PA) is a midlevel medical practitioner who works under the supervision of a licensed physician. The PA came about in the 1960s as a response to the need for more clinicians (there was a shortage of family physicians) and to improve access to care. The first

PA program was developed by Dr. Eugene Stead, chairman of the Department of Medicine at Duke University, to train PAs for rural areas with dwindling numbers of physicians and nurses. Although there is not yet a requirement to hold a degree beyond the bachelor's level, most PAs have a master's degree.

Education and Training

The National Commission on Certification of Physician Assistants accredits PA training programs. Each state in the United States has its own specific licensing and practicing restrictions for PAs. Most states require PAs to pass the certification examination of the National Commission on Certification of Physician Assistants.

To practice as a PA, most states require a master's degree and a degree from an accredited PA program. Candidates must meet state requirements pertaining to a PA.

Most PA programs have little training in the area of addiction. During their clinical rotation series, students usually train for 6 to 10 weeks in the area of behavioral science, which may or may not include addiction medicine. PA students must often use elective time during school to obtain training in addiction principles. PAs interested in addiction medicine may require extra training in addiction prior to encountering patients. Few PA programs offer specific postgraduate training in addiction medicine, complicating a PA's path to becoming involved in addiction treatment. Some national courses exist to train PAs in addiction principles. A national society for PAs involved in addiction medicine offers opportunities for continuing education and networking.

Role and Scope

PAs evaluate patients under the supervision of a licensed physician. Although the physician need not be present during the time the PA performs his or her duties, there must be a method of contact between the supervising physician and the PA at all times. The PA must be competent in the duties he or she is performing, and the physician for whom the PA is working must also be licensed and trained to perform the relevant duties. Examples of the duties of a general PA include

- Medical histories and physical examinations: a PA can usually perform histories and physical examinations that do not go beyond a particular level.
- Laboratory tests: a PA can order any test which he or she is competent to interpret and provide the appropriate treatment.
- Follow-up: PAs follow patients through their hospital course, their course of treatment in a clinic setting, and so on.

Many private insurers and health plans sometimes require advanced degrees and/or certifications for PA specifically in behavioral health as a prerequisite for payment. Some companies do not pay for services delegated to PAs, even if the delegated service is within the PA's legal scope of practice.

Counselors

Definition

A *licensed chemical dependency counselor* (LCDC) provides counseling and education for substance abuse problems, but may not diagnose or provide official treatment.

Education and Training Requirements

A high school diploma is usually required to work in this field. Counselors generally are trained on the job. Training programs vary in length from 6 weeks to 2 years. Some colleges also offer training programs for counselors. These programs usually last 2 years and include courses on

the effects of alcohol and other drugs. Students may also learn crisis intervention—a way of handling emergency situations. Graduates are usually awarded an associate's degree. Students may also obtain certification from the National Board for Certified Counselors. For some positions, a bachelor's degree or higher in sociology, psychology, or a related field may be required. An increasing number of substance abuse counselors are obtaining master's degrees in mental health counseling.

Evaluation of Competency and Ethical Conduct The individual signs an affidavit to abide by the canon of ethical principles and arranges to have three individuals complete an evaluation of competency and ethical conduct on his/her behalf. All evaluators must have direct knowledge of his/her work experience observed for a minimum of 6 months. One evaluator must be the individual's current clinical supervisor, one must be a Credentialed Alcoholism and Substance Abuse Counselor (CASAC) or hold reciprocal-level credential issued by another member of the International Certification and Reciprocity Consortium/Alcohol and Other Drug Abuse (ICRC/AODA). The third evaluator must be a qualified health professional with at least 1 year of experience in substance abuse treatment.

Work Experience

The individual must document a minimum of 6,000 hours (approximately 3 years) of supervised, full-time equivalent experience in an approved work setting as a provider or supervisor of direct patient services. A minimum of 2,000 hours must be paid. The work experience must have been obtained within 10 years prior to submission of application and include 18 consecutive months during the 5 years leading up to the application. The individual must have performed professional tasks, including, but not limited to, diagnostic assessment, evaluation, intervention, referral, substance abuse counseling in both individual and group setting. Furthermore, there is a need for a minimum weekly, on-site, and documented clinical supervision by a qualified health professional and must include a minimum of 300 hours of supervised practical training in 12 core functions performed for a minimum of 10 hours, under the supervision of a qualified health professional. Office of Alcoholism and Substance Abuse Services (OASAS) of New York State strongly recommends the majority of your work experience be devoted to the practice of substance abuse counseling.

In addition, the following academic degree substitutions may be claimed toward satisfying the 6,000-hour work experience requirement:

- A master's (or higher) degree in an approved human services field from an accredited college or institution may be substituted for the remaining 4,000 hours of work experience, provided that the 2,000 hours of paid work experience occurred within 5 years prior to submission of the application.
- A bachelor's degree in an approved human services field from an accredited college or institution may be substituted for 2,000 hours of work experience. A maximum of 2,000 hours of full-time equivalent voluntary or other nonpaid work experience (including a formal internship or formal field placement) that occurred within 5 years prior to submission of the application may also be claimed, providing it involved appropriately supervised direct patient services in an approved work setting.

Education and Training The individual must document education and a total of 350 hours of training. The minimum requirements include hours ranging from 45 to 150 in knowledge of alcoholism and substance abuse; training with focus on alcoholism and substance abuse counseling and assessment; clinical evaluation; treatment planning; case management; patient, family, and community education; and professional and ethical responsibilities. All these must have occurred within 10 years prior to date of submission of the application.

Long-distance learning is acceptable as long as the institution is OASAS-approved. However, no more than 30 hours of training through participation in conferences by professional organizations is acceptable. A formal internship or formal field placement may be claimed as work experience or education and training based on the academic credit associated with completion, but not both. One should calculate the need to claim a formal internship or formal field placement as either work experience or education and training.

Conclusion and Future Direction

Many disciplines serve within the substance use field; however, no standard/uniform curriculum, policies, or strategies exist to train professionals in the field of addiction. Fellowships and certification trainings are available; however, these programs do not necessarily follow any standard. These uncertain credentialing practices may contribute to the variable practice standards in addiction. PA training in addiction is limited, although the potential for PA service in the field is large. As is common among physician-extenders, PAs usually gain experience in this field through their regular encounter with addiction population. The in-school training in addiction for PAs and the opportunities for postgraduate training could be expanded and standardized to prepare PAs to work in the addiction field. Some addiction counselors receive education and training; however, standards vary from state to state in credentialing. Some standardized certificates exist, but most counselors remain uncertified. Statewide or nationwide certification practices could ensure that addiction counselors receive adequate basic training in counseling before encountering individuals with SUDs.

Suggested Readings

Baird C. Specialty certification: is it for you? *J Addict Nurs*. 2007;18(4):217–218.

Chossis I, Lane C, Gache P, et al. Effect of training on primary care residents' performance in brief alcohol intervention: a randomized controlled trial. *J Gen Intern Med*. 2007;22(8):1144–1149.

da Silva Cardoso E, Pruett SR, Chan F, et al. Substance abuse assessment and treatment: the current training and practice of APA division 22 members. *Rehabil Psychol*. 2006;51:175–178.

DiNitto, DM and McNeese, CA. Addictions and social work practice. In: DiNitto, DM and McNeese, CA, eds. *Social Work Issues and Opportunities in a Challenging Profession*. Chicago, IL: Lyceum Books, Inc. 2008:171–192.

Kerwin ME, Walker-Smith K, Kirby KC. Comparative, analysis of state requirements for the training of substance abuse and mental health counselors. *J Subst Abuse Treat*. 2006;30:173–181.

50 Forensics

The addiction specialist's role as expert in forensic matters has grown significantly over the past decades reflecting the growth of the accredited specialty of addiction psychiatry and addiction medicine and of the maturation of this subspecialty in general. Addiction specialists are being preferentially sought after by attorneys for consultation and expert testimony about the effects of intoxicant use instead of continuing to resort to general psychiatrists, psychologists, or other mental health professionals.

Being Qualified as an Expert

Although there are federal and state standards that govern expert testimony, there is little consistency between and within jurisdictions about the qualifications of expert witnesses. Determining who should be an expert witness for "psychologic" matters has been a difficult task for the courts. Often, decisions regarding who qualifies as an "expert" are made on pragmatic rather than jurisprudential grounds. Some courts have permitted (or precluded) a wide range of individuals, including case workers, police officers, and even lay witnesses, to testify about a variety of psychologic issues (including the question of sanity). Other courts have been unwilling to recognize the expertise of psychiatrists, physicians, psychologists, and others, and have refused to admit their testimony in selected matters. Examples include compulsive gambling, the effects of drugs on witness credibility, and satanic ritual murder.

Rationale for the Admission of Expert Testimony

The Federal Rule of Evidence 702 provides that "if scientific, technical, or other specialized knowledge will assist the trier of fact [judge or jury] to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise." Most states have a rule of evidence that parallels the Federal Rule of Evidence 702, although a few states have adopted different and confusing rules on this point. The states also have tended to follow Federal Rule of Evidence 704, which limits expert testimony to an explanation of the defendant's diagnosis and the characteristics of the disease or defect. This rule specifically precludes expert opinion on "whether the defendant did or did not have the mental state or condition constituting an element of the crime charged or of a defense thereto."

How the Law Views Expert Testimony

Under prevailing rules of evidence, the testimony of expert witnesses is presented to the court in the form of expert opinion. As such, it does not enjoy the same privileged status as "fact" testimony. It is up to the judge or the jury (the trier of fact) to evaluate the credibility, reliability, relevance, and applicability of any expert testimony introduced. Thus, even what is considered accepted medical "fact" is considered only "opinion" when expressed in expert testimony, and as such, it may be accepted, discounted, or rejected in whole or in part.

The Role of the Expert in Addiction Medicine

The professional mandate as an expert witness is to assist the court. It is important to remember that the role of the expert witness is not that of an advocate. The expert testimony responsibility is to provide the judge and jury with information that is truthful, intelligible, and clear and to offer opinions that are unbiased, carefully reasoned, and based on the expert's understanding of the facts in evidence.

The Pretrial Phase

The addiction specialist should make a preliminary assessment of all available background materials of prospective witnesses to identify any possible clinical (i.e., medical, neuropsychiatric, or addiction) issues that require investigation. The addiction specialist can also help the attorney to prepare for depositions by (a) drafting specific questions to be posed, (b) doing content and psycholinguistic analyses of taped or written evidence (e.g., statements or depositions made by the defendant or witnesses), and (c) suggesting strategies and tactics for conducting interviews or depositions. It is often important to interview family members, friends, former teachers, or others who may have particular knowledge or a different perspective of the defendant or witness.

The addiction specialist also can assist the attorney if the other side will be calling an addiction expert by (a) evaluating that expert's credentials, (b) anticipating the nature of the testimony, (c) analyzing the strengths and weaknesses of both expert positions, and (d) drafting appropriate questions for the attorney to ask in cross-examination.

The Trial Phase

The two most common types of cases in which an addiction specialist will be engaged in are those in which a person either is accused of having committed a crime while drug-involved (i.e., while experiencing the acute, subacute, chronic, or residual effects of previous intoxicant use, dependence, or withdrawal) or is on trial as the result of statements made to law enforcement officers or testimony given by witnesses who themselves are or have been drug-involved. Typically, the first type of case requires testimony about the nature and effects of intoxicant use on the defendant. Common issues include the impact of specific intoxicants on (a) the physical and mental ability to have committed the crime, (b) the state of mind required for the offense charged, or (c) the formation of the requisite intent. Other questions may involve the special issues of diminished capacity or insanity. The second type of case usually involves testimony about the effects of acute and/or chronic intoxicant use on cognition and memory, and how such use might affect the credibility of witnesses.

The Postconviction Phase

The postconviction phase, at sentencing, often offers the opportunity for the addiction expert's most valuable contribution to a case. During the sentencing phase, the rules governing the nature, content, form, and scope of expert testimony are far more liberal at this phase than at trial and most jurisdictions permit the defense to present evidence (including expert testimony) in support of mitigation during the sentencing process. At sentencing, an expert may be permitted to (a) discuss the defendant's entire intoxicant history, (b) comment on the influence of intoxicant use on the acts constituting the crime charged, (c) make prescriptive treatment recommendations, or (d) propose an alternative sentencing plan, such as providing for dispositions, for example, supervised release probation, community control (home confinement), or community service. In offering sentencing recommendations to the judge, it is important to be cognizant of the fact that the court has the awesome responsibility of balancing between the needs of the community for protection and justice and those of the defendant for treatment and rehabilitation.

Criminal Responsibility and Intoxicants

Although the connection between the use of intoxicants and crime has been universally recognized, the explosive increase in drug-related crime over the past two decades has had only minimal impact on substantive criminal law. The recognition (albeit equivocal) of substance use disorders (SUDs) as "diseases" and the growth of a professional field and industry around the field has had significant social and professional consequences and instructive (although surprisingly limited) effects on the legal rules.

Disease, Disorder, Defect, and Dysfunction

The addiction specialist must be prepared to confront the distinctions between "disease," "disorder," and "dysfunction." The first two terms have long and tortuous histories in the law of every jurisdiction, whereas the concept of cerebral "dysfunction" has virtually none. And yet, it is precisely in terms of cognitive, emotional, and behavioral dysfunction that one can best explain (and even quantify) the effects of acute, subacute, and chronic intoxicant use. Most defendants seeking to avail themselves of an intoxicant-based defense will have grossly normal findings on objective neuropsychiatric diagnostic tests as the electroencephalography, CT scan, or MRI scan. Even when administered using the latest enhanced techniques, these modalities are of limited value in demonstrating cerebral dysfunction. Although the newer brain imaging technologies, such as the quantitative electroencephalogram, single-photon emission computed tomography, and brain electrical activity mapping, promise considerable future utility, at present, valid norms for these modalities are still in the earliest stages of development, because the legal tests applied by the courts for the admissibility of scientific evidence based on "newer" technologies are strict and narrow. Historically, the courts are slow to recognize the evidentiary validity of emerging scientific technologies, although facilitation of integrating scientific knowledge and evidence-based practice (EBP) into forensic practices is an active topic of debate.

Use, Misuse, Abuse, Dependence, and Addiction

Terminology in the field of addictive disease remains an unsettled area. One might argue that substance dependence is a medical disease, whereas substance addiction is a social issue. It is crucial to be consistent with the use of terminology, making certain to define the usage of the term at the outset, recognizing that not all use qualifies as abuse. There is no reference to quantity of use within the definitions of abuse or dependence, but that has not stopped the lay public from assuming that any use of heroin constitutes abuse, whereas only high volumes of alcohol intake would amount to abuse. Use of a substance does not establish the presence of a disease, but it does establish the presence of potentially intoxicating effects.

The Elements of the Offense

Definitions of both common law and statutory crimes require the voluntary commission of a bad act or harmful omission (*actus reus*) in conjunction with a bad state of mind (*mens rea*). However, these fundamental concepts have resisted enduring definition. Most older common law crimes have been redefined in modern criminal statutes. Criminal codifications often use adverbial qualifiers such as "knowingly," "willfully," or "intentionally" to designate as voluntary an act performed consciously as the result of effort or determination.

The Exculpatory Doctrine in Common Law

Over time, scientific views of human behavior gradually supplanted moral ones. Concurrently, there was a substantial increase in the consumption of alcohol in all social and economic strata. In response to these societal changes, the common law evolved what came to be known as "the exculpatory doctrine." This doctrine permitted the presentation of evidence of specified mental conditions (including intoxication) in legal proceedings as a means of mitigating culpability, liability, or responsibility. Such evidence could be introduced in the form of an assertion of a defendant's insanity or lack of the "specific" intent required as an element of the offense charged. New and more difficult problems arose almost immediately.

The Enduring Problematic Concept of "Intent"

The early cases in which the exculpatory doctrine was applied involved alcohol intoxication. The courts gradually realized that "common sense" suggested that a distinction should be made between a crime committed by an intoxicated and a sober person. But traditional moral attitudes stigmatizing intoxication as a vice indicated the impropriety of complete exculpation. The criminal rules on "intent" provided an expedient, if inadequate, means of mediation.

The meaning of "intent" in the criminal law has always been obscure. Traditionally, intent was defined to include elements of both knowledge and volition. In the modern era, a statutory distinction generally is made between the mental states of knowledge and intent. Obviously, certain intoxicants, when used in certain ways by certain persons, affect certain cognitive, emotional, and behavioral functions in certain ways. Defining, distinguishing, and presenting these to the jury in nontechnical, readily intelligible language is the responsibility of the addiction expert. Successful communication of these clinical complexities to the jury by the expert is the cornerstone of a viable intoxicant-based defense.

The implicit public policy in the prevailing law reflects society's historical vacillation and expedient compromises between the punishment of intoxicant-influenced offenders in complete disregard of their condition (i.e., viewing them as ordinary criminals) and the total exculpation often suggested by the clinical evidence (i.e., viewing them as patients).

Intoxication as a Defense

Today, the effect of intoxication on criminal responsibility is well established but only precariously settled. At law, intoxication can be either (a) involuntary, where the intoxicant is ingested as the result of force or duress, deceit or trickery, medical advice, or lack of awareness of a susceptibility to a recognized atypical reaction to that substance, as in pathologic intoxication; or (b) voluntary, where the intoxicant is ingested for effect, as in recreational drug use. Many jurisdictions have recognized involuntary intoxication as a complete defense to criminal behavior in appropriate circumstances. Most jurisdictions, however, adhere to the view that voluntary intoxication does not excuse a criminal act unless the actor, because of his intoxication, could not form the intent required in the statutory definition of the crime. That is, voluntary intoxication may be raised to negative an element of an offense. Unfortunately, neither the distinctions between voluntary and involuntary intoxication nor those between general and specific intent are clear or consistent.

Dependence as a Defense

Dependence on an intoxicant, or active intoxication, does not provide a complete defense in any jurisdiction. The nature, course, and effects of dependence on specific substances on cognition, emotion, or behavior have not been recognized by the law.

Interestingly, opioid intoxication (but not dependence) may be of such extent as to negate the "knowingly" element of criminal intent. But neither opioid intoxication nor dependence has been held to negate the "willfully" element of criminal intent. Intoxication (but not dependence) induced by any substance may be sufficient to render a person incapable of the "deliberation" or "premeditation" required as an element of a specific degree of an offense, as in first-degree murder. In no jurisdiction has dependence on specific intoxicants been differentiated from that of alcohol, thereby warranting special consideration. Until recently, attempts to use dependence as a defense to criminal responsibility were couched in terms of insanity, by characterizing dependence or addiction as a mental disorder that rendered the defendant insane and therefore not criminally responsible. For the most part, these attempts have been unsuccessful.

Withdrawal as a Defense

Defenses based upon the argument that the criminal act at issue was the direct or indirect product of withdrawal from an intoxicant have not prevailed, except in the limited and infrequent circumstance where a defendant in withdrawal commits an act while semiconscious or unconscious. An action that, while purposive, is not spontaneous, and therefore is not voluntary, is defined at law as an "automatism" and does not incur criminal responsibility.

Intoxicant-Induced Insanity as a Defense

An insanity defense asserts that at the time the accused committed the act for which he or she is charged, a mental illness precluded him from having the required bad state of mind to be convicted of the act. The insanity defense has been a part of English and American jurisprudence for several hundred years. It reflects a shared belief that only those individuals who have chosen to commit wrongful acts should be punished, and that those without the capacity to appreciate the wrongfulness of their conduct should be absolved. The roots of the insanity defense are ultimately embedded in the Judeo-Christian tradition of linking moral responsibility with punishment and absolution.

Insanity that arises from either acute or chronic intoxicant use has not been distinguished from insanity produced by other causes. Thus, whether temporary insanity caused by voluntary intoxication will be exculpatory largely depends on the legal test for insanity used in that jurisdiction. Several states have statutorily excluded this defense.

The Concept of Partial Responsibility

Partial responsibility, or diminished capacity, is a difficult and muddled concept in the law, with little coherence or consistency. Many courts appear to reject or not understand it.

Insanity of the legal type is considered a complete defense to criminal acts in most jurisdictions. A mental disorder that constitutes "something less than insanity" is not considered a complete defense to a crime, but is widely thought to lessen the degree of criminal responsibility, at least for crimes where there is a lesser degree of responsibility or severity available (as in murder, which might be reducible from first degree to second or a lesser degree). Today, mitigation, not exculpation, is the most common application of the concept of diminished capacity.

Intoxicant Use and Effects as Mitigating Factors

Although many states now require judges to adhere to legislatively prescribed sentencing guidelines, in some jurisdictions judges have retained limited discretion to consider a convicted defendant's complete drug history (including intoxication and dependence) as a mitigating factor. However, it is a general rule that the nature, extent, and effects of the intoxicant history must be introduced into evidence before being eligible for consideration at sentencing. There are marked differences between jurisdictions regarding the type of evidence (expert testimony, corroborating witnesses, etc.) required or admissible to establish the extent and effects of intoxication in support of mitigation.

The Addictive Processes

The concept of behaviors involving addictive processes, rather than intoxicating substances, as in "compulsive" or "pathologic" gambling, is of exceptional theoretical importance for the criminal law and the addictions field. The concept has required a reexamination of many fundamental legal postulates, precedents, and assumptions about criminal responsibility and intentionality. If viewed as addictive disorders (as in "compulsive gambling") in which no exogenous intoxicating substance is ingested, such processes raise profound questions about the paradigms that inform research, theory, and practice in the addictions field. If viewed as impulse control disorders (as in "pathologic gambling"), these processes raise difficult questions about the causal and temporal relationships between a person's impulses and the acts issuing therefrom. Unfortunately, in recent years, addiction terminology has been used to refer to everything from Internet usage ("Internet addiction") to dedication to one's career ("workaholic"), thus lessening its applicability and meaning with respect to physiologic addictive disease. To lessen the potential for difficulties, precise usage of terminology is called for.

Pathologic Gambling

What we find in the fact patterns of cases involving pathologic gambling is not a total or even substantial incapacity to carry out simple (or even complex) acts that can be reasonably attributed to the "disease." Nor do we find such a compromise of intellectual function as to entirely exclude purposeful conduct. Instead, we observe an apparent blunting of ethical sensitivity sufficient to destroy the understanding, appreciation, or regard for the moral quality of the criminal act, combined with a drastic, often protracted, lapse of inhibition. Rarely do we find a lapse of conscious awareness of the criminal act itself. Because pathologic gambling is a chronic disorder with a recognizable natural history, these mental elements typically can be identified before, during, and after the crime is committed. In this sense, the problem behavior seen in pathologic gambling is more like a process than like a state. In its effects, it more closely resembles "insanity" of both legally recognized varieties—the inability to distinguish right from wrong or the inability to resist an impulse—than it does any state of intoxication. Before being widely rejected, the "capacity to conform" test for an insanity defense highlighted the problem of defining a "mental disease or defect." The *Freeman* court held that "an abnormality manifested only by repeated criminal or otherwise anti-social conduct" was not a disease.

Clinical and Forensic Distinctions

It is recognized clinically that at least some compulsive gamblers who commit crimes are impaired physically and psychologically, and thus may be only partially responsible for their misconduct. In this sense, at law they resemble the inebriate, whose reason has been temporarily compromised; and for them the rules governing intoxication often seem more applicable than do those for insanity. Although they are only very rarely psychotic, and only a few may

even be neurotic, they are nonetheless considered abnormal by many clinicians, even though in ways of questionable relevance. Hence, for this subgroup of "impaired" compulsive gamblers, neither complete exculpation nor full responsibility seems appropriate. One might argue that as applied to pathologic gamblers who commit crimes, the legal rules should be applied not in terms of lack of intent, but in terms of lack of understanding of the ethical quality of the act and/or the ability to control behavior. But the legal rules have not adopted this view. The link between compulsive gambling and a criminal offense is too tenuous to permit the court to find that the defendant lacks substantial capacity to conform his behavior to the requirements of the law as a result of his compulsive gambling disorder.

Sexual Addiction

In recent years, the diagnosis of "compulsive sexuality" or "sexual addiction" has been offered as the basis for exculpation or mitigation in cases involving sexual, as well as less obviously related, offenses. A few courts have admitted expert testimony about this controversial condition. In no jurisdiction has such a defense prevailed. A number of courts have admitted a defendant's alleged "sexual addiction" as a mitigating factor at sentencing. Limited treatment programs (most based on 12-step or other self-help principles) are available in the federal prison system and in that of most states.

Eating Disorders

There have been a few cases involving shoplifting and petty theft from groceries where an eating disorder (bulimia) was advanced as a defense. In none of these cases did the defense exculpate the accused. In two cases, after the defendants were convicted of the crimes charged, the sentencing judge recognized the eating disorder as a legitimate "mental disorder" that constituted a valid mitigating factor. Both defendants were sentenced to community supervision and service and to mandatory professional treatment instead of incarceration.

Compulsive Spending or Shopping

Recently, support groups based on 12-step principles and other self-help models have emerged for persons with the "diseases" of "compulsive spending" and "compulsive shopping." Advocates in these movements have adopted or endorsed addiction-derived explanations, language, and treatment approaches for these problems. The application of an addiction paradigm to these behaviors is of dubious validity, and neither problem has been widely recognized as an addictive disorder by professionals in the field.

Criminal defenses based on the "diseases" of compulsive spending or shopping have been rejected by the courts. In a few cases involving petty theft and shoplifting, expert clinical testimony about these excessive behaviors, although admitted, had little mitigatory impact at sentencing.

The Effects of Intoxicants on Memory

Expert Testimony about the Memory of Witnesses

Human memory is a complex phenomenon. One would expect the literature on the effects of intoxicants on human cognition, particularly memory, to be extensive—it is not. In cases where the defendant has been accused by persons who are or have been drug-involved, an expert must

assess the potential impact of their intoxicant use on their credibility as witnesses. The focus must be on the effect of the relevant intoxicant(s) on memory and its constituent cognitive processes. To be an effective expert in this area, the addiction specialist requires a broad and deep understanding of human memory. Authoritative texts on research and theory about human memory written from both the clinical and legal perspectives need to be studied closely.

Cocaine-Related Memory Dysfunction in Criminal Proceedings

Although any of the intoxicants can have potentially deleterious effects on selected memory functions, the effects of cocaine raise the most serious and frequent concerns. A significant number of today's large-scale cocaine trafficking cases are founded principally or solely on the testimony of alleged or self-styled coconspirators, who, more often than not, were themselves using large amounts of cocaine (and usually other intoxicants as well) during the period about which they will testify in great detail as to time, place, person, sequence, and events. In evaluating the credibility of such witnesses, it is critical to look for any possible effects of intoxicant use on their memory functions. It is always important and often productive to look for predicates and indicia of (cocaine-induced) confabulation that may taint their testimony. To establish the possibility that testimony may contain confabulated elements and therefore be subject to "reasonable doubt," it is necessary to assess the circumstances, frequency, extent, and detail of the witness's prior statements, depositions, narratives, or conferences with the authorities. Evidence of high-dose cocaine use, extensive "testimonial schooling," and progressively detailed and inclusive recall provides a sufficient predicate for an addiction medicine expert to consider reasonably and responsibly the possibility that confabulation is present.

The Phenomenon of Confabulation

Confabulation is a neuropsychiatric symptom that is characteristic of diffuse organic brain disease and/or dysfunction. It refers to the unconscious filling in of memory gaps by imagined experiences, fabricated stories, or grossly distorted accounts of recent or remote events. It is absolutely distinct from lying, which implies both motive and awareness of the distortion or untruth. Confabulatory recall is inconsistent; it may change from moment to moment; and it may be induced unwittingly by suggestion. Characteristically, isolated events and information from the past are retained in fragmented form but are at times related without regard for the intervals that separated these or for their proper temporal sequence. Sometimes, in confabulating, a person will telescope events, compressing time, thereby linking as cause and effect events that were widely separated in time and causally unrelated. These memory fragments may be cued, intentionally or unintentionally, during conversation (a) by suggestion, (b) by presentation of selected data about recent or remote events as if it were unequivocal fact, or (c) by provision of a cogent, internally consistent narrative explanation of some situation or event. The dysfunctional brain, in an attempt to maintain consistency with this apparent "reality," may fill in any memory gaps with associative, derivative, or suggested data.

Cocaine-Induced Confabulation

Confabulation may be seen in two phases of high-dose cocaine use. During the acute intoxication phase, the profound confusion, grandiosity, emotional lability, false sense of mastery, illusions, delusions, and hallucinations occasionally can induce certain users to confabulate "in real time." During the convalescent phase, after a period of abstinence from cocaine, the person gradually recalls fragments of past experience (many of which may have been originally misperceived) in a distorted way. In an attempt to preserve logical consistency, these may be linked with confabulated material. The more often such confabulated material is ratified by the social setting and in particular by authority figures (e.g., physicians, attorneys, or law

enforcement officers), the more likely it is to become a fully integrated and unquestioned part of that person's self-history. It even may go on to become the basis for future thoughts, conclusions, and actions.

Regulatory and Administrative Proceedings

Members of licensed, regulated, or otherwise supervised professions (e.g., health-care professionals, attorneys, airline pilots, interstate truckers) can find their licenses at risk for a number of reasons involving intoxicants. Two, however, are of exceptional importance and are discussed here: (a) allegations of "impairment" consequent to intoxicant use and, (b) for physicians, allegations of the "inappropriate" prescribing of opioids for the long-term management of chronic nonmalignant pain. In cases involving professional impairment, it has identified two fundamental and very serious medical–legal issues: (a) the common presumption that "use equals abuse equals addiction equals impairment" and (b) that only a few regulatory agencies (e.g., the Federal Aviation Administration for pilots and the Department of Transportation for interstate truck drivers) have normative data defining the cognitive, sensory, or motor skills required of a normal, that is, a "nonimpaired" practitioner. With the exception of the blood alcohol concentration, which, as a matter of public policy, has been adopted in every state as an objective, affirmative indicium of impairment for the operation of a motorized vehicle, there are no similarly established norms for any other intoxicants, nor for alcohol-mediated impairment in other contexts.

Professional Impairment

In the assessment of professional impairment, regulatory policies do not reflect the clinically significant, specific differences between intoxicants in terms of their effects, patterns of use, routes of administration, nature of the dependence and/or withdrawal syndromes (if applicable), or resultant substance-related disabilities. Although there are a few regulatory and legal cases where (limited) consideration was given to these crucial distinctions, such deliberations are clearly the exception, not the rule.

All too often the proverbial deck is stacked against the accused professional, who, upon being accused of even the mere use of an intoxicant, is presumed to be impaired consequent thereto. Contrary to the traditions of Anglo-American jurisprudence, the accused professional then has the effective burden of proving his or her "innocence" in the face of the presumption of guilt. These prosecutions are invariably legitimized and justified as necessary to protect patients or clients, institutions, or professions from the harmful actions of impaired practitioners. But in practice, the hearing panels are often biased, punitive, and easily influenced by professional or institutional interests and politics. Even the isolated or occasional use of an intoxicant is often conflated with impairment, and harsh sanctions are imposed. If the accused admits to any use of intoxicants, impairment is usually presumed. If the accused denies use of intoxicants, the conclusion that accused is in "denial" will likely be drawn and considered as evidence of "addiction" and, consequently, of "impairment."

Prescribing Opioids for Pain in Private Practice

Each year the prescribing profiles for controlled substances (class II opioids, in particular) of thousands of physicians are routinely (often automatically) monitored, sampled, or otherwise scanned, and evaluated by state regulatory bodies. Despite the dubious ethics and questionable purposes/efficacy of such monitoring programs, these practices are increasingly being "justified" by state regulatory bodies in the name of public health and safety, which

are (presumptively) privileged over issues of individual privacy and confidentiality. The legal authority for these actions and the regulation of opioid prescribing for pain is provided by health (medical) practice acts legislated at the state level and by federal and state acts governing the use of controlled substances. Hundreds of physicians whose prescribing profiles are deemed "questionable" are then more thoroughly investigated. Such investigations and prosecutions may be initiated by even the brief treatment of a single patient! Of course, there are physicians whose prescribing of opioids is clinically inappropriate and/or unethical. Some in this group simply lack adequate current knowledge about the indications for opioid analgesia and/or the rational choice of appropriate opioid agents. Others are motivated by simple greed or sexual interest. Others are innocently duped, manipulated, or otherwise pressured by cunning and/or demanding patients.

The two most frequent bases upon which regulators found allegations that a physician's use of long-term opioid therapy for chronic, nonmalignant pain is inappropriate are that such therapy "creates addicts" and that opioid therapy is contraindicated in any patient with a history of substance abuse. Both assertions are highly controversial, and the underlying assumptions, concerns, and issues of both have been comprehensively examined and challenged by specialists in pain management and addiction medicine. In any event, every chronic pain patient being considered for long-term opioid therapy must undergo a comprehensive, multidimensional evaluation, which must include an analysis of their (a) pain (etiology, history, character), (b) prior experience with all modalities of pain management (including opioids), and (c) prior and current use of all classes of psychoactive drugs, prescribed or otherwise. The clinician in the pain clinic, private practice, or other settings must make a conscious effort to identify prior or current addictive disease, and must also attempt to identify those patients who are in active recovery.

For even the most-knowledgeable, best-intentioned, and best-prepared practitioner accused of opioid prescribing violations, exculpation is by no means assured, and ultimate vindication should never be assumed. However, documentation of the following material in the medical record often has proved to be the pivotal element in the successful defense of such cases:

1. A comprehensive evaluation and assessment of the etiology, history, and character of the patient's pain.
2. Clinical records or summaries from the specialists or subspecialists who have diagnosed and treated the primary medical or surgical conditions thought to be producing the patient's pain.
3. An appropriately executed (signed, witnessed, and notarized) document of the patient's "informed consent to treatment with opioid drugs." Because the law on informed consent varies substantially from state to state and is subject to increasingly frequent review and revision, this critical document must be drafted in close consultation with an attorney who is experienced and absolutely up to date in this area of the law.
4. Frequent multidimensional assessment and documentation of the efficacy of opioid therapy, the absence of drug toxicity, and the absence of indicia of "addiction" (including periodic urine toxicology screening). Multidimensional assessment of the frequency and distress illuminates the impact of symptoms and the efficacy of treatment on a patient's quality of life.
5. Annual (or more frequent if indicated) "letters of indemnification" from an appropriate surgical or medical specialist stating that the specialist has reexamined the patient found that the underlying medical or surgical condition is still present and/or unchanged, that there have been no treatment innovations or technological breakthroughs from which the patient might be expected to benefit, and that therefore continued management of the patient's pain is clinically justifiable.

6. If the physician prescribing the opioids is not a credentialed expert or specialist in either pain management or addiction medicine, letters of consultation from a specialist in both of these areas are essential. Moreover, even if the prescribing physician is an expert in one of these two areas, a consultation letter from an expert in the other area is critical.
7. It is early yet to determine whether the availability of buprenorphine for the office-based practitioner will lead to significant legal difficulties. However, given the strict supervision being administered in terms of specialized Drug Enforcement Agency (DEA) certification, specialized training requirements, and limitations on patient quantity, it is certainly likely to be a closely examined process.

Administrative Proceedings

The effects of intoxicants of different classes have not been differentiated in administrative hearings or other proceedings involving employment eligibility, benefits, restriction, discrimination, supervision, discipline, or termination. In these venues, as in professional regulatory contexts, the prevailing presumption reflects the false and dangerous syllogism that "use equals abuse equals addiction equals impairment." Moreover, routine screening for intoxicant use in the workplace is technically problematic as well as legally and ethically questionable. Well-established principles of administrative law procedure are often violated and fundamental legal rights (e.g., due process) often ignored. Despite their being treated like criminal "defendants," the accused in these proceedings are neither guaranteed adequate legal representation nor provided with the funds and resources (e.g., expert witnesses) necessary to present an adequate defense. Data and conclusions from questionably valid screening protocols and dubious testing methods and procedures often go unchallenged. It is vital that an addiction medicine specialist (preferably one with added qualifications as a medical review officer) (a) reviews all of the technical data, (b) examines the accused to assess the nature and extent of any intoxicant-related problems or disabilities that might be relevant to job performance, and (c) provides testimony to the administrative review body to explain the meaning, significance, and implications of the findings. There is no other way to assure fairness for all parties.

Given the cultural prejudices about intoxicant use and the pressures on employers to maintain a "drug-free workplace," an employee who is accused of intoxicant use cannot safely assume that he or she will get a fair hearing or receive an equitable disposition. Addiction medicine specialists must be aware of these prevailing inequities. The need and opportunities for professional involvement in intoxicant-related matters of administrative law are great.

Conclusion

Forensic issues involving addiction psychiatry encompass a wide range of problems within a complex clinical and biopsychosocial context. Substance-related problems with forensic implications may range from problems originating from an occasional problematic use to SUDs, such as abuse or dependence and a vast array of substances. Areas of forensic psychiatry may involve criminal, civil and administrative, professional, and monitoring issues. The forensic arena presents a set of specific definitions, requirements, and criteria that the addiction specialist experts should become familiar with, including the role, expectations, and the court's consideration and view of the latitude of the expert testimony throughout the different phases of the trial. The role of the addiction expert in forensics has become essential, given the expanding knowledge in the field of addiction psychiatry and substance use, the secular increase in the prevalence of substance abuse, and the periodic introduction of new trends of patterns

and types of substance abuse. The multiplicity of conceptual problems in this field reflects the complexity of the historical and contextual social determinants that shaped these concepts over time. New discoveries in sciences and the interdisciplinary collaboration between the practitioners of law and the doctrines of jurisprudence and medical addiction sciences may ultimately help clarify these conceptual issues, although this may occur at what has been a slow pace. Practicing in the forensic arena presents a wide array of significant challenges for the addiction specialists; some of them, such as heightened adversarial role, are at odd with the predominant "helping" attitudes of the health profession. Other significant challenges include working within the constricting rules of criminal proceedings or facing ethical concerns, opinions, attitudes, and values. On the other hand, addiction experts, adhering to their role, may be instrumental in clarifying the many lingering stigmatizing misconceptions and help bring into focus modern concepts, based on knowledge and objective considerations, which would ultimately enhance the function of justice.

Suggested Readings

Fishbain D, Johnson S, Webster L, et al. Review of regulatory programs and new opioid technologies in chronic pain management: balancing the risk of medication abuse with medical need. *J Manag Care Pharm*. 2010;16(4):276–287.

Glancy GD, Saini M. The confluence of evidence-based practice and Daubert within the fields of forensic psychiatry and the law. *J Am Acad Psychiatry Law*. 2009;37(4):438–441.

Heffernan TM. The impact of excessive alcohol use on prospective memory: a brief review. *Curr Drug Abuse Rev*. 2008;1(1):36–41.

Silva JA. Forensic psychiatry, neuroscience, and the law. *J Am Acad Psychiatry Law*. 2009;37(4):489–502.

Victor TW, Alvarez NA, Gould E. Opioid prescribing practices in chronic pain management: guidelines do not sufficiently influence clinical practice. *J Pain*. 2009;10(10):1051–1057.

INDEX