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01 - 20.1 Introduction and Overview

20.1 Introduction and Overview

Substance Use and Addictive Disorders 20.1 Introduction and Overview The most commonly used drugs have been part of human existence for thousands of years. For example, opium has been used for medicinal purposes for at least 3,500 years, references to cannabis (marijuana) as a medicinal can be found in ancient Chinese herbals, wine is mentioned frequently in the Bible, and the natives of the Western Hemisphere smoked tobacco and chewed coca leaves. As new drugs were discovered and new routes of administration developed, new problems related to their use emerged. Substance use disorders are complicated psychiatric conditions and like other psychiatric disorders, both biological factors and environmental circumstances are etiologically significant. This chapter covers substance dependence and substance abuse with descriptions of the clinical phenomena associated with the use of 11 designated classes of pharmacological agents: alcohol; amphetamines or similarly acting agents; caffeine; cannabis; cocaine; hallucinogens; inhalants; nicotine; opioids; phencyclidine (PCP) or similar agents; and a group that includes sedatives, hypnotics, and anxiolytics. A residual 12th category includes a variety of agents not in the 11 designated classes, such as anabolic steroids and nitrous oxide. TERMINOLOGY Various terms have been used over the years to refer to drug abuse. For example, the term dependence has been and is used in one of two ways when discussing substance use disorders. In behavioral dependence, substance-seeking activities and related evidence of pathological use patterns are emphasized, whereas physical dependence refers to the physical (physiological) effects of multiple episodes of substance use. Psychological dependence, also referred to as habituation, is characterized by a continuous or intermittent craving (i.e., intense desire) for the substance to avoid a dysphoric state. Behavioral, physical, and psychological dependence are the hallmark of substance use disorders. Somewhat related to dependence are the related words addiction and addict. The word addict has acquired a pejorative connotation that ignores the concept of substance abuse as a medical disorder. Addiction has also been trivialized in popular usage, as in the terms TV addiction and money addiction; however, the term still has value. There are common neurochemical and neuroanatomical substrates found among all addictions, whether it is to substances or to gambling, sex, stealing, or eating. These various

addictions may have similar effects on the activities of specific reward areas of the brain, such as the ventral tegmental area, the locus ceruleus, and the nucleus accumbens. Other Terms Codependence. The terms coaddiction and, more commonly, codependency or codependence are used to designate the behavioral patterns of family members who have been significantly affected by another family member's substance use or addiction. The terms have been used in various ways and no established criteria for codependence exist. Enabling. Enabling was one of the first, and more agreed on, characteristics of codependence or coaddiction. Sometimes, family members feel that they have little or no control over the enabling acts. Either because of the social pressures for protecting and supporting family members or because of pathological interdependencies, or both, enabling behavior often resists modification. Other characteristics of codependence include unwillingness to accept the notion of addiction as a disease. The family members continue to behave as if the substance-using behavior were voluntary and willful (if not actually spiteful), and the user cares more for alcohol and drugs than for family members. This results in feelings of anger, rejection, and failure. In addition to those feelings, family members may feel guilty and depressed because addicts, in an effort to deny loss of control over drugs and to shift the focus of concern away from their use, often try to place the responsibility for such use on other family members, who often seem willing to accept some or all of it. Denial. Family members, as with the substance users themselves, often behave as if the substance use that is causing obvious problems were not really a problem; that is, they engage in denial. The reasons for the unwillingness to accept the obvious vary. Sometimes denial is self-protecting, in that the family members believe that if a drug or alcohol problem exists, then they are responsible. As with the addicts themselves, codependent family members seem unwilling to accept the notion that outside intervention is needed and, despite repeated failures, continue to believe that greater willpower and greater efforts at control can restore tranquility. When additional efforts at control fail, they often attribute the failure to themselves rather than to the addict or the disease process, and along with failure come feelings of anger, lowered self-esteem, and depression. A summary of some key terms related to substance use disorders is given in Table 20.1-1. Table 20.1-1 Terms Used in Substance-Related Disorders

EPIDEMIOLOGY The National Institute of Drug Abuse (NIDA) and other agencies, such as the National Survey of Drug Use and Health (NSDUH), conduct periodic surveys of the use of illicit drugs in the United States. As of 2012, it is estimated that more than 22 million persons older than the age of 12 years (about 10 percent of the total US population) were classified as having a substance-related disorder. Of this group, almost 15 million were dependent on, or abused, alcohol (Fig. 20.1-1). FIGURE 20.1-1 Substance dependence or abuse in the past year among persons age 12 or over: 2002– 2012. (From Substance Abuse and Mental Health Services Administration, Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH

Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.) Figure 20.1-2 shows data from the surveys on the percentage of respondents who reported using various drugs. In 2012, 669,000 persons were dependent on, or abused, heroin; 1.7 percent (4.3 million) abused marijuana; 0.4 percent (1 million) abused cocaine; and 2 million were classified as dependent on, or abuse of, pain relievers. FIGURE 20.1-2 Dependence on, or abuse of, specific illicit drugs within the past year among persons age 12 or older: 2010. (From Substance Abuse and Mental Health Services Administration,

Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.) With regard to age at first use, those who started to use drugs at an earlier age (14 years or younger) were more likely to become addicted than those who started at a later age. This applied to all substances of abuse, but particularly to alcohol. Among adults aged 21 or older who first tried alcohol at age 14 or younger, 15 percent were classified as alcoholics compared with only 3 percent who first used alcohol at age 21 or older. Rates of abuse also varied according to age (Table 20.1-2). In 2012, the rate for dependence or abuse is highest among adults age 18 to 25 (19 percent) compared to youths age 12 to 17 (6 percent) and adults age 26 or older (7 percent). After age 21, a general decline occurred with age. By age 65, only about 1 percent of persons have used an illicit substance within the past year, which lends credence to the clinical observation that addicts tend to “burn out” as they age. Table 20.1-2 Illicit Drug Use in Lifetime, Past Year, and Past Month, by Detailed Age

Category: Percentages, 2011 and 2012 Table 20.1-3 summarizes data about the demographic characteristics of those who use illicit drugs. More men than women use drugs; the highest lifetime rate is among American Indian or Alaska Natives; whites are more affected than blacks or African Americans; those with some college education use more substances than those with less education; and the unemployed have higher rates that those with either part-time or fulltime employment. Table 20.1-3 Illicit Drug Use in Lifetime, Past Year, and Past Month among Persons Aged 18 or Older, by Demographic Characteristics: Percentages, 2011 and 2012

Rates of substance dependence or abuse varied by region in the United States. In 2010, rates were slightly higher in the West (9 percent) and Midwest (9 percent) than in the Northeast (8 percent) and South (8 percent). Rates were similar in small metropolitan counties and large metropolitan counties (both at 9 percent) and were lowest in completely rural counties (7 percent). Rates are also higher among persons on parole or on supervised release from jail (34 percent vs. 9 percent). The number of persons driving while under the influence of drugs or alcohol is on a decline. The percentage driving under the influence of alcohol decreased from 14 percent in 2002 to

11 percent in 2010, and those driving under the influence of drugs decreased from 5 percent to 4 percent during the same period. A comprehensive survey of drug use and trends in the United States is available at www.samhsa.gov. ETIOLOGY The model of substance use disorders is the result of a process in which multiple interacting factors influence drug-using behavior and the loss of judgment with respect to decisions about using a given drug. Although the actions of a given drug are critical in the process, it is not assumed that all people who become dependent on the same drug experience its effects in the same way or are motivated by the same set of factors. Furthermore, it is postulated that different factors may be more or less important at different stages of the process. Thus, drug availability, social acceptability, and peer pressures may be the major determinants of initial experimentation with a drug, but other factors, such as personality and individual biology, probably are more important in how the effects of a given drug are perceived and the degree to which repeated drug use produces changes in the central nervous system (CNS). Still other factors, including the particular actions of the drug, may be primary determinants of whether drug use progresses to drug dependence, whereas still others may be important influences on the likelihood that drug use (1) leads to adverse effects or (2) to successful recovery from dependence. It has been asserted that addiction is a “brain disease,” that the critical

processes that transform voluntary drug-using behavior to compulsive drug use are changes in the structure and neurochemistry of the brain of the drug user. Sufficient evidence now indicates that such changes in relevant parts of the brain do occur. The perplexing and unanswered question is whether these changes are both necessary and sufficient to account for the drug-using behavior. Many argue that they are not, that the capacity of drug-dependent individuals to modify their drug-using behavior in response to positive reinforcers or aversive contingencies indicates that the nature of addiction is more complex and requires the interaction of multiple factors. Figure 20.1-3 illustrates how various factors might interact in the development of drug dependence. The central element is the drug-using behavior itself. The decision to use a drug is influenced by immediate social and psychological situations as well as by the person's more remote history. Use of the drug initiates a sequence of consequences that can be rewarding or aversive and which, through a process of learning, can result in a greater or lesser likelihood that the drug-using behavior will be repeated. For some drugs, use also initiates the biological processes associated with tolerance, physical dependence, and (not shown in the figure) sensitization. In turn, tolerance can reduce some of the adverse effects of the drug, permitting or requiring the use of larger doses, which then can accelerate or intensify the development of physical dependence. Above a certain threshold, the aversive qualities of a withdrawal syndrome provide a distinct recurrent motive for further drug use. Sensitization of motivational systems can increase the salience of drug-related stimuli.

FIGURE 20.1-3 World Health Organization schematic model of drug use and dependence. (From Edwards G, Arif A, Hodgson R. Nomenclature and classification of drug-and alcoholrelated problems. A WHO memorandum. Bull WHO. 1981;59:225, with permission.) Psychodynamic Factors The range of psychodynamic theories about substance abuse reflects the various popular theories during the last 100 years. According to classic theories, substance abuse is a masturbatory equivalent (some heroin users describe the initial "rush" as similar to a prolonged sexual orgasm), a defense against anxious impulses, or a manifestation of oral regression (i.e., dependency). Recent psychodynamic formulations relate substance use as a reflection of disturbed ego functions (i.e., the inability to deal with reality). As a form of self-medication, alcohol may be used to control panic, opioids to diminish anger, and amphetamines to alleviate depression. Some addicts have great difficulty recognizing their inner emotional states, a condition called alexithymia (i.e., being unable to find words to describe their feelings). Learning and Conditioning. Drug use, whether occasional or compulsive, can be viewed as behavior maintained by its consequences. Drugs can reinforce antecedent behaviors by terminating some noxious or aversive state such as pain, anxiety, or depression. In some social situations, the drug use, apart from its pharmacological effects, can be reinforcing if it results in special status or the approval of friends. Each use of the drug evokes rapid positive reinforcement, either as a result of the rush (the drug-induced euphoria), alleviation of disturbed affects, alleviation of withdrawal

symptoms, or any combination of these effects. In addition, some drugs may sensitize neural systems to the reinforcing effects of the drug. Eventually, the paraphernalia (needles, bottles, cigarette packs) and behaviors associated with substance use can become secondary reinforcers, as well as cues signaling availability of the substance, and in their presence, craving or a desire to experience the effects increases. Drug users respond to the drug-related stimuli with increased activity in limbic regions, including the amygdala and the anterior cingulate. Such drug-related activation of limbic areas has been demonstrated with a variety of drugs, including cocaine, opioids, and cigarettes (nicotine). Of interest, the same regions activated by cocainerelated stimuli

in cocaine users are activated by sexual stimuli in both normal controls and cocaine users. In addition to the operant reinforcement of drug-using and drug-seeking behaviors, other learning mechanisms probably play a role in dependence and relapse. Opioid and alcohol withdrawal phenomena can be conditioned (in the Pavlovian or classic sense) to environmental or interoceptive stimuli. For a long time after withdrawal (from opioids, nicotine, or alcohol), the addict exposed to environmental stimuli previously linked with substance use or withdrawal may experience conditioned withdrawal, conditioned craving, or both. The increased feelings of craving are not necessarily accompanied by symptoms of withdrawal. The most intense craving is elicited by conditions associated with the availability or use of the substance, such as watching someone else use heroin or light a cigarette or being offered some drug by a friend. Those learning and conditioning phenomena can be superimposed on any preexisting psychopathology, but preexisting difficulties are not required for the development of powerfully reinforced substance-seeking behavior. Genetic Factors Strong evidence from studies of twins, adoptees, and siblings brought up separately indicates that the cause of alcohol abuse has a genetic component. Many less conclusive data show that other types of substance abuse or substance dependence have a genetic pattern in their development. Researchers recently have used restriction fragment length polymorphism (RFLP) in the study of substance abuse and substance dependence, and associations to genes that affect dopamine production have been postulated. Neurochemical Factors Receptors and Receptor Systems. With the exception of alcohol, researchers have identified particular neurotransmitters or neurotransmitter receptors involved with most substances of abuse. Some researchers base their studies on such hypotheses. The opioids, for example, act on opioid receptors. A person with too little endogenous opioid activity (e.g., low concentrations of endorphins) or with too much activity of an endogenous opioid antagonist may be at risk for developing opioid dependence. Even in a person with completely normal endogenous receptor function and neurotransmitter

concentration, the long-term use of a particular substance of abuse may eventually modulate receptor systems in the brain so that the presence of the exogenous substance is needed to maintain homeostasis. Such a receptor-level process may be the mechanism for developing tolerance within the CNS. Demonstrating modulation of neurotransmitter release and neurotransmitter receptor function has proved difficult, however, and recent research focuses on the effects of substances on the second-messenger system and on gene regulation. Pathways and Neurotransmitters The major neurotransmitters possibly involved in developing substance abuse and substance dependence are the opioid, catecholamine (particularly dopamine), and γaminobutyric acid (GABA) systems. The dopaminergic neurons in the ventral tegmental area are particularly important. These neurons project to the cortical and limbic regions, especially the nucleus accumbens. This pathway is probably involved in the sensation of reward and may be the major mediator of the effects of such substances as amphetamine and cocaine. The locus ceruleus, the largest group of adrenergic neurons, probably mediates the effects of the opiates and the opioids. These pathways have collectively been called the brain-reward circuitry. COMORBIDITY Comorbidity is the occurrence of two or more psychiatric disorders in a single patient at the same time. A high prevalence of additional psychiatric disorders is found among persons seeking treatment for alcohol, cocaine, or opioid dependence; some studies have shown that up to 50 percent of addicts have a comorbid psychiatric disorder. Although opioid, cocaine, and alcohol abusers with current psychiatric problems are more likely to seek treatment, those who do not seek treatment are not necessarily free of comorbid psychiatric problems; such persons may have

social supports that enable them to deny the impact that drug use is having on their lives. Two large epidemiological studies have shown that even among representative samples of the population, those who meet the criteria for alcohol or drug abuse and dependence (excluding tobacco dependence) are also far more likely to meet the criteria for other psychiatric disorders also. In various studies, a range of 35 to 60 percent of patients with substance abuse or substance dependence also meets the diagnostic criteria for antisocial personality disorder. The range is even higher when investigators include persons who meet all the antisocial personality disorder diagnostic criteria, except the requirement that the symptoms started at an early age. That is, a high percentage of patients with substance abuse or substance dependence diagnoses have a pattern of antisocial behavior, whether it was present before the substance use started or developed during the course of the substance use. Patients with substance abuse or substance dependence diagnoses who have antisocial personality disorder are likely to use more illegal substances; to have more psychopathology; to be less satisfied with their lives; and to be more impulsive, isolated, and depressed than patients with antisocial personality disorders alone.

Depression and Suicide. Depressive symptoms are common among persons diagnosed with substance abuse or substance dependence. About one third to one half of all those with opioid abuse or opioid dependence and about 40 percent of those with alcohol abuse or alcohol dependence meet the criteria for major depressive disorder sometime during their lives. Substance use is also a major precipitating factor for suicide. Persons who abuse substances are about 20 times more likely to die by suicide than the general population. About 15 percent of persons with alcohol abuse or alcohol dependence have been reported to commit suicide. This frequency of suicide is second only to the frequency in patients with major depressive disorder. DIAGNOSTIC CLASSIFICATION There are four major diagnostic categories in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5): (1) Substance Use Disorder; (2) Substance Intoxication; (3) Substance Withdrawal; and (4) Substance-Induced Mental Disorder. Substance Use Disorder Substance use disorder is the diagnostic term applied to the specific substance abused (e.g., alcohol use disorder, opioid use disorder) that results from the prolonged use of the substance. The following points should be considered in making this diagnosis. These criteria apply to all substances of abuse. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by 2 (or more) of the following, occurring within a 12-month period:

1. recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
2. recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
3. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)
4. tolerance, as defined by either of the following: a. a need for markedly increased amounts of the substance to achieve intoxication or desired effect b. markedly diminished effect with continued use of the same amount of the substance

5. withdrawal, as manifested by either of the following: a. the characteristic withdrawal syndrome for the substance b. the same (or a closely related) substance is taken to relieve or avoid withdrawal

symptoms 6. the substance is often taken in larger amounts or over a longer period than was intended 7. there is a persistent desire or unsuccessful efforts to cut down or control substance use 8. a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects 9. important social, occupational, or recreational activities are given up or reduced because of substance use 10. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance 11. craving or a strong desire or urge to use a specific substance. Substance Intoxication Substance intoxication is the diagnosis used to describe a syndrome (e.g., alcohol intoxication or simple drunkenness) characterized by specific signs and symptoms resulting from recent ingestion or exposure to the substance. A general description of substance intoxication includes the following points: The development of a reversible substance-specific syndrome due to recent ingestion of (or exposure to) a substance. Note: Different substances may produce similar or identical syndromes. Clinically significant maladaptive behavioral or psychological changes that are due to the effect of the substance on the central nervous system (e.g., belligerence, mood lability, cognitive impairment, impaired judgment, impaired social or occupational functioning) and develop during or shortly after use of the substance. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder. Substance Withdrawal Substance withdrawal is the diagnosis used to describe a substance specific syndrome that results from the abrupt cessation of heavy and prolonged use of a substance (e.g., opioid withdrawal). A general description of substance withdrawal requires the following criteria to be met: The development of a substance-specific syndrome due to the cessation of (or reduction in) substance use that has been heavy and prolonged. The substance-specific syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms are not due to a general medical condition and are not better

accounted for by another mental disorder. In the discussion of each substance in the sections that follow, the generic tables listed above, derived from the DSM-5 can be applied. Thus, in place of the word substance, the clinician should indicate the specific substance or drug that is used or that caused intoxication or withdrawal. TREATMENT AND REHABILITATION Some persons who develop substance-related problems recover without formal treatment, especially as they age. For those patients with less severe disorders, such as nicotine addiction, relatively brief interventions are often as effective as more intensive treatments. Because these brief interventions do not change the environment, alter druginduced brain changes, or provide new skills, a change in the patient’s motivation (cognitive change) probably has the best impact on the drug-using behavior. For those individuals who do not respond or whose dependence is more severe, a variety of interventions described below appear to be effective. It is useful to distinguish among specific procedures or techniques (e.g., individual therapy, family therapy, group therapy, relapse prevention, and pharmacotherapy) and treatment programs. Most programs use a number of specific procedures and involve several professional disciplines as well as nonprofessionals who have special skills or personal experience with the substance problem being treated. The best treatment programs combine specific procedures and disciplines to meet the needs of the individual patient after a

careful assessment. No classification system is generally accepted for either the specific procedures used in treatment or programs using various combinations of procedures. This lack of standardized terminology for categorizing procedures and programs presents a problem, even when the field of interest is narrowed from substance problems in general to treatment for a single substance, such as alcohol, tobacco, or cocaine. Except in carefully monitored research projects, even the definitions of specific procedures (e.g., individual counseling, group therapy, and methadone maintenance) tend to be so imprecise that usually just what transactions are supposed to occur cannot be inferred. Nevertheless, for descriptive purposes, programs are often broadly grouped on the basis of one or more of their salient characteristics: whether the program is aimed at merely controlling acute withdrawal and consequences of recent drug use (detoxification) or is focused on longer-term behavioral change; whether the program makes extensive use of pharmacological interventions; and the degree to which the program is based on individual psychotherapy, Alcoholics Anonymous (AA) or other 12-step principles, or therapeutic community principles. For example, government agencies recently categorized publicly funded treatment programs for drug dependence as (1) methadone maintenance (mostly outpatient), (2) outpatient drug-free programs, (3) therapeutic communities, or (4) short-term inpatient programs. Selecting a Treatment

Not all interventions are applicable to all types of substance use or dependence, and some of the more coercive interventions used for illicit drugs are not applicable to substances that are legally available, such as tobacco. Addictive behaviors do not change abruptly, but through a series of stages. Five stages in this gradual process have been proposed: precontemplation, contemplation, preparation, action, and maintenance. For some types of addictions the therapeutic alliance is enhanced when the treatment approach is tailored to the patient’s stage of readiness to change. Interventions for some drug use disorders may have a specific pharmacological agent as an important component; for example, disulfiram, naltrexone (ReVia), or acamprosate for alcoholism; methadone (Dolophine), levomethadyl acetate (ORLAAM), or buprenorphine (Buprenex) for heroin addiction; and nicotine delivery devices or bupropion (Zyban) for tobacco dependence. Not all interventions are likely to be useful to health care professionals. For example, many youthful offenders with histories of drug use or dependence are now remanded to special facilities (boot camps); other programs for offenders (and sometimes for employees) rely almost exclusively on the deterrent effect of frequent urine testing; and a third group are built around religious conversion or rededication in a specific religious sect or denomination. In contrast to the numerous studies suggesting some value for brief interventions for smoking and for problem drinking, few controlled studies are conducted of brief interventions for those seeking treatment for dependence on illicit drugs. In general, brief interventions (e.g., a few weeks of detoxification, whether in or out of a hospital) used for persons who are severely dependent on illicit opioids have limited effect on outcome measured a few months later. Substantial reductions in illicit drug use, antisocial behaviors, and psychiatric distress among patients dependent on cocaine or heroin are much more likely following treatment lasting at least 3 months. Such a time-in-treatment effect is seen across very different modalities, from residential therapeutic communities to ambulatory methadone maintenance programs. Although some patients appear to benefit from a few days or weeks of treatment, a substantial percentage of users of illicit drugs drop out (or are dropped) from treatment before they have achieved significant benefits. Some of the variance in treatment outcomes can be attributed to differences in the characteristics of patients entering treatment and by events and conditions following treatment. Programs based on similar philosophical principles

and using what seem to be similar therapeutic procedures vary greatly in effectiveness, however. Some of the differences among programs that seem to be similar reflect the range and intensity of services offered. Programs with professionally trained staffs that provide more comprehensive services to patients with more severe psychiatric difficulties are more likely able to retain those patients in treatment and help them make positive changes. Differences in the skills of individual counselors and professionals can strongly affect outcomes. Such generalizations concerning programs serving illicit drug users may not hold for programs dealing with those seeking treatment for alcohol, tobacco, or even cannabis problems uncomplicated by heavy use of illicit drugs. In such cases, relatively brief

periods of individual or group counseling can produce long-lasting reductions in drug use. The outcomes usually considered in programs dealing with illicit drugs have typically included measures of social functioning, employment, and criminal activity, as well as decreased drug-using behavior. Treatment of Comorbidity Treatment of the severely mentally ill (primarily those with schizophrenia and schizoaffective disorders) who are also drug dependent continues to pose problems for clinicians. Although some special facilities have been developed that use both antipsychotic drugs and therapeutic community principles, for the most part, specialized addiction agencies have difficulty treating these patients. Generally, integrated treatment in which the same staff can treat both the psychiatric disorder and the addiction is more effective than either parallel treatment (a mental health and a specialty addiction program providing care concurrently) or sequential treatment (treating either the addiction or the psychiatric disorder first and then dealing with the comorbid condition). Services and Outcome The extension of managed care into the public sector has produced a major reduction in the use of hospital-based detoxification and virtual disappearance of residential rehabilitation programs for alcoholics. Managed-care organizations, however, tend to assume that the relatively brief courses of outpatient counseling that are effective with private-sector alcoholic patients are also effective with patients who are dependent on illicit drugs and who have minimal social supports. For the present, the trend is to provide the care that costs the least over the short term and to ignore studies showing that more services can produce better long-term outcomes. Treatment is often a worthwhile social expenditure. For example, treatment of antisocial illicit drug users in outpatient settings can decrease antisocial behavior and reduce rates of human immunodeficiency virus (HIV) seroconversion that more than offset the treatment cost. Treatment in a prison setting can decrease post-release costs associated with drug use and rearrests. Despite such evidence, problems exist in maintaining public support for treatment of substance dependence in both the public and private sectors. This lack of support suggests that these problems continue to be viewed, at least in part, as moral failings rather than as medical disorders. REFERENCES Bonder BR. Substance-related disorders. In: Bonder BR. Psychopathology and Function. 4thed. Thorofare, NJ: SLACK Inc.; 2010:103. Clark R, Samnaliev M, McGovern MP. Impact of substance disorders on medical expenditures for Medicaid beneficiaries with behavioral health disorders. Psychiatr Serv. 2009;60:35. Ersche KD, Jones PS, Williams GB, Turton AJ, Robbins TW, Bullmore ET: Abnormal brain structure implicated in

02 - 20.2 Alcohol Related Disorders

20.2 Alcohol-Related Disorders

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of the body that cessation of use can precipitate a withdrawal syndrome usually marked by insomnia, evidence of hyperactivity of the autonomic nervous system, and feelings of anxiety. Therefore, in an adequate evaluation of life problems and psychiatric symptoms in a patient, the clinician must consider the possibility that the clinical situation reflects the effects of alcohol.

EPIDEMIOLOGY Psychiatrists need to be concerned about alcoholism because this condition is common; intoxication and withdrawal mimic many major psychiatric disorders, and the usual person with alcoholism does not fit the stereotype (i.e., so called “nasty knock-down drinkers”). Prevalence of Drinking At some time during life, 90 percent of the population in the United States drinks, with most people beginning their alcohol intake in the early to middle teens (Table 20.2-1). By the end of high school, 80 percent of students have consumed alcohol, and more than 60 percent have been intoxicated. At any time, two of three men are drinkers, with a ratio of persisting alcohol intake of approximately 1.3 men to 1.0 women, and the highest prevalence of drinking from the middle or late teens to the mid-20s. Table 20.2-1 Alcohol Epidemiology Men and women with higher education and income are most likely to imbibe, and, among religious denominations, Jews have the highest proportion who consume alcohol but among the lowest rates of alcohol dependence. Other ethnicities, such as the Irish, have higher rates of severe alcohol problems, but they also have significantly higher rates of abstentions. Some estimates show that more than 60 percent of men and women in some Native American and Inuit tribes have been alcohol dependent at some time. In the United States, the average adult consumes 2.2 gallons of absolute alcohol a year, a decrease from 2.7 gallons per capita in 1981. Drinking alcohol-containing beverages is generally considered an acceptable habit in the United States. About 90 percent of all US residents have had an alcohol-containing drink at least once in their lives, and about 51 percent of all US adults are current users of alcohol. After heart disease and cancer, alcohol-related disorders constitute the third largest health problem in the United States today. Beer accounts for about one half of all alcohol consumption, liquor for about one third, and wine for about one sixth. About 30 to 45 percent of all adults in the United States have had at least one transient episode of an alcohol-related problem, usually an alcohol-induced amnestic episode (e.g., a blackout), driving a motor vehicle while intoxicated, or missing school or work because

of excessive drinking. About 10 percent of women and 20 percent of men have met the diagnostic criteria for alcohol abuse during their lifetimes, and 3 to 5 percent of women and 10 percent of men have met the diagnostic criteria for the more serious diagnosis of alcohol dependence during their lifetimes. About 200,000 deaths each year are directly related to alcohol abuse. The common causes of death among persons with the alcoholrelated disorders are suicide, cancer, heart disease, and hepatic disease. Although persons involved in automotive fatalities do not always meet the diagnostic criteria for an alcohol-related disorder, drunk drivers are involved in about 50 percent of all automotive fatalities, and this percentage increases to about 75 percent when only accidents occurring in the late evening are considered. Alcohol use and alcohol-related disorders are associated with about 50 percent of all homicides and 25 percent of all suicides. Alcohol abuse reduces life expectancy by about 10 years, and alcohol leads all other substances in substance-related deaths. Table 20.2-2 lists other epidemiological data about alcohol use. Table 20.2-2 Epidemiological Data for Alcohol-Related Disorders COMORBIDITY The psychiatric diagnoses most commonly associated with the alcohol-related disorders are other substance-related disorders, antisocial personality disorder, mood disorders, and anxiety disorders. Although the data are somewhat controversial, most suggest that persons with alcohol-related disorders have a markedly

higher suicide rate than the general population.

Antisocial Personality Disorder A relation between antisocial personality disorder and alcohol-related disorders has frequently been reported. Some studies suggest that antisocial personality disorder is particularly common in men with an alcohol-related disorder and can precede the development of the alcohol-related disorder. Other studies, however, suggest that antisocial personality disorder and alcohol-related disorders are completely distinct entities that are not causally related. Mood Disorders About 30 to 40 percent of persons with an alcohol-related disorder meet the diagnostic criteria for major depressive disorder sometime during their lifetimes. Depression is more common in women than in men with these disorders. Several studies reported that depression is likely to occur in patients with alcohol-related disorders who have a high daily consumption of alcohol and a family history of alcohol abuse. Persons with alcohol-related disorders and major depressive disorder are at great risk for attempting suicide and are likely to have other substance-related disorder diagnoses. Some clinicians recommend antidepressant drug therapy for depressive symptoms that remain after 2 to 3 weeks of sobriety. Patients with bipolar I disorder are thought to be at risk for developing an alcohol-related disorder; they may use alcohol to self-medicate their manic episodes. Some studies have shown that persons with both alcohol-related disorder and depressive disorder diagnoses have concentrations of dopamine metabolites (homovanillic acid) and γ-aminobutyric acid (GABA) in their cerebrospinal fluid (CSF). Anxiety Disorders Many persons use alcohol for its efficacy in alleviating anxiety. Although the comorbidity between alcohol-related disorders and mood disorders is fairly widely recognized, it is less well known that perhaps 25 to 50 percent of all persons with alcohol-related disorders also meet the diagnostic criteria for an anxiety disorder. Phobias and panic disorder are particularly frequent comorbid diagnoses in these patients. Some data indicate that alcohol may be used in an attempt to self-medicate symptoms of agoraphobia or social phobia, but an alcohol-related disorder is likely to precede the development of panic disorder or generalized anxiety disorder. Suicide Most estimates of the prevalence of suicide among persons with alcohol-related disorders range from 10 to 15 percent, although alcohol use itself may be involved in a much higher percentage of suicides. Some investigators have questioned whether the suicide rate among persons with alcohol-related disorders is as high as the numbers suggest. Factors that have been associated with suicide among persons with alcohol-related disorders include the presence of a major depressive episode, weak psychosocial support systems, a serious coexisting medical condition, unemployment, and living alone. ETIOLOGY Many factors affect the decision to drink, the development of temporary alcohol-related difficulties in the teenage years and the 20s, and the development of alcohol dependence. The initiation of alcohol intake probably depends largely on social, religious, and psychological factors, although genetic characteristics might also

contribute. The factors that influence the decision to drink or those that contribute to temporary problems might differ, however, from those that add to the risk for the severe, recurring problems of alcohol dependence. A similar interplay between genetic and environmental influences contributes to many medical and psychiatric conditions, and, thus, a review of these factors in alcoholism offers information about complex genetic disorders overall. Dominant or recessive genes, although important, explain only relatively rare conditions. Most disorders have some level of genetic predisposition that usually relates to a series of different genetically influenced characteristics, each of which increases or decreases the risk for the disorder. It is likely that a series of genetic influences combine to explain approximately 60 percent of the proportion of risk

for alcoholism, with environment responsible for the remaining proportion of the variance. The divisions offered in this section, therefore, are more heuristic than real, because it is the combination of a series of psychological, sociocultural, biological, and other factors that are responsible for the development of severe, repetitive alcohol-related life problems. Psychological Theories A variety of theories relate to the use of alcohol to reduce tension, increase feelings of power, and decrease the effects of psychological pain. Perhaps the greatest interest has been paid to the observation that people with alcohol-related problems often report that alcohol decreases their feelings of nervousness and helps them cope with the day-to-day stresses of life. The psychological theories are built, in part, on the observation among nonalcoholic people that the intake of low doses of alcohol in a tense social setting or after a difficult day can be associated with an enhanced feeling of well-being and an improved ease of interactions. In high doses, especially at falling blood alcohol levels, however, most measures of muscle tension and psychological feelings of nervousness and tension are increased. Thus, tension-reducing effects of this drug might have an impact most on light to moderate drinkers or add to the relief of withdrawal symptoms, but play a minor role in causing alcoholism. The theories that focus on alcohol's potential to enhance feelings of being powerful and sexually attractive and to decrease the effects of psychological pain are difficult to evaluate definitively. Psychodynamic Theories Perhaps related to the disinhibiting or anxiety-lowering effects of lower doses of alcohol is the hypothesis that some people may use this drug to help them deal with self-punitive harsh superegos and to decrease unconscious stress levels. In addition, classic psychoanalytical theory hypothesizes that at least some alcoholic people may have become fixated at the oral stage of development and use alcohol to relieve their frustrations by taking the substance by mouth. Hypotheses regarding arrested phases of psychosexual development, although heuristically useful, have had little effect on the usual treatment approaches and are not the focus of extensive ongoing research. Similarly, most studies have not been able to document an "addictive personality" present in most alcoholics and associated with a propensity to lack control of intake of a wide range of substances and foods. Although pathological scores on personality tests are often seen during intoxication, withdrawal, and early recovery, many of these characteristics are not found to predate alcoholism, and most disappear with abstinence. Similarly, prospective studies of children of alcoholics who themselves have no co-occurring disorders usually document high risks mostly for alcoholism. As is described later in this text, one partial exception occurs

with the extreme levels of impulsivity seen in the 15 to 20 percent of alcoholic men with antisocial personality disorder, because they have high risks for criminality, violence, and multiple substance dependencies. Behavioral Theories Expectations about the rewarding effects of drinking, cognitive attitudes toward responsibility for one's behavior, and subsequent reinforcement after alcohol intake all contribute to the decision to drink again after the first experience with alcohol and to continue to imbibe despite problems. These issues are important in efforts to modify drinking behaviors in the general population, and they contribute to some important aspects of alcoholic rehabilitation. Sociocultural Theories Sociocultural theories are often based on extrapolations from social groups that have high and low rates of alcoholism. Theorists hypothesize that ethnic groups, such as Jews, who introduce children to modest levels of drinking in a family atmosphere and eschew drunkenness have low rates of alcoholism. Some other groups, such as Irish men or some American Indian tribes with high rates of abstention but a tradition of drinking to the point of drunkenness among drinkers, are believed to have high rates of alcoholism. These theories, however, often depend on stereotypes that tend to be erroneous, and prominent exceptions to

these rules exist. For example, some theories based on observations of the Irish and the French have incorrectly predicted high rates of alcoholism among the Italians. Yet, environmental events, presumably including cultural factors, account for as much as 40 percent of the alcoholism risk. Thus, although these are difficult to study, it is likely that cultural attitudes toward drinking, drunkenness, and personal responsibility for consequences are important contributors to the rates of alcohol-related problems in a society. In the final analysis, social and psychological theories are probably highly relevant, because they outline factors that contribute to the onset of drinking, the development of temporary alcohol-related life difficulties, and even alcoholism. The problem is how to gather relatively definitive data to support or refute the theories. Childhood History Researchers have identified several factors in the childhood histories of persons with later alcohol-related disorders and in children at high risk for having an alcohol-related disorder because one or both of their parents are affected. In experimental studies, children at high risk for alcohol-related disorders have been found to possess, on average, a range of deficits on neurocognitive testing, low amplitude of the P300 wave on evoked potential testing, and a variety of abnormalities on electroencephalography (EEG) recordings. Studies of high-risk offspring in their 20s have also shown a generally blunted effect of alcohol compared with that seen in persons whose parents have not been diagnosed with alcohol-related disorder. These findings suggest that a heritable biological brain function may predispose a person to an alcohol-related disorder. A childhood history of attention-deficit/hyperactivity disorder (ADHD), conduct disorder, or both, increases a child’s risk for an alcohol-related disorder as an adult. Personality disorders, especially antisocial personality disorder, as noted earlier, also predispose a person to an alcohol-related disorder.

Genetic Theories Importance of Genetic Influences. Four lines of evidence support the conclusion that alcoholism is genetically influenced. First, a threefold to fourfold increased risk for severe alcohol problems is seen in close relatives of alcoholic people. The rate of alcohol problems increases with the number of alcoholic relatives, the severity of their illness, and the closeness of their genetic relationship to the person under study. The family investigations do little to separate the importance of genetics and environment, and the second approach, twin studies, takes the data a step further. The rate of similarity, or concordance, for severe alcohol-related problems is significantly higher in identical twins of alcoholic individuals than in fraternal twins in most investigations, which estimate that genes explain 60 percent of the variance, with the remainder relating to nonshared, probably adult environmental influences. Third, the adoption-type studies have all revealed a significantly enhanced risk for alcoholism in the offspring of alcoholic parents, even when the children had been separated from their biological parents close to birth and raised without any knowledge of the problems within the biological family. The risk for severe alcohol-related difficulties is not further enhanced by being raised by an alcoholic adoptive family. Finally, studies in animals support the importance of a variety of yet-to-be-identified genes in the free-choice use of alcohol, subsequent levels of intoxication, and some consequences. EFFECTS OF ALCOHOL The term alcohol refers to a large group of organic molecules that have a hydroxyl group (-OH) attached to a saturated carbon atom. Ethyl alcohol, also called ethanol, is the common form of alcohol; sometimes referred to as beverage alcohol, ethyl alcohol is used for drinking. The chemical formula for ethanol is CH3-CH2-OH. The characteristic tastes and flavors of alcohol-containing beverages result from their methods of production, which produce various congeners in the final product, including methanol, butanol, aldehydes, phenols, tannins, and trace amounts of various metals. Although the congeners may confer some differential psychoactive effects on the various alcohol-containing beverages, these differences are minimal compared with the effects of

ethanol itself. A single drink is usually considered to contain about 12 g of ethanol, which is the content of 12 ounces of beer (7.2 proof, 3.6 percent ethanol in the United States), one 4-ounce glass of nonfortified wine, or 1 to 1.5 ounces of an 80-proof (40 percent ethanol) liquor (e.g., whiskey or gin). In calculating patients' alcohol intake, however, clinicians should be aware that beers vary in their alcohol content, that beers are available in small and large cans and mugs, that glasses of wine range from 2 to 6 ounces, and that mixed drinks at some bars and in most homes contain 2 to 3 ounces of liquor. Nonetheless, using the moderate sizes of drinks, clinicians can estimate that a single drink increases the blood alcohol level of a 150-pound man by 15 to 20 mg/dL, which is about the concentration of alcohol that an average person can metabolize in 1 hour. The possible beneficial effects of alcohol have been publicized, especially by the makers and the distributors of alcohol. Most attention has been focused on some epidemiological data that suggest that one or two glasses of red wine each day lower the incidence of cardiovascular disease; these findings, however, are highly controversial.

Absorption About 10 percent of consumed alcohol is absorbed from the stomach, and the remainder from the small intestine. Peak blood concentration of alcohol is reached in 30 to 90 minutes and usually in 45 to 60 minutes, depending on whether the alcohol was ingested on an empty stomach (which enhances absorption) or with food (which delays absorption). The time to peak blood concentration also depends on the time during which the alcohol was consumed; rapid drinking reduces the time to peak concentration, slower drinking increases it. Absorption is most rapid with beverages containing 15 to 30 percent alcohol (30 to 60 proof). There is some dispute about whether carbonation (e.g., in champagne and in drinks mixed with seltzer) enhances the absorption of alcohol. The body has protective devices against inundation by alcohol. For example, if the concentration of alcohol in the stomach becomes too high, mucus is secreted and the pyloric valve closes. These actions slow the absorption and keep the alcohol from passing into the small intestine, where there are no significant restraints on absorption. Thus, a large amount of alcohol can remain unabsorbed in the stomach for hours. Furthermore, pylorospasm often results in nausea and vomiting. Once alcohol is absorbed into the bloodstream, it is distributed to all body tissues. Because alcohol is uniformly dissolved in the body's water, tissues containing a high proportion of water receive a high concentration of alcohol. The intoxicating effects are greater when the blood alcohol concentration is rising than when it is falling (the Mellanby effects). For this reason, the rate of absorption bears directly on the intoxication response. Metabolism About 90 percent of absorbed alcohol is metabolized through oxidation in the liver; the remaining 10 percent is excreted unchanged by the kidneys and lungs. The rate of oxidation by the liver is constant and independent of the body's energy requirements. The body can metabolize about 15 mg/dL per hour, with a range of 10 to 34 mg/dL per hour. That is, the average person oxidizes three fourths of an ounce of 40 percent (80 proof) alcohol in an hour. In persons with a history of excessive alcohol consumption, upregulation of the necessary enzymes results in rapid alcohol metabolism. Alcohol is metabolized by two enzymes: alcohol dehydrogenase (ADH) and aldehyde dehydrogenase. ADH catalyzes the conversion of alcohol into acetaldehyde, which is a toxic compound; aldehyde dehydrogenase catalyzes the conversion of acetaldehyde into acetic acid. Aldehyde dehydrogenase is inhibited by disulfiram (Antabuse), often used in the treatment of alcohol-related disorders. Some studies have shown that women have a lower ADH blood content than men; this fact may account for woman's tendency to become more intoxicated than men after drinking the same amount of alcohol. The decreased function of alcohol-metabolizing enzymes in some Asian persons can also lead to easy intoxication and toxic symptoms. Effects on the Brain Biochemistry.

In contrast to most other substances of abuse with identified receptor targets—such as the N-methyl-D-aspartate (NMDA) receptor of phencyclidine (PCP)—no single molecular target has been identified as the mediator for the effects of alcohol. The longstanding theory about the biochemical effects of alcohol concerns its effects on the membranes of neurons. Data support the hypothesis that alcohol produces its effects by intercalating itself into membranes and, thus, increasing fluidity of the membranes with short-term use. With long-term use, however, the theory hypothesizes

that the membranes become rigid or stiff. The fluidity of the membranes is critical to normal functioning of receptors, ion channels, and other membrane-bound functional proteins. In recent studies, researchers have attempted to identify specific molecular targets for the effects of alcohol. Most attention has been focused on the effects of alcohol at ion channels. Specifically, studies have found that alcohol ion channel activities associated with the nicotinic acetylcholine, serotonin 5-hydroxytryptamine3 (5-HT3), and GABA type A (GABAA) receptors are enhanced by alcohol, whereas ion channel activities associated with glutamate receptors and voltage-gated calcium channels are inhibited. Behavioral Effects. As the net result of the molecular activities, alcohol functions as a depressant much like the barbiturates and the benzodiazepines, with which alcohol has some cross-tolerance and cross-dependence. At a level of 0.05 percent alcohol in the blood, thought, judgment, and restraint are loosened and sometimes disrupted. At a concentration of 0.1 percent, voluntary motor actions usually become perceptibly clumsy. In most states, legal intoxication ranges from 0.1 to 0.15 percent blood alcohol level. At 0.2 percent, the function of the entire motor area of the brain is measurably depressed, and the parts of the brain that control emotional behavior are also affected. At 0.3 percent, a person is commonly confused or may become stuporous; at 0.4 to 0.5 percent, the person falls into a coma. At higher levels, the primitive centers of the brain that control breathing and heart rate are affected, and death ensues secondary to direct respiratory depression or the aspiration of vomitus. Persons with long-term histories of alcohol abuse, however, can tolerate much higher concentrations of alcohol than can alcohol-naïve persons; their alcohol tolerance may cause them to falsely appear less intoxicated than they really are. Sleep Effects. Although alcohol consumed in the evening usually increases the ease of falling asleep (decreased sleep latency), alcohol also has adverse effects on sleep architecture. Specifically, alcohol use is associated with a decrease in rapid eye movement sleep (REM or dream sleep) and deep sleep (stage 4) and more sleep fragmentation, with more and longer episodes of awakening. Therefore, the idea that drinking alcohol helps persons fall asleep is a myth. Other Physiological Effects Liver. The major adverse effects of alcohol use are related to liver damage. Alcohol use, even as short as week-long episodes of increased drinking, can result in an accumulation of fats and proteins, which produce the appearance of a fatty liver, sometimes found on physical examination as an enlarged liver. The association between fatty infiltration of the liver and serious liver damage remains unclear. Alcohol use, however, is associated with the development of alcoholic hepatitis and hepatic cirrhosis.

Gastrointestinal System. Long-term heavy drinking is associated with developing esophagitis, gastritis, achlorhydria, and gastric ulcers. The development of esophageal varices can accompany particularly heavy alcohol abuse; the rupture of the varices is a medical emergency often resulting in death by exsanguination. Disorders of the small intestine occasionally occur, and pancreatitis, pancreatic insufficiency, and pancreatic cancer are also associated with heavy alcohol use. Heavy alcohol intake can interfere with the normal processes of food digestion and absorption; as a result, consumed food is inadequately digested. Alcohol abuse also appears to inhibit the intestine’s

capacity to absorb various nutrients, such as vitamins and amino acids. This effect, coupled with the often poor dietary habits of those with alcohol-related disorders, can cause serious vitamin deficiencies, particularly of the B vitamins. Other Bodily Systems. Significant intake of alcohol has been associated with increased blood pressure, dysregulation of lipoprotein and triglyceride metabolism, and increased risk for myocardial infarction and cerebrovascular disease. Alcohol has been shown to affect the hearts of nonalcoholic persons who do not usually drink, increasing the resting cardiac output, the heart rate, and the myocardial oxygen consumption. Evidence indicates that alcohol intake can adversely affect the hematopoietic system and can increase the incidence of cancer, particularly head, neck, esophageal, stomach, hepatic, colonic, and lung cancer. Acute intoxication may also be associated with hypoglycemia, which, when unrecognized, may be responsible for some of the sudden deaths of persons who are intoxicated. Muscle weakness is another side effect of alcoholism. Recent evidence shows that alcohol intake raises the blood concentration of estradiol in women. The increase in estradiol correlates with the blood alcohol level. Laboratory Tests. The adverse effects of alcohol appear in common laboratory tests, which can be useful diagnostic aids in identifying persons with alcohol-related disorders. The γ-glutamyl transpeptidase levels are high in about 80 percent of those with alcohol-related disorders, and the mean corpuscular volume (MCV) is high in about 60 percent, more so in women than in men. Other laboratory test values that may be high in association with alcohol abuse are those of uric acid, triglycerides, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Drug Interactions The interaction between alcohol and other substances can be dangerous, even fatal. Certain substances, such as alcohol and phenobarbital (Luminal), are metabolized by the liver, and their prolonged use can lead to acceleration of their metabolism. When persons with alcohol-related disorders are sober, this accelerated metabolism makes them unusually tolerant to many drugs such as sedatives and hypnotics; when they are intoxicated, however, these drugs compete with the alcohol for the same detoxification mechanisms, and potentially toxic concentrations of all involved substances can accumulate in the blood. The effects of alcohol and other central nervous system (CNS) depressants are usually

synergistic. Sedatives, hypnotics, and drugs that relieve pain, motion sickness, head colds, and allergy symptoms must be used with caution by persons with alcohol-related disorders. Narcotics depress the sensory areas of the cerebral cortex and can produce pain relief, sedation, apathy, drowsiness, and sleep; high doses can result in respiratory failure and death. Increasing the dosages of sedative-hypnotic drugs, such as chloral hydrate (Noctec) and benzodiazepines, especially when they are combined with alcohol, produces a range of effects from sedation to motor and intellectual impairment to stupor, coma, and death. Because sedatives and other psychotropic drugs can potentiate the effects of alcohol, patients should be instructed about the dangers of combining CNS depressants and alcohol, particularly when they are driving or operating machinery. DISORDERS Alcohol Use Disorder Diagnosis and Clinical Features. In the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), all substance use disorders use the same general criteria for dependence and abuse (see Section 20.1). A need for daily use of large amounts of alcohol for adequate functioning, a regular pattern of heavy drinking limited to weekends, and long periods of sobriety interspersed with binges of heavy alcohol intake lasting for weeks or months strongly suggest alcohol dependence and alcohol abuse. The drinking patterns are often associated with certain behaviors: the inability to cut down or stop drinking; repeated efforts to control or reduce excessive drinking by “going on the wagon” (periods of temporary abstinence) or by restricting drinking to certain times of the day; binges (remaining intoxicated

throughout the day for at least 2 days); occasional consumption of a fifth of spirits (or its equivalent in wine or beer); amnestic periods for events occurring while intoxicated (blackouts); the continuation of drinking despite a serious physical disorder that the person knows is exacerbated by alcohol use; and drinking nonbeverage alcohol, such as fuel and commercial products containing alcohol. In addition, persons with alcohol dependence and alcohol abuse show impaired social or occupational functioning because of alcohol use (e.g., violence while intoxicated, absence from work, job loss), legal difficulties (e.g., arrest for intoxicated behavior and traffic accidents while intoxicated), and arguments or difficulties with family members or friends about excessive alcohol consumption. Mark, a 45-year-old divorced man, was examined in a hospital emergency room because he had been confused and unable to care for himself of the preceding 3 days. His brother, who brought him to the hospital, reported that the patient has consumed large quantities of beer and wine daily for more than 5 years. His home and job lives were reasonably stable until his divorce 5 years prior. The brother indicated that Mark's drinking pattern since the divorce has been approximately 5 beers and a fourth of wine a day. Mark often experienced blackouts from drinking and missed

days of work frequently. As a result, Mark has lost several jobs in the past 5 years. Although he usually provides for himself marginally with small jobs, 3 days earlier he ran out of money and alcohol and resorted to panhandling on the streets for cash to buy food. Mark had been poorly nourished, having one meal per day at best and was evidently relying on beer as his prime source of nourishment. On examination, Mark alternates between apprehension and chatty, superficial warmth. He is pretty keyed up and talks constantly in a rambling and unfocused manner. His recognition of the physician varies; at times he recognizes him and other times he becomes confused and believes the doctor to be his other brother who lives in another state. On two occasions he referred to the physician by said brother's name and asked when he arrived in town, evidently having lost track of the interview up to that point. He has a gross hand tremor at rest and is disoriented to time. He believes he's in a parking lot rather than a hospital. Efforts at memory and calculation testing fail because Mark's attention shifts so rapidly. Subtypes of Alcohol Dependence. Various researchers have attempted to divide alcohol dependence into subtypes based primarily on phenomenological characteristics. One recent classification notes that type A alcohol dependence is characterized by late onset, few childhood risk factors, relatively mild dependence, few alcohol-related problems, and little psychopathology. Type B alcohol dependence is characterized by many childhood risk factors, severe dependence, an early onset of alcohol-related problems, much psychopathology, a strong family history of alcohol abuse, frequent polysubstance abuse, a long history of alcohol treatment, and a lot of severe life stresses. Some researchers have found that type A persons who are alcohol dependent may respond to interactional psychotherapies, whereas type B persons who are alcohol dependent may respond to training in coping skills. Other subtyping schemes of alcohol dependence have received fairly wide recognition in the literature. One group of investigators proposed three subtypes: earlystage problem drinkers, who do not yet have complete alcohol dependence syndromes; affiliative drinkers, who tend to drink daily in moderate amounts in social settings; and schizoid-isolated drinkers, who have severe dependence and tend to drink in binges and often alone. Another investigator described gamma alcohol dependence, which is thought to be common in the United States and represents the alcohol dependence seen in those who are active in Alcoholics Anonymous (AA). This variant concerns control problems in which persons are unable to stop drinking once they start. When drinking is terminated as a result of ill health or lack of money,

these persons can abstain for varying periods. In delta alcohol dependence, perhaps more common in Europe than in the United States, persons who are alcohol dependent must drink a certain amount each day but are unaware of a lack of control. The alcohol use disorder may not be discovered until a person who must stop drinking for some reason exhibits withdrawal symptoms. Another researcher has suggested a type I, male-limited variety of alcohol dependence,

characterized by late onset, more evidence of psychological than of physical dependence, and the presence of guilt feelings. Type II, male-limited alcohol dependence is characterized by onset at an early age, spontaneous seeking of alcohol for consumption, and a socially disruptive set of behaviors when intoxicated. Four subtypes of alcoholism were postulated by still another investigator. The first is antisocial alcoholism, typically with a predominance in men, a poor prognosis, early onset of alcohol-related problems, and a close association with antisocial personality disorder. The second is developmentally cumulative alcoholism, with a primary tendency for alcohol abuse that is exacerbated with time as cultural expectations foster increased opportunities to drink. The third is negative-affect alcoholism, which is more common in women than in men; according to this hypothesis, women are likely to use alcohol for mood regulation and to help ease social relationships. The fourth is developmentally limited alcoholism, with frequent bouts of consuming large amounts of alcohol; the bouts become less frequent as persons age and respond to the increased expectations of society about their jobs and families. Alcohol Intoxication The DSM-5 diagnostic criteria for alcohol intoxication (also called simple drunkenness) are based on evidence of recent ingestion of ethanol, maladaptive behavior, and at least one of several possible physiological correlates of intoxication (Table 20.2-3). As a conservative approach to identifying blood levels that are likely to have major effects on driving abilities, the legal definition of intoxication in most states in the United States requires a blood concentration of 80 or 100 mg ethanol per deciliter of blood (mg/dL), which is the same as 0.08 to 0.10 g/dL. The following is an outline of the rough estimates of the levels of impairment likely to be seen at various blood alcohol concentrations, for most people. Evidence of behavioral changes, a slowing in motor performance, and a decrease in the ability to think clearly occurs at doses as low as 20 to 30 mg/dL, as shown in Table 20.2-4. Blood concentrations between 100 and 200 mg/dL are likely to increase the impairment in coordination and judgment to severe problems with coordination (ataxia), increasing lability of mood, and progressively greater levels of cognitive deterioration. Anyone who does not show significant levels of impairment in motor and mental performance at approximately 150 mg/dL probably has significant pharmacodynamic tolerance. In that range, most people without significant tolerance also experience relatively severe nausea and vomiting. With blood alcohol concentrations in the 200 to 300 mg/dL range, the slurring of speech is likely to become more intense, and memory impairment (anterograde amnesia or alcoholic blackouts) becomes pronounced. Further increases in blood alcohol concentration result in the first level of anesthesia, and the nontolerant person who reaches 400 mg/dL or more risks respiratory failure, coma, and death. Table 20.2-3 Signs of Alcohol Intoxication

Table 20.2-4 Impairment Likely to be Seen at Different Blood Alcohol Concentrations Alcohol Withdrawal Alcohol withdrawal, even without delirium, can be serious; it can include seizures and autonomic hyperactivity. Conditions that may predispose to, or aggravate, withdrawal symptoms include fatigue, malnutrition, physical illness, and depression. The DSM-5 criteria for alcohol withdrawal require the cessation or reduction of alcohol use that was heavy and prolonged as well as the presence of specific physical or neuropsychiatric symptoms. The diagnosis also allows for

the specification “with perceptual disturbances.” One positron emission tomography (PET) study of blood flow during alcohol withdrawal in otherwise healthy persons with alcohol dependence reported a globally low rate of metabolic activity, although, with further inspection of the data, the authors concluded that activity was especially low in the left parietal and right frontal areas. The classic sign of alcohol withdrawal is tremulousness, although the spectrum of symptoms can expand to include psychotic and perceptual symptoms (e.g., delusions and hallucinations), seizures, and the symptoms of delirium tremens (DTs), called alcohol delirium in DSM-5. Tremulousness (commonly called the “shakes” or the “jitters”) develops 6 to 8 hours after the cessation of drinking, the psychotic and perceptual symptoms begin in 8 to 12 hours, seizures in 12 to 24 hours, and DTs anytime during the first 72 hours, although physicians should watch for the development of DTs for the first week of withdrawal. The syndrome of withdrawal sometimes skips the usual progression and, for example, goes directly to DTs. The tremor of alcohol withdrawal can be similar to either physiological tremor, with a continuous tremor of great amplitude and of more than 8 Hz, or familial tremor, with bursts of tremor activity slower than 8 Hz. Other symptoms of withdrawal include general irritability, gastrointestinal symptoms (e.g., nausea and vomiting), and

sympathetic autonomic hyperactivity, including anxiety, arousal, sweating, facial flushing, mydriasis, tachycardia, and mild hypertension. Patients experiencing alcohol withdrawal are generally alert but may startle easily. Twenty-nine-year-old Mr. F had been a heavy drinker for 8 years. One evening after work, he started drinking with friends and drank throughout the evening. He fell asleep in the early morning hours and upon awakening had a strong desire to drink and decided not to attend work. He had several Bloody Marys instead of food because food did not appeal to him. He went to a local bar in the afternoon and consumed large quantities of beer. That evening he met with some friends and continued to drink. This drinking pattern continued for the next week. The beginning of the following week he attempted to have a cup of coffee and found that he hands were shaking so much that he could not get the cup to his mouth to drink. He eventually managed to pour himself some wine in a glass and drank as much as he could. His hands then became less shaky, but he now felt nauseous and began having dry heaves. He tried to drink repeatedly but he could not keep the alcohol down. He felt very ill and anxious so he contacted his physician who recommended he report to a hospital. Upon evaluation, Mr. F was alert. He had a marked resting and intention tremor of the hands, and his tongue and eyelids were tremulous. He was oriented and had no memory impairment. When inquired about his drinking, Mr. F admits to drinking several drinks each day for the past 8 years, but claims that his drinking never interfered with his work or his relations with colleagues or friends. He denies having any aftereffects from his drinking other than mild hangovers. He denies ever having a binge such as this before and denies ever needing to drink daily in order to function adequately. He admits, however, that he has never tried to reduce or stop drinking. Withdrawal Seizures. Seizures associated with alcohol withdrawal are stereotyped, generalized, and tonic–clonic in character. Patients often have more than one seizure 3 to 6 hours after the first seizure. Status epilepticus is relatively rare and occurs in less than 3 percent of patients. Although anticonvulsant medications are not required in the management of alcohol withdrawal seizures, the cause of the seizures is difficult to establish when a patient is first assessed in the emergency room; thus, many patients with withdrawal seizures receive anticonvulsant medications, which are then discontinued once the cause of the seizures is recognized. Seizure activity in patients with known alcohol abuse histories should still prompt clinicians to consider other causative factors, such as head injuries, CNS infections, CNS neoplasms, and other cerebrovascular diseases; long-term severe alcohol abuse

can result in hypoglycemia, hyponatremia, and hypomagnesemia—all of which can also be associated with seizures. Treatment. The primary medications to control alcohol withdrawal symptoms are

the benzodiazepines (Table 20.2-5). Many studies have found that benzodiazepines help control seizure activity, delirium, anxiety, tachycardia, hypertension, diaphoresis, and tremor associated with alcohol withdrawal. Benzodiazepines can be given either orally or parenterally; neither diazepam (Valium) nor chlordiazepoxide (Librium), however, should be given intramuscularly (IM) because of their erratic absorption by this route. Clinicians must titrate the dosage of the benzodiazepine, starting with a high dosage and lowering the dosage as the patient recovers. Sufficient benzodiazepines should be given to keep patients calm and sedated but not so sedated that they cannot be aroused for clinicians to perform appropriate procedures, including neurological examinations. Table 20.2-5 Drug Therapy for Alcohol Intoxication and Withdrawal Although benzodiazepines are the standard treatment for alcohol withdrawal, studies have shown that carbamazepine (Tegretol) in daily doses of 800 mg is as effective as benzodiazepines and has the added benefit of minimal abuse liability. Carbamazepine use is gradually becoming common in the United States and Europe. The β-adrenergic receptor antagonists and clonidine (Catapres) have also been used to block the symptoms of sympathetic hyperactivity, but neither drug is an effective treatment for seizures or delirium. Delirium Diagnosis and Clinical Features. Patients with recognized alcohol withdrawal symptoms should be carefully monitored to prevent progression to alcohol withdrawal delirium, the most severe form of the withdrawal syndrome, also known as DTs. Alcohol withdrawal delirium is a medical emergency that can result in significant morbidity and mortality. Patients with delirium are a danger to themselves and to others. Because of the unpredictability of their behavior, patients with delirium may be assaultive or suicidal or may act on hallucinations or delusional thoughts as if they were genuine dangers. Untreated, DTs has a mortality rate of 20 percent, usually as a result of an intercurrent medical illness such as pneumonia, renal disease, hepatic insufficiency, or heart failure. Although withdrawal seizures commonly precede the development of alcohol withdrawal delirium, delirium can also appear unheralded. The essential feature of the syndrome is delirium occurring within 1 week after a person stops drinking or reduces the intake of alcohol. In addition to the symptoms of delirium, the features of

alcohol intoxication delirium include autonomic hyperactivity such as tachycardia, diaphoresis, fever, anxiety, insomnia, and hypertension; perceptual distortions, most frequently visual or tactile hallucinations; and fluctuating levels of psychomotor activity, ranging from hyperexcitability to lethargy. About 5 percent of persons with alcohol-related disorders who are hospitalized have DTs. Because the syndrome usually develops on the third hospital day, a patient admitted for an unrelated condition may unexpectedly have an episode of delirium, the first sign of a previously undiagnosed alcohol-related disorder. Episodes of DTs usually begin in a patient’s 30s or 40s after 5 to 15 years of heavy drinking, typically of the binge type. Physical illness (e.g., hepatitis or pancreatitis) predisposes to the syndrome; a person in good physical health rarely has DTs during alcohol withdrawal. Mr. R, a 40-year-old man, was admitted to the orthopedic department of a general hospital after experiencing a fall down stairs and breaking his leg. On the third day of his hospital stay, he became increasingly nervous and started to tremble. He was unable to sleep at night, talked incoherently, and was obviously very anxious. Mr. R, when asked, denied an alcohol problem other than an occasional glass of wine. When asked directly, his wife admitted that Mr. R

drank large quantities of wine for over 4 years. During the previous year, his drinking would begin every evening when he came home from work and would not end until he fell asleep. On the evening of admittance, the fall occurred before he was able to consume any alcohol. During the few weeks prior to his admittance, Mr. R had eaten very little. On several occasions, Mrs. R noticed that Mr. R was unable to recall even important events from the previous day. He had a car accident 3 years prior but without major injury. Mr. R had no other major health problems. His relationship with Mrs. R became very difficult after he began drinking and Mrs. R was seriously contemplating divorce. Mr. R had a tense relationship with his four children and he often argued with them. Recently, the children tried to avoid Mr. R as much as possible. On examination, Mr. R's speech was rambling and incoherent. He believed that he was still at work and that he had a job to finish. At times he thought the physicians and nurses were his co-workers. At times he picked at bugs that he could see on his bed sheets. He was disoriented in time and was startled easily by sounds from outside the room. He sweat profusely and could not hold a glass without spilling some of the contents. Treatment. The best treatment for DTs is prevention. Patients withdrawing from alcohol who exhibit withdrawal phenomena should receive a benzodiazepine, such as 25 to 50 mg of chlordiazepoxide every 2 to 4 hours until they seem to be out of danger. Once the delirium appears, however, 50 to 100 mg of chlordiazepoxide should be given every 4 hours orally, or lorazepam (Ativan) should be given intravenously (IV) if oral medication is not possible (Table 20.2-5). Antipsychotic medications that may reduce the

seizure threshold in patients should be avoided. A high-calorie, high-carbohydrate diet supplemented by multivitamins is also important. Physically restraining patients with the DTs is risky; they may fight against the restraints to a dangerous level of exhaustion. When patients are disorderly and uncontrollable, a seclusion room can be used. Dehydration, often exacerbated by diaphoresis and fever, can be corrected with fluids given by mouth or IV. Anorexia, vomiting, and diarrhea often occur during withdrawal. Antipsychotic medications should be avoided because they can reduce the seizure threshold in the patient. The emergence of focal neurological symptoms, lateralizing seizures, increased intracranial pressure, or evidence of skull fractures or other indications of CNS pathology should prompt clinicians to examine a patient for additional neurological disease. Nonbenzodiazepine anticonvulsant medication is not useful in preventing or treating alcohol withdrawal convulsions, although benzodiazepines are generally effective. Warm, supportive psychotherapy in the treatment of DTs is essential. Patients are often bewildered, frightened, and anxious because of their tumultuous symptoms, and skillful verbal support is imperative. Alcohol-Induced Persisting Dementia Alcohol-induced persisting dementia is a poorly studied, heterogeneous long-term cognitive problem that can develop in the course of alcoholism. Global decreases in intellectual functioning, cognitive abilities, and memory are observed, but recent memory difficulties are consistent with the global cognitive impairment, an observation that helps to distinguish this from alcohol-induced persisting amnestic disorder. Brain functioning tends to improve with abstinence, but perhaps half of all affected patients have long-term and even permanent disabilities in memory and thinking. Approximately 50 to 70 percent of these patients evidence increased size of the brain ventricles and shrinkage of the cerebral sulci, although these changes appear to be partially or completely reversible during the first year of complete abstinence. Alcohol-Induced Persisting Amnestic Disorder Diagnosis and Clinical Features. The essential feature of alcohol-induced persisting amnestic disorder is a disturbance in short-term memory caused by prolonged heavy use of alcohol. Because the disorder usually occurs in persons who have been drinking heavily for many years, the disorder is rare in persons younger than age

35. Wernicke-Korsakoff Syndrome. The classic names for alcohol-induced persisting amnestic disorder are Wernicke’s encephalopathy (a set of acute symptoms) and Korsakoff’s syndrome (a chronic condition). Whereas Wernicke’s encephalopathy is completely reversible with treatment, only about 20 percent of patients with Korsakoff’s syndrome recover. The pathophysiological connection between the two syndromes is thiamine deficiency, caused either by poor nutritional habits or by malabsorption

problems. Thiamine is a cofactor for several important enzymes and may also be involved in conduction of the axon potential along the axon and in synaptic transmission. The neuropathological lesions are symmetrical and paraventricular, involving the mammillary bodies, the thalamus, the hypothalamus, the midbrain, the pons, the medulla, the fornix, and the cerebellum. Wernicke’s encephalopathy, also called alcoholic encephalopathy, is an acute neurological disorder characterized by ataxia (affecting primarily the gait), vestibular dysfunction, confusion, and a variety of ocular motility abnormalities, including horizontal nystagmus, lateral orbital palsy, and gaze palsy. These eye signs are usually bilateral but not necessarily symmetrical. Other eye signs may include a sluggish reaction to light and anisocoria. Wernicke’s encephalopathy may clear spontaneously in a few days or weeks or may progress into Korsakoff’s syndrome. Treatment. In the early stages, Wernicke’s encephalopathy responds rapidly to large doses of parenteral thiamine, which is believed to be effective in preventing the progression into Korsakoff’s syndrome. The dosage of thiamine is usually initiated at 100 mg by mouth two to three times daily and is continued for 1 to 2 weeks. In patients with alcohol-related disorders who are receiving IV administration of glucose solution, it is good practice to include 100 mg of thiamine in each liter of the glucose solution. Korsakoff’s syndrome is the chronic amnestic syndrome that can follow Wernicke’s encephalopathy, and the two syndromes are believed to be pathophysiologically related. The cardinal features of Korsakoff’s syndrome are impaired mental syndrome (especially recent memory) and anterograde amnesia in an alert and responsive patient. The patient may or may not have the symptom of confabulation. Treatment of Korsakoff’s syndrome is also thiamine given 100 mg by mouth two to three times daily; the treatment regimen should continue for 3 to 12 months. Few patients who progress to Korsakoff’s syndrome ever fully recover, although many have some improvement in their cognitive abilities with thiamine and nutritional support. Blackouts. Blackouts are similar to episodes of transient global amnesia in that they are discrete episodes of anterograde amnesia that occur in association with alcohol intoxication. The periods of amnesia can be particularly distressing when persons fear that they have unknowingly harmed someone or behaved imprudently while intoxicated. During a blackout, persons have relatively intact remote memory but experience a specific short-term memory deficit in which they are unable to recall events that happened in the previous 5 or 10 minutes. Because their other intellectual faculties are well preserved, they can perform complicated tasks and appear normal to casual observers. The neurobiological mechanisms for alcoholic blackouts are now known at the molecular level; alcohol blocks the consolidation of new memories into old memories, a process that is thought to involve the hippocampus and related temporal lobe structures. Alcohol-Induced Psychotic Disorder

Diagnosis and Clinical Features. Approximately 3 percent of alcoholic persons experience auditory hallucinations or paranoid delusions in the context of heavy drinking or withdrawal. The most common auditory hallucinations are voices, but they are often unstructured. The voices are characteristically maligning, reproachful, or threatening, although some patients report that the

voices are pleasant and nondisruptive. The hallucinations usually last less than a week, but during that week impaired reality testing is common. After the episode, most patients realize the hallucinatory nature of the symptoms. Hallucinations after alcohol withdrawal are considered rare, and the syndrome is distinct from alcohol withdrawal delirium. The hallucinations can occur at any age, but usually appear in persons abusing alcohol for a long time. Although the hallucinations usually resolve within a week, some linger; in these cases, clinicians must consider other psychotic disorders in the differential diagnosis. Alcohol withdrawal-related hallucinations are differentiated from the hallucinations of schizophrenia by the temporal association with alcohol withdrawal, the absence of a classic history of schizophrenia, and their usually short-lived duration. Alcohol withdrawal-related hallucinations are differentiated from the DTs by the presence of a clear sensorium in patients. Mr. G was a 40-year-old unemployed man living alone in a studio apartment and was brought to the hospital by the police. He contacted them complaining that he heard voices of men on the street below his window talking about him and threatening to kill him. He stated that every time he looked out the window the men had always disappeared. Mr. G had a 15-year history of almost daily alcohol use. He was intoxicated each day and often experienced shakes upon awakening in the morning. On the previous day, he had only one glass of beer instead of his usual four because of gastrointestinal problems. He was fully alert and oriented. Treatment. The treatment of alcohol withdrawal-related hallucinations is much like the treatment of DTs—benzodiazepines, adequate nutrition, and fluids, if necessary. If this regimen fails or for long-term cases, antipsychotics may be used. Alcohol-Induced Mood Disorder Heavy intake of alcohol over several days results in many of the symptoms observed in major depressive disorder, but the intense sadness markedly improves within several days to 1 month of abstinence. Eighty percent of people with alcoholism report histories of intense depression, including 30 to 40 percent who were depressed for 2 or more weeks at a time. However, only 10 to 15 percent of alcoholic persons have ever had depression that meets the criteria for major depressive disorder when they have not

been drinking heavily. Even severe substance-induced depressions are likely to improve fairly rapidly with abstinence, without medication or intensive psychotherapy aimed at the depressive symptoms. A logical approach for these substance-induced conditions is to teach the patient how to best view and deal with the temporary sadness through education and cognitive-behavioral treatment, and to watch and wait at least 2 to 4 weeks before starting antidepressant medications. A consultation was requested on a 42-year-old woman with alcohol dependence who complained of persisting severe depressive symptoms despite 5 days of abstinence. In the initial stage of the interview, she noted that she had “always been depressed” and felt that she “drank to cope with the depressive symptoms.” Her current complaint included a prominent sadness that had persisted for several weeks, difficulties concentrating, initial and terminal insomnia, and a feeling of hopelessness and guilt. In an effort to distinguish between an alcohol-induced mood disorder and an independent major depressive episode, a time-line–based history was obtained. This focused on the age of onset of alcohol dependence, periods of abstinence that extended for several months or more since the onset of dependence, and the ages of occurrence of clear major depressive episodes lasting several weeks or more at a time. Despite this patient’s original complaints, it became clear that there had been no major depressive episodes prior to her mid-20s when alcohol dependence began, and that during a 1-year period of abstinence related to the gestation and neonatal period of her son, her mood had significantly improved. A provisional diagnosis of an alcohol-induced mood disorder was made. The patient was offered education, reassurance, and cognitive therapy to help her to deal with the depressive symptoms, but no antidepressant

medications were prescribed. The depressive symptoms remained at their original intensity for several additional days and then began to improve. By approximately 3 weeks abstinent the patient no longer met criteria for a major depressive episode, although she demonstrated mood swings similar to dysphemia for several additional weeks. This case is a fairly typical example of an alcohol-induced mood disorder in an individual with alcohol dependence. (Courtesy of Marc A. Shuckit, M.D.) Alcohol-Induced Anxiety Disorder Anxiety symptoms fulfilling the diagnostic criteria for alcohol-induced anxiety disorder are also common in the context of acute and protracted alcohol withdrawal. Almost 80 percent of alcoholic persons report panic attacks during at least one acute withdrawal episode; their complaints can be sufficiently intense for the clinician to consider diagnosing panic disorder. Similarly, during the first 4 weeks or so of abstinence, people with severe alcohol problems are likely to avoid some social situations for fear of being overwhelmed by anxiety (i.e., they have symptoms resembling social phobia); their

problems can at times be severe enough to resemble agoraphobia. However, when psychological or physiological symptoms of anxiety are observed in alcoholic persons only in the context of heavy drinking or within the first several weeks or month of abstinence, the symptoms are likely to diminish and subsequently disappear with time alone. A 48-year-old woman was referred for evaluation and treatment of her recent onset of panic attacks. These episodes occurred two to three times per week over the preceding 6 months, with each lasting typically between 10 and 20 minutes. Panic symptoms occurred regardless of levels of life stress and could not be explained by current medications or medical conditions. The workup included an evaluation of her laboratory test values, which revealed a carbohydrate-deficient transferrin (CDT) level of 28 U/L, a uric acid level of 7.1 mg, and a γ-glutamyltransferase value of 47. All other blood tests were within normal limits. The atypical age of onset of the panic attacks, along with the blood results, encouraged the clinician to probe further regarding the pattern of alcohol-related life problems with both the patient and, separately, her spouse. This step documented a history of alcohol dependence with an onset at approximately 35 years of age, with no evidence of panic disorder before that date. Nor did the patient have repetitive panic attacks beyond 2 weeks of abstinence during her frequent periods of nondrinking, which often lasted for 3 or 4 months. A working diagnosis of alcohol dependence with an alcohol-induced anxiety disorder characterized by panic attacks was made, and the patient was encouraged to abstain and was appropriately treated for possible withdrawal symptoms. Over the subsequent 3 weeks after a taper of benzodiazepines used for the treatment of withdrawal, the panic symptoms diminished in intensity and subsequently disappeared. (Courtesy of Marc A. Schuckit, M.D.) Alcohol-Induced Sexual Dysfunction The formal diagnosis of symptoms of sexual dysfunction associated with alcohol intoxication is alcohol-induced sexual dysfunction (see Section 17.2). Alcohol-Induced Sleep Disorder The diagnostic criteria for alcohol-induced sleep disorders with an onset during either alcohol intoxication or alcohol withdrawal are found in the sleep disorders section (see Section 16.2). Unspecified Alcohol-Related Disorder The diagnosis of unspecified alcohol-related disorder is used for alcohol-related disorders that do not meet the diagnostic criteria for any of the other diagnoses.

Idiosyncratic Alcohol Intoxication Whether there is such a diagnostic entity as idiosyncratic alcohol intoxication is under debate. Several well-controlled studies of persons who supposedly have the disorder have raised questions about the validity of the designation. The condition has been variously called pathologic, complicated, atypical, and paranoid alcohol intoxication; all these terms indicate that a severe behavioral syndrome develops rapidly after a person consumes a

small amount of alcohol that would have minimal behavioral effects on most persons. The diagnosis is important in the forensic arena because alcohol intoxication is not generally accepted as a reason for judging persons not responsible for their activities. Idiosyncratic alcohol intoxication, however, can be used in a person's defense if a defense lawyer can argue successfully that the defendant has an unexpected, idiosyncratic, pathological reaction to a minimal amount of alcohol. In anecdotal reports, persons with idiosyncratic alcohol intoxication have been described as confused and disoriented and as experiencing illusions, transitory delusions, and visual hallucinations. Persons may display greatly increased psychomotor activity and impulsive, aggressive behavior. They can be dangerous to others and they may also exhibit suicidal ideation and make suicide attempts. The disorder, usually described as lasting for a few hours, terminates in prolonged sleep, and those affected cannot recall the episodes on awakening. The cause of the condition is unknown, but it is reported to be most common in persons with high levels of anxiety. According to one hypothesis, alcohol causes sufficient disorganization and loss of control to release aggressive impulses. Another suggestion is that brain damage, particularly encephalitic or traumatic damage, predisposes some persons to an intolerance for alcohol and thus to abnormal behavior after they ingest only small amounts. Other predisposing factors may include advancing age, using sedative-hypnotic drugs, and feeling fatigued. A person's behavior while intoxicated tends to be atypical; after one weak drink, a quiet, shy person becomes belligerent and aggressive. In treating idiosyncratic alcohol intoxication, clinicians must help protect patients from harming themselves and others. Physical restraint may be necessary, but is difficult because of the abrupt onset of the condition. Once a patient has been restrained, injection of an antipsychotic drug, such as haloperidol (Haldol), is useful for controlling assaultiveness. This condition must be differentiated from other causes of abrupt behavioral change, such as complex partial epilepsy. Some persons with the disorder reportedly showed temporal lobe spiking on an EEG after ingesting small amounts of alcohol. Other Alcohol-Related Neurological Disorders Only the major neuropsychiatric syndromes associated with alcohol use have been discussed here. The complete list of neurological syndromes is lengthy (Table 20.2-6). Alcoholic pellagra encephalopathy is one diagnosis of potential interest to psychiatrists presented with a patient who appears to have Wernicke-Korsakoff syndrome but who

does not respond to thiamine treatment. The symptoms of alcoholic pellagra encephalopathy include confusion, clouding of consciousness, myoclonus, oppositional hypertonias, fatigue, apathy, irritability, anorexia, insomnia, and sometimes delirium. Patients have a niacin (nicotinic acid) deficiency, and the specific treatment is 50 mg of niacin by mouth four times daily or 25 mg parenterally two to three times daily. Table 20.2-6 Neurological and Medical Complications of Alcohol Use Fetal Alcohol Syndrome. Data indicate that women who are pregnant or are breast-feeding should not drink alcohol. Fetal alcohol syndrome, the leading cause of intellectual disability in the United States, occurs when mothers who drink alcohol expose fetuses to alcohol in utero. The alcohol inhibits intrauterine growth and postnatal development. Microcephaly, craniofacial malformations, and limb and heart defects are common in affected infants. Short adult stature and development of a range of adult maladaptive behaviors have also been associated with fetal alcohol syndrome. Women with alcohol-related disorders have a 35 percent risk of having a child with defects. Although the precise mechanism of the damage to the fetus is unknown, the damage seems to result from exposure in utero to ethanol or to its metabolites; alcohol

may also cause hormone imbalances that increase the risk of abnormalities. PROGNOSIS Between 10 and 40 percent of alcoholic persons enter some kind of formal treatment program during the course of their alcohol problems. A number of prognostic signs are favorable. First is the absence of preexisting antisocial personality disorder or a diagnosis of other substance abuse or dependence. Second, evidence of general life stability with a job, continuing close family contacts, and the absence of severe legal problems also bodes well for the patient. Third, if the patient stays for the full course of the initial rehabilitation (perhaps 2 to 4 weeks), the chances of maintaining abstinence are good. The combination of these three attributes predicts at least a 60 percent chance for 1 or more years of abstinence. Few studies have documented the long-term course, but researchers agree that 1 year of abstinence is associated with a good chance for continued abstinence over an extended period. Alcoholic persons with severe drug problems (especially intravenous drug use or cocaine or amphetamine dependence) and those who are homeless may have only a 10 to 15 percent chance of achieving 1 year of abstinence, however. Accurately predicting whether any specific person will achieve or maintain abstinence is impossible, but the prognostic factors listed earlier are associated with an increased likelihood of abstinence. The factors reflecting life stability, however, probably explain only 20 percent or less of the course of alcohol use disorders. Many forces that are difficult to measure affect the clinical course significantly; they are likely to include such intangibles as motivational level and the quality of the patient’s social support system. In general, alcoholic persons with preexisting independent major psychiatric disorders —such as antisocial personality disorder, schizophrenia, and bipolar I disorder—are likely to run the course of their independent psychiatric illness. Thus, for example, clinicians must treat the patient with bipolar I disorder who has secondary alcoholism with appropriate psychotherapy and lithium (Eskalith), use relevant psychological and behavioral techniques for the patient with antisocial personality disorder, and offer appropriate antipsychotic medications on a long-term basis to the patient with schizophrenia. The goal is to minimize the symptoms of the independent psychiatric disorder in the hope that greater life stability will be associated with a better prognosis for the patient’s alcohol problems. TREATMENT AND REHABILITATION Three general steps are involved in treating the alcoholic person after the disorder has been diagnosed: intervention, detoxification, and rehabilitation. These approaches assume that all possible efforts have been made to optimize medical functioning and to address psychiatric emergencies. Thus, for example, an alcoholic person with symptoms of depression sufficiently severe to be suicidal requires inpatient hospitalization for at least several days until the suicidal ideation disappears. Similarly, a person presenting with cardiomyopathy, liver difficulties, or gastrointestinal bleeding first needs adequate

treatment of the medical emergency. The patient with alcohol abuse or dependence must then be brought face-to-face with the reality of the disorder (intervention), be detoxified if needed, and begin rehabilitation. The essentials of these three steps for an alcoholic person with independent psychiatric syndromes closely resemble the approaches used for the primary alcoholic person without independent psychiatric syndromes. In the former case, however, the treatments are applied after the psychiatric disorder has been stabilized to the extent possible. Intervention The goal in the intervention step, which has also been called confrontation, is to break through feelings of denial and help the patient recognize the adverse consequences likely to occur if the disorder is not treated. Intervention is a process aimed at maximizing the motivation for treatment and continued abstinence. This step often involves convincing patients that they are responsible for their own actions while reminding them of how alcohol has created significant life impairments. The

psychiatrist often finds it useful to take advantage of the person’s chief presenting complaint, whether it is insomnia, difficulties with sexual performance, an inability to cope with life stresses, depression, anxiety, or psychotic symptoms. The psychiatrist can then explain how alcohol has either created or contributed to these problems and can reassure the patient that abstinence can be achieved with a minimum of discomfort. JP, a 47-year-old physician, was confronted regarding his alcohol-related behaviors by his wife and 21-year-old daughter. They told him about his slurred speech on several recent occasions when the daughter called home, as well as a large number of wine bottles in the trash each week. JP’s wife complained of the hours he spent alone in his study and his practice of staying up after she went to bed, retiring later with alcohol on his breath. She also related her concern about his consumption of about 10 or 12 drinks at a recent party, with the resulting tendency to isolate himself from the other guests. She then reminded him of his need to pack liquor when they go on trips where alcohol may not be readily available, and the tremor of his hands some mornings after being drunk the night before. The family shared their concern directly with JP at a time when he was not actively intoxicated, emphasizing specific times and events when his impairment with alcohol occurred. They had also made an appointment with the clinician at an alcohol and drug treatment program so that a next step could be established if the intervention was successful. (Adapted from Marc A. Schuckit, M.D.) A physician intervening with a patient can use the same nonjudgmental but persistent approach each time an alcohol-related impairment is identified. It is the persistence rather than exceptional interpersonal skills that usually gets results. A single

intervention is rarely sufficient. Most alcoholic persons need a series of reminders of how alcohol contributed to each developing crisis before they seriously consider abstinence as a long-term option. Family The family can be of great help in the intervention. Family members must learn not to protect the patient from the problems caused by alcohol; otherwise, the patient may not be able to gather the energy and the motivation necessary to stop drinking. In addition, during the intervention stage, the family can suggest that the patient meet with persons who are recovering from alcoholism, perhaps through AA, and family members can meet with groups, such as Al-Anon, that reach out to family members. Those support groups for families meet many times a week and help family members and friends see that they are not alone in their fears, worry, and feelings of guilt. Participants share coping strategies and help each other find community resources. The groups can be most useful in helping family members rebuild their lives, even if the alcoholic person refuses to seek help. Detoxification Most persons with alcohol dependence have relatively mild symptoms when they stop drinking. If the patient is in relatively good health, is adequately nourished, and has a good social support system, the depressant withdrawal syndrome usually resembles a mild case of the flu. Even intense withdrawal syndromes rarely approach the severity of symptoms described by some early textbooks in the field. The essential first step in detoxification is a thorough physical examination. In the absence of a serious medical disorder or combined drug abuse, severe alcohol withdrawal is unlikely. The second step is to offer rest, adequate nutrition, and multiple vitamins, especially those containing thiamine. Mild or Moderate Withdrawal. Withdrawal develops because the brain has physically adapted to the presence of a brain depressant and cannot function adequately in the absence of the drug. Giving sufficient brain depressant on the first day to diminish symptoms and then weaning the patient off the drug over the next 5 days offers most patients optimal relief and minimizes the possibility that severe withdrawal will develop. Any depressant—including alcohol, barbiturates, or any of the benzodiazepines—can work, but most clinicians choose a benzodiazepine for its relative safety.

Adequate treatment can be given with either short-acting drugs (e.g., lorazepam), or long-acting substances (e.g., chlordiazepoxide and diazepam). An example of treatment is the administration of 25 mg of chlordiazepoxide by mouth three or four times a day on the first day, with a notation to skip a dose if the patient is asleep or feeling sleepy. An additional one or two 25-mg doses can be given during the first 24 hours if the patient is jittery or shows signs of increasing tremor or autonomic dysfunction. Whatever benzodiazepine dosage is required on the first day can be decreased by 20 percent each subsequent day, with a resulting need for no further medication after 4 or 5 days. When giving a long-acting agent, such as chlordiazepoxide, the

clinician must avoid producing excessive sleepiness through overmedication; if the patient is sleepy, the next scheduled dose should be omitted. When taking a short-acting drug, such as lorazepam, the patient must not miss any dose because rapid changes in benzodiazepine concentrations in the blood can precipitate severe withdrawal. A social model program of detoxification saves money by avoiding medications while using social supports. This lessexpensive regimen can be helpful for mild or moderate withdrawal syndromes. Some clinicians have also recommended βadrenergic receptor antagonists (e.g., propranolol [Inderal]) or α-adrenergic receptor agonists (e.g., clonidine), although these medications do not appear to be superior to the benzodiazepines. Unlike the brain depressants, these other agents do little to decrease the risk of seizures or delirium. Severe Withdrawal. For the approximately 1 percent of alcoholic patients with extreme autonomic dysfunction, agitation, and confusion—that is, those with alcoholic withdrawal delirium, or DTs—no optimal treatment has yet been developed. The first step is to ask why such a severe and relatively uncommon withdrawal syndrome has occurred; the answer often relates to a severe concomitant medical problem that needs immediate treatment. The withdrawal symptoms can then be minimized through the use of either benzodiazepines (in which case high doses are sometimes required) or antipsychotic agents, such as haloperidol. Once again, on the first or second day, doses are used to control behavior, and the patient can be weaned off the medication by about the fifth day. Another 1 percent of patients may have a single grand mal convulsion; the rare person has multiple fits, with the peak incidence on the second day of withdrawal. Such patients require neurological evaluation, but in the absence of evidence of a seizure disorder, they do not benefit from anticonvulsant drugs. Protracted Withdrawal. Symptoms of anxiety, insomnia, and mild autonomic overactivity are likely to continue for 2 to 6 months after the acute withdrawal has disappeared. Although no pharmacological treatment for this syndrome appears appropriate, it is possible that some of the medications used for the rehabilitation phase, especially acamprosate (Campral), may work by diminishing some of these symptoms. It is important that the clinician warn the patient that some level of sleep problems or feelings of nervousness might remain after acute withdrawal and discuss cognitive and behavioral approaches that might be appropriate to helping the patient feel more comfortable. These protracted withdrawal symptoms may enhance the probability of relapse. Rehabilitation For most patients, rehabilitation includes three major components: (1) continued efforts to increase and maintain high levels of motivation for abstinence; (2) work to help the patient readjust to a lifestyle free of alcohol; and (3) relapse prevention. Because these steps are carried out in the context of acute and protracted withdrawal syndromes and life crises, treatment requires repeated presentations of similar materials that remind the patient how important abstinence is and that help the patient develop new day-today support systems and coping styles.

No single major life event, traumatic life period, or identifiable psychiatric disorder is known to be a unique cause of alcoholism. In addition, the effects of any causes of alcoholism are likely to have been diluted by the effects of alcohol on the brain and the years of an altered lifestyle, so that the alcoholism has developed a life of its own. This is true even though many alcoholic persons believe that the cause was depression, anxiety, life stress, or pain syndromes. Research, data from records, and resource persons usually reveal that alcohol contributed to the mood disorder, accident, or life stress, not vice versa. The same general treatment approach is used in inpatient and outpatient settings. Selection of the more expensive and intensive inpatient mode often depends on evidence of additional severe medical or psychiatric syndromes, the absence of appropriate nearby outpatient groups and facilities, and the patient's history of having failed in outpatient care. The treatment process in either setting involves intervention, optimizing physical and psychological functioning, enhancing motivation, reaching out to family, and using the first 2 to 4 weeks of care as an intensive period of help. Those efforts must be followed by at least 3 to 6 months of less frequent outpatient care. Outpatient care uses a combination of individual and group counseling, judicious avoidance of psychotropic medications unless needed for independent disorders, and involvement in such self-help groups as AA. Counseling. Counseling efforts in the first several months should focus on day-today life issues to help patients maintain a high level of motivation for abstinence and to enhance their functioning. Psychotherapy techniques that provoke anxiety or that require deep insights have not been shown to be of benefit during the early months of recovery and, at least theoretically, may actually impair efforts at maintaining abstinence. Thus, this discussion focuses on the efforts likely to characterize the first 3 to 6 months of care. Counseling or therapy can be carried out in an individual or group setting; few data indicate that either approach is superior. The technique used is not likely to matter greatly and usually boils down to simple day-to-day counseling or almost any behavioral or psychotherapeutic approach focusing on the here and now. To optimize motivation, treatment sessions should explore the consequences of drinking, the likely future course of alcohol-related life problems, and the marked improvement that can be expected with abstinence. Whether in an inpatient or an outpatient setting, individual or group counseling is usually offered a minimum of three times a week for the first 2 to 4 weeks, followed by less intense efforts, perhaps once a week, for the subsequent 3 to 6 months. Much time in counseling deals with how to build a lifestyle free of alcohol. Discussions cover the need for a sober peer group, a plan for social and recreational events without drinking, and approaches for reestablishing communication with family members and friends. The third major component, relapse prevention, first identifies situations in which the risk for relapse is high. The counselor must help the patient develop modes of coping to

be used when the craving for alcohol increases or when any event or emotional state makes a return to drinking likely. An important part of relapse prevention is reminding the patient about the appropriate attitude toward slips. Short-term experiences with alcohol can never be used as an excuse for returning to regular drinking. The efforts to achieve and maintain a sober lifestyle are not a game in which all benefits are lost with that first sip. Rather, recovery is a process of trial and error; patients use slips that occur to identify high-risk situations and to develop more appropriate coping techniques. Most treatment efforts recognize the effects that alcoholism has on the significant persons in the patient's life, and an important aspect of recovery involves helping family members and close friends understand alcoholism and realize that rehabilitation is an ongoing process that lasts for 6 to 12 or more months. Couples and family counseling and support groups for relatives and friends help the persons involved to rebuild relationships, to learn how to avoid

protecting the patient from the consequences of any drinking in the future, and to be as supportive as possible of the alcoholic patient's recovery program. Medications. If detoxification has been completed and the patient is not one of the 10 to 15 percent of alcoholic persons who have an independent mood disorder, schizophrenia, or anxiety disorder, little evidence favors prescribing psychotropic medications for the treatment of alcoholism. Lingering levels of anxiety and insomnia as part of a reaction to life stresses and protracted abstinence should be treated with behavior modification approaches and reassurance. Medications for these symptoms (including benzodiazepines) are likely to lose their effectiveness much faster than the insomnia disappears; thus, the patient may increase the dose and have subsequent problems. Similarly, sadness and mood swings can linger at low levels for several months. Controlled clinical trials, however, indicate no benefit in prescribing antidepressant medications or lithium to treat the average alcoholic person who has no independent or long-lasting psychiatric disorder. The mood disorder will clear before the medications can take effect, and patients who resume drinking while on the medications face significant potential dangers. With little or no evidence that the medications are effective, the dangers significantly outweigh any potential benefits from their routine use. One possible exception to the proscription against the use of medications is the alcohol-sensitizing agent disulfiram. Disulfiram is given in daily doses of 250 mg before the patient is discharged from the intensive first phase of outpatient rehabilitation or from inpatient care. The goal is to place the patient in a condition in which drinking alcohol precipitates an uncomfortable physical reaction, including nausea, vomiting, and a burning sensation in the face and stomach. Few data prove that disulfiram is more effective than a placebo, however, probably because most persons stop taking the disulfiram when they resume drinking. Many clinicians have stopped routinely prescribing the agent, partly in recognition of the dangers associated with the drug itself: mood swings, rare instances of psychosis, the possibility of increased peripheral neuropathies, the relatively rare occurrence of other significant neuropathies, and

potentially fatal hepatitis. Moreover, patients with preexisting heart disease, cerebral thrombosis, diabetes, and a number of other conditions cannot be given disulfiram because an alcohol reaction to the disulfiram could be fatal. Two additional promising pharmacological interventions have recently been studied. The first involves the opioid antagonist naltrexone (ReVia), which at least theoretically is believed possibly to decrease the craving for alcohol or blunt the rewarding effects of drinking. In any event, two relatively small (approximately 90 patients on the active drug across the studies) and short-term (3 months of active treatment) investigations using 50 mg per day of this drug had potentially promising results. Evaluating the full impact of this medication, however, will require longer-term studies of relatively large groups of more diverse patients. The second medication of interest, acamprosate (Campral), has been tested in more than 5,000 alcohol-dependent patients in Europe. This drug is not yet available in the United States. Used in dosages of approximately 2,000 mg per day, this medication was associated with approximately 10 to 20 percent more positive outcomes than placebo when used in the context of the usual psychological and behavioral treatment regimens for alcoholism. The mechanism of action of acamprosate is not known, but it may act directly or indirectly at GABA receptors or at NMDA sites, the effects of which alter the development of tolerance or physical dependence on alcohol. A summary of medications used for alcohol dependence is given in Table 20.2-7. Table 20.2-7 Medications for Treating Alcohol Dependence

Another medication with potential promise in the treatment of alcoholism is the nonbenzodiazepine antianxiety drug buspirone (BuSpar), although the effect of this drug on alcohol rehabilitation is inconsistent between studies. No evidence exists that antidepressant medications, such as the selective serotonin reuptake inhibitors (SSRIs), lithium, or antipsychotic medications, are significantly effective in the treatment of alcoholism. Alcoholics Anonymous. Clinicians must recognize the potential importance of self-help groups such as AA. Members of AA have help available 24 hours a day, associate with a sober peer group, learn that it is possible to participate in social functions without drinking, and are given a model of recovery by observing the

accomplishments of sober members of the group. Learning about AA usually begins during inpatient or outpatient rehabilitation. The clinician can play a major role in helping patients understand the differences between specific groups. Some are composed only of men or women, and others are mixed; some meetings are composed mostly of blue collar men and women, whereas others are mostly for professionals; some groups place great emphasis on religion, and others are eclectic. Patients with coexisting psychiatric disorders may need some additional education about AA. The clinician should remind them that some members of AA may not understand their special need for medications and should arm the patients with ways of coping when group members inappropriately suggest that the required medications be stopped. Although difficult to evaluate using double-blind controls, most studies indicate that participation in AA is associated with improved outcomes, and incorporation into treatment programs saves money. REFERENCES Baillie AJ, Sannibale C, Stapinski LA, Teesson M, Rapee RM, Haber PS. An investigator-blinded randomized study to compare the efficacy of combined CBT for alcohol use disorders and social anxiety disorder versus CBT focused on alcohol alone in adults with comorbid disorders: The Combined Alcohol Social Phobia (CASP) trial protocol. BMC Psych. 2013;13:199. Choo ED, McGregor AJ, Mello MJ, Baird J. Gender, violence and brief interventions for alcohol in the emergency department. Drug Alcohol Depend. 2013;127:115. Incerti M, Vink J, Roberson R, Benassou I, Abebe D, Spong CY. Prevention of the alcohol-induced changes in brain-derived neurotrophic factor expression using neuroprotective peptides in a model of fetal alcohol syndrome. Am J Obstet Gynecol. 2010;202(5):457. Jackson KM, Bucholz KK, Wood PK, Steinley D, Grant JD, Sher KJ. Towards the characterization and validation of alcohol use disorder subtypes: integrating consumption and symptom data. Psychol Med . 2014;44(01):143–159. Johnson BA. Medication treatment of different types of alcoholism. Am J Psychiatry. 2010; 167:630. Johnson BA, Marzani-Nissen G. Alcohol. Clinical Aspects. In: Johnson BA, ed. Addiction Medicine: Science and Practice. New York: Springer; 2011:381. MacKillop J, Miranda R, Jr., Monti PM, Ray LA, Murphy JG, Rohsenow DJ, McGeary JE, Swift RM, Tidey JW, Gwaltney CJ. Alcohol demand, delayed reward discounting, and craving in relation to drinking and alcohol use disorders. J Abnorm Psychol. 2010;11:106. Moberg CA, Curtin JJ. Alcohol selectively reduces anxiety but not fear: startle response during unpredictable versus predictable threat. J Abnorm Psychol. 2009;118(2):335. Morgan T, White H, Mun E. Changes in drinking before a mandated brief intervention with college students. J Stud Alcohol Drugs. 2008;69:286. Nilsen P. Brief alcohol intervention—where to from here? Challenges remain for research and practice. Addiction. 2010;105(6):954. Oreskovich MR, Kaups KL, Balch CM, Hanks JB, Satele D, Sloan J, Meredith C, Buhl A, Dyrbye LN, Shanafelt TD. Prevalence of alcohol use disorders among American surgeons. JAMA Arch Surg. 2012;147(2):168. Rasmussen C, Bisnaz J. Executive functioning in children with Fetal Alcohol Spectrum Disorders: Profiles and age-related differences. Child Neuropsych. 2009;15(3):201. Schuckit MA. Alcohol-related disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook

03 - 20.3 Caffeine Related Disorders

20.3 Caffeine-Related Disorders

of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1268. Vergés A, Jackson KM, Bucholz KK, Grant JD, Trull TJ, Wood PK, Sher KJ. Deconstructing the age-prevalence curve of alcohol dependence: Why “maturing out” is only a small piece of the puzzle. J Abnormal Psychol. 2012;121:511. 20.3 Caffeine-Related Disorders Caffeine is the most widely consumed psychoactive substance in the world. Caffeine is found in more than 60 species of plants and belongs to the methylxanthine class of alkaloids, which also includes theobromine (found in chocolate) and theophylline (often used in the treatment of asthma). In the United States, 87 percent of children and adults consume foods and beverages containing caffeine. Caffeine affects various neurobiological and physiological systems and produces significant psychological effects. Caffeine is not associated with any life-threatening illnesses, but its use can result in psychiatric symptoms and disorders. The habitual use of caffeine and its widely accepted integration into daily customs can lead to an underestimation of the role that caffeine may play in one’s daily life and can make the recognition of caffeine-associated disorders particularly challenging. Hence, it is important for the clinician to be familiar with caffeine, its effects, and problems that can be associated with its use. Caffeine use is associated with five disorders: caffeine use disorder, caffeine intoxication, caffeine withdrawal, caffeine-induced anxiety disorder, and caffeineinduced sleep disorder. EPIDEMIOLOGY Caffeine is contained in drinks, foods, prescription medicines, and over-the-counter medicines (Table 20.3-1). An adult in the United States consumes about 200 mg of caffeine per day on average, although 20 to 30 percent of all adults consume more than 500 mg per day. The per capita use of coffee in the United States is 10.2 pounds per year. A cup of coffee generally contains 100 to 150 mg of caffeine; tea contains about one third as much. Many over-the-counter medications contain one third to one half as much caffeine as a cup of coffee, and some migraine medications and over-the-counter stimulants contain more caffeine than a cup of coffee. Cocoa, chocolate, and soft drinks contain significant amounts of caffeine, enough to cause some symptoms of caffeine intoxication in small children when they ingest a candy bar and a 12-ounce cola drink. Table 20.3-1 Common Sources of Caffeine and Representative Decaffeinated Products

Caffeine consumption also varies by age. The average daily caffeine consumption of caffeine consumers of all ages is 2.79 mg/kg of body weight in the United States. A substantial amount of

caffeine is consumed even by young children (i.e., more than 1 mg/kg for children between the ages of 1 and 5 years). Worldwide, estimates place the average daily per capita caffeine consumption at about 70 mg. Up to 85 percent of adults consume caffeine in any given year. COMORBIDITY Persons with caffeine-related disorders are more likely to have additional substancerelated disorders than are those without diagnoses of caffeine-related disorders. About two thirds of those who consume large amounts of caffeine daily also use sedative and hypnotic drugs. ETIOLOGY After exposure to caffeine, continued caffeine consumption can be influenced by several different factors, such as the pharmacological effects of caffeine, caffeine's reinforcing effects, genetic predispositions to caffeine use, and personal attributes of the consumer.

Neuropharmacology Caffeine, a methylxanthine, is more potent than another commonly used methylxanthine, theophylline (Primatene). The half-life of caffeine in the human body is 3 to 10 hours, and the time of peak concentration is 30 to 60 minutes. Caffeine readily crosses the blood–brain barrier. Caffeine acts primarily as an antagonist of the adenosine receptors. Adenosine receptors activate an inhibitory G protein (Gi) and, thus, inhibit the formation of the second-messenger cyclic adenosine monophosphate (cAMP). Caffeine intake, therefore, results in an increase in intraneuronal cAMP concentrations in neurons with adenosine receptors. Three cups of coffee are estimated to deliver so much caffeine to the brain that about 50 percent of the adenosine receptors are occupied by caffeine. Several experiments indicate that caffeine, especially at high doses or concentrations, can affect dopamine and noradrenergic neurons. Specifically, dopamine activity may be enhanced by caffeine, a hypothesis that could explain clinical reports associating caffeine intake with an exacerbation of psychotic symptoms in patients with schizophrenia. Activation of noradrenergic neurons has been hypothesized to be involved in the mediation of some symptoms of caffeine withdrawal. Subjective Effects and Reinforcement Single low to moderate doses of caffeine (i.e., 20 to 200 mg) can produce a profile of subjective effects in humans that is generally identified as pleasurable. Thus, studies have shown that such doses of caffeine result in increased ratings on measures such as well-being, energy and concentration, and motivation to work. In addition, these doses of caffeine produce decreases in ratings of feeling sleepy or tired. Doses of caffeine in the range of 300 to 800 mg (the equivalent of several cups of brewed coffee ingested at once) produce effects that are often rated as being unpleasant, such as anxiety and nervousness. Although animal studies have generally found it difficult to demonstrate that caffeine functions as a reinforcer, well-controlled studies in humans have shown that people choose caffeine over placebo when given the choice under controlled experimental conditions. In habitual users, the reinforcing effects of caffeine are potentiated by the ability to suppress low-grade withdrawal symptoms after overnight abstinence. Thus, the profile of caffeine's subjective effects and its ability to function as a reinforcer contribute to the regular use of caffeine. Genetics and Caffeine Use Some genetic predisposition may exist to continued coffee use after exposure to coffee. Investigations comparing coffee or caffeine use in monozygotic and dizygotic twins have shown higher concordance rates for monozygotic twins for total caffeine consumption, heavy use, caffeine tolerance, caffeine withdrawal, and caffeine intoxication, with heritabilities ranging between 35 and 77 percent. Multivariate structural equation modeling of caffeine use, cigarette smoking, and alcohol use suggests that a common genetic factor—polysubstance use—underlies use of these three substances. Age, Sex, and Race The relationship between long-term chronic caffeine use and demographical features, such as age, sex, and race, has not been widely studied. Some evidence suggests that middle-aged people may use more caffeine, although caffeine use in adolescents is not uncommon. No known evidence

indicates that caffeine use differs between men and women, and no data specifically address caffeine use for different races. Some evidence suggests that, for both children and adults in the United States, whites consume more caffeine than blacks.

Special Populations Cigarette smokers consume more caffeine than nonsmokers. This observation may reflect a common genetic vulnerability to caffeine use and cigarette smoking. It may also be related to increased rates of caffeine elimination in cigarette smokers. Preclinical and clinical studies indicate that regular caffeine use can potentiate the reinforcing effects of nicotine. Heavy use and clinical dependence on alcohol is associated with heavy use and clinical dependence on caffeine as well. Individuals with anxiety disorders tend to report lower levels of caffeine use, although one study showed that a greater proportion of heavy caffeine consumers also use benzodiazepines. Several studies have also shown high daily amounts of caffeine use in psychiatric in-patients. For example, several studies have found that such patients consume the equivalent of an average of five or more cups of brewed coffee each day. Finally, high daily caffeine consumption has also been noted in prisoners. Personality Although attempts have been made to link preferential use of caffeine to particular personality types, results from these studies do not suggest that any particular personality type is especially linked to caffeine use. Effects on Cerebral Blood Flow Most studies have found that caffeine results in global cerebral vasoconstriction, with a resultant decrease in cerebral blood flow (CBF), although this effect may not occur in persons over 65 years of age. According to one recent study, tolerance does not develop to these vasoconstrictive effects, and the CBF shows a rebound increase after withdrawal from caffeine. Some clinicians believe that caffeine use can cause a similar constriction in the coronary arteries and produce angina in the absence of atherosclerosis. DIAGNOSIS The diagnosis of caffeine intoxication or other caffeine-related disorders depends primarily on a comprehensive history of a patient’s intake of caffeine-containing products. The history should cover whether a patient has experienced any symptoms of caffeine withdrawal during periods when caffeine consumption was either stopped or severely reduced. The differential diagnosis for caffeine-related disorders should include the following psychiatric diagnoses: generalized anxiety disorder, panic disorder with or without agoraphobia, bipolar II disorder, attention-deficit/hyperactivity disorder (ADHD), and sleep disorders. The differential diagnosis should include the abuse of caffeine-containing over-the-counter medications, anabolic steroids, and other stimulants, such as amphetamines and cocaine. A urine sample may be needed to screen for these substances. The differential diagnosis should also include hyperthyroidism and pheochromocytoma. Caffeine Intoxication The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

diagnostic criteria for caffeine intoxication includes the recent consumption of caffeine, usually in excess of 250 mg. The annual incidence of caffeine intoxication is an estimated 10 percent, although some clinicians and investigators suspect that the actual incidence is much higher. The common symptoms associated with caffeine intoxication include anxiety, psychomotor agitation, restlessness, irritability, and psychophysiological complaints such as muscle twitching, flushed face, nausea, diuresis, gastrointestinal distress, excessive perspiration, tingling in the fingers and toes, and insomnia. Consumption of more than 1 g of caffeine can produce rambling speech, confused thinking, cardiac arrhythmias, inexhaustibleness, marked agitation, tinnitus, and mild visual hallucinations (light flashes). Consumption of more than 10 g of caffeine can cause generalized tonic–clonic seizures, respiratory failure, and death. Ms. B, a 30-year-old, went for consultation due to “anxiety attacks.” The attacks occurred mid- to late afternoon, when Ms. B

became restless, nervous, and easily excited and sometimes was noticed to be flushed, sweating, and, according to coworkers, “talking a mile a minute.” In response to questioning, Ms. B admitted to consuming six to seven cups of coffee each day before the time the attacks usually occurred. Caffeine Withdrawal The appearance of withdrawal symptoms reflects the tolerance and physiological dependence that develop with continued caffeine use. Several epidemiological studies have reported symptoms of caffeine withdrawal in 50 to 75 percent of all caffeine users studied. The most common symptoms are headache and fatigue; other symptoms include anxiety, irritability, mild depressive symptoms, impaired psychomotor performance, nausea, vomiting, craving for caffeine, and muscle pain and stiffness. The number and severity of the withdrawal symptoms are correlated with the amount of caffeine ingested and the abruptness of the withdrawal. Caffeine withdrawal symptoms have their onset 12 to 24 hours after the last dose; the symptoms peak in 24 to 48 hours and resolve within 1 week. The induction of caffeine withdrawal can sometimes be iatrogenic. Physicians often ask their patients to discontinue caffeine intake before certain medical procedures, such as endoscopy, colonoscopy, and cardiac catheterization. In addition, physicians often recommend that patients with anxiety symptoms, cardiac arrhythmias, esophagitis, hiatal hernias, fibrocystic disease of the breast, and insomnia stop caffeine intake. Some persons simply decide that it would be good for them to stop using caffeine-containing products. In all these situations, caffeine users should taper the use of caffeinecontaining products over a 7- to 14-day period rather than stop abruptly. Mr. F was a 43-year-old attorney who was brought for a psychiatric consultation by

his wife. Mr. F had been complaining of fatigue, loss of motivation, sleepiness, headache, nausea, and difficulty concentrating. His symptoms occurred mostly over the weekends. He withdrew from weekend social activities due to his symptoms, which worried Mrs. F because he seems fine during the week. Mr. F is in good health with no recent history of medical disorders. Mr. F worked in a very busy law practice, many times working 60-hour weeks, and barely sees his family during the week. At work he is often anxious, restless, and constantly busy. He worries about his job so much that he has difficulty sleeping on weeknights. He denies any marital or family problems, other than those caused by his not wanting to do anything over the weekend. At work, Mr. F regularly consumes approximately 4 to 5 cups of coffee per day. He cut out coffee on the weekends because he felt that it may be contributing to his anxiety and sleeplessness. Caffeine-Induced Anxiety Disorder The anxiety related to caffeine use can resemble that of generalized anxiety disorder. Patients with the disorder may be perceived as “wired,” overly talkative, and irritable; they may complain of not sleeping well and of having energy to burn. Caffeine can induce and exacerbate panic attacks in persons with a panic disorder, and although a causative association between caffeine and a panic disorder has not yet been demonstrated, patients with panic disorder should avoid caffeine. Mr. B was a 28-year-old single African American male graduate student who was in good health and had no history of previous psychiatric evaluation or treatment. He took no medications, did not smoke or consume alcohol, and had no current or past history of illicit drug use. His chief complaint was that he had begun feeling mounting “anxiety” when working in the laboratory where he was pursuing his graduate studies. His work had been progressive well, he felt his relationship with his advisor was good and supportive, and he could not identify any problems with staff or peers that might explain his anxiety. He had been working long hours, but found the work interesting and had recently had his first paper accepted for publication. Despite these successes, he reported feeling a “crescendoing anxiety” as his day would progress. He noted that by the afternoon he would be experiencing palpitations, bursts of his heart racing, tremors in his hands, and an overall feeling of

“being on the edge.” He also noted a nervous energy in the afternoons. These experiences were occurring daily and seemed confined to the laboratory (although he admitted he was in the laboratory every day of the week). When reviewing Mr. B’s caffeine intake, it was found that he was consuming excessive amounts of coffee. Staff made a large urn of caffeinated coffee each morning, and Mr. B routinely started with a large mug of coffee. Over the course of

the morning he would consume three to four mugs of coffee (the equivalent of about six or eight 6-oz cups of coffee), and continued this level of use throughout the afternoon. He occasionally had a single can of a caffeinated soft drink, and used no other forms of caffeine on a regular basis. Mr. B estimated that he drank a total of six to eight or more mugs of coffee per day (which was estimated to be at least 1,200 mg of caffeine per day). Once pointed out to him, he realized that this level of caffeine consumption was considerably higher than at any other time in his life. He admitted he liked the taste of coffee and felt a burst of energy in the morning when he drank coffee that helped him start his day. Mr. B and his physician developed a plan to decrease his caffeine use by tapering off caffeine. Mr. B was successful in decreasing his caffeine use and had good resolution of his anxiety symptoms once his daily caffeine use had markedly decreased. (Courtesy of Laura M. Juliano, Ph.D., and Roland R. Griffiths, Ph.D.) Caffeine-Induced Sleep Disorder Caffeine is associated with delay in falling asleep, inability to remain asleep, and early morning awakening. Caffeine Use Disorder A diagnosis of caffeine use disorder can be given in some people with problematic caffeine consumption. It is included in Section III of DSM-5, which is reserved for conditions that require further research. No studies have examined the course and prognosis for patients with a diagnosis of caffeine use disorder. Subjects with caffeine use disorder have reported continued use of caffeine despite repeated efforts to discontinue their caffeine use. Ms. G was a 35-year-old married, white homemaker with three children, aged 8, 6, and 2. She took no prescription medications, took a multivitamin and vitamins C and E on a daily basis, did not smoke, and had no history of psychiatric problems. She drank moderate amounts of alcohol on the weekends, had smoked marijuana in college but had not used it since, and had no other history of illicit drug use. She had started consuming caffeinated beverages while in college, and her current beverage of choice was caffeinated diet cola. Ms. G had her first soft drink early in the morning, shortly after getting out of bed, and she jokingly called it her “morning hit.” She spaced out her bottles of soft drinks over the course of the day, with her last bottle at dinnertime. She typically drank four to five 20-oz bottles of caffeinated diet cola each day. She and her husband had argued about her caffeinated soft drink use in the past, and her husband had believed she should not drink caffeinated soft drinks while pregnant. However, she had continued to do so during each of her pregnancies.

Despite a desire to stop drinking caffeinated soft drinks, she was unable to do so. She described having a strong desire to drink caffeinated soft drinks, and if she resisted this desire, she found that she could not think of anything else. She drank caffeinated soft drinks in her car, which had a manual transmission, and noted that she fumbled while shifting and holding the soft drink and spilled it in the car. She also noted that her teeth had become yellowed, and she suspected this was related to her tendency to swish soft drink in her mouth before swallowing it. When asked to describe a time when she stopped using soft drinks, she reported that she had run out of it on the day one of her children was to have a birthday party, and she did not have time to leave her home to buy more. In the early afternoon of that day, a few hours before the scheduled start of the party, she felt extreme lethargy, a severe headache, irritability, and craving for a soft drink. She called

her husband and told him she planned to cancel the party. She then went to the grocery store to buy soft drinks, and after drinking two bottles, she felt well enough to host the party. Although initially expressing interest in decreasing or stopping her caffeinated soft drink use, Ms. G did not attend scheduled follow-up appointments after her first evaluation. When finally contacted at home, she reported she had only sought help initially at her husband's request, and she had decided to try to cut down on her caffeine use on her own. (Courtesy of Eric Stain, M.D.) Caffeine-Related Disorder Not Elsewhere Classified This category is used for caffeine-related disorders that do not meet the criteria for caffeine use disorder, caffeine intoxication, caffeine withdrawal, caffeine-induced anxiety disorder, or caffeine-induced sleep disorder. CLINICAL FEATURES Signs and Symptoms After the ingestion of 50 to 100 mg of caffeine, common symptoms include increased alertness, a mild sense of well-being, and a sense of improved verbal and motor performance. Caffeine ingestion is also associated with diuresis, cardiac muscle stimulation, increased intestinal peristalsis, increased gastric acid secretion, and (usually mildly) increased blood pressure. Caffeine Use and Nonpsychiatric Illnesses Despite numerous studies examining the relationship between caffeine use and physical illness, significant health risk from nonreversible pathological consequences of caffeine use, such as cancer, heart disease, and human reproduction, has not been conclusively demonstrated. Nonetheless, caffeine use is often considered to be contraindicated for various conditions, including generalized anxiety disorder, panic disorder, primary insomnia, gastroesophageal reflux, and pregnancy. In addition, the modest ability of

caffeine to increase blood pressure and the documented cholesterol-elevating compounds of unfiltered coffee have raised the issue of the relationship of caffeine and coffee use to cardiovascular disease. Finally, there may be a mild association between higher daily caffeine use in women and delayed conception and slightly lower birth weight. Studies, however, have not found such associations, and effects, when found, are usually with relatively high daily dosages of caffeine (e.g., the equivalent of five cups of brewed coffee per day). For a woman who is considering pregnancy, especially if there is some difficulty in conceiving, it may be useful to counsel the elimination of caffeine use. Similarly, for a woman who becomes pregnant and has moderate to high daily caffeine consumption, a discussion about decreasing her daily caffeine use may be warranted. TREATMENT Analgesics, such as aspirin, almost always can control the headaches and muscle aches that may accompany caffeine withdrawal. Rarely do patients require benzodiazepines to relieve withdrawal symptoms. If benzodiazepines are used for this purpose, they should be used in small dosages for a brief time, about 7 to 10 days at the longest. The first step in reducing or eliminating caffeine use is to have patients determine their daily consumption of caffeine. This can best be accomplished by having the patient keep a daily food diary. The patient must recognize all sources of caffeine in the diet, including forms of caffeine (e.g., beverages, medications), and accurately record the amount consumed. After several days of keeping such a diary, the clinician can meet with the patient, review the diary, and determine the average daily caffeine dose in milligrams. The patient and clinician should then decide on a fading schedule for caffeine consumption. Such a schedule could involve a decrease in increments of 10 percent every few days. Because caffeine is typically consumed in beverage form, the patient can use a substitution procedure in which a decaffeinated beverage is gradually used in place of the caffeinated beverage. The diary should be maintained during this time, so that the patient's progress can be monitored. The fading should be individualized for each patient, so that the rate of decrease in caffeine consumption minimizes withdrawal symptoms. The patient should probably avoid stopping all caffeine use abruptly, because withdrawal symptoms are likely to develop with

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plants may contain up to 15 or 20 percent THC.

FIGURE 20.4-1 Marijuana (Cannabis sativa). EPIDEMIOLOGY Prevalence and Recent Trends Based on the 2012 National Surveys on Drug Use and Health (NSDUH), an estimated 19 million persons age 12 years and older (7 percent) had used marijuana in the past month. Of this age group, 2.4 million initiated use within the last year, 57 percent of which initiated use before age 18 years. The Monitoring the Future survey of adolescents in school indicates recent increases in lifetime, annual, current (within the past 30 days), and daily use of marijuana by eighth and tenth graders, continuing a trend that began in the early 1990s. In 1996, about 23 percent of eighth graders and about 40 percent of tenth graders reported having used marijuana and, in 1998 and 1999, more than a quarter of marijuana initiates were aged 14 years or younger. The average age was 17. In 2012, approximately 1 percent of eighth graders, 4 percent of tenth graders, and 7 percent of twelfth graders reported daily use of marijuana. Demographic Correlates

The rate of past year and current marijuana use by males was almost twice the rate for females overall among those aged 26 and older. This gap between the sexes narrows with younger users; at ages 12 to 17, there are no significant differences. Race and ethnicity were also related to marijuana use, but the relationships varied by age group. Among those aged 12 to 17, whites had higher rates of lifetime and past-year marijuana use than blacks. Among those 17 to 34 years of age, whites reported higher levels of lifetime use than blacks and Hispanics. But among those 35 and older, whites and blacks reported the same levels of use. The lifetime rates for black adults were significantly higher than those for Hispanics. NEUROPHARMACOLOGY As stated above, the principal component of cannabis is Δ9-THC; however, the cannabis plant contains more than 400 chemicals, of which about 60 are chemically related to Δ9THC. In humans, Δ9-THC is rapidly converted into 11-hydroxy-Δ9-THC, the metabolite that is active in the central nervous system (CNS). A specific receptor for the cannabinols has been identified, cloned, and characterized. The cannabinoid receptor, a member of the G-protein-linked family of receptors, is linked to the inhibitory G protein (Gi), which is linked to adenylyl cyclase in an inhibitory fashion. The cannabinoid receptor is found in highest concentrations in the basal ganglia, the hippocampus, and the cerebellum, with lower concentrations in the cerebral cortex (Figure 20.4-2). This receptor is not found in the brainstem, a fact consistent with cannabis's minimal effects on respiratory and cardiac functions. Studies in animals have shown that the cannabinoids affect the monoamine and γ-aminobutyric acid (GABA) neurons. FIGURE 20.4-2 Autoradiography of cannabinoid receptor distribution in a sagittal section of rat brain.

Binding of tritiated ligand is dense in the hippocampus (Hipp), the globus pallidus (GP), the entopeduncular nucleus (EP), the substantia nigra pars reticulata (SNr), and the cerebellum (Cer). Binding is moderate in the cerebral cortex (Cx) and the caudate putamen (CP) and sparse in the brainstem (Br St) and spinal cord. (From Howlett AC, Bidaut-Russell M, Devane WA, Melvin LS, Johnson MR, Herkenham M. The cannabinoid receptor: Biochemical anatomical, and behavioral characterization. Trends Neurosci. 1990;13:422, with permission.) According to most studies, animals do not self-administer cannabinoids as they do most other substances of abuse. Moreover, some debate questions whether the cannabinoids stimulate the so-called reward centers of the brain, such as the dopaminergic neurons of the ventral tegmental area. Tolerance to cannabis does develop, however, and psychological dependence has been found, although the evidence for physiological dependence is not strong. Withdrawal symptoms in humans are limited to modest

increases in irritability, restlessness, insomnia, and anorexia and mild nausea; all these symptoms appear only when a person abruptly stops taking high doses of cannabis. When cannabis is smoked, the euphoric effects appear within minutes, peak in about 30 minutes, and last 2 to 4 hours. Some motor and cognitive effects last 5 to 12 hours. Cannabis can also be taken orally when it is prepared in food, such as brownies and cakes. About two to three times as much cannabis must be taken orally to be as potent as cannabis taken by inhaling its smoke. Many variables affect the psychoactive properties of cannabis, including the potency of the cannabis used, the route of administration, the smoking technique, the effects of pyrolysis on the cannabinoid content, the dose, the setting, and the user's past experience, expectations, and unique biological vulnerability to the effects of cannabinoids. DIAGNOSIS AND CLINICAL FEATURES The most common physical effects of cannabis are dilation of the conjunctival blood vessels (red eye) and mild tachycardia. At high doses, orthostatic hypotension may appear. Increased appetite—often referred to as "the munchies"—and dry mouth are common effects of cannabis intoxication. That no clearly documented case of death caused by cannabis intoxication alone reflects the substance's lack of effect on the respiratory rate. The most serious potential adverse effects of cannabis use are those caused by inhaling the same carcinogenic hydrocarbons present in conventional tobacco, and some data indicate that heavy cannabis users are at risk for chronic respiratory disease and lung cancer. The practice of smoking cannabis-containing cigarettes to their very ends, so-called "roaches," further increases the intake of tar (particulate matter). Many reports indicate that long-term cannabis use is associated with cerebral atrophy, seizure susceptibility, chromosomal damage, birth defects, impaired immune reactivity, alterations in testosterone concentrations, and dysregulation of menstrual cycles; these reports, however, have not been conclusively

replicated, and the association between these findings and cannabis use is uncertain. Cannabis Use Disorder The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes the diagnosis of cannabis use disorder. People who use cannabis daily over weeks to months are most likely to become dependent. The risk of developing dependence is around one in ten for anyone who uses cannabis. The earlier the age of first use, the more often cannabis has been used, and the longer it has been used, the higher the risk of dependence. Cannabis Intoxication Cannabis intoxication commonly heightens users' sensitivities to external stimuli, reveals new details, makes colors seem brighter and richer, and subjectively slows the appreciation of time. In high doses, users may experience depersonalization and derealization. Motor skills are impaired by cannabis use, and the impairment in motor skills remains after the subjective, euphoriant effects have resolved. For 8 to 12 hours after using cannabis, users' impaired motor skills interfere with the operation of motor vehicles and other heavy machinery. Moreover, these effects are additive to those of alcohol, which is commonly used in combination with cannabis. Mr. M was an unemployed 20-year-old man who lived with his parents. He was brought to a hospital by some friends in a state of anxiety and agitation. He had been out for the evening with some friends at a restaurant, and after a couple of beers, he decided to have some cannabis. He had smoked cannabis on previous occasions; however, this time he ate a lump of cannabis despite warnings from his friends. After about half an hour, Mr. M appeared tense and anxious and complained that everything was changing. He could see the faces of his friends increasing to about three times their natural size. The room became distorted, and its proportions and colors kept altering. He felt that the other guests in the restaurant were talking about him and his friends in a menacing way, so he suddenly rushed outside because he felt that he was in danger. He became increasingly agitated and started running down the middle of the street, dodging in and out among the traffic.

Eventually, his friends were able to catch him. They were unable to quiet his anxiety, however, and had a hard time persuading him to go with them to the hospital. On examination Mr. M appeared tense and apprehensive, looking around the room as if he felt uneasy with the surroundings, but he denied perceptual symptoms and did not really believe that he was the subject of persecution. He was fully aware of his surroundings, but his attention was fleeting, and he did not always answer questions. There was no marked impairment of memory, and he was fully oriented. Physical examination revealed conjunctival injection and an increased pulse rate of 120 beats per minute, but otherwise no abnormalities were found. Neurological

examination also revealed no abnormalities. In the course of a few hours, he quieted down. When he felt recovered, he left the hospital with his friends. Cannabis Intoxication Delirium The delirium associated with cannabis intoxication is characterized by marked impairment on cognition and performance tasks. Even modest doses of cannabis impair memory, reaction time, perception, motor coordination, and attention. High doses that also impair users' levels of consciousness have marked effects on cognitive measures. Cannabis Withdrawal Studies have shown that cessation of use in daily cannabis users results in withdrawal symptoms within 1 to 2 weeks of cessation. Withdrawal symptoms include irritability, cannabis cravings, nervousness, anxiety, insomnia, disturbed or vivid dreaming, decreased appetite, weight loss, depressed mood, restlessness, headache, chills, stomach pain, sweating, and tremors. Cannabis-Induced Psychotic Disorder Cannabis-induced psychotic disorder is diagnosed in the presence of a cannabis-induced psychosis. Cannabis-induced psychotic disorder is rare; transient paranoid ideation is more common. Florid psychosis is somewhat common in countries in which some persons have longterm access to cannabis of particularly high potency. The psychotic episodes are sometimes referred to as "hemp insanity." Cannabis use rarely causes a "bad-trip" experience, which is often associated with hallucinogen intoxication. When cannabisinduced psychotic disorder does occur, it may be correlated with a preexisting personality disorder in the affected person. Cannabis-Induced Anxiety Disorder Cannabis-induced anxiety disorder is a common diagnosis for acute cannabis intoxication, which in many persons induces short-lived anxiety states often provoked by paranoid thoughts. In such circumstances, panic attacks may be induced, based on illdefined and disorganized fears. The appearance of anxiety symptoms is correlated with the dose and is the most frequent adverse reaction to the moderate use of smoked cannabis. Inexperienced users are much more likely to experience anxiety symptoms than are experienced users. A 35-year-old white married male who was naïve to cannabis use was given two "joints" by a friend. He smoked the first of the two in the same manner that he normally smoked a cigarette (in about 3 to 5 minutes). Noting no major effects, he

proceeded immediately to smoke the second in the same amount of time. Within 30 minutes, he began to experience rapid heartbeat, dry mouth, mounting anxiety and the delusional belief that his throat was closing up and that he was going to die. That belief induced further panic and the patient was brought to the emergency room in the midst of the experience. Reassurance that he would not die had no effect. He was sedated with diazepam and some of his anxiety diminished. He eventually went to sleep and on awakening in about 5 hours he was asymptomatic with full recall of previous events. Unspecified Cannabis-Related Disorders DSM-5 includes the category unspecified cannabis-related disorders for cannabis disorders that cannot be classified as cannabis use disorder, cannabis intoxication, cannabis intoxication delirium, cannabis withdrawal, cannabis-induced psychotic disorder, or cannabis-induced anxiety disorder. Cannabis intoxication can be

associated with depressive symptoms, although such symptoms may suggest long-term cannabis use. Hypomania, however, is a common symptom in cannabis intoxication. When either sleep disorder or sexual dysfunction symptoms are related to cannabis use, they almost always resolve within days or a week after cessation of cannabis use. Flashbacks. There are case reports of persons who have experienced—at times significantly—sensations related to cannabis intoxication after the short-term effects of the substance have disappeared. Continued debate concerns whether flashbacks are related to cannabis use alone or to the concomitant use of hallucinogens or of cannabis tainted with phencyclidine (PCP). Cognitive Impairment. Clinical and experimental evidence indicates that the long-term use of cannabis may produce subtle forms of cognitive impairment in the higher cognitive functions of memory, attention, and organization and in the integration of complex information. This evidence suggests that the longer the period of heavy cannabis use, the more pronounced the cognitive impairment. Nonetheless, because the impairments in performance are subtle, it remains to be determined how significant they are for everyday functioning. It also remains to be investigated whether these impairments can be reversed after an extended period of abstinence from cannabis. Amotivational Syndrome. A controversial cannabis-related syndrome is amotivational syndrome. Whether the syndrome is related to cannabis use or reflects characterological traits in a subgroup of persons regardless of cannabis use is under debate. Traditionally, the amotivational syndrome has been associated with long-term heavy use and has been characterized by a person’s unwillingness to persist in a task—be it at school, at work, or in any setting that requires prolonged attention or tenacity.

Persons are described as becoming apathetic and anergic, usually gaining weight, and appearing slothful. TREATMENT AND REHABILITATION Treatment of cannabis use rests on the same principles as treatment of other substances of abuse—abstinence and support. Abstinence can be achieved through direct interventions, such as hospitalization, or through careful monitoring on an outpatient basis by the use of urine drug screens, which can detect cannabis for up to 4 weeks after use. Support can be achieved through the use of individual, family, and group psychotherapies. Education should be a cornerstone for both abstinence and support programs. A patient who does not understand the intellectual reasons for addressing a substance-abuse problem has little motivation to stop. For some patients, an antianxiety drug may be useful for short-term relief of withdrawal symptoms. For other patients, cannabis use may be related to an underlying depressive disorder that may respond to specific antidepressant treatment. Medical Use of Marijuana Marijuana has been used as a medicinal herb for centuries, and cannabis was listed in the US Pharmacopeia until the end of the 19th century as a remedy for anxiety, depression, and gastrointestinal disorders, among others. Currently, cannabis is a controlled substance with a high potential for abuse and no medical use recognized by the Drug Enforcement Agency (DEA); however, it is used to treat various disorders, such as the nausea secondary to chemotherapy, multiple sclerosis (MS) chronic pain, acquired immune deficiency syndrome (AIDS), epilepsy, and glaucoma. In 1996, California residents approved the California Compensation Use Act that allowed state residents to grow and use marijuana for these disorders: in 2001, however, the U.S. Supreme Court ruled 8 to 0 that the manufacture and distribution of marijuana are illegal under any circumstances. In addition, the Court held that patients using marijuana for medical purposes can be prosecuted; however, as of 2013, 20 states—Alaska, Arizona, California, Colorado, Connecticut, Delaware, Hawaii, Illinois, Maine, Massachusetts, Michigan, Montana, Nevada, New Hampshire, New Jersey, New Mexico, Oregon, Rhode Island, Vermont and Washington—and the District of Columbia have passed laws exempting patients who use cannabis under a physician’s supervision from state

criminal penalties. In addition to the Supreme Court ruling, periodically the federal government attempts to prosecute doctors who prescribe the drug for medical use with the threat of loss of licensure or jail sentences. In a strongly worded editorial, the New England Journal of Medicine urged that “Federal authorities should rescind their prohibition of the medical use of marijuana for seriously ill patients and allow physicians to decide which patients to treat.” The editorial concluded by commenting on the role of the physician: “Some physicians will have the courage to challenge the continued proscription of marijuana for the sick. Eventually, their actions will force the courts to adjudicate between the rights of those at death’s door and the absolute power of bureaucrats whose decisions are based more on reflexive ideology and political correctness

than on compassion.” Dronabinol, a synthetic form of THC, has been approved by the U.S. Food and Drug Administration (FDA); some researchers believe, however, that when taken orally, it is not as effective as smoking the entire plant product. In 2006, regulatory officials authorized the first U.S. clinical trial investigating the efficacy of Sativex, an oral spray consisting of natural cannabis extracts, for the treatment of cancer pain. Sativex is currently available by prescription in Canada and on a limited basis in Spain and Great Britain for patients with neuropathic pain, multiple sclerosis, and other conditions. Sativex can be prescribed in the United States only with a special exemption granted by the FDA for use in certain patients. In 2013, a product called Epidiolex which contains cannabidiol was granted orphan drug status for the treatment of certain rare, intractable types of epilepsy in children. REFERENCES Agrawal A, Wetherill L, Dick DM, Xuei X, Hinrichs A, Hesselbrock V, Kramer J, Nurnberger Jr. JI, Schuckit M, Bierut LJ, Edenberg HJ, Foroud T. Evidence for association between polymorphisms in the cannabinoid receptor 1 (CNR1) gene and cannabis dependence. Am J Med Genet. 2009;150B:736. Buckner JD, Silgado J, Schmidt NB. Marijuana craving during a public speaking challenge: Understanding marijuana use vulnerability among women and those with social anxiety disorder. J Behav Ther Exp Psychiatry. 2011;42:104. Carter GT, Flanagan AM, Earleywine M, Abrams DI, Aggarwal SK, Grinspoon L. Cannabis in palliative medicine: Improving care and reducing opioid-related morbidity. Am J Hosp Palliat Care. 2011;28:297. Cohen AS, Buckner JD, Najolia GM, Stewart DW. Cannabis and psychometrically-defined schizotypy: Use, problems and treatment considerations. J Psychiatr Res. 2011;45:548. Crean RD, Crane NA, Mason BJ. An evidence-based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med. 2011;5:1. Crean RD, Tapert SF, Minassian A, MacDonald K, Crane NA, Mason BJ. Effects of chronic, heavy cannabis use on executive functions. J Addict Med. 2011;5:9. Ehlers CL, Gizer IR, Vieten C, Wilhelmsen KC. Linkage analyses of cannabis dependence, craving, and withdrawal in the San Francisco family study. Am J Med Genet. 2010;153B:802. Fridberg DJ, Skosnik PD, Hetrick WP, O’Donnell BF. Neural correlates of performance monitoring in chronic cannabis users and cannabis-naïve controls. J Psychopharm. 2013;27:515. Griffin O, Fritsch AL, Woodward VH, Mohn RS. Sifting through the hyperbole: One hundred year of marijuana coverage in The New York Times. Deviant Behav. 2013;34:767. Hall WD, Degenhardt L. Cannabis-related disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1309. Hurd YL, Michaelides M, Miller ML, Jutras-Aswad D. Trajectory of adolescent cannabis use on addiction vulnerability. Neuropharmacology. 2014;76:416–424. Nickerson LD, Ravichandran C, Lundahl LH, Rodolico J, Dunlap S, Trksak GH, Lukas SE. Cue reactivity in cannabisdependent adolescents. Psychol Addict Behav. 2011;25:168. Pacek LR, Martins SS, Crum RM. The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: results from a national sample. J Affect Disord. 2013;148:188. Svrakic

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Overview of Representative Hallucinogens

Phencyclidine (PCP; 1-1 [phenylcyclohexyl] piperidine), also known as angel dust, was first developed as a novel anesthetic in the late 1950s. This drug and the closely related compound ketamine were termed dissociative anesthetics, because they produced a condition in which subjects were awake but apparently insensitive to, or dissociated from, the environment. Phencyclidine and ketamine exert their unique behavioral effects by blocking N-methyl-D-aspartate (NMDA)–type receptors for the excitatory neurotransmitter glutamate. Their intoxication can present with a variety of symptoms, from anxiety to psychosis. Phencyclidine and ketamine are classified as Schedule II and Schedule III controlled substances, respectively. Although different in pharmacology and clinical effects, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes PCP and ketamine within the hallucinogen category due to their hallucinogenic effects. EPIDEMIOLOGY The incidence of hallucinogen use has exhibited two notable periods of increase. Between 1965 and 1969, there was a tenfold increase in the estimated annual number of initiates. This increase was driven primarily by the use of LSD. The second period of increase in first-time hallucinogen use occurred from around 1992 until 2000, fueled mainly by increases in use of ecstasy (i.e., MDMA). Decreases in initiation of both LSD

and ecstasy were evident between then and 2013, coinciding with an overall drop in hallucinogen incidence from 1.6 million to 1.1 million. The National Survey on Drug Use and Health (NSDUH) found that approximately 10 percent of persons age 12 years or older reported lifetime use of hallucinogens. Of this group, 9 percent reported lifetime use of LSD, 6 percent reported lifetime use of ecstasy, and 3 percent reported lifetime use of PCP. The highest rates of current use are among 18 to 25 year olds (2 percent) followed by 12 to 17 year olds (0.9 percent) and adults 25 years or older (0.2 percent). Males (9 percent) are more likely than females (11 percent) to use hallucinogens. Approximately 331,000 persons age 12 years or older were dependent on or abused hallucinogens within the past year. Hallucinogen use is most common among young (15 to 35 years of age) white men. The ratio of whites to blacks who have used a hallucinogen is 2:1; the white to Hispanic ratio is about 1.5:1. Men represent 62 percent of those who have used a hallucinogen at some time and 75 percent of those who have used a hallucinogen in the preceding month. Persons 26 to 34 years of age show the highest use of hallucinogens, with 16 percent having used a hallucinogen at least once. Persons 18 to 25 years of age have the highest recent use of a hallucinogen. Cultural factors influence the use of hallucinogens; their use in the western United States is significantly higher than in the southern United States. Hallucinogen use is associated with less morbidity and less mortality than use of some other substances. For example, one study found that only 1 percent of substance-related emergency room visits were related to hallucinogens, compared with 40 percent for cocaine-related problems. Of persons visiting the emergency room for hallucinogen-related reasons, however, more than 50 percent were younger than 20 years of age. Resurgence in the popularity of hallucinogens has been reported. Phencyclidine Phencyclidine and some related substances are relatively easy to synthesize in illegal laboratories and relatively inexpensive to buy on the street. The variable quality of the laboratories, however, results in a range of potency and purity. PCP use varies most markedly with geography. Most users of PCP also use other substances, particularly alcohol, but also opiates, opioids, marijuana, amphetamines, and cocaine. PCP is frequently added to marijuana, with severe untoward effects on users. The actual rate of PCP dependence and abuse is not known, but PCP is associated with 3 percent of substance abuse deaths and 32 percent of substance-related

emergency room visits nationally. In the United States, 2.5 percent of those ages 12 and older acknowledged ever using PCP. The highest lifetime prevalence was in those aged 26 to 34 years (4 percent), whereas the highest proportion using PCP in the prior year (0.7 percent) was in those aged 12 to 17 years. Some areas of some cities have a tenfold higher usage rate of PCP than other areas. The highest PCP use in the United States is in Washington, DC, where PCP accounts for

18 percent of all substance-related deaths and more than 1,000 emergency room visits per year. In Los Angeles, Chicago, and Baltimore, the comparable figure is 6 percent. Overall, most users are between 18 and 25 years of age and they account for 50 percent of cases. Patients are more likely to be male rather than female, especially those who visit emergency rooms. There are twice as many white as blacks users, although blacks account for more visits to hospitals for PCP-related disorders than do whites. PCP use appears to be rising, with some reports showing a 50 percent increase, particularly in urban areas. NEUROPHARMACOLOGY Although most hallucinogenic substances vary in their pharmacological effects, LSD can serve as a hallucinogenic prototype. The pharmacodynamic effect of LSD remains controversial, although it is generally agreed that the drug acts on the serotonergic system, either as an antagonist or as an agonist. Data at this time suggest that LSD acts as a partial agonist at postsynaptic serotonin receptors. Most hallucinogens are well absorbed after oral ingestion, although some are ingested by inhalation, smoking, or intravenous injection. Tolerance for LSD and other hallucinogens develops rapidly and is virtually complete after 3 or 4 days of continuous use. Tolerance also reverses quickly, usually in 4 to 7 days. Neither physical dependence nor withdrawal symptoms occur with hallucinogens, but a user can develop a psychological dependence on the insight-inducing experiences of episodes of hallucinogen use. Phencyclidine Phencyclidine and its related compounds are variously sold as a crystalline powder, paste, liquid, or drug-soaked paper (blotter). PCP is most commonly used as an additive to a cannabis- or parsley-containing cigarette. Experienced users report that the effects of 2 to 3 mg of smoked PCP occur in about 5 minutes and plateau in 30 minutes. The bioavailability of PCP is about 75 percent when taken by intravenous administration and about 30 percent when smoked. The half-life of PCP in humans is about 20 hours, and the half-life of ketamine in humans is about 2 hours. The primary pharmacodynamic effect of PCP and ketamine is as an antagonist at the NMDA subtype of glutamate receptors. PCP binds to a site within the NMDA-associated calcium channel and prevents the influx of calcium ions. PCP also activates the dopaminergic neurons of the ventral tegmental area, which project to the cerebral cortex and the limbic system. Activation of these neurons is usually involved in mediating the reinforcing qualities of PCP. Tolerance for the effects of PCP occurs in humans, although physical dependence generally does not occur. In animals that are administered more PCP per pound for longer times than most humans, PCP does induce physical dependence, however, with marked withdrawal symptoms of lethargy, depression, and craving. Physical symptoms of withdrawal in humans are rare, probably as a function of dose and duration of use.

Although physical dependence on PCP is rare in humans, psychological dependence on both PCP and ketamine are common, and some users become psychologically dependent on the PCP-induced psychological state. That PCP is made in illicit laboratories contributes to the increased likelihood of impurities in the final product. One such contaminant is 1-piperidenocyclohexane carbonitrite, which releases hydrogen cyanide in small quantities when ingested. Another contaminant is piperidine, which can be recognized by its strong, fishy odor. DIAGNOSIS Hallucinogen Use Disorder Long-term hallucinogen use is not common. Some long-term users of

PCP are said to be “crystallized,” a syndrome characterized by dulled thinking, decreased reflexes, loss of memory, loss of impulse control, depression, lethargy, and impaired concentration. Although psychological dependence occurs, it is rare, in part because each LSD experience is different and in part because there is no reliable euphoria. B, a 16-year-old boy from divorced parents, was admitted to the psychiatric unit of a local hospital. He had slashed his wrists with a knife, severing nerves and tendons in his left hand, and drifted in and out of consciousness during the night. He finally contacted the mother of a friend who lived nearby in the morning who immediately brought him to the hospital. B had a history of juvenile delinquency from the age of 13 when he began hanging out with some older boys at his junior high school. He and his friends shoplifted, stole, smoked marijuana, and took LSD. B’s grades dropped and he got in trouble at school on two occasions for getting into fights with other students. On admission, B stated that he did not intend on committing suicide when he slashed his wrist. After some questioning, he revealed that he had been “dropping acid” with some friend and after they left he thought he heard the sirens of police cars approaching his home. He did not wish to get arrested, so he slashed his wrist and then lost consciousness. He denies feeling depressed, although he claims his life is pointless and that he felt it made no difference whether he lived or died. Hallucinogen Intoxication Intoxication with hallucinogens is characterized by maladaptive behavioral and perceptual changes and by certain physiological signs (Table 20.5-2). The differential diagnosis for hallucinogen intoxication includes anticholinergic and amphetamine intoxication and alcohol withdrawal. The preferred treatment for hallucinogen intoxication is talking down the patient; during this process, guides can reassure patients that the symptoms are drug induced, that they are not going crazy, and that the

symptoms will resolve shortly. In the most severe cases, dopaminergic antagonists—for example, haloperidol (Haldol)—or benzodiazepines—for example, diazepam (Valium)— can be used for a limited time. Hallucinogen intoxication usually lacks a withdrawal syndrome. Table 20.5-2 Physiological Changes from Hallucinogens Short-term PCP intoxication can have potentially severe complications and must often be considered a psychiatric emergency. Some patients may be brought to psychiatric attention within hours of ingesting PCP, but often 2 to 3 days elapse before psychiatric help is sought. Persons who lose consciousness are brought for help earlier than those who remain conscious. Most patients recover completely within a day or two, but some remain psychotic for as long as 2 weeks. Patients who are first seen in a coma often exhibit disorientation, hallucinations, confusion, and difficulty communicating on regaining consciousness. These symptoms may also be seen in noncomatose patients, but their symptoms appear to be less severe than those of comatose patients. Behavioral disturbances sometimes are severe; they can include public masturbation, stripping off clothes, violence, urinary incontinence, crying, and inappropriate laughing. Patients frequently have amnesia for the entire period of the psychosis. A 17-year-old male patient was brought to the emergency room by the police, having been found disoriented on the street. As the police attempted to question him, he became increasingly agitated; when they attempted to restrain him, he became assaultive. Attempts to question or to examine him in the emergency department evoked increased agitation. Initially, it was impossible to determine vital signs or to draw blood. Based on the observation of horizontal, vertical, and rotator nystagmus, a diagnosis of PCP intoxication was entertained. Within a few minutes of being placed in a darkened examination room, his agitation markedly decreased. Blood pressure was 170/100; other vital signs were within normal limits. Blood was drawn for toxicological examination. The patient agreed to take 20 mg of diazepam (Valium) orally. Thirty minutes later, he was less agitated and could be interviewed, although he responded to questions in a fragmented fashion and was slightly

dysarthic. He stated that he must have inadvertently taken a larger-than-usual dose of “dust,” which he reported having used once or twice a week for several years. He denied use of any other substance and any history of mental disorder. He was disoriented to time and place. The qualitative toxicology screen revealed PCP and no other drugs. Results of

neurological examination were within normal limits, but brisk deep tendon reflexes were noted. Some 90 minutes after arrival, his temperature, initially normal, was elevated to 38°C, his blood pressure had increased to 182/110, and he was poorly responsive to stimulation. He was admitted to a medical bed. His blood pressure and level of consciousness continued to fluctuate over the ensuing 18 hours. Results of hematological and biochemical analyses of blood, as well as urinalyses, remained within normal limits. A history obtained from his family revealed that the patient had had multiple emergency room visits for complications from PCP use during the previous several years. He had completed a 30-day residential treatment program and had participated in several outpatient programs but had consistently relapsed. The patient was discharged after vital signs and level of consciousness had been within normal limits for 8 hours. At discharge, nystagmus and dysarthria were no longer present. A referral to an outpatient treatment program was made. (Courtesy of Daniel C. Javitt, M.D., Ph.D., and Stephen R. Zukin, M.D.) Hallucinogen Persisting Perception Disorder Long after ingesting a hallucinogen, a person can experience a flashback of hallucinogenic symptoms. This syndrome is diagnosed as hallucinogen persisting perception disorder in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). According to studies, from 15 to 80 percent of users of hallucinogens report having experienced flashbacks. The differential diagnosis for flashbacks includes migraine, seizures, visual system abnormalities, and posttraumatic stress disorder. The following can trigger a flashback: emotional stress; sensory deprivation, such as monotonous driving; or use of another psychoactive substance, such as alcohol or marijuana. Flashbacks are spontaneous, transitory recurrences of the substance-induced experience. Most flashbacks are episodes of visual distortion, geometric hallucinations, hallucinations of sounds or voices, false perceptions of movement in peripheral fields, flashes of color, trails of images from moving objects, positive afterimages and halos, macropsia, micropsia, time expansion, physical symptoms, or relived intense emotion. The episodes usually last a few seconds to a few minutes, but sometimes last longer. Most often, even in the presence of distinct perceptual disturbances, the person has insight into the pathological nature of the disturbance. Suicidal behavior, major depressive disorder, and panic disorders are potential complications. A 20-year-old undergraduate presented with a chief complaint of seeing the air. The visual disturbance consisted of perception of white pinpoint specks too numerous to count in both the central and peripheral visual fields. They were constantly present and were accompanied by the perception of trails of moving objects left behind as they passed through the patient’s visual field. Attending a hockey game was difficult, as the brightly dressed players left streaks of their own images against the white of

the ice for seconds at a time. The patient also described the false perception of movement in stable objects, usually in his peripheral visual fields; halos around objects; and positive and negative afterimages. Other symptoms included mild depression, daily bitemporal headache, and a loss of concentration in the last year. The visual syndrome had gradually emerged over the last 3 months following experimentation with the hallucinogenic drug LCD-25 on three separate occasions. He feared he had sustained some kind of “brain damage” from the drug experience. He denied use of any other agents, including amphetamines, phencyclidine, narcotics, or alcohol, to

excess. He had smoked marijuana twice a week for a period of 7 months at age 17. The patient had consulted two ophthalmologists, both of whom confirmed that the white pinpoint specks were not vitreous floaters (diagnostically insignificant particulate matter floating in the vitreous humor of the eye that can cause the perception of “specks”). A neurologist’s examination also proved negative. A therapeutic trial of an anticonvulsant medication resulted in a 50 percent improvement in the patient’s visual symptoms and remission of his depression. Hallucinogen Intoxication Delirium Hallucinogen intoxication delirium is a relatively rare disorder beginning during intoxication in those who have ingested pure hallucinogens. An estimated 25 percent of all PCP-related emergency room patients may meet the criteria for hallucinogen intoxication delirium. Hallucinogens are often mixed with other substances, however, and the other components or their interactions with the hallucinogens can produce clinical delirium. Hallucinogen-Induced Psychotic Disorders If psychotic symptoms are present in the absence of retained reality testing, a diagnosis of hallucinogen-induced psychotic disorder may be warranted. The most common adverse effect of LSD and related substances is a “bad trip,” an experience resembling the acute panic reaction to cannabis but sometimes more severe; a bad trip can occasionally produce true psychotic symptoms. The bad trip generally ends when the immediate effects of the hallucinogen wear off, but its course is variable. Occasionally, a protracted psychotic episode is difficult to distinguish from a nonorganic psychotic disorder. Whether a chronic psychosis after drug ingestion is the result of the drug ingestion, is unrelated to the drug ingestion, or is a combination of both the drug ingestion and predisposing factors is currently unanswerable. Occasionally, the psychotic disorder is prolonged, a reaction thought to be most common in persons with preexisting schizoid personality disorder and prepsychotic personalities, an unstable ego balance, or much anxiety. Such persons cannot cope with the perceptual changes, body-image distortions, and symbolic unconscious material stimulated by the hallucinogen. The rate of previous mental instability in persons

hospitalized for LSD reactions is high. Adverse reactions occurred in the late 1960s when LSD was being promoted as a self-prescribed psychotherapy for emotional crises in the lives of seriously disturbed persons. Now that this practice is less frequent, prolonged adverse reactions are less common. A 22-year-old female photography student presented to the hospital with inappropriate mood and bizarre thinking. She had no prior psychiatric history. Nine days before admission, she ingested one or two psilocybin mushrooms. Following the immediate ingestion, the patient began to giggle. She then described euphoria, which progressed to auditory hallucinations and belief in the ability to broadcast her thoughts on the media. Two days later she repeated the ingestion, and continued to exhibit psychotic symptoms to the day of admission. When examined she heard voices telling her she could be president, and reported the sounds of “lambs crying.” She continued to giggle inappropriately, bizarrely turning her head from side to side ritualistically. She continued to describe euphoria, but with an intermittent sense of hopelessness in a context of thought blocking. Her self-description was “feeling lucky.” She was given haloperidol, 10 mg twice a day, along with benztropine (Cogentin) 1 mg three times a day and lithium carbonate (Eskalith) 300 mg twice a day. On this regimen her psychosis abated after 5 days. Hallucinogen-Induced Mood Disorder Unlike cocaine-induced mood disorder and amphetamine-induced mood disorder, in which the symptoms are somewhat predictable, mood disorder symptoms accompanying hallucinogen abuse can vary. Abusers may experience manic-like symptoms with grandiose delusions or depression-like feelings and ideas or mixed symptoms. As with the hallucinogen-induced psychotic disorder symptoms, the symptoms of hallucinogeninduced mood disorder usually resolve once the

drug has been eliminated from the person’s body. Hallucinogen-Induced Anxiety Disorder Hallucinogen-induced anxiety disorder also varies in its symptom pattern, but few data about symptom patterns are available. Anecdotally, emergency room physicians who treat patients with hallucinogen-related disorders frequently report panic disorder with agoraphobia. Anxiety is probably the most common symptom causing a PCP-intoxicated person to seek help in an emergency room. Unspecified Hallucinogen-Related Disorder When a patient with a hallucinogen-related disorder does not meet the diagnostic criteria for any of the standard hallucinogen-related disorders, the patient may be classified as having unspecified hallucinogen-related disorder. DSM-5 does not have a

diagnostic category of hallucinogen withdrawal, but some clinicians anecdotally report a syndrome with depression and anxiety after cessation of frequent hallucinogen use. Such a syndrome may best fit the diagnosis of unspecified hallucinogen-related disorder. CLINICAL FEATURES Lsysergic Acid Diethylamide A large class of hallucinogenic compounds with well-studied structure–activity relationships is represented by the prototype LSD. LSD is a synthetic base derived from the lysergic acid nucleus from the ergot alkaloids. That family of compounds was discovered in rye fungus and was responsible for lethal outbreaks of St. Anthony’s fire in the Middle Ages. The compounds are also present in morning glory seeds in low concentrations. Many homologs and analogs of LSD have been studied. None of them has potency exceeding that of LSD. Physiological symptoms from LSD are typically few and relatively mild. Dilated pupils, increased deep tendon motor reflexes and muscle tension, and mild motor incoordination and ataxia are common. Increased heart rate, respiration, and blood pressure are modest in degree and variable, as are nausea, decreased appetite, and salivation. The usual sequence of changes follows a pattern of somatic symptoms appearing first, then mood and perceptual changes, and, finally, psychological changes, although effects overlap and, depending on the particular hallucinogen, the time of onset and offset varies. The intensity of LSD effects in a nontolerant user generally is proportional to dose, with 25 µg as an approximate threshold dose. The syndrome produced by LSD resembles that produced by mescaline, psilocybin, and some of the amphetamine analogs. The major difference among LSD, psilocybin, and mescaline is potency. A 1.5 µg/kg dose of LSD is roughly equivalent to 225 µg/kg of psilocybin, which is equivalent to 5 mg/kg of mescaline. With mescaline, onset of symptoms is slower and more nausea and vomiting occurs but in general, the perceptual effects are more similar than different. Tolerance, particularly to the sensory and other psychological effects, is evident as soon as the second or third day of successive LSD use. Four to 6 days free of LSD are necessary to lose significant tolerance. Tolerance is associated with frequent use of any of the hallucinogens. Cross-tolerance among mescaline, psilocybin, and LSD occurs, but not between amphetamine and LSD, despite the chemical similarity of amphetamine and mescaline. Previously distributed as tablets, liquid, powder, and gelatin squares, in recent years, LSD has been commonly distributed as “blotter acid.” Sheets of paper are soaked with LSD, and dried and perforated into small squares. Popular designs are stamped on the paper. Each sheet contains as many as a few hundred squares; one square containing 30 to 75 µg of LSD is one chewed dose, more or less. Planned massive ingestion is uncommon but massive ingestion happens by accident. The onset of action of LSD occurs within an hour, peaks in 2 to 4 hours, and lasts 8 to

12 hours. The sympathomimetic effects of LSD include tremors, tachycardia, hypertension, hyperthermia, sweating, blurring of vision, and mydriasis. Death caused by cardiac or cerebrovascular pathology related to hypertension or hyperthermia can occur with hallucinogenic

use. A syndrome similar to neuroleptic malignant syndrome has reportedly been associated with LSD. Death can also be caused by a physical injury when LSD use impairs judgment about traffic or a person’s ability to fly, for example. The psychological effects are usually well tolerated, but when persons cannot recall experiences or appreciate that the experiences are substance induced, they may fear the onset of insanity. With hallucinogen use, perceptions become unusually brilliant and intense. Colors and textures seem to be richer, contours sharpened, music more emotionally profound, and smells and tastes heightened. Synesthesia is common; colors may be heard or sounds seen. Changes in body image and alterations of time and space perception also occur. Hallucinations are usually visual, often of geometric forms and figures, but auditory and tactile hallucinations are sometimes experienced. Emotions become unusually intense and may change abruptly and often; two seemingly incompatible feelings may be experienced at the same time. Suggestibility is greatly heightened, and sensitivity or detachment from other persons may arise. Other common features are a seeming awareness of internal organs, the recovery of lost early memories, the release of unconscious material in symbolic form, and regression and the apparent reliving of past events, including birth. Introspective reflection and feelings of religious and philosophical insight are common. The sense of self is greatly changed, sometimes to the point of depersonalization, merging with the external world, separation of self from body, or total dissolution of the ego in mystical ecstasy. There is no clear evidence of a drastic personality change or chronic psychosis produced by long-term LSD use by moderate users not otherwise predisposed to these conditions. Some heavy users of hallucinogens, however, may experience chronic anxiety or depression and may benefit from a psychological or pharmacological approach that addresses the underlying problem. Many persons maintain that a single experience with LSD has given them increased creative capacity, new psychological insight, relief from neurotic or psychosomatic symptoms, or a desirable change in personality. In the 1950s and 1960s, psychiatrists showed great interest in LSD and related substances, both as potential models for functional psychosis and as possible pharmacotherapeutic agents. The availability of these compounds to researchers in the basic neurosciences has led to many scientific advances. Phenethylamines Phenethylamines are compounds with chemical structures similar to those of the neurotransmitters dopamine and norepinephrine. Mescaline (3,4,5trimethoxyphenethylamine), a classic hallucinogen in every sense of the term, was the first hallucinogen isolated from the peyote cactus that grows in the southwestern United States and northern Mexico. Mescaline human pharmacology was characterized in 1896 and its structure verified by synthesis 23 years later. Although many psychoactive plants have been recognized dating to before recorded history, mescaline was the only structurally identified hallucinogen until LSD was described in 1943. Mescaline

Mescaline is usually consumed as peyote “buttons,” picked from the small blue-green cacti Lophophora williamsii and Lophophora diffusa. The buttons are the dried, round, fleshy cacti tops. Mescaline is the active hallucinogenic alkaloid in the buttons. Use of peyote is legal for the Native American Church members in some states. Adverse reactions to peyote are rare during structured religious use. Peyote usually is not consumed casually because of its bitter taste and sometimes severe nausea and vomiting that precede the hallucinogenic effects. Many structural variations of mescaline have been investigated and structural activity relationships fairly well characterized. One analog, 2,5-dimethoxy-4methylamphetamine (DOM), also known as STP, an unusually potent amphetamine with hallucinogen properties, had a relatively brief period of illicit popularity and notoriety in the 1960s, but it appears to have disappeared from the illicit market. Another series of

phenethylamine analogs with hallucinogenic properties is the 3,4methylenedioxyamphetamine (MDA)–related amphetamines. The currently most popular and, to society, most troublesome member of this large family of drugs is MDMA, or ecstasy, more a relatively mild stimulant than hallucinogen. MDMA produces an altered state of consciousness with sensory changes and, most important for some users, a feeling of enhanced personal interactions. Many plants contain N,N-dimethyltryptamine (DMT), which is also found normally in human biofluids at very low concentrations. When DMT is taken parenterally or by sniffing, a brief, intense hallucinogenic episode can result. As with mescaline in the phenethylamine group, DMT is one of the oldest, best documented, but least potent of the tryptamine hallucinogens. Synthesized homologs of DMT have been evaluated in humans and structure activity relationships have been reasonably well described. Psilocybin Analogs An unusual collection of tryptamines has its origin in the world of fungi. The natural prototype is psilocybin itself. That and related homologs have been found in as many as 100 species of mushroom, largely of the Psilocybe genus. Psilocybin is usually ingested as mushrooms. Many species of psilocybin-containing mushrooms are found worldwide. In the United States, large Psilocybe cubensis (gold caps) grow in Florida and Texas and are easily grown with cultivation kits advertised in drug-oriented magazines and on the Internet. The tiny Psilocybe semilanceata (liberty cap) grows in lawns and pastures in the Pacific Northwest. Psilocybin remains active when the mushrooms are dried or cooked into omelets or other foods. Psilocybin mushrooms are used in religious activities by Mexican Indians. They are valued in Western society by users who prefer to ingest a mushroom rather than a synthetic chemical. Of course, one danger of eating wild mushrooms is misidentification and ingestion of a poisonous variety. At a large American university, 24 percent of students reported using psychedelic mushrooms or mescaline, compared with 17 percent who reported LSD use. Psilocybin sold as pills or capsules usually contains phencyclidine (PCP) or LSD instead.

Studies are underway in several medical centers in the United States (including New York University) to examine the use of psilocybin in terminally ill patients. Preliminary reports indicate that the psilocybin is helpful in reducing morbid anxiety about death and dying. It may play an important role in palliative care medicine in the future. Phencyclidine The amount of PCP varies greatly from PCP-laced cigarette to cigarette; 1 g may be used to make as few as four or as many as several dozen cigarettes. Less than 5 mg of PCP is considered a low dose, and doses above 10 mg are considered high. Dose variability makes it difficult to predict the effect, although smoking PCP is the easiest and most reliable way for users to titrate the dose. Persons who have just taken PCP are frequently uncommunicative, appear to be oblivious, and report active fantasy production. They experience speedy feelings, euphoria, bodily warmth, tingling, peaceful floating sensations, and, occasionally, feelings of depersonalization, isolation, and estrangement. Sometimes, they have auditory and visual hallucinations. They often have striking alterations of body image, distortions of space and time perception, and delusions. They may experience intensified dependence feelings, confusion, and disorganization of thought. Users may be sympathetic, sociable, and talkative at one moment but hostile and negative at another. Anxiety is sometimes reported; it is often the most prominent presenting symptom during an adverse reaction. Nystagmus, hypertension, and hyperthermia are common effects of PCP. Head-rolling movements, stroking, grimacing, muscle rigidity on stimulation, repeated episodes of vomiting, and repetitive chanting speech are sometimes observed. The short-term effects last 3 to 6 hours and sometimes give way to a mild depression in which the user becomes irritable, somewhat paranoid, and occasionally belligerent, irrationally assaultive, suicidal, or homicidal. The effects can last for

several days. Users sometimes find that it takes 1 to 2 days to recover completely; laboratory tests show that PCP can remain in the patient's blood and urine for more than a week. Ketamine Ketamine is a dissociative anesthetic agent, originally derived from PCP, which is available for use in human and veterinary medicine. It has become a drug of abuse, with sources exclusively from stolen supplies. It is available as a powder or in solution for intranasal, oral, inhalational, or (rarely) intravenous use. Ketamine functions by working at the NMDA receptor and, as with PCP, can cause hallucinations and a dissociated state in which the patient has an altered sense of the body and reality and little concern for the environment. Ketamine causes cardiovascular stimulation and no respiratory depression. On physical examination, the patient may be hypertensive and tachycardic, have increased salivation and bidirectional or rotary nystagmus, or both. The onset of action is within

seconds when used intravenously, and analgesia lasting 40 minutes and dissociative effects lasting for hours have been described. Cardiovascular status should be monitored and supportive care administered. A dystonic reaction has been described, as have flashbacks, but a more common complication is related to a lack of concern for the environment or personal safety. Ketamine has a briefer duration of effect than PCP. Peak ketamine levels occur approximately 20 minutes after intramuscular injection. After intranasal administration, the duration of effect is approximately 1 hour. Ketamine is N-demethylated by liver microsomal cytochrome P450 (CYP), especially CYP3A, into norketamine. Ketamine, norketamine, and dehydronorketamine can be detected in urine, with half-lives of 3, 4, and 7 hours, respectively. Urinary ketamine and norketamine levels vary widely from individual to individual and can range from 10 to 7,000 ng/mL after intoxication. As of yet, the relationship between serum ketamine levels and clinical symptoms has not been formally studied. Ketamine is often used in combination with other drugs of abuse, especially cocaine. Ketamine does not appear to interfere with, and may enhance, cocaine metabolism. Ketamine is being studied for use in the treatment of depression. ADDITIONAL HALLUCINOGENS Canthinones Canthinones are alkaloids similar to amphetamines naturally found in the khat plant and synthetically made and known as "bath salts." They are CNS stimulants that cause a massive release of dopamine, and a single dose can last up to 8 hours. They produce profound toxic effects that can lead to seizures, strokes, and/or death. Hallucinations and delusions are common. They are swallowed, injected, or "snorted" to produce the desired euphoric effect. Ibogaine Ibogaine is a complex alkaloid found in the African shrub Tabernanthe iboga. Ibogaine is a hallucinogen at the 400 mg dose range. The plant originates in Africa and traditionally is used in sacramental initiation ceremonies. Although it has not been a popular hallucinogen because of its unpleasant somatic effects when taken at hallucinogenic doses, patients exposed to ibogaine may be encountered by a psychiatrist because of the therapeutic claims. Ayahuasca Ayahuasca, much discussed on Internet hallucinogen websites, originally referred to a decoction from one or more South American plants. The substance contains the alkaloids harmaline and harmine. Both of those β-carboline alkaloids have hallucinogenic properties, but the resulting visual sensory alterations are accompanied by considerable nausea. Amazon native tribes discovered that adding leaves from plants containing substantial amounts of DMT markedly enhanced the visual and sacramental impact of ayahuasca. Thus, neither component in the ayahuasca plant mixture works well alone but when taken in combination an extremely effective hallucinogenic agent results. In recent years, the term ayahuasca has evolved to a less specific term to refer to any mixture of two things that are hallucinogenic when taken in combination. For example, harmine and harmaline are available as fine chemicals and when taken along with many botanicals containing DMT result in a mixture with

hallucinogen properties, initially intense but

usually of brief duration. Salvia Divinorum American Indians in northern Oaxaca, Mexico, have used Salvia divinorum as a medicine and as a sacred sacrament, which is now widely discussed, advertised, and sold on the Internet. When the plant is chewed or dried leaves smoked, it produces hallucinogen effects. Salvinorin-A, an active component in the plant, is parenterally potent, active at 250-µg doses when smoked, and of scientific and potential medical interest because it binds to the opioid κ-receptor. TREATMENT Hallucinogen Intoxication A basic principle in treatment is providing reassurance and supportive care. Patients experiencing intense and unpleasant hallucinogen intoxication can be helped by a quiet environment, verbal reassurance, and the passage of time. More rapid relief of intense anxiety is likely after oral administration of 20 mg of diazepam (Valium) or, if oral administration presents problems, an equivalent parenteral dose of a benzodiazepine. Anxiety and other symptoms generally diminish within 20 minutes of medication administration, compared to hours with only psychological and environmental support; however, perceptual symptoms may persist. Patients may need gentle restraint if they are in danger to themselves or others, but restraints should be avoided if possible. Neuroleptic medications, particularly if given at excessive doses, may worsen symptoms and are best avoided unless the diagnosis remains unclear and behavior cannot otherwise be managed. The marketing of lower doses of LSD and a more sophisticated approach to treatment of casualties by drug users themselves have combined to reduce the appearance of this once-common disorder in psychiatric treatment facilities. Hallucinogen Persisting Disorder Treatment for hallucinogen persisting perception disorder is palliative. The first step in the process is correct identification of the disorder; it is not uncommon for the patient to consult a number of specialists before the diagnosis is made. Pharmacological approaches include long-lasting benzodiazepines, such as clonazepam (Klonopin) and, to a lesser extent, anticonvulsants including valproic acid (Depakene) and carbamazepine (Tegretol). Currently, no drug is completely effective in ablating symptoms. Antipsychotic agents should be used only in the treatment of hallucinogeninduced psychoses, because they may have a paradoxical effect and exacerbate symptoms. A second dimension of treatment is behavioral. The patient must be instructed to avoid gratuitous stimulation in the form of over-the-counter drugs, caffeine, and alcohol, and avoidable physical and emotional stressors. Marijuana smoke is a particularly strong intensifier of the disorder, even when passively inhaled. Finally, three comorbid conditions are associated with hallucinogen persisting perception disorder: panic disorder, major depression, and alcohol dependence. All these conditions

require primary prevention and early intervention. Hallucinogen-Induced Psychosis Treatment of hallucinogen-induced psychosis does not differ from conventional treatment for other psychoses. In addition to antipsychotic medications, a number of agents are reportedly effective, including lithium carbonate, carbamazepine, and electroconvulsive therapy. Antidepressant drugs, benzodiazepines, and anticonvulsant agents may each have a role in treatment as well. One hallmark of this disorder is that, as opposed to schizophrenia, in which negative symptoms and poor interpersonal relatedness may commonly be found, patients with hallucinogen-induced psychosis exhibit the positive symptoms of hallucinations and delusions while retaining the ability to relate to the psychiatrist. Medical therapies are best applied in a context of supportive, educational, and family therapies. The goals of treatment are the control of symptoms, a minimal use of hospitals, daily work, the development and preservation of social relationships, and the management of comorbid illnesses such as alcohol dependence. Phencyclidine Treatment of PCP

intoxication aims to reduce systemic PCP levels and to address significant medical, behavioral, and psychiatric issues. For intoxication and PCP-induced psychotic disorder, although resolution of current symptoms and signs is paramount, the long-term goal of treatment is to prevent relapse to PCP use. PCP levels can fluctuate over many hours or even days, especially after oral administration. A prolonged period of clinical observation is therefore mandatory before concluding that no serious or lifethreatening complications will ensue. Trapping of ionized PCP in the stomach has led to the suggestion of continuous nasogastric suction as a treatment for PCP intoxication. This strategy, however, can be needlessly intrusive and can induce electrolyte imbalances. Administration of activated charcoal is safer, and it binds PCP and diminishes toxic effects of PCP in animals.

Trapping of ionized PCP in urine has led to the suggestion of urinary acidification as an aid to drug elimination. This strategy, however, may be ineffective and is potentially dangerous. Only a small portion of PCP is excreted in urine, metabolic acidosis itself carries significant risks, and acidic urine can increase the risk of renal failure secondary to rhabdomyolysis. Because of the extremely large volume of distribution of PCP, neither hemodialysis nor hemoperfusion can significantly promote drug clearance. No drug is known to function as a direct PCP antagonist. Any compound binding to the PCP receptor, which is located within the ion channel of the NMDA receptor, would block NMDA receptor–mediated ion fluxes as does PCP itself. NMDA-receptor mechanisms predict that pharmacological strategies promoting NMDA receptor activation (e.g., administration of a glycine site agonist drug) would promote rapid dissociation of PCP from its binding sites. No clinical trials of NMDA agonists for PCP or ketamine intoxication in humans have been carried out to date. Treatment must therefore be supportive and directed at specific symptoms and signs of toxicity. Classic measures should be used for medical crises, including seizures, hypothermia, and hypertensive crisis. Because PCP disrupts sensory input, environmental stimuli can cause unpredictable, exaggerated, distorted, or violent reactions. A cornerstone of treatment, therefore, is minimization of sensory inputs to PCP-intoxicated patients. Patients should be evaluated and treated in an environment that is as quiet and isolated as possible. Precautionary physical restraint is recommended by some authorities, with the risk of rhabdomyolysis from struggle against the restraints balanced by the avoidance of violent or disruptive behavior. Pharmacological sedation can be accomplished with oral or intramuscular (IM) antipsychotics or benzodiazepines; no convincing evidence indicates that either class of compounds is clinically superior. Because of the anticholinergic actions of PCP at high doses, neuroleptics with potent intrinsic anticholinergic properties should be avoided. REFERENCES Bokor G, Anderson PD. Ketamine: An Update on Its Abuse. J Pharm Pract. 2014 Mar. [Epub ahead of print] Catts VS, Catts SV. Psychotomimetic effects of PCP, LSD, and ecstasy: Pharmacological models of schizophrenia? In: Sachdev PS, Keshavan MS, eds. Secondary Schizophrenia. New York: Cambridge University Press; 2010:141. Crane CA, Easton CJ, Devine S. The association between phencyclidine use and partner violence: An initial examination. J Addictive Disord. 2013;32:150. Fantegrossi WE, Murnane KS, Reissig CJ. The behavioral pharmacology of hallucinogens. Biochem Pharmacol. 2008;75:17. Fontanilla D, Johannessen D, Hajipour AR, Cozzi NV, Jackson MB, Ruoho AE. The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. Science. 2009;323:934. Geraci MJ, Peele J, McCoy SL, Elias B. Phencyclidine false positive induced by lamotrigine (Lamictal) on a rapid urine toxicology screen. Int J Emerg Med. 2010;3(4):327. Javitt DC, Zukin SR. Phencyclidine (or phencyclidine-like)-related disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams

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gases (e.g., nitrous oxide and ether) and short-acting vasodilators (e.g., amyl nitrite) from the inhalant-related disorders, which are classified as other (or unknown) substance-related disorders and are discussed in Section 20.12. EPIDEMIOLOGY Inhalant substances are easily available, legal, and inexpensive. These three factors contribute to the high use of inhalants among poor persons and young persons.

Approximately 6 percent of persons in the United States had used inhalants at least once, and about 1 percent of persons are current users. Among young adults 18 to 25 years of age, 11 percent had used inhalants at least once, and 2 percent were current users. Among adolescents 12 to 17 years of age, 7 percent had used inhalants at least once, and 1.1 percent were current users. In one study of high school seniors, 18 percent reported having used inhalants at least once, and 2.7 percent reported having used inhalants within the preceding month. White users of inhalants are more common than either black or Hispanic users. Most users (up to 80 percent) are male. Some data suggest that inhalant use may be more common in suburban communities in the United States than in urban communities. Inhalant use accounts for 1 percent of all substance-related deaths and less than 0.5 percent of all substance-related emergency room visits. About 20 percent of the emergency room visits for inhalant use involve persons younger than 18 years of age. Inhalant use among adolescents may be most common in those whose parents or older siblings use illegal substances. Inhalant use among adolescents is also associated with an increased likelihood of conduct disorder or antisocial personality disorder. NEUROPHARMACOLOGY Inhalants most used by American adolescents are (in descending order) gasoline, glue (which usually contains toluene), spray paint, solvents, cleaning fluids, and assorted other aerosols. Sniffing vapor through the nose or huffing (taking deep breaths) through the mouth leads to transpulmonary absorption with very rapid drug access to the brain. Breathing through a solvent-soaked cloth, inhaling fumes from a glue-containing bag, huffing vapor sprayed into a plastic bag, or breathing vapor from a gasoline can are common. Approximately 15 to 20 breaths of 1 percent gasoline vapor produce several hours of intoxication. Inhaled toluene concentrations from a glue-containing bag may reach 10,000 ppm, and vapors from several tubes of glue may be inhaled each day. By comparison, one study of just 100 ppm of toluene showed that a 6-hour exposure produced a temporary neuropsychological performance decrement of approximately 10 percent. Inhalants generally act as a central nervous system (CNS) depressant. Tolerance for inhalants can develop, although withdrawal symptoms are usually fairly mild. Inhalants are rapidly absorbed through the lungs and rapidly delivered to the brain. The effects appear within 5 minutes and can last for 30 minutes to several hours, depending on the inhalant substance and the dose. The concentrations of many inhalant substances in blood are increased when used in combination with alcohol, perhaps because of competition for hepatic enzymes. Although about one fifth of an inhalant substance is excreted unchanged by the lungs, the remainder is metabolized by the liver. Inhalants are detectable in the blood for 4 to 10 hours after use, and blood samples should be taken in the emergency room when inhalant use is suspected. Much like alcohol, inhalants have specific pharmacodynamic effects that are not well understood. Because their effects are generally similar and additive to the effects of

other CNS depressants (e.g., ethanol, barbiturates, and benzodiazepines), some investigators have suggested that inhalants operate by enhancing the γ-aminobutyric acid (GABA) system. Other investigators have suggested that inhalants work through membrane fluidization, which has also been hypothesized to be a pharmacodynamic effect of ethanol. DIAGNOSIS Inhalant Use Disorder Most persons probably use inhalants for a short time without developing a pattern of long-term use

resulting in dependence and abuse. Nonetheless, dependence and abuse of inhalants occur and are diagnosed according to the DSM-5 (see page 621). Inhalant Intoxication The diagnostic criteria for inhalant intoxication specify the presence of maladaptive behavioral changes and at least two physical symptoms. The intoxicated state is often characterized by apathy, diminished social and occupational functioning, impaired judgment, and impulsive or aggressive behavior, and it can be accompanied by nausea, anorexia, nystagmus, depressed reflexes, and diplopia. With high doses and long exposures, a user's neurological status can progress to stupor and unconsciousness, and a person may later be amnestic for the period of intoxication. Clinicians can sometimes identify a recent user of inhalants by rashes around the patient's nose and mouth; unusual breath odors; the residue of the inhalant substances on the patient's face, hands, or clothing; and irritation of the patient's eyes, throat, lungs, and nose. The disorder can be chronic, as in the following case. A 16-year-old single Hispanic female was referred to a university substancetreatment program for evaluation. The patient had been convicted for auto theft, menacing with a weapon, and being out of control by her family. By age 15, she had regularly been using inhalants and drinking alcohol heavily. She had tried typewritererasing fluid, bleach, tile cleaner, hairspray, nail polish, glue, and gasoline, but preferred spray paint. She had sniffed paint many times each day for about 6 months at age 15, using a maximum of eight paint cans per day. The patient said, "It blacks out everything." Sometimes she had lost consciousness, and she believed that the paint had impaired her memory and made her "dumb." (Courtesy of Thomas J. Crowley, M.D.) Inhalant Intoxication Delirium Delirium can be induced by the effects of the inhalants themselves, by pharmacodynamic interactions with other substances, and by the hypoxia that may be

associated with either the inhalant or its method of inhalation. If the delirium results in severe behavioral disturbances, short-term treatment with a dopamine receptor antagonist, such as haloperidol (Haldol), may be necessary. Benzodiazepines should be avoided because of the possibility of increasing the patient's respiratory depression. Inhalant-Induced Persisting Dementia Inhalant-induced persisting dementia, as with delirium, may result from the neurotoxic effects of the inhalants themselves; the neurotoxic effects of the metals (e.g., lead) commonly used in inhalants; or the effects of frequent and prolonged periods of hypoxia. The dementia caused by inhalants is likely to be irreversible in all but the mildest cases. Inhalant-Induced Psychotic Disorder Clinicians can specify hallucinations or delusions as the predominant symptoms. Paranoid states are probably the most common psychotic syndromes during inhalant intoxication. Inhalant-Induced Mood Disorder and Inhalant-Induced Anxiety Disorder Inhalant-induced mood disorder and inhalant-induced anxiety disorder allow the classification of inhalant-related disorders characterized by prominent mood and anxiety symptoms. Depressive disorders are the most common mood disorders associated with inhalant use, and panic disorders and generalized anxiety disorder are the most common anxiety disorders. Other Inhalant-Induced Disorders Other Inhalant-Induced Disorder is the recommended DSM-5 diagnosis for inhalantrelated disorders that do not fit into one of the diagnostic categories discussed earlier. CLINICAL FEATURES In small initial doses, inhalants can be disinhibiting and produce feelings of euphoria and excitement as well as pleasant floating sensations, the effects for which persons presumably use the drugs. High doses of inhalants can cause psychological symptoms of fearfulness, sensory illusions, auditory and visual hallucinations, and distortions of body size. The neurological symptoms can include slurred speech, decreased speed of talking, and ataxia. Long-term use can be associated with irritability, emotional lability, and impaired memory. Tolerance for the inhalants does develop for some users; a withdrawal syndrome can accompany the cessation of inhalant use. The withdrawal syndrome does

not occur frequently; when it does, it can be characterized by sleep disturbances, irritability, jitteriness, sweating, nausea, vomiting, tachycardia, and (sometimes) delusions and

hallucinations. Organ Pathology and Neurological Effects Inhalants are associated with many potentially serious adverse effects. The most serious of these is death, which can result from respiratory depression, cardiac arrhythmias, asphyxiation, aspiration of vomitus, or accident or injury (e.g., driving while intoxicated with inhalants). Placing an inhalant-soaked rag and one's head into a plastic bag, a common procedure for inhalant users, can cause coma and suffocation. Chronic inhalant users may have numerous neurological problems. Computed tomography (CT) and magnetic resonance imaging (MRI) reveal diffuse cerebral, cerebellar, and brainstem atrophy with white matter disease, a leukoencephalopathy. Single photon emission CT (SPECT) of former solvent-abusing adolescents showed both increases and decreases of blood flow in different cerebral areas. Several studies of house painters and factory workers who have been exposed to solvents for long periods also have found evidence of brain atrophy on CT scans, with decreased cerebral blood flow. Neurological and behavioral signs and symptoms can include hearing loss, peripheral neuropathy, headache, paresthesias, cerebellar signs, persisting motor impairment, parkinsonism, apathy, poor concentration, memory loss, visual-spatial dysfunction, impaired processing of linguistic material, and lead encephalopathy. White matter changes, or pontine atrophy on MRI, have been associated with worse intelligence quotient (IQ) test results. The combination of organic solvents with high concentrations of copper, zinc, and heavy metals has been associated with the development of brain atrophy, temporal lobe epilepsy, decreased IQ, and a variety of electroencephalography (EEG) changes. Other serious adverse effects associated with long-term inhalant use include irreversible hepatic disease or renal damage (tubular acidosis) and permanent muscle damage associated with rhabdomyolysis. Additional adverse effects include cardiovascular and pulmonary symptoms (e.g., chest pain and bronchospasm) as well as gastrointestinal (GI) symptoms (e.g., pain, nausea, vomiting, and hematemesis). There are several clinical reports of toluene embryopathy, with signs such as those of fetal alcohol syndrome. These include low birth weight, microcephaly, shortened palpebral fissures, small face, low-set ears, and other dysmorphic signs. These babies reportedly develop slowly, show hyperactivity, and have cerebellar dysfunction. No convincing evidence indicates, however, that toluene, the best-studied inhalant, produces genetic damage in somatic cells. TREATMENT Inhalant intoxication, as with alcohol intoxication, usually requires no medical attention and resolves spontaneously. However, effects of the intoxication, such as coma, bronchospasm, laryngospasm, cardiac arrhythmias, trauma, or burns, need treatment. Otherwise, care primarily involves reassurance, quiet support, and attention to vital

signs and level of consciousness. Sedative drugs, including benzodiazepines, are contraindicated because they worsen inhalant intoxication. No established treatment exists for the cognitive and memory problems of inhalantinduced persisting dementia. Street outreach and extensive social service support have been offered to severely deteriorated, inhalant-dependent, homeless adults. Patients may require extensive support within their families or in foster or domiciliary care. The course and treatment of inhalant-induced psychotic disorder are like those of inhalant intoxication. The disorder is brief, lasting a few hours to (at most) a very few weeks beyond the intoxication. Appropriate is vigorous treatment of such lifethreatening complications as respiratory or cardiac arrest, together with conservative management of the intoxication itself. Confusion, panic, and psychosis mandate special attention to patient safety. Severe agitation may require cautious

control with haloperidol (5 mg intramuscularly per 70 kg body weight). Sedative drugs should be avoided because they may aggravate the psychosis. Inhalant-induced anxiety and mood disorders may precipitate suicidal ideation, and patients should be carefully evaluated for that possibility. Antianxiety medications and antidepressants are not useful in the acute phase of the disorder; they may be of use in cases of a coexisting anxiety or depressive illness. Day Treatment and Residential Programs Day treatment and residential programs have been used successfully, especially for adolescent abusers with combined substance dependence and other psychiatric disorders. Treatment addresses the comorbid state which, in most cases, is conduct disorder or, in other instances, may be attention-deficit/hyperactivity disorder (ADHD), major depressive disorder, dysthymic disorder, and posttraumatic stress disorder (PTSD). Attention is also directed to experiences of abuse or neglect, which is very common in these patients. Both group and individual therapy are used that are behaviorally oriented, with immediate rewards for progress toward objectively defined goals in treatment and punishments for lapses to previous behaviors. Patients attend on-site schools with special education teachers, together with planned recreational activities, and the programs provide birth control consultations. The patients' families, often very chaotic, are engaged in modifications of structural family therapy or multisystemic therapy, both of which have good empirical support. Participation in 12-step programs is required. Treatment interventions are coordinated closely with interventions by community social workers and probation officers. Progress is monitored with urine and breath samples analyzed for alcohol and other drugs at intake and frequently during treatment. Treatment usually lasts 3 to 12 months. Termination is considered successful if the youth has practiced a plan to stay abstinent; is showing fewer antisocial behaviors; has a plan to continue any needed psychiatric treatment (e.g., treatment for comorbid depression); has a plan to live in a supportive, drug-free environment; is interacting with the family in a more productive way; is working or attending school; and is

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associating with drug-free, nondelinquent peers. REFERENCES Balster RL, Cruz SL, Howard MO, Dell CA, Cottler LB. Classification of abused inhalants. Addiction. 2009;104:878. Baltazar A, Hopkins G, McBride D, Vanderwaal C, Pepper S, Mackey S. Parental influence on inhalant use. J Child Adolesc Substance Abuse. 2013; 22(1):25–37. Bender E. Troubling trends found in teen inhalant use. Psychiatric News. 2009;44:6. Cairney S, O'Connor N, Dingwall KM. A prospective study of neurocognitive changes 15 years after chronic inhalant abuse. Addiction. Jun 2013;108(6):1107–1114. Clark CT, Richards EM, Antoine DG II, Chisolm MS. Perinatal toluene use: Associated risks and considerations. Addict Disord Treat. 2011;10:1. Garland EL, Howard MO. Adverse consequences of acute inhalant intoxication. Exp Clin Psychopharmacol. 2011;19:134. Garland EL, Howard MO. Phenomenology of adolescent inhalant intoxication. Exp Clin Psychopharmacol. 2010;18:498. Hall MT, Edwards JD, Howard MO. Accidental deaths due to inhalant misuse in North Carolina: 2000–2008. Subst Use Misuse. 2010;45:1330. Howard MO, Bowen SE, Garland EL, Perron BE, Vaughn MG. Inhalant use and inhalant use disorders in the United States. Addict Sci Clin Pract. 2011;6:18. Perron BE, Glass JE, Ahmedani BK, Vaughn MG, Roberts DE, Wu LT. The prevalence and clinical significance of inhalant withdrawal symptoms among a national sample. Subst Abuse Rehabil. 2011;2:69. Perron BE, Howard MO, Maitra S, Vaughn MG. Prevalence, timing, and predictors of transitions from inhalant use to inhalant use disorders. Drug Alcohol Depend. 2009;100:277. Perron BE, Mowbray O, Bier S, Vaughn MG, Krentzman A, Howard MO. Service use and treatment barriers among inhalant users. J Psychoactive Drugs. 2011;43:69. Sakai JT, Crowley TJ. Inhalant-related disorder. In: Sadock BJ, Sadock, VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1341. Sanchez ZM, Ribeiro LA, Moura YG, Noto AR, Martins SS. Inhalants as intermediate drugs between legal and illegal drugs among middle and high school students. J Add Dis. 2013;32(2):217–226. Scott KD, Scott AA. Adolescent inhalant use and executive cognitive functioning. Child Care Health Dev. 2014;40(1):20–8. Vilar-Lopez R, Takagi M, Lubman DI. The effects of inhalant misuse on attentional networks. Develop Neuropsychol. Feb 2013;38(2):126–136. 20.7 Opioid-Related Disorders Opioids have been used for analgesic and other medicinal purposes for thousands of years, but they also have a long history of misuse for their psychoactive effects. Continued opioid misuse can result in syndromes of abuse and

dependence and cause disturbances in mood, behavior, and cognition that can mimic other psychiatric disorders. In developed countries, the opioid drug most frequently associated with abuse and dependence is heroin; however, there is growing public health concern about prescription opioids, which are widely available, have significant abuse liability, and are used increasingly for purposes. Opioid addiction affects the young and the old, the wealthy and the poor, and the professional and the unemployed. Over the last few

decades there have been significant advances in treatment and understanding of opioid dependence. It is increasingly accepted that opioid dependence is often a chronic, relapsing disorder amenable to medical treatment and intervention. Table 20.7-1 lists various opioids that are used therapeutically in the United States, with the exception of heroin. Table 20.7-1 Opioids Opioid dependence is a cluster of physiological, behavioral, and cognitive symptoms, which together indicate repeated and continuing use of opioid drugs, despite significant problems related to such use. Drug dependence, in general, has been defined by the World Health Organization (WHO) as a syndrome in which the use of a drug or class of drugs takes on a much higher priority for a given person than other behaviors that once had a higher value. These brief definitions each have as their central features an emphasis on the drug-using behavior itself, its maladaptive nature, and how the choice to engage in that behavior shifts and becomes constrained as a result of interaction with the drug over time. Opioid abuse is a term used to designate a pattern of maladaptive use of an opioid drug leading to clinically significant impairment or distress and occurring within a 12-month period, but one in which the symptoms have never met the criteria for opioid dependence. The opioid-induced disorders include such common phenomena as opioid use disorder, opioid intoxication, opioid withdrawal, opioid-induced sleep disorder, and opioidinduced sexual dysfunction. Opioid intoxication delirium is occasionally seen in hospitalized patients. Opioid-induced psychotic disorder, opioid-induced mood disorder, and opioid-induced anxiety disorder, by contrast, are quite uncommon with μ-agonist opioids, but have been seen with certain mixed agonist–antagonist opioids acting at other receptors. The diagnosis of opioid-related disorder not elsewhere classified is used for situations that do not meet the criteria for any of the other opioid-related disorders.

In addition to the morbidity and mortality associated directly with the opioid-related disorders, the association between the transmission of the human immunodeficiency virus (HIV) and intravenous opioid and opiate use is now recognized as a leading national health concern. The words opiate and opioid come from the word opium, the juice of the opium poppy, Papaver somniferum, which contains approximately 20 opium alkaloids, including morphine. Many synthetic opioids have been manufactured, including meperidine (Demerol), methadone (Dolophine), pentazocine (Talwin), and propoxyphene (Darvon). Methadone is the current gold standard in the treatment of opioid dependence. Opioid antagonists have been synthesized to treat opioid overdose and opioid dependence. This class of drugs includes naloxone (Narcan), naltrexone (ReVia), nalorphine, levallorphan, and apomorphine. Compounds with mixed agonist and antagonist activity at opioid receptors have been synthesized and include pentazocine, butorphanol (Stadol), and buprenorphine (Buprenex). Studies have found buprenorphine to be an effective treatment for opioid dependence. EPIDEMIOLOGY The use and dependence rates derived from national surveys do not accurately reflect fluctuations in drug use among opioid-dependent and previously opioid-dependent populations. When the supply of illicit heroin increases in purity or decreases in price, use among that vulnerable population tends to increase, with subsequent increases in adverse

consequences (emergency room visits) and requests for treatment. The number of current heroin users in the United States has been estimated to be between 600,000 and 800,000. The number of people estimated to have used heroin at any time in their lives (lifetime users) is estimated at approximately 3 million. In 2010, an estimated 140,000 persons had used heroin for the first time within the past 12 months. The average age of first use among recent initiates was 21.3 years in 2010. Opioid use in the United States experienced a resurgence in the 1990s, with emergency department visits related to heroin abuse doubling between 1990 and 1995. This increase in heroin use was associated with an increase in heroin purity and a decrease in its street price. In the late 1990s, heroin use increased among people who were 18 to 25 years of age, and a brief upsurge was seen in the use of oxycodone (OxyContin). Methods of administration other than injecting, such as smoking and snorting, increased in popularity. In 2010, the number of new nonmedical users of psychiatry of oxycodone was 598,000, with an average age at first use of 22.8 years. Comparable data on past year oxycodone initiation are not available for prior years, but calendar year estimates of oxycodone initiation show a steady increase in the number of initiates from 1995, the year this drug was first available, through 2003. The male-to-female ratio of persons with heroin dependence is about 3:1. Users of opioids typically started to use substances in their teens and early 20s; currently, most persons with opioid dependence are in their 30s and 40s. The tendency for dependence to remit generally begins after age 40 years and has been called “maturing out.” Many persons,

however, have remained opioid dependent for 50 years or longer. In the United States, persons tend to experience their first opioid-induced experience in their early teens or even as young as 10 years of age. Early induction into the drug culture is likely in communities in which substance abuse is rampant and in families in which the parents are substance abusers. A heroin habit can cost a person hundreds of dollars a day; thus, a person with opioid dependence needs to obtain money through criminal activities and prostitution. The involvement of persons with opioid dependence in prostitution accounts for much of the spread of HIV. The lifetime prevalence for heroin use is about 1 percent, with 0.2 percent having taken the drug during the prior year. NEUROPHARMACOLOGY The primary effects of the opioid drugs are mediated via the opioid receptors, which were discovered in the first half of the 1970s (published in 1973). The μ-opioid receptors are involved in the regulation and mediation of analgesia, respiratory depression, constipation, and drug dependence; the κ-opioid receptors, with analgesia, diuresis, and sedation; and the Δ-opioid receptors, with analgesia. In 1975, the enkephalins, two endogenous pentapeptides with opioid-like actions, were identified. This discovery led to the identification of three classes of endogenous opioids within the brain, including the endorphins, the dynorphins, and the enkephalins. The term “endorphin” (a contraction of “endogenous” and “morphine”) was coined by Dr. Eric Simon, Professor of psychiatry at NYU School of Medicine, one of the scientists who discovered the opioid receptors, to serve as a generic name for all molecules with morphine-like activity found in the brain. Endorphins are involved in neural transmission and pain suppression. They are released naturally in the body when a person is physically hurt or severely stressed and are thought to account for the absence of pain during acute injuries. The endogenous opioids also have significant interactions with other neuronal systems, such as the dopaminergic and noradrenergic neurotransmitter systems. Several types of data indicate that the addictive rewarding properties of opioids are mediated through activation of the ventral tegmental area dopaminergic neurons that project to the cerebral cortex and the limbic system (Fig. 20.7-1).

FIGURE 20.7-1 Scheme illustrating opioid actions in the locus ceruleus (LC). Opioids acutely inhibit LC neurons by increasing the conductance of a K+ channel (light cross-hatch) via coupling with subtypes of Gi and/or Go and by decreasing an Na+-dependent inward current (dark cross-hatch) via coupling with Gi/o and the consequent inhibition of adenylyl cyclase. Reduced levels of cAMP decrease PKA and the phosphorylation of the responsible channel or pump. Inhibition of the cyclic adenosine monophosphate (cAMP) pathway also decreases phosphorylation of numerous other proteins and thereby affects many additional processes in the neuron. For example, it reduces the phosphorylation state of CREB, which may initiate some of the longer-term changes in LC function. Upper bold arrows summarize effects of repeated morphine administration in the LC. Repeated morphine administration increases levels of adenylyl cyclase, PKA, and several phosphoproteins, including CREB. These changes contribute to the altered phenotype of the drug-addicted state. For example, the intrinsic excitability of LC neurons is increased via enhanced activity of the cAMP pathway and Na+-dependent inward current, which contributes to the tolerance, dependence, and withdrawal exhibited by the these neurons. This altered phenotypic state appears to be maintained, in part, by upregulation of CREB expression. (From Nestler EJ. Molecular mechanisms underlying opiate addiction: Implications for medications development. Semin Neurosci. 1997;9:84, with permission.) Heroin, the most commonly abused opioid, is more lipid soluble than morphine. This allows it to cross the blood–brain barrier faster and have a more rapid and pleasurable onset than morphine. Heroin was first introduced as a treatment for morphine addiction, but heroin, in fact, is more dependence producing than morphine. Codeine,

which occurs naturally as about 0.5 percent of the opiate alkaloids in opium, is absorbed easily through the gastrointestinal tract and is subsequently transformed into morphine in the body. Results of at least one study using positron emission tomography (PET) have suggested that one effect of all opioids is decreased cerebral blood flow in selected brain regions in persons with opioid dependence. There is interesting evidence indicating that the endorphins are involved in other addictions, such as alcoholism, cocaine, and cannabinoid addiction. The opioid antagonist, naltrexone, has shown value in mitigating alcohol addiction. The discovery of this new endorphinergic neuromodulatory system has led to the discovery of an endogenous cannabinoid system and has stimulated many outstanding laboratories to do research toward improved pain management and prevention and treatment of narcotic addiction. Tolerance and Dependence Tolerance to all actions of opioid drugs does not develop uniformly. Tolerance to some actions of opioids can be so high that a 100-fold increase in dose is required to produce the original effect. For example, terminally ill cancer patients may need 200 to 300 mg a day of morphine, whereas a dose of 60 mg can easily be fatal to an opioid-naive person. The symptoms of opioid withdrawal do not appear unless a person has been using opioids for a long time or when cessation is particularly abrupt, as occurs functionally when an opioid antagonist is given. The long-term use of opioids results in changes in the number and sensitivity of opioid receptors, which mediate at least some of the effects of tolerance and withdrawal. Although long-term use is associated with increased sensitivity of the dopaminergic, cholinergic, and serotonergic neurons, the effect of opioids on the noradrenergic neurons is probably the primary mediator of the symptoms of opioid withdrawal. Short-term use of opioids apparently decreases the activity of the noradrenergic neurons in the locus ceruleus; long-term use activates a compensatory homeostatic mechanism within the neurons; and opioid withdrawal results in rebound hyperactivity. This hypothesis also provides an explanation for why clonidine (Catapres), an α2-adrenergic receptor agonist that decreases the release of norepinephrine, is useful in the treatment of opioid withdrawal symptoms. COMORBIDITY

About 90 percent of persons with opioid dependence have an additional psychiatric disorder. The most common comorbid psychiatric diagnoses are major depressive disorder, alcohol use disorders, antisocial personality disorder, and anxiety disorders. About 15 percent of persons with opioid dependence attempt to commit suicide at least once. The high prevalence of comorbidity with other psychiatric diagnoses (Table 20.72) highlights the need to develop a broad-based treatment program that also addresses patients' associated psychiatric disorders.

Table 20.7-2 Non–Substance-Related Psychiatric Disorders in Opioid Users ETIOLOGY Psychosocial Factors Opioid dependence is not limited to low socioeconomic status (SES), although the incidence of opioid dependence is greater in these groups than in higher SES groups. Social factors associated with urban poverty probably contribute to opioid dependence. About 50 percent of urban heroin users are children of single parents or divorced parents and are from families in which at least one other member has a substancerelated disorder. Children from such settings are at high risk for opioid dependence, especially if they also evidence behavioral problems in school or other signs of conduct disorder. Some consistent behavior patterns seem to be especially pronounced in adolescents with opioid dependence. These patterns have been called the heroin behavior syndrome: underlying depression, often of an agitated type and frequently accompanied by anxiety symptoms; impulsiveness expressed by a passive-aggressive orientation; fear of failure; use of heroin as an antianxiety agent to mask feelings of low self-esteem, hopelessness, and aggression; limited coping strategies and low frustration tolerance, accompanied by the need for immediate gratification; sensitivity to drug contingencies, with a keen awareness of the relation between good feelings and the act of drug taking; feelings of behavioral impotence counteracted by momentary control over the life situation by means of substances; disturbances in social and interpersonal relationships with peers

maintained by mutual substance experiences. Biological and Genetic Factors Evidence now exists for common and drug-specific, genetically transmitted vulnerability factors that increase the likelihood of developing drug dependence. Individuals who abuse a substance from any category are more likely to abuse substances from other categories. Monozygotic twins are more likely than dizygotic twins to be concordant for opioid dependence. Multivariate modeling techniques have indicated that not only was the genetic contribution high for heroin abuse in this group, but also a higher proportion of the variance because of genetic factors was not shared with the common vulnerability factor—that is, it was specific for opioids. A person with an opioid-related disorder may have had genetically determined hypoactivity of the opiate system. Researchers are investigating the possibility that such hypoactivity may be caused by too few, or less-sensitive, opioid receptors, by release of too little endogenous opioid, or by overly high concentrations of a hypothesized endogenous opioid antagonist. A biological predisposition to an opioid-related disorder may also be associated with abnormal functioning in either the dopaminergic or the noradrenergic neurotransmitter system. Psychodynamic Theory In psychoanalytic literature, the behavior of persons addicted to narcotics has been described in terms of libidinal fixation, with regression to pregenital, oral, or even more archaic levels of psychosexual development. The need to explain the relation of drug abuse, defense mechanisms, impulse control, affective disturbances, and adaptive mechanisms led to the shift from psychosexual formulations to formulations emphasizing ego psychology. Serious ego pathology, often thought to be associated with substance abuse, is considered to indicate profound developmental disturbances. Problems of the relation between the ego and affects emerge as a key area of difficulty. DIAGNOSIS Opioid Use Disorder Opioid use

disorder is a pattern of maladaptive use of an opioid drug, leading to clinically significant impairment or distress and occurring within a 12-month period. A 42-year-old executive in a public relations firm was referred for psychiatric consultation by his surgeon, who discovered him sneaking large quantities of a codeine-containing cough medicine into the hospital. The patient had been a heavy cigarette smoker for 20 years and had a chronic, hacking cough. He had come into the hospital for a hernia repair and found the pain from the incision unbearable when he coughed.

An back operation 5 years previously had led his doctors to prescribe codeine to help relieve the incisional pain at that time. Over the intervening 5 years, however, the patient had continued to use codeine-containing tablets and had increased his intake to 60–90 mg daily. He stated that he often “just took them by the handful—not to feel good, you understand, just to get by.” He spent considerable time and effort developing a circle of physicians and pharmacists to whom he would “make the rounds” at least three times a week to obtain new supplies of pills. He had tried several times to stop using codeine, but had failed. During this period he lost two jobs because of lax work habits and was divorced by his wife of 11 years. Opioid Intoxication Opioid intoxication includes maladaptive behavioral changes and specific physical symptoms of opioid use. In general, altered mood, psychomotor retardation, drowsiness, slurred speech, and impaired memory and attention in the presence of other indicators of recent opioid use strongly suggest a diagnosis of opioid intoxication. Opioid Withdrawal The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) diagnostic criteria for opioid withdrawal are listed in Table 20.7-3. The general rule about the onset and duration of withdrawal symptoms is that substances with short durations of action tend to produce short, intense withdrawal syndromes and substances with long durations of action produce prolonged, but mild, withdrawal syndromes. An exception to the rule, narcotic antagonist-precipitated withdrawal after long-acting opioid dependence can be severe. Table 20.7-3 DSM-5 Diagnostic Criteria for Opioid Withdrawal

An abstinence syndrome can be precipitated by administration of an opioid antagonist. The symptoms can begin within seconds of such an intravenous injection and peak in about 1 hour. Opioid craving rarely occurs in the context of analgesic administration for pain from physical disorders or surgery. The full withdrawal syndrome, including intense craving for opioids, usually occurs only secondary to abrupt cessation of use in persons with opioid dependence. Morphine and Heroin. The morphine and heroin withdrawal syndrome begins 6 to 8 hours after the last dose, usually after a 1- to 2-week period of continuous use or after the administration of a narcotic antagonist. The withdrawal syndrome reaches its peak intensity during the second or third day and subsides during the next 7 to 10 days, but some symptoms may persist for 6 months or longer. Meperidine. The withdrawal syndrome from meperidine begins quickly, reaches a peak in 8 to 12 hours, and ends in 4 to 5 days. Methadone. Methadone withdrawal usually begins 1 to 3 days after the last dose and ends in 10 to 14 days. Symptoms. Opioid withdrawal consists of severe muscle cramps and bone aches, profuse diarrhea, abdominal cramps, rhinorrhea, lacrimation, piloerection or gooseflesh (from which comes the term cold turkey for the abstinence syndrome), yawning, fever,

pupillary dilation, hypertension, tachycardia, and temperature dysregulation, including hypothermia and hyperthermia. Persons with opioid dependence seldom die from opioid withdrawal, unless they have a severe preexisting physical illness such as cardiac disease. Residual symptoms—such as insomnia, bradycardia, temperature dysregulation, and a craving for

opioids—can persist for months after withdrawal. Associated features of opioid withdrawal include restlessness, irritability, depression, tremor, weakness, nausea, and vomiting. At any time during the abstinence syndrome, a single injection of morphine or heroin eliminates all the symptoms. Opioid Intoxication Delirium Opioid intoxication delirium is most likely to happen when opioids are used in high doses, are mixed with other psychoactive compounds, or are used by a person with preexisting brain damage or a central nervous system (CNS) disorder (e.g., epilepsy). Opioid-Induced Psychotic Disorder Opioid-induced psychotic disorder can begin during opioid intoxication. Clinicians can specify whether hallucinations or delusions are the predominant symptoms. Opioid-Induced Mood Disorder Opioid-induced mood disorder can begin during opioid intoxication. Opioid-induced mood disorder symptoms can have a manic, depressed, or mixed nature, depending on a person's response to opioids. A person coming to psychiatric attention with opioidinduced mood disorder usually has mixed symptoms, combining irritability, expansiveness, and depression. Opioid-Induced Sleep Disorder and Opioid-Induced Sexual Dysfunction Hypersomnia is likely to be more common with opioids than insomnia. The most common sexual dysfunction is likely to be impotence. Unspecified Opioid-Related Disorder The DSM-5 includes diagnoses for other opioid-related disorders with symptoms of delirium, abnormal mood, psychosis, abnormal sleep, and sexual dysfunction. Clinical situations that do not fit into these categories exemplify appropriate cases for the use of the DSM-5 diagnosis of unspecified opioid-related disorder. CLINICAL FEATURES Opioids can be taken orally, snorted intranasally, and injected intravenously or subcutaneously (Fig. 20.7-2). Opioids are subjectively addictive because of the euphoric high (the rush) that users experience, especially those who take the substances

intravenously. The associated symptoms include a feeling of warmth, heaviness of the extremities, dry mouth, itchy face (especially the nose), and facial flushing. The initial euphoria is followed by a period of sedation, known in street parlance as "nodding off." Opioid use can induce dysphoria, nausea, and vomiting in opioid-naive persons. FIGURE 20.7-2 Skin popper. Circular depressed scars, often with underlying chronic abscesses, can result from skin popping. (Courtesy of Michael Baden, M.D.) The physical effects of opioids include respiratory depression, pupillary constriction, smooth muscle contraction (including the ureters and the bile ducts), constipation, and changes in blood pressure, heart rate, and body temperature. The respiratory depressant effects are mediated at the level of the brainstem. Adverse Effects The most common and most serious adverse effect associated with the opioid-related disorders is the potential transmission of hepatitis and HIV through the use of contaminated needles by more than one person. Persons can experience idiosyncratic allergic reactions to opioids, which result in anaphylactic shock, pulmonary edema, and death if they do not receive prompt and adequate treatment. Another serious adverse effect is an idiosyncratic drug interaction between meperidine and monoamine oxidase inhibitors (MAOIs), which can produce gross autonomic instability, severe behavioral agitation, coma, seizures, and death. Opioids and MAOIs should not be given together for this reason. Opioid Overdose Death from an overdose of an opioid is usually attributable to respiratory arrest from the respiratory depressant effect of the drug. The symptoms of overdose include marked unresponsiveness, coma, slow respiration, hypothermia, hypotension, and bradycardia. When presented with the clinical triad of coma, pinpoint pupils, and respiratory depression, clinicians should consider opioid overdose as a primary diagnosis. They can

also inspect the patient's body for needle tracks in the arms, legs, ankles, groin, and even the dorsal vein of the penis. MPTP-Induced Parkinsonism In 1976, after ingesting an opioid

contaminated with methyl-phenyltetrahydropyridine (MPTP), several persons developed a syndrome of irreversible parkinsonism. The mechanism for the neurotoxic effect is as follows: MPTP is converted into 1methyl-4-phenylpyridinium (MPP+) by the enzyme monoamine oxidase and is then taken up by dopaminergic neurons. Because MPP+ binds to melanin in substantia nigra neurons, MPP+ is concentrated in these neurons and eventually kills the cells. PET studies of persons who ingested MPTP but remained asymptomatic have shown a decreased number of dopamine-binding sites in the substantia nigra. This decrease reflects a loss in the number of dopaminergic neurons in that region. TREATMENT AND REHABILITATION Overdose Treatment The first task in overdose treatment is to ensure an adequate airway. Tracheopharyngeal secretions should be aspirated; an airway may be inserted. The patient should be ventilated mechanically until naloxone, a specific opioid antagonist, can be given. Naloxone is administered intravenously at a slow rate—initially about 0.8 mg per 70 kg of body weight. Signs of improvement (increased respiratory rate and pupillary dilation) should occur promptly. In opioid-dependent patients, too much naloxone may produce signs of withdrawal as well as reversal of overdosage. If no response to the initial dosage occurs, naloxone administration may be repeated after intervals of a few minutes. Previously, it was thought that if no response was observed after 4 to 5 mg, the CNS depression was probably not caused solely by opioids. The duration of action of naloxone is short compared with that of many opioids, such as methadone and levomethadyl acetate, and repeated administration may be required to prevent recurrence of opioid toxicity. Medically Supervised Withdrawal and Detoxification Opioid Agents for Treating Opioid Withdrawal METHADONE. Methadone is a synthetic narcotic (an opioid) that substitutes for heroin and can be taken orally. When given to addicts to replace their usual substance of abuse, the drug suppresses withdrawal symptoms. A daily dose of 20 to 80 mg suffices to stabilize a patient, although daily doses of up to 120 mg have been used. The duration of action for methadone exceeds 24 hours; thus, once-daily dosing is adequate. Methadone maintenance is continued until the patient can be withdrawn from methadone, which itself causes dependence. An abstinence syndrome occurs with methadone withdrawal, but patients are detoxified from methadone more easily than from heroin. Clonidine (0.1 to 0.3 mg three to four times a day) is usually given during

the detoxification period. Methadone maintenance has several advantages. First, it frees persons with opioid dependence from using injectable heroin and, thus, reduces the chance of spreading HIV through contaminated needles. Second, methadone produces minimal euphoria and rarely causes drowsiness or depression when taken for a long time. Third, methadone allows patients to engage in gainful employment instead of criminal activity. The major disadvantage of methadone use is that patients remain dependent on a narcotic. Other Opioid Substitutes LEVOMETHADYL (LAAM). LAAM is an opioid agonist that suppresses opioid withdrawal. It is no longer used, however, because some patients developed prolonged QT intervals associated with potentially fatal arrhythmias (torsades de pointes). BUPRENORPHINE. As with methadone and LAAM, buprenorphine is an opioid agonist approved for opioid dependence in 2002. It can be dispensed on an outpatient basis, but prescribing physicians must demonstrate that they have received special training in its use. Buprenorphine in a daily dose of 8 to 10 mg appears to reduce heroin use. Buprenorphine also is effective in thrice-weekly dosing because of its slow dissociation from opioid receptors. After repeated administration, it attenuates or blocks the subjective effects of parenterally administered opioids such as heroin or morphine. A mild opioid withdrawal syndrome occurs if the drug is abruptly discontinued after chronic administrations. Opioid Antagonists. Opioid antagonists block or antagonize the effects of opioids. Unlike methadone, they do not exert narcotic effects and do not

cause dependence. Opioid antagonists include naloxone, which is used in the treatment of opioid overdose because it reverses the effects of narcotics, and naltrexone, the longest-acting (72 hours) antagonist. The theory for using an antagonist for opioid-related disorders is that blocking opioid agonist effects, particularly euphoria, discourages persons with opioid dependence from substance-seeking behavior and, thus, deconditions this behavior. The major weakness of the antagonist treatment model is the lack of any mechanism that compels a person to continue to take the antagonist. Pregnant Women with Opioid Dependence Neonatal addiction is a significant problem. About three fourths of all infants born to addicted mothers experience the withdrawal syndrome. Neonatal Withdrawal. Although opioid withdrawal rarely is fatal for the otherwise healthy adult, it is hazardous to the fetus and can lead to miscarriage or fetal death. Maintaining a pregnant woman with opioid dependence on a low dose of methadone (10 to 40 mg daily) may be the least hazardous course to follow. At this dose, neonatal withdrawal is usually mild and can be managed with low doses of

paregoric. If pregnancy begins while a woman is taking high doses of methadone, the dosage should be reduced slowly (e.g., 1 mg every 3 days), and fetal movements should be monitored. If withdrawal is necessary or desired, it is least hazardous during the second trimester. Fetal AIDS Transmission. Acquired immune deficiency syndrome (AIDS) is the other major risk to the fetus of a woman with opioid dependence. Pregnant women can pass HIV, the causative agent of AIDS, to the fetus through the placental circulation. An HIV-infected mother can also pass HIV to the infant through breast-feeding. The use of zidovudine (Retrovir) alone or in combination with other anti-HIV medication in infected women can decrease the incidence of HIV in newborns. Psychotherapy The entire range of psychotherapeutic modalities is appropriate for treating opioidrelated disorders. Individual psychotherapy, behavioral therapy, cognitive-behavioral therapy, family therapy, support groups (e.g., Narcotics Anonymous [NA]), and social skills training may all prove effective for specific patients. Social skills training should be particularly emphasized for patients with few social skills. Family therapy is usually indicated when the patient lives with family members. Therapeutic Communities Therapeutic communities are residences in which all members have a substance abuse problem. Abstinence is the rule; to be admitted to such a community, a person must show a high level of motivation. The goals are to effect a complete change of lifestyle, including abstinence from substances; to develop personal honesty, responsibility, and useful social skills; and to eliminate antisocial attitudes and criminal behavior. The staff members of most therapeutic communities are persons with former substance dependence who often put prospective candidates through a rigorous screening process to test their motivation. Self-help through the use of confrontational groups and isolation from the outside world and from friends associated with the drug life are emphasized. The prototypical community for persons with substance dependence is Phoenix House, where the residents live for long periods (usually 12 to 18 months) while receiving treatment. They are allowed to return to their old environments only when they have demonstrated their ability to handle increased responsibility within the therapeutic community. Therapeutic communities can be effective but require large staffs and extensive facilities. Moreover, dropout rates are high; up to 75 percent of those who enter therapeutic communities leave within the first month. Education and Needle Exchange. Although the essential treatment of opioid use disorders is encouraging persons to abstain from opioids, education about the transmission of HIV must receive equal attention. Persons with opioid dependence who use intravenous or subcutaneous routes of administration must be taught available safe-

sex practices. Free needle-exchange programs are often subject to intense political and societal pressures but, where allowed, should be made available to persons with opioid dependence. Several studies have indicated that unsafe needle sharing is common when it is difficult to obtain enough clean needles and is also common in persons with legal difficulties, severe substance problems, and psychiatric symptoms. These are just the persons most likely to be involved in transmitting HIV. Narcotic Anonymous Narcotics Anonymous is a self-help group of abstinent drug addicts modeled on the 12step principles of Alcoholics Anonymous (AA). Such groups now exist in most large cities and can provide useful group support. The outcome for patients treated in 12-step programs is generally good, but the anonymity that is at the core of the 12-step model has made detailed evaluation of its efficacy in treating opioid dependence difficult. REFERENCES Barry DT, Beitel M, Cutter CJ, Joshi D, Falcioni J, Schottenfeld RS. Conventional and nonconventional pain treatment utilization among opioid dependent individuals with pain seeking methadone maintenance treatment: A needs assessment study. J Addict Med. 2010;4:81. Bohnert ASB, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011;305:1315. Comer SD, Sullivan MA, Whittington RA, Vosburg SK, Kowalczyk WJ. Abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. Neuropsychopharmacology. 2008;33(5):1179. Gros DF, Milanak ME, Brady KT, Back SE. Frequency and severity of comorbid mood and anxiety disorders in prescription opioid dependence. Am J Addict. 2013;22(3):261–265. Haller DL, Acosta MC. Characteristics of pain patients with opioid-use disorder. Psychosomatics. 2010;51:257. Howe CQ, Sullivan MD. The missing ‘P’ in pain management: how the current opioid epidemic highlights the need for psychiatric services in chronic pain care. Gen Hosp Psychiatry. 2014;36(1):99–104. Jones HE. Treating opioid use disorders during pregnancy: Historical, current, and future directions. Substance Abuse. 2013;34(2):89–91. Ling W, Casadonte P, Bigelow G, Kampman KM, Patkar A, Bailey GL, Rosenthal RN, Beebe KL. Buprenorphine implants for treatment of opioid dependence. JAMA. 2010;304:1576. Marino EN, Rosen KD, Gutierrez A, Eckmann M, Ramamurthy S, Potter JS. Impulsivity but not sensation seeking is associated with opioid analgesic misuse risk in patients with chronic pain. Addict Beh. 2013;38(5):2154–2157. Martins SS, Keyes KM, Storr CL, Zhu H, Chilcoat HD. Pathways between nonmedical opioid use/dependence and psychiatric disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend. 2009;103:16. Oviedo-Joekes E, Brissette S, Marsh DC, Lauzon P, Guh D, Anis A, Schechter MT. Diacetylmorphine versus methadone for the treatment of opioid addiction. N Engl J Med. 2009;361:777. Renner JA, Suzuki J. Opiates and prescription drugs. In: Johnson BA, ed. Addiction Medicine: Science and Practice. Vol. 1. New York: Springer, LLC; 2011:463. Rich BA, Webster LR. A review of forensic implications of opioid prescribing with examples from malpractice cases involving opioid-related overdose. Pain Med. 2011;12:S59.

08 - 20.8 Sedative , Hypnotic , or Anxiolytic Rela

20.8 Sedative-, Hypnotic-, or Anxiolytic-Related Disorders

Smith HS, Kirsh KL, Passik SD. Chronic opioid therapy issues associated with opioid abuse potential. J Opioid Manag. 2009;5:287. Strain EC, Lofwall MR, Jaffe JH. Opioid-related disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1360. Unger A, Jung E, Winklbaur B, Fischer G. Gender issues in the pharmacotherapy of opioid-addicted women: Buprenorphine. J Addict Dis. 2010;29:217. Webster LR, Dasgupta N. Obtaining adequate data to determine causes of opioid-related overdose deaths. Pain Med. 2011;12:S86. Wu LT, Ringwalt CL, Yang C, Reeve BB, Pan JJ, Blazer DG. Construct and differential item functioning in the assessment of prescription opioid use disorders among American adolescents. J Am Acad Child Adolesc Psychiatry. 2009;48:563. 20.8 Sedative-, Hypnotic-, or Anxiolytic-Related Disorders The drugs discussed in this section are referred to as anxiolytic or sedative–hypnotic drugs. Their sedative or calming effects are on a continuum with their hypnotic or sleepinducing effects. In addition to their psychiatric indications, these drugs are also used as antiepileptics, muscle relaxants, anesthetics, and anesthetic adjuvants. Alcohol and all drugs of this class are cross-tolerant, and their effects are additive. Physical and psychological dependence develops to these drugs, and all are associated with withdrawal symptoms. In the practice of psychiatry and addiction medicine, the drug class that is most important clinically is the benzodiazepines. The three major groups of drugs associated with this class of substance-related disorders are benzodiazepines, barbiturates, and barbiturate-like substances. Each group is discussed below. BENZODIAZEPINES Many benzodiazepines, differing primarily in their half-lives, are available in the United States. Examples of benzodiazepines are diazepam, flurazepam (Dalmane), oxazepam (Serax), and chlordiazepoxide (Librium). Benzodiazepines are used primarily as anxiolytics, hypnotics, antiepileptics, and anesthetics, as well as for alcohol withdrawal. After their introduction in the United States in the 1960s, benzodiazepines rapidly became the most prescribed drugs; about 15 percent of all persons in the United States have had a benzodiazepine prescribed by a physician. Increasing awareness of the risks for dependence on benzodiazepines and increased regulatory requirements, however, have decreased the number of benzodiazepine prescriptions. The Drug Enforcement Agency (DEA) classifies all benzodiazepines as Schedule IV controlled substances. Flunitrazepam (Rohypnol), a benzodiazepine used in Mexico, South America, and Europe but not available in the United States,

has become a drug of abuse. When taken with alcohol, it has been associated with promiscuous sexual behavior and rape. It is illegal to bring flunitrazepam into the United States. Although misused in the United States, it remains a standard anxiolytic in many countries. Non-benzodiazepine sedatives such as zolpidem (Ambien) zaleplon (Sonata), and

eszopiclone (Lunesta)—the so called Z drugs—have clinical effects similar to the benzodiazepines and are also subject to misuse and dependence. BARBITURATES Before the introduction of benzodiazepines, barbiturates were frequently prescribed, but because of their high abuse potential, their use is much rarer today. Secobarbital (popularly known as “reds,” “red devils,” “seggies,” and “downers”), pentobarbital (Nembutal) (known as “yellow jackets,” “yellows,” and “nembies”), and a secobarbital– amobarbital combination (known as “reds and blues,” “rainbows,” “double-trouble,” and “tooies”) are easily available on the street from drug dealers. Pentobarbital, secobarbital, and amobarbital (Amytal) are now under the same federal legal controls as morphine. The first barbiturate, barbital (Veronal), was introduced in the United States in 1903. Barbital and phenobarbital (Solfoton, Luminal), which was introduced shortly thereafter, are long-acting drugs with half-lives of 12 to 24 hours. Amobarbital is an intermediate-acting barbiturate with a half-life of 6 to 12 hours. Pentobarbital and secobarbital are short-acting barbiturates with half-lives of 3 to 6 hours. Although barbiturates are useful and effective sedatives, they are highly lethal with only ten times the normal dose producing coma and death. BARBITURATE-LIKE SUBSTANCES The most commonly abused barbiturate-like substance is methaqualone, which is no longer manufactured in the United States. It is often used by young persons who believe that the substance heightens the pleasure of sexual activity. Abusers of methaqualone commonly take one or two standard tablets (usually 300 mg per tablet) to obtain the desired effects. The street names for methaqualone include “mandrakes” (from the United Kingdom preparation Mandrax) and “soapers” (from the brand name Sopor). “Luding out” (from the brand name Quaalude) means getting high on methaqualone, which is often combined with excessive alcohol intake. Other barbiturate-like substances include meprobamate (Equanil), a carbamate derivative that has weak efficacy as an antianxiety agent but has muscle-relaxant effects and is used for that purpose; chloral hydrate, a hypnotic that is highly toxic to the gastrointestinal (GI) system and, when combined with alcohol, is known as a “mickey finn”; and ethchlorvynol, a rapidly acting sedative agent with anticonvulsant and muscle-relaxant properties. All are subject to abuse. EPIDEMIOLOGY About 6 percent of individuals have used either sedatives or tranquilizers illicitly, including 0.3 percent who reported illicit use of sedatives in the prior year and 0.1 percent who reported use of sedatives in the prior month. The age group with the highest lifetime prevalence of sedative (3 percent) or tranquilizer (6 percent) use was 26

to 34 years of age, and those aged 18 to 25 were most likely to have used sedatives or tranquilizers in the prior year. About one fourth to one third of all substance-related emergency room visits involve substances of this class. The patients have a female-tomale ratio of 3:1 and a white-to-black ratio of 2:1. Some persons use benzodiazepines alone, but persons who use cocaine often use benzodiazepines to reduce withdrawal symptoms, and opioid abusers use them to enhance the euphoric effects of opioids. Because they are easily obtained, benzodiazepines are also used by abusers of stimulants, hallucinogens, and phencyclidine (PCP) to help reduce the anxiety that can be caused by those substances. Whereas barbiturate abuse is common among mature adults who have long histories of abuse of these substances, benzodiazepines are abused by a younger age group, usually those under 40 years of age. This group may have a slight male

predominance and has a white-to-black ratio of about 2:1. Benzodiazepines are probably not abused as frequently as other substances for the purpose of getting “high,” or inducing a euphoric feeling. Rather, they are used when a person wishes to experience a general relaxed feeling. NEUROPHARMACOLOGY The benzodiazepines, barbiturates, and barbiturate-like substances all have their primary effects on the γ-aminobutyric acid (GABA) type A (GABAA) receptor complex, which contains a chloride ion channel, a binding site for GABA, and a well-defined binding site for benzodiazepines. The barbiturates and barbiturate-like substances are also believed to bind somewhere on the GABAA receptor complex. When a benzodiazepine, barbiturate, or barbiturate-like substance does bind to the complex, the effect is to increase the affinity of the receptor for its endogenous neurotransmitter, GABA, and to increase the flow of chloride ions through the channel into the neuron. The influx of negatively charged chloride ions into the neuron is inhibitory, and hyperpolarizes the neuron relative to the extracellular space. Although all the substances in this class induce tolerance and physical dependence, the mechanisms behind these effects are best understood for the benzodiazepines. After long-term benzodiazepine use, the receptor effects caused by the agonist are attenuated. Specifically, GABA stimulation of the GABAA receptors results in less chloride influx than was caused by GABA stimulation before the benzodiazepine administration. This downregulation of receptor response is not caused by a decrease in receptor number or by decreased affinity of the receptor for GABA. The basis for the downregulation seems to be in the coupling between the GABA binding site and the activation of the chloride ion channel. This decreased efficiency in coupling may be regulated within the GABAA receptor complex itself or by other neuronal mechanisms. DIAGNOSIS

Sedative, Hypnotic, or Anxiolytic Use Disorder Sedative, hypnotic, or anxiolytic use disorder is diagnosed according to the general criteria in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for substance use disorder (see page 621). Sedative, Hypnotic, or Anxiolytic Intoxication The intoxication syndromes induced by all these drugs are similar, and include incoordination, dysarthria, nystagmus, impaired memory, gait disturbance, and in severe cases stupor, coma, or death. The diagnosis of intoxication by one of this class of substances is best confirmed by obtaining a blood sample for substance screening. Benzodiazepines. Benzodiazepine intoxication can be associated with behavioral disinhibition, potentially resulting in hostile or aggressive behavior in some persons. The effect is perhaps most common when benzodiazepines are taken in combination with alcohol. Benzodiazepine intoxication is associated with less euphoria than is intoxication by other drugs in this class. This characteristic is the basis for the lower abuse and dependence potential of benzodiazepines than of barbiturates. Barbiturates and Barbiturate-like Substances. When barbiturates and barbiturate-like substances are taken in relatively low doses, the clinical syndrome of intoxication is indistinguishable from that associated with alcohol intoxication. The symptoms include sluggishness, incoordination, difficulty thinking, poor memory, slow speech and comprehension, faulty judgment, disinhibited sexual aggressive impulses, narrowed range of attention, emotional lability, and exaggerated basic personality traits. The sluggishness usually resolves after a few hours, but depending primarily on the half-life of the abused substance, impaired judgment, distorted mood, and impaired motor skills may remain for 12 to 24 hours. Other potential symptoms are hostility, argumentativeness, moroseness, and, occasionally, paranoid and suicidal ideation. The neurological effects include nystagmus, diplopia, strabismus, ataxic gait, positive Romberg’s sign, hypotonia, and decreased superficial reflexes. Sedative, Hypnotic, or Anxiolytic Withdrawal Benzodiazepines. The severity of the withdrawal syndrome associated with the benzodiazepines varies significantly depending on

the average dose and the duration of use, but a mild withdrawal syndrome can follow even short-term use of relatively low doses of benzodiazepines. A significant withdrawal syndrome is likely to occur at cessation of dosages in the range of 40 mg a day for diazepam, for example, although 10 to 20 mg a day, taken for a month, can also result in a withdrawal syndrome when drug administration is stopped. The onset of withdrawal symptoms usually occurs 2 to 3 days after the cessation of use, but with long-acting drugs, such as diazepam, the latency before onset can be 5 or 6 days. The symptoms include anxiety, dysphoria, intolerance

for bright lights and loud noises, nausea, sweating, muscle twitching, and sometimes seizures (generally at dosages of 50 mg a day or more of diazepam). Table 20.8-1 lists the signs and symptoms of benzodiazepine withdrawal. Table 20.8-1 Signs and Symptoms of the Benzodiazepine Discontinuation Syndrome Barbiturates and Barbiturate-like Substances. The withdrawal syndrome for barbiturate and barbiturate-like substances ranges from mild symptoms (e.g., anxiety, weakness, sweating, and insomnia) to severe symptoms (e.g., seizures, delirium, cardiovascular collapse, and death). Persons who have been abusing phenobarbital in the range of 400 mg a day may experience mild withdrawal symptoms; those who have been abusing the substance in the range of 800 mg a day can experience orthostatic hypotension, weakness, tremor, and severe anxiety. About 75 percent of these persons have withdrawal-related seizures. Users of dosages higher than 800 mg a day may experience anorexia, delirium, hallucinations, and repeated seizures. Most symptoms appear in the first 3 days of abstinence, and seizures generally occur on the second or third day, when the symptoms are worst. If seizures do occur, they always precede the development of delirium. The symptoms rarely occur more than a week after stopping the substance. A psychotic disorder, if it develops, starts on the third to eighth day. The various associated symptoms generally run their course within 2 to 3 days, but can last as long as 2 weeks. The first episode of the syndrome usually occurs after 5 to 15 years of heavy substance use. Other Sedative-, Hypnotic-, or Anxiolytic-Induced Disorders Delirium. Delirium that is indistinguishable from delirium tremens associated with alcohol withdrawal is seen more commonly with barbiturate withdrawal than with benzodiazepine withdrawal. Delirium associated with intoxication can be seen with either barbiturates or benzodiazepines if the dosages are sufficiently high. Persisting Dementia. The existence of the sedative/hypnotic-induced persisting

dementia is controversial, because uncertainty exists whether a persisting dementia is caused by the substance use itself or by associated features of the substance use. Persisting Amnestic Disorder. Amnestic disorders associated with sedatives and hypnotics may be underdiagnosed. One exception is the increased number of reports of amnestic episodes associated with short-term use of benzodiazepines with short half-lives (e.g., triazolam [Halcion]). Psychotic Disorders. The psychotic symptoms of barbiturate withdrawal can be indistinguishable from those of alcohol-associated delirium tremens. Agitation, delusions, and hallucinations are usually visual, but sometimes tactile or auditory features develop after about 1 week of abstinence. Psychotic symptoms associated with intoxication or withdrawal are more common with barbiturates than with benzodiazepines. They are diagnosed in DSM-5 as sedative, hypnotic, or anxiolytic withdrawal with perceptual disturbances when reality testing is intact (the individual is aware the drug is causing the psychotic symptoms). If reality testing is not intact (the individual believes the hallucinations are real), a diagnosis of substance/medicationinduced psychotic disorder is more appropriate. Clinicians can further specify whether delusions or hallucinations are the predominant symptoms, including the type (e.g. auditory, visual, or tactile). Other Disorders. Sedative and hypnotic use has

also been associated with mood disorders, anxiety disorders, sleep disorders, and sexual dysfunctions. Unspecified Sedative-, Hypnotic-, or Anxiolytic-Related Disorder. When none of the previously discussed diagnostic categories is appropriate for a person with sedative-, hypnotic-, or anxiolytic-related disorder, and he or she does not meet the diagnostic criteria for any general substance-related disorder (see page 621), the appropriate diagnosis is unspecified sedative-, hypnotic-, or anxiolytic-related disorder. CLINICAL FEATURES Patterns of Abuse Oral Use. Sedatives and hypnotics can all be taken orally, either occasionally to achieve a time-limited specific effect or regularly to obtain a constant, usually mild, intoxication state. The occasional use pattern is associated with young persons who take the substance to achieve specific effects—relaxation for an evening, intensification of sexual activities, and a short-lived period of mild euphoria. The user's personality and expectations about the substance's effects and the setting in which the substance is taken also affect the substance-induced experience. The regular use pattern is associated with middle-aged, middle-class persons who usually obtain the substance from a family physician as a prescription for insomnia or anxiety. Abusers of this type may have prescriptions from several physicians, and the pattern of abuse may go undetected until

obvious signs of abuse or dependence are noticed by the person's family, coworkers, or physicians. Intravenous Use. A severe form of abuse involves the intravenous use of this class of substances. The users are mainly young adults who are intimately involved with illegal substances. Intravenous barbiturate use is associated with a pleasant, warm, drowsy feeling, and users may be inclined to use barbiturates more than opioids because barbiturates are less costly. The physical dangers of injection include transmission of the human immunodeficiency virus (HIV), cellulitis, vascular complications from accidental injection into an artery, infections, and allergic reactions to contaminants. Intravenous use is associated with rapid and profound tolerance and dependence and a severe withdrawal syndrome. Overdose Benzodiazepines. In contrast to the barbiturates and the barbiturate-like substances, the benzodiazepines have a large margin of safety when taken in overdoses, a feature that has contributed significantly to their rapid acceptance. The ratio of lethal dose to effective dose is about 200 to 1 or higher, because of the minimal degree of respiratory depression associated with the benzodiazepines. A list of equivalent therapeutic doses of benzodiazepines is given in Table 20.8-2. Even when grossly excessive amounts (more than 2 g) are taken in suicide attempts, the symptoms include only drowsiness, lethargy, ataxia, some confusion, and mild depression of the user's vital signs. A much more serious condition prevails when benzodiazepines are taken in overdose in combination with other sedative-hypnotic substances, such as alcohol. In such cases, small doses of benzodiazepines can cause death. The availability of flumazenil (Romazicon), a specific benzodiazepine antagonist, has reduced the lethality of the benzodiazepines. Flumazenil can be used in emergency rooms to reverse the effects of the benzodiazepines. Table 20.8-2 Approximate Therapeutic Equivalent Doses of Benzodiazepines

Barbiturates. Barbiturates are lethal when taken in overdose because they induce respiratory depression. In addition to intentional suicide attempts, accidental or unintentional overdoses are common. Barbiturates in home medicine cabinets are a common cause of fatal drug overdoses in children. As with benzodiazepines, the lethal effects of the barbiturates are additive to those of other sedatives or hypnotics, including alcohol and benzodiazepines. Barbiturate overdose is characterized by the induction of coma, respiratory arrest, cardiovascular failure, and death. The lethal dose varies with the route of administration and the degree of tolerance for the substance

after a history of long-term abuse. For the most commonly abused barbiturates, the ratio of lethal dose to effective dose ranges between 3:1 and 30:1. Dependent users often take an average daily dose of 1.5 g of a short-acting barbiturate, and some have been reported to take as much as 2.5 g a day for months. The lethal dose is not much greater for the long-term abuser than for the neophyte. Tolerance develops quickly, to the point at which withdrawal in a hospital becomes necessary to prevent accidental death from overdose. Barbiturate-like Substances. The barbiturate-like substances vary in their lethality and are usually intermediate between the relative safety of the benzodiazepines and the high lethality of the barbiturates. An overdose of methaqualone, for example, can result in restlessness, delirium, hypertonia, muscle spasms, convulsions, and, in very high doses, death. Unlike barbiturates, methaqualone rarely causes severe cardiovascular or respiratory depression, and most fatalities result from combining methaqualone with alcohol. TREATMENT AND REHABILITATION Withdrawal Benzodiazepines. Because some benzodiazepines are eliminated from the body slowly, symptoms of withdrawal can continue to develop for several weeks. To prevent seizures and other withdrawal symptoms, clinicians should gradually reduce the dosage. Several reports indicate that carbamazepine (Tegretol) may be useful in the treatment of benzodiazepine withdrawal. Table 20.8-3 lists guidelines for treating benzodiazepine withdrawal. Table 20.8-3 Guidelines for Treatment of Benzodiazepine Withdrawal

Barbiturates. To avoid sudden death during barbiturate withdrawal, clinicians must follow conservative clinical guidelines. Clinicians should not give barbiturates to a comatose or grossly intoxicated patient. A clinician should attempt to determine a patient’s usual daily dose of barbiturates and then verify the dosage clinically. For example, a clinician can give a test dose of 200 mg of pentobarbital every hour until a mild intoxication occurs but withdrawal symptoms are absent (Table 20.8-4). The clinician can then taper the total daily dose at a rate of about 10 percent of the total daily dose. Once the correct dosage is determined, a long-acting barbiturate can be used for the detoxification period. During this process, the patient may begin to experience withdrawal symptoms, in which case the clinician should halve the daily decrement. Table 20.8-4 Pentobarbital Test Dose Procedure for Barbiturate Withdrawal

In the withdrawal procedure, phenobarbital can be substituted for the more commonly abused short-acting barbiturates. The effects of phenobarbital last longer, and because barbiturate blood levels fluctuate less, phenobarbital does not cause observable toxic signs or a serious overdose. An adequate dose is 30 mg of phenobarbital for every 100 mg of the short-acting substance. The user should be maintained for at least 2 days at that level before the dose is reduced further. The regimen is analogous to the substitution of methadone for heroin. After withdrawal is complete, the patient must overcome the desire to start taking the substance again. Although substitution of nonbarbiturate sedatives or hypnotics for barbiturates has been suggested as a preventive therapeutic measure, this often results in replacing one substance dependence with another. If a user is to remain substance free, follow-up treatment, usually with psychiatric help and community support, is vital. Otherwise, a patient will almost certainly return to barbiturates or a substance with similar hazards. Overdose The treatment of overdose of this class of substances involves gastric lavage, activated charcoal, and careful monitoring of vital signs and central nervous system (CNS) activity. Patients who overdose and come to medical attention while awake should be kept from slipping into unconsciousness. Vomiting should be induced, and activated charcoal should be administered to delay gastric absorption. If a patient is comatose, the clinician must establish an intravenous fluid line, monitor the patient’s vital signs, insert an endotracheal tube to maintain a

patent airway, and provide mechanical ventilation, if necessary. Hospitalization of a comatose patient in an intensive care unit is usually required during the early stages of recovery from such overdoses. EXPERT OPINION The International Study of Expert Judgment on Therapeutic Use of Benzodiazepines and Other Psychotherapeutic Medications was designed to gather systematic data on the opinions of leading clinicians concerning the benefits and risks of benzodiazepines and alternative treatments of anxiety. This survey study addressed the relative risks of

benzodiazepines compared with other agents and comparative risks within the class. The expert panel assessed risk based on a drug's potential to produce tolerance, rebound symptoms, a withdrawal syndrome, and ease of discontinuation. Two thirds of the expert panel reported that long-term use of benzodiazepines for the treatment of anxiety disorders does not pose a high risk of dependence and abuse. Although agreement was that the pharmacological properties of the medication may be the most important contributor to development of withdrawal symptoms, no consensus existed on whether benzodiazepines with shorter and longer half-lives have similar dependence potential. A clear consensus was that the differences in withdrawal symptoms are clinically negligible with gradual dose tapering. Because differences in abuse liability among the various benzodiazepines have not been demonstrated in humans, and because the benefits of benzodiazepine treatment clearly outweigh the risks, most physicians on the expert panel opposed increased restrictions on benzodiazepine prescribing. Despite the expert opinion stated earlier, state and federal agencies have attempted to restrict the distribution of benzodiazepines by requiring special reporting forms. For example, in New York State, through the use of a newly enacted prescription monitoring program (PMP) called I-STOP, effective since August 27, 2013, doctors cannot write a prescription for a benzodiazepine unless they first search a computerized database that contains the names of all persons in the state who were ever prescribed benzodiazepines and other controlled substances. Governments have taken these and other such measures in an attempt to stem the tide of abuse. However most abuse results from the illicit manufacture, sale, and diversion of substances, particularly to cocaine and opioid addicts, not from physicians' prescriptions or legitimate pharmaceutical companies. These programs do not stem the tide of illegal use of valuable medications and interfere in the practice of medicine and in the confidential relationship between doctor and patient. REFERENCES Auta J, Kadriu B, Giusti P, Costa E, Guidotti A. Anticonvulsant, anxiolytic, and non-sedating actions of imidazenil and other imidazo-benzodiazepine carboxamide derivatives. Pharmacol Biochem Behav. 2010;95(4):383. Barceloux DG. Barbiturates (Amobarbital, Butalbital, Pentobarbital, Secobarbital). In: Medical Toxicology of Drugs Abuse: Synthesized Chemicals and Psychoactive Plants. Hoboken, NJ: John Wiley & Sons, Inc.; 2012:467. Barnett SR, Riddle MA. Anxiolytics and sedative/hypnotics: Benzodiazepines, buspirone, and other. In: Martin A, Scahill L, Kratochvil C, eds. Pediatric Psychopharmacology: Principles and Practice. New York: Oxford University Press, Inc.; 2011:338. Ciraulo DA, Sarid-Segal O. Sedative-, hypnotic-, or anxiolytic-related disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1397. Hall MT, Howard MO, McCabe SE. Subtypes of adolescent sedative/anxiolytic misusers: A latent profile analysis. Addict Behav. 2010;35(10):882. Hoque R, Chesson Jr. AL. Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: Fluorine-18flourodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem. J Clin Sleep Med. 2009;5(5):471. Houston CM, McGee TP, MacKenzie G, Troyano-Cuturi K, Rodriguez PM, Kutsarova E, Diamanti E, Hosie AM, Frank NP, Brickley SG. Are extrasynaptic GABAA receptors important targets for sedative/hypnotic drugs? J

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These drugs go by such street names as ice, crystal, crystal meth, and speed. As a general class, the amphetamines are referred to as analeptics, sympathomimetics, stimulants, and psychostimulants. The typical amphetamines are used to increase performance and to induce a euphoric feeling, for example, by students studying for examinations, by long-distance truck drivers on trips, by business people

with important deadlines, by athletes in competition, and by soldiers during wartime. Although not as addictive as cocaine, amphetamines are nonetheless addictive drugs. Other amphetamine-like substances are ephedrine, pseudoephedrine, and phenylpropanolamine (PPA). These drugs, PPA in particular, can dangerously exacerbate hypertension, precipitate a toxic psychosis, cause intestinal infarction, or result in death. The safety margin for PPA is particularly narrow, and three to four times the normal dose can result in life-threatening hypertension. In 2005, medications containing PPA were recalled by the FDA, and in 2006, the FDA prohibited the sale of over-the-counter medications containing ephedrine and regulated the sale of over-thecounter medications containing pseudoephedrine, which was being used illegally to make methamphetamine. Amphetamine-type drugs with abuse potential also include phendimetrazine (Preludin), which is included in Schedule II of the Controlled Substance Act (CSA), and diethylpropion (Tenuate), benzphetamine (Didrex), and phentermine (Ionamin), which are included in Schedules III or IV of the CSA. It is presumed that all of these drugs are capable of producing all of the listed amphetamine-induced disorders. Modafinil (Provigil), used in the treatment of narcolepsy, also has stimulant and euphorigenic effects in humans, but its toxicity and likelihood of producing amphetamine-induced disorders are unknown. Methamphetamine is a potent form of amphetamine that abusers of the substance inhale, smoke, or inject intravenously. Its psychological effects last for hours and are described as particularly powerful. Unlike cocaine (see discussion later in this section), which must be imported, methamphetamine is a synthetic drug that can be manufactured domestically in illicit laboratories. Other agents called substituted or designer amphetamines are discussed separately later in this section. Epidemiology Amphetamine-type stimulant abuse represents major public health and law enforcement problems in the United States and abroad, primarily due to the consumption of methamphetamine. According to the Community Epidemiology Work Group, methamphetamine abuse occurs at epidemic levels in Hawaii, on the West Coast, and in some Southern states, and continues to spread eastward. Nationally, treatment admission rates for methamphetamine dependence more than doubled between 1995 and 2012, and in the western United States, treatment admission rates for methamphetamine dependence are higher than those of either cocaine or heroin. According to the National Association of Counties, nearly half (48 percent) of 500 county law enforcement agencies in the United States name methamphetamine as the primary drug problem, more than cocaine (22 percent), marijuana (22 percent), and heroin (2 percent) combined. Similarly, almost 40 percent of state and local law enforcement agencies identify methamphetamine as their greatest drug threat, second only to cocaine, a higher percentage than any other drug.

On a global basis, use of amphetamine-type stimulants, including methamphetamine, is also a major concern, ranking as the second most widely used substance, following marijuana, according to a report from the United Nations Office on Drugs and Crime. According to the 2010 National Survey on Drug Use and Health (NSDUH), 353,000 persons 12 years or older were current users of methamphetamine (0.1 percent). Neuropharmacology All the amphetamines are rapidly absorbed orally and have a rapid onset of action, usually within 1 hour when taken orally. The classic

amphetamines are also taken intravenously and have an almost immediate effect by this route. Nonprescribed amphetamines and designer amphetamines are also inhaled (“snorting”). Tolerance develops with both classic and designer amphetamines, although amphetamine users often overcome the tolerance by taking more of the drug. Amphetamine is less addictive than cocaine, as evidenced by experiments on rats in which not all animals spontaneously self-administered low doses of amphetamine. The classic amphetamines (i.e., dextroamphetamine, methamphetamine, and methylphenidate) produce their primary effects by causing the release of catecholamines, particularly dopamine, from presynaptic terminals. The effects are particularly potent for the dopaminergic neurons projecting from the ventral tegmental area to the cerebral cortex and the limbic areas. This pathway has been termed the reward circuit pathway, and its activation is probably the major addicting mechanism for the amphetamines. The designer amphetamines cause the release of catecholamines (dopamine and norepinephrine) and of serotonin, the neurotransmitter implicated as the major neurochemical pathway for hallucinogens. Therefore, the clinical effects of designer amphetamines are a blend of the effects of classic amphetamines and those of hallucinogens. COCAINE Cocaine has been used in its raw form for more than 15 centuries. In the United States, cycles of widespread stimulant misuse and associated problems have occurred for more than 100 years. Cocaine and cocaine use disorders became a major public health issue in the 1980s when an epidemic of use spread throughout the country. Due to education and intervention, cocaine use has since declined. However, high rates of legal, psychiatric, medical, and social problems related to cocaine use still exist, thus cocaine related disorders remain an important public health issue. Cocaine is an alkaloid derived from the shrub Erythroxylum coca, which is indigenous to South America, where the leaves of the shrub are chewed by local inhabitants to obtain the stimulating effects (Fig. 20.9-1). The cocaine alkaloid was first isolated in 1855 and first used as a local anesthetic in 1880. It is still used as a local anesthetic, especially for eye, nose, and throat surgery, for which its vasoconstrictive and analgesic effects are helpful. In 1884, Sigmund Freud made a study of cocaine’s general pharmacological effects and, for a period of time, according to his biographers, was addicted to the drug. In the 1880s and 1890s, cocaine was widely touted as a cure for many ills and was listed in the 1899 Merck Manual. It

was the active ingredient in the beverage Coca-Cola until 1903. In 1914, however, once its addictive and adverse effects had been recognized, cocaine was classified as a narcotic, along with morphine and heroin. FIGURE 20.9-1 Cocaine is an alkaloid obtained from coca leaves. Epidemiology Cocaine Use. In 2012, 1.5 million (0.6 percent) persons aged 12 years or older used cocaine in the past month. Persons aged 18 to 25 (1.5 percent) had a higher rate of past month cocaine use than persons aged 26 or older (0.5 percent) and youths aged 12 to 17 (0.9 percent). Males (0.8 percent) were twice as likely as females (0.4 percent) to have used cocaine in the past year. Asians had the lowest rate of past year cocaine use (0.5 percent) compared with other racial or ethnic groups. Cocaine Abuse and Dependence. In 2012 more than 1.0 million (0.4 percent) persons aged 12 or older met the criteria for abuse of, or dependence on, cocaine in the past year. Persons aged 18 to 25 (0.9 percent) had the highest rate of past year cocaine abuse or dependence, followed by persons aged 26 or older (0.4 percent) and youths aged 12 to 17 (0.2 percent). Males (0.9 percent) were more than twice as likely as females (0.4 percent) to have met the criteria for cocaine abuse or dependence. Blacks

(1.1 percent) and Hispanics (0.9 percent) had higher rates of cocaine abuse or dependence than whites (0.5 percent), and the rate for Asians (0.1 percent) was lower than that for blacks, Hispanics, whites, American Indians or Alaskan Natives (1.2 percent), and non-Hispanic persons who identified themselves with two or more races (0.9 percent). Crack Cocaine. An estimated 1.1 million (0.4 percent) persons aged 12 or older used crack cocaine in the past year, and 492,000 (0.2 percent) persons used crack cocaine in the past month. Persons aged 18 to 25 (0.5 percent) had the highest rate of past year crack use, followed by persons aged 26 or older (0.4 percent) and youths aged 12 to 17 (0.1 percent). Males (0.5 percent) were twice as likely as females (0.3 percent) to have used crack cocaine in the past year. Asians had the lowest rate of past year crack cocaine use (0.1 percent) compared with other racial or ethnic groups. Blacks (0.9 percent), whites (0.4 percent), Hispanics or Latinos (0.3 percent), and persons who identified themselves with two or more non-Hispanic races (0.9 percent) had higher rates of past year crack cocaine use than American Indians or Alaska Natives (0.2 percent) and Native Hawaiians or Other Pacific Islanders (0.1 percent). Current cocaine use is on the decline, primarily because of increased awareness of cocaine's risks, as well as a comprehensive public campaign about cocaine and its effects. The societal effects of the decrease in cocaine use, however, have been somewhat offset by the frequent use over the past years of crack. Comorbidity As with other substance-related disorders, cocaine-related disorders are often accompanied by additional psychiatric disorders. The development of mood disorders and alcohol-related disorders usually follows the onset of cocaine-related disorders, whereas anxiety disorders, antisocial personality disorder, and ADHD are thought to precede the development of cocaine-related disorders. Most studies of comorbidity in patients with cocaine-related disorders have shown that major depressive disorder, bipolar II disorder, cyclothymic disorder, anxiety disorders, and antisocial personality disorder are the most commonly associated psychiatric diagnoses. The percentages of comorbidity in cocaine users are presented in Table 20.9-1. Table 20.9-1 Additional Psychiatric Diagnoses among Cocaine Users Seeking Treatment (New Haven Cocaine Diagnostic Study Results, Percentages)

Etiology Genetic Factors. The most convincing evidence to date of a genetic influence on cocaine dependence comes from studies of twins. Monozygotic twins have higher concordance rates for stimulant dependence (cocaine, amphetamines, and amphetamine-like drugs) than dizygotic twins. The analyses indicate that genetic factors and unique (unshared) environmental factors contribute about equally to the development of stimulant dependence. Sociocultural Factors. Social, cultural, and economic factors are powerful determinants of initial use, continuing use, and relapse. Excessive use is far more likely in countries where cocaine is readily available. Different economic opportunities may influence certain groups more than others to engage in selling illicit drugs, and selling is more likely to be carried out in familiar communities than in communities where the seller runs a high risk of arrest. Learning and Conditioning. Learning and conditioning are also considered important in perpetuating cocaine use. Each inhalation or injection of cocaine yields a "rush" and a euphoric experience that reinforces the antecedent drug-taking behavior. In addition, the environmental cues associated with substance use become associated with the euphoric state so that long after a period of cessation, such cues (e.g., white powder and paraphernalia) can elicit memories of the euphoric state and reawaken craving for cocaine. In cocaine abusers (but not in normal controls), cocaine-related stimuli activate brain regions subserving episodic and working memory and produce electroencephalography (EEG) arousal (desynchronization). Increased metabolic activity in the limbic-related regions, such as the amygdala, parahippocampal gyrus, and dorsolateral prefrontal cortex, reportedly correlates with reports of craving for cocaine, but the

degree of EEG arousal does not.

Pharmacological Factors. As a result of actions in the central nervous system (CNS), cocaine can produce a sense of alertness, euphoria, and well-being. Users may experience decreased hunger and less need for sleep. Performance impaired by fatigue is usually improved. Some users believe that cocaine enhances sexual performance. Neuropharmacology Cocaine's primary pharmacodynamic action related to its behavioral effects is competitive blockade of dopamine reuptake by the dopamine transporter. This blockade increases the concentration of dopamine in the synaptic cleft and results in increased activation of both dopamine type 1 (D1) and type 2 (D2) receptors. The effects of cocaine on the activity mediated by D3, D4, and D5 receptors are not yet well understood, but at least one preclinical study has implicated the D3 receptor. Although the behavioral effects are attributed primarily to the blockade of dopamine reuptake, cocaine also blocks the reuptake of norepinephrine and serotonin. The behavioral effects related to these activities are receiving increased attention in the scientific literature. The effects of cocaine on cerebral blood flow and cerebral glucose use have also been studied. Results in most studies generally showed that cocaine is associated with decreased cerebral blood flow and possibly with the development of patchy areas of decreased glucose use. The behavioral effects of cocaine are felt almost immediately and last for a relatively brief time (30 to 60 minutes); thus users require repeated doses of the drug to maintain the feelings of intoxication. Despite the short-lived behavioral effects, metabolites of cocaine can be present in the blood and urine for up to 10 days. Cocaine has powerful addictive qualities. Because of its potency as a positive reinforcer of behavior, psychological dependence on cocaine can develop after a single use. With repeated administration, both tolerance and sensitivity to various effects of cocaine can arise, although the development of tolerance or sensitivity is apparently caused by many factors and is not easily predicted. Physiological dependence on cocaine does occur, although cocaine withdrawal is mild compared with withdrawal from opiates and opioids. Researchers recently reported that positron emission tomography (PET) scans of the brains of patients being treated for cocaine addiction show high activation in the mesolimbic dopamine system when addicts profoundly crave a drug. Researchers exposed patients to cues that had previously caused them to crave cocaine, and patients described feelings of intense cravings for the drug while PET scans showed activation in areas from the amygdala and the anterior cingulate to the tip of both temporal lobes. Some researchers claim that the mesolimbic dopamine system is also active in patients with nicotine addiction, and the same system has been linked to cravings for heroin, morphine, amphetamines, marijuana, and alcohol. The D2 receptors in the mesolimbic dopamine system have been held responsible for the heightened activity during periods of craving. PET scans of patients recovering from cocaine addiction are reported to show a drop in neuronal activity consistent with a lessened ability to receive dopamine, and the reduction in this ability, although it decreases over time, is apparent as long as a year and a half after withdrawal. The pattern of reduced brain activity reflects the course of the craving; between the third and fourth weeks of withdrawal, the activity is at its lowest level, and the risk of patient relapse is highest. After about 1 year, the brains of former addicts are almost back to normal, although whether the dopamine cells ever return to a completely normal state is debatable. Methods of Use Because drug dealers often dilute cocaine powder with sugar or procaine, street cocaine varies greatly in purity. Cocaine is sometimes cut with amphetamine. The most common

method of using cocaine is inhaling the finely chopped powder into the nose, a practice referred to as “snorting” or “tooting.” Other methods of ingesting cocaine are subcutaneous or intravenous injection and smoking (freebasing). Freebasing involves mixing street cocaine with chemically extracted pure cocaine alkaloid (the freebase) to get an increased effect. Smoking is also the method used to ingest crack cocaine. Inhaling is the least dangerous method of cocaine use; intravenous injection and smoking are the most dangerous. The most direct methods of ingestion are often associated with cerebrovascular diseases, cardiac abnormalities, and death. Although cocaine can be taken orally, it is rarely ingested via this, the least effective, route. Crack. Crack, a freebase form of cocaine, is extremely potent. It is sold in small, ready-to-smoke amounts, often called “rocks.” Crack cocaine is highly addictive; even one or two experiences with the drug can cause intense craving for more. Users have been known to resort to extremes of behavior to obtain the money to buy more crack. Reports from urban emergency rooms have also associated extremes of violence with crack abuse. DIAGNOSIS AND CLINICAL FEATURES Stimulant Use Disorder The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for stimulant use disorder are similar to the criteria used for other substance use disorders (see page 621). Amphetamine dependence can result in a rapid downward spiral of a person’s abilities to cope with work- and family-related obligations and stresses. A person who abuses amphetamines requires increasingly high doses of amphetamine to obtain the usual high, and physical signs of amphetamine abuse (e.g., decreased weight and paranoid ideas) almost always develop with continued abuse. Mr. H, a 35-year-old married man, was admitted to a psychiatric hospital because he felt persecuted by gang members who were out to kill him. He could not explain why they wished to kill him, but he heard voices from people whom he suspected to be mob drug dealers and they were discussing that they should kill him. He used methamphetamine for several years, so he had dealt with drug dealers before. He began using at age 27 at the persuasion of a friend to try it. After an injection of 20 mg, he felt good and powerful and his sleepiness and fatigue disappeared. After a few tries Mr. H found that he could not stop using it. He constantly thought about how he would obtain the drug and started increasing the dosage he used. During times that he could not get methamphetamine, he felt lethargic and sleepy and became irritable and dysphoric. Mr. H’s wife learned of his drug use and attempted to persuade him to stop using it. He lost his job 2 months prior to his admission because he was repeatedly abusive to work colleagues because he felt that they were trying to harm him. With no

income, Mr. H had to cut down his use of methamphetamine to only occasional usage. He finally decided to quit when his wife threatened to divorce him. Once he stopped using, he felt very tired, seemed gloomy, and often sat in his favorite chair and did nothing. After a few weeks, Mr. H told his wife that he did not wish to leave the house because he had heard dealers on the street talking about him. He wanted all doors and windows locked, and he refused to eat in fear that the food may be poisoned. On examination, Mr. H seemed withdrawn, only giving short answers to questions. He was in clear consciousness and fully oriented and showed no marked impairment of cognitive functions. Physical and neurological testing showed no abnormalities except needle scars on his arms from methamphetamine injections. An EEG was normal. Clinically and practically, cocaine use disorder can be suspected in patients who evidence unexplained changes in personality. Common changes associated with cocaine use are irritability, impaired ability to concentrate, compulsive behavior, severe insomnia, and weight loss. Colleagues at work and family members may notice a person’s general and increasing inability to perform the expected tasks associated with work and family life. The patient may show new evidence of increased debt or

inability to pay bills on time because of the large sums used to buy cocaine. Cocaine abusers often excuse themselves from work or social situations every 30 to 60 minutes to find a secluded place to inhale more cocaine. Because of the vasoconstricting effects of cocaine, users almost always develop nasal congestion, which they may attempt to selfmedicate with decongestant sprays. Mr. D, a 45-year-old married man, was referred by his therapist to a private outpatient substance abuse treatment program for evaluation and treatment of a possible cocaine problem. According to the therapist, Mr. D's wife expressed concern for a possible substance abuse problem on several occasions. A few days prior, Mr. D admitted to the therapist and his wife that he "occasionally" used cocaine for the past year. His wife insisted that he obtain treatment for his drug problem or else she would file for divorce. Mr. D reluctantly conceded to treatment, but insisted that his cocaine use was not a problem and that he felt capable of stopping without entering a treatment program. During the initial evaluation interview, Mr. D reported that he currently used cocaine, intranasally, 3 to 5 days a week, and that this pattern has been continuing for a year and a half. On average, he consumes a total of 1 to 2 grams of cocaine weekly. He mostly uses cocaine at work, in his office or in the bathroom. He usually started thinking about cocaine during his drive to work in the morning and once at work was unable avoid thinking about the cocaine in his desk drawer. Despites his attempts at distraction and postponing use, he usually takes his first line of cocaine within an hour of arriving at work. On some days he will take another two to three lines over the course of the day, but, on days where he is frustrated and stressed, he

may take a line or two every hour from morning until late afternoon. He rarely uses cocaine at home and never uses in front of his wife or his three daughters. He occasionally takes a line or two during a weekday evening or weekends at home when everyone else is out of the house. He denies current use of alcohol or any other illicit drug. He denies any history of alcohol or drug abuse and any history of emotional or marital problems. Stimulant Intoxication The diagnostic criteria for stimulant intoxication emphasize behavioral and physical signs and symptoms of stimulant use (Table 20.9-2). Persons use stimulants for their characteristic effects of elation, euphoria, heightened self-esteem, and perceived improvement on mental and physical tasks. With high doses, symptoms of intoxication include agitation, irritability, impaired judgment, impulsive and potentially dangerous sexual behavior, aggression, a generalized increase in psychomotor activity, and potentially, symptoms of mania. The major associated physical symptoms are tachycardia, hypertension, and mydriasis. Table 20.9-2 Signs and Symptoms of Stimulant Intoxication Mrs. T, a 45-year-old married business woman, was admitted to psychiatric service after a 3-month period in which she became increasing mistrustful of others and suspicious of business associates. She took statements from others out of context, twisting their words, and making inappropriately hostile and accusatory comments. On one occasion, Mrs. T physically attacked a coworker in a bar accusing her of having an affair with her husband and plotting with other coworkers to kill her. One year previously, Mrs. T was prescribed methylphenidate for narcolepsy due to daily irresistible sleep attacks and episodes of sudden loss of muscle tone when she became emotionally excited. After taking the medication, Mrs. T became asymptomatic and was able to work effectively and have an active social life with family and friends. In the 5 months before admission, Mrs. T had been using increasingly large doses of methylphenidate to maintain alertness late at night because of an increased amount

of work that could not be handled during the day. She reported that during this time she often could feel her heart race and that she had trouble sitting still. Mr. P, an 18-year-old man, was

brought to a hospital emergency room via ambulance in the middle of the night. He was accompanied by a friend who decided to call an ambulance because he felt Mr. P was going to die. Mr. P was agitated and argumentative, his breathing was irregular and rapid, his pulse was rapid, and his pupils were dilated. His friend eventually admitted that they used a lot of cocaine that evening. When his mother arrived at the hospital, Mr. P's condition had somewhat improved, although his loud singing created a commotion in the emergency room. His mother states Mr. P has some disciplinary problems; he is disobedient, resentful, and violently argumentative. He had been arrested on a few occasions for shoplifting and for driving while intoxicated. His mother suspected that Mr. P was using drugs due to his behavior and because she heard him talk to his friends about drugs, however, she has no direct proof of his use. Within 24 hours, Mr. P was well and willing to talk. He boastfully stated that he had been using alcohol and various drugs regularly since he was 13. It started with just alcohol and marijuana, but once he entered high school and became acquainted with older youths, he experimented with other drugs such as speed and cocaine. By the time he was 16, he was using combinations of alcohol, speed, marijuana, and cocaine. He settled on just cocaine after a year of mixing drugs. Mr. P frequently skipped school and when he attended school he was usually intoxicated. To support his habit, he acquired money in various schemes, such as borrowing money from friends that he had no intention of paying back or stealing car radios or stealing from his mother. Despite his blatant admission of drug use, Mr. P denies having a problem. When asked about his ability to control his drug use, he defensively replies "Of course I can. No problem. I just don't see any damn reason to stop." Stimulant Withdrawal After stimulant intoxication, a "crash" occurs with symptoms of anxiety, tremulousness, dysphoric mood, lethargy, fatigue, nightmares (accompanied by rebound rapid eye movement [REM] sleep), headache, profuse sweating, muscle cramps, stomach cramps, and insatiable hunger. The withdrawal symptoms generally peak in 2 to 4 days and are resolved in 1 week. The most serious withdrawal symptom is depression, which can be particularly severe after the sustained use of high doses of stimulants and which can be associated with suicidal ideation or behavior. A person in the state of withdrawal can experience powerful and intense cravings for cocaine, especially because taking cocaine can eliminate the unpleasant withdrawal symptoms. Persons experiencing cocaine withdrawal often attempt to self-medicate with alcohol, sedatives, hypnotics, or antianxiety agents such as diazepam (Valium).

Stimulant Intoxication Delirium Delirium associated with stimulant use generally results from high doses of a stimulant or from sustained use, and so sleep deprivation affects the clinical presentation. The combination of stimulants with other substances and the use of stimulants by a person with preexisting brain damage can also cause development of delirium. It is not uncommon for university students who are using amphetamines to cram for examinations to exhibit this type of delirium. Stimulant-Induced Psychotic Disorder The hallmark of stimulant-induced psychotic disorder is the presence of paranoid delusions and hallucinations, which occurs in up to 50 percent of stimulant users. Auditory hallucinations are also common, but visual and tactile hallucinations are less common than paranoid delusions. The sensation of bugs crawling beneath the skin (formication) has been reported to be associated with cocaine use. The presence of these symptoms depends on the dose, duration of use, and the user's sensitivity to the substance. Cocaine-induced psychotic disorders are most common with intravenous use and crack users, and the psychotic symptoms are more common in men than in women. The treatment of choice for amphetamine-induced psychotic disorder is the short-term use of an antipsychotic medication such as haloperidol (Haldol). Mr. H is a 20-year-old college student who was functioning well until the

weeks of his finals, when he began taking large amounts of cocaine because he felt he was unprepared for his tests. He began having delusional beliefs that he was being followed by the police and a detective at the request of his parents in order to spy on him. He also believed that his roommate would give reports to the detective about his study habits and social life. He was brought to the emergency room after he threatened to harm his roommate if he continued to report on him. During evaluation, Mr. P reported sleeplessness and auditory hallucinations that told him that his roommate was conspiring against him. He was very agitated and paced continuously. After admission to the hospital, Mr. P was given antipsychotics and sleeping medications and recovered in 3 days. Stimulant-Induced Mood Disorder The DSM-5 allows for the diagnoses of stimulant-induced bipolar disorder and stimulantinduced depressive disorder, either of which can begin during either intoxication or withdrawal. In general, intoxication is associated with manic or mixed mood features, whereas withdrawal is associated with depressive mood features. Stimulant-Induced Anxiety Disorder

The DSM-5 allows for the diagnosis of stimulant-induced anxiety disorder. The onset of stimulant-induced anxiety disorder can also occur during intoxication or withdrawal. Stimulants can induce symptoms similar to those seen in panic disorder, and phobic disorders, in particular. Stimulant-Induced Obsessive-Compulsive Disorder The DSM-5 allows for the diagnosis of stimulant-induced obsessive-compulsive disorder. The onset can occur during intoxication or withdrawal. After high doses of stimulants, some individuals develop time-limited stereotyped behaviors or rituals (i.e., picking at clothing, and arranging and rearranging items purposelessly) that share some features with the type of compulsions seen in obsessive-compulsive disorder. Stimulant-Induced Sexual Dysfunction The DSM-5 allows for the diagnosis of stimulant-induced sexual dysfunction. Amphetamines may be prescribed as an antidote to the sexual side effects of serotonergic agents such as fluoxetine (Prozac), but stimulants are often misused by persons to enhance sexual experiences. High doses and long-term use are associated with erectile disorder and other sexual dysfunctions. Stimulant-Induced Sleep Disorder Stimulant-induced sleep disorder can begin during either intoxication or withdrawal, and sleep dysfunction can vary depending on the onset. Stimulant intoxication can produce insomnia and sleep deprivation, whereas persons undergoing stimulant withdrawal can experience hypersomnolence and nightmares. ADVERSE EFFECTS Amphetamines Physical. Amphetamine abuse can produce adverse effects, the most serious of which include cerebrovascular, cardiac, and gastrointestinal effects. Among the specific life-threatening conditions are myocardial infarction, severe hypertension, cerebrovascular disease, and ischemic colitis. A continuum of neurological symptoms, from twitching to tetany to seizures to coma and death, is associated with increasingly high amphetamine doses. Intravenous use of amphetamines can transmit human immunodeficiency virus (HIV) and hepatitis and further the development of lung abscesses, endocarditis, and necrotizing angiitis. Several studies have shown that abusers of amphetamines knew little—or did not care—about safe-sex practices and the use of condoms. The non–life-threatening adverse effects of amphetamine abuse include flushing, pallor, cyanosis, fever, headache, tachycardia, palpitations, nausea, vomiting, bruxism (teeth grinding), shortness of breath, tremor, and ataxia. Pregnant women who use amphetamines often have babies with low birthweight, small head circumference,

early gestational age, and growth retardation. Psychological. The adverse psychological effects associated with amphetamine use include restlessness, dysphoria, insomnia, irritability, hostility, and confusion. Amphetamine use can also induce symptoms of anxiety disorders, such as

generalized anxiety disorder and panic disorder, as well as ideas of reference, paranoid delusions, and hallucinations. Cocaine A common adverse effect associated with cocaine use is nasal congestion; serious inflammation, swelling, bleeding, and ulceration of the nasal mucosa can also occur. Long-term use of cocaine can also lead to perforation of the nasal septa. Freebasing and smoking crack can damage the bronchial passages and the lungs. The intravenous use of cocaine can result in infection, embolisms, and the transmission of human immunodeficiency virus (HIV). Minor neurological complications with cocaine use include the development of acute dystonia, tics, and migraine-like headaches. The major complications of cocaine use, however, are cerebrovascular, epileptic, and cardiac. About two thirds of these acute toxic effects occur within 1 hour of intoxication, about one fifth occur in 1 to 3 hours, and the remainder occurs up to several days later. Cerebrovascular Effects. The most common cerebrovascular diseases associated with cocaine use are nonhemorrhagic cerebral infarctions. When hemorrhagic infarctions do occur, they can include subarachnoid, intraparenchymal, and intraventricular hemorrhages. Transient ischemic attacks have also been associated with cocaine use. Although these vascular disorders usually affect the brain, spinal cord hemorrhages have also been reported. The obvious pathophysiological mechanism for these vascular disorders is vasoconstriction, but other pathophysiological mechanisms have also been proposed. Seizures. Seizures have been reported to account for 3 to 8 percent of cocainerelated emergency room visits. Cocaine is the substance of abuse most commonly associated with seizures; the second most common substance is amphetamine. Cocaineinduced seizures are usually single events, although multiple seizures and status epilepticus are also possible. A rare and easily misdiagnosed complication of cocaine use is partial complex status epilepticus, which should be considered as a diagnosis in a patient who seems to have cocaine-induced psychotic disorder with an unusually fluctuating course. The risk of having cocaine-induced seizures is highest in patients with a history of epilepsy who use high doses of cocaine as well as crack. Cardiac Effects. Myocardial infarctions and arrhythmias are perhaps the most common cocaine-induced cardiac abnormalities. Cardiomyopathies can develop with long-term use of cocaine, and cardioembolic cerebral infarctions can be a further

complication of cocaine-induced myocardial dysfunction. Death. High doses of cocaine are associated with seizures, respiratory depression, cerebrovascular diseases, and myocardial infarctions—all of which can lead to death in persons who use cocaine. Users may experience warning signs of syncope or chest pain but may ignore these signs because of the irrepressible desire to take more cocaine. Deaths have also been reported with the ingestion of “speedballs,” which are combinations of opioids and cocaine. Other Agents Substituted Amphetamines. MDMA (3,4-methylene-dioxymethamphetamine) is one of a series of substituted amphetamines that also includes MDEA, MDA (3,4methylene-dioxyamphetamine), DOB (2,5-dimethoxy-4-bromoamphetamine), PMA (paramethoxyamphetamine), and others. These drugs produce subjective effects resembling those of amphetamine and LSD (lysergic acid diethylamide), and in that sense, MDMA and similar analogues may represent a distinct category of drugs. A methamphetamine derivative that came into use in the 1980s, MDMA was not technically subject to legal regulation at the time. Although it has been labeled a “designer drug” in the belief that it was deliberately synthesized to evade legal regulation, it was actually synthesized and patented in 1914. Several psychiatrists used it as an adjunct to psychotherapy and concluded that it had value. At one time, it was advertised as legal and was used in psychotherapy for its subjective effects. It was never approved by the FDA, however. Its use raised questions of both safety and legality, because the related amphetamine derivatives MDA, DOB, and PMA had caused a number of

overdose deaths, and MDA was known to cause extensive destruction of serotonergic nerve terminals in the CNS. Using emergency scheduling authority, the Drug Enforcement Agency made MDMA a Schedule I drug under the CSA, along with LSD, heroin, and marijuana. Despite its illegal status, MDMA continues to be manufactured, distributed, and used in the United States, Europe, and Australia. Its use is common in Australia and Great Britain at extended dances (“raves”) popular with adolescents and young adults. MECHANISMS OF ACTION. The unusual properties of the drugs may be a consequence of the different actions of the optical isomers: the R(–) isomers produce LSD-like effects and the amphetamine-like properties are linked to S(+) isomers. The LSD-like actions, in turn, may be linked to the capacity to release serotonin. The various derivatives may exhibit significant differences in subjective effects and toxicity. Animals in laboratory experiments will self-administer the drugs, suggesting prominent amphetamine-like effects. SUBJECTIVE EFFECTS. After taking usual doses (100 to 150 mg), MDMA users experience elevated mood and, according to various reports, increased self-confidence and sensory sensitivity; peaceful feelings coupled with insight, empathy, and closeness to persons; and decreased appetite. Difficulty concentrating and an increased capacity to focus have both been reported. Dysphoric reactions, psychotomimetic effects, and psychosis have also been reported. Higher doses seem more likely to produce psychotomimetic effects. Sympathomimetic effects of tachycardia, palpitation, increased blood pressure,

sweating, and bruxism are common. The subjective effects are reported to be prominent for about 4 to 8 hours, but they may not last as long or may last longer, depending on the dose and route of administration. The drug is usually taken orally but is also snorted and injected. Both tachyphylaxis and some tolerance are reported by users. TOXICITY. Although it is not as toxic as MDA, various somatic toxicities have been attributed to MDMA use as well as fatal overdoses. It does not appear to be neurotoxic when injected into the brains of animals, but it is metabolized to MDA in both animals and humans. In animals, MDMA produces selective, long-lasting damage to serotonergic nerve terminals. It is not certain if the levels of the MDA metabolite reached in humans after the usual doses of MDMA suffice to produce lasting damage. Users of MDMA show differences in neuroendocrine responses to serotonergic probes, and studies of former MDMA users show global and regional decreases in serotonin transporter binding, as measured by PET (Fig. 20.9-2). FIGURE 20.9-2 Positron emission tomography (PET) images obtained 75 to 95 minutes postinjection of [11C]McN5652 and [11C]DASB in a representative control subject and a representative 3,4-methylenedioxymethamphetamine (MDMA) subject, demonstrating the reductions in serotonin transporter (SERT) binding in the MDMA subject with both radioligands. PET images are normalized to a common maximum. (Reprinted from McCann UD, Szabo Z, Seckin E, Rosenblatt P, Mathews WB. Quantitative PET studies of serotonin transporter MDMA users and controls using [11C]McN5652 and [11C]DASB. Neuropsychopharmacology. 2005;30[9]:1741, with permission.) Currently, no established clinical uses exist for MDMA, although before its regulation, there were several reports of its beneficial effects as an adjunct to psychotherapy. Khat. The fresh leaves of Catha edulis, a bush native to East Africa, have been used as a stimulant in the Middle East, Africa, and the Arabian Peninsula for at least 1,000

years. Khat is still widely used in Ethiopia, Kenya, Somalia, and Yemen. The amphetamine-like effects of khat have long been recognized, and although efforts to isolate the active ingredient were first undertaken in the 19th century, only since the 1970s has cathinone (S[–] α-aminopropiophenone or S[–]2-amino-1-phenyl-1propanone) been identified as the substance

responsible. Cathinone is a precursor moiety that is normally enzymatically converted in the plant to the less-active entities norephedrine and cathine (norpseudoephedrine), which explains why only the fresh leaves of the plant are valued for their stimulant effects. Cathinone has most of the CNS and peripheral actions of amphetamine and appears to have the same mechanism of action. In humans, it elevates mood, decreases hunger, and alleviates fatigue. At high doses, it can induce an amphetamine-like psychosis in humans. Because it is typically absorbed buccally after chewing the leaf and because the alkaloid is metabolized relatively rapidly, high toxic blood levels are rarely reached. Concern about khat use is linked to its dependence-producing properties rather than to its acute toxicity. It is estimated that five million doses are consumed each day, despite prohibition of its use in a number of African and Arab countries. In the 1990s, several clandestine laboratories began synthesizing methcathinone, a drug with actions similar to those of cathinone. Known by a number of street names (e.g., bath salts, “CAT,” “goob,” and “crank”), its popularity is primarily owing to its ease of synthesis from ephedrine or pseudoephedrine, which were readily available until placed under special controls. Methcathinone has been moved to Schedule I of the CSA. The patterns of use, adverse effects, and complications closely resemble those reported for amphetamine. “Club Drugs”. The use of a certain group of substances popularly called club drugs is often associated with dance clubs, bars, and all-night dance parties (raves). The group includes LSD, γ-hydroxybutyrate (GHB), ketamine, methamphetamine, MDMA (ecstasy), and Rohypnol or “roofies” (flunitrazepam). These substances are not all in the same drug class, and they do not produce the same physical or subjective effects. GHB, ketamine, and Rohypnol have been called date rape drugs because they produce disorienting and sedating effects, and often users cannot recall what occurred during all or part of an episode under the influence of the drug. Hence, it is alleged that these drugs might be surreptitiously placed in a beverage, or a person might be convinced to take the drug and then not recall clearly what occurred after ingestion. Emergency department mentions of GHB, ketamine, and Rohypnol are relatively few. Of the club drugs, methamphetamine is the substance that accounts for the largest share of treatment admissions. TREATMENT AND REHABILITATION Amphetamines The treatment of amphetamine-related (or amphetamine-like) disorders shares with

cocaine-related disorders the difficulty of helping patients remain abstinent from the drug, which is powerfully reinforcing and induces craving. An inpatient setting and the use of multiple therapeutic methods (individual, family, and group psychotherapy) are usually necessary to achieve lasting abstinence. The treatment of specific amphetamineinduced disorders (e.g., amphetamine-induced psychotic disorder and amphetamineinduced anxiety disorder) with specific drugs (e.g., antipsychotic and anxiolytics) may be necessary on a short-term basis. Antipsychotics may be prescribed for the first few days. In the absence of psychosis, diazepam (Valium) is useful to treat patients’ agitation and hyperactivity. Physicians should establish a therapeutic alliance with patients to deal with the underlying depression, personality disorder, or both. Because many patients are heavily dependent on the drug, however, psychotherapy may be especially difficult. Comorbid conditions, such as depression, may respond to antidepressant medication. Bupropion (Wellbutrin) may be of use after patients have withdrawn from amphetamine. It has the effect of producing feelings of well-being as these patients cope with the dysphoria that may accompany abstinence. Cocaine Detoxification. The cocaine withdrawal syndrome is distinct from that of opioids, alcohol, or sedative-hypnotic agents, because no physiological disturbances necessitate inpatient or residential drug withdrawal. Thus, it is generally possible to engage in a therapeutic trial of outpatient withdrawal before deciding whether a more intensive or controlled setting is

required for patients unable to stop without help in limiting their access to cocaine. Patients withdrawing from cocaine typically experience fatigue, dysphoria, disturbed sleep, and some craving; some may experience depression. No pharmacological agents reliably reduce the intensity of withdrawal, but recovery over a week or two is generally uneventful. It may take longer, however, for sleep, mood, and cognitive function to recover fully. Most cocaine users do not come to treatment voluntarily. Their experience with the substance is too positive, and the negative effects are perceived as too minimal, to warrant seeking treatment. Those who do not seek treatment often have polysubstancerelated disorder, fewer negative consequences associated with cocaine use, fewer workor family-related obligations, and increased contact with the legal system and with illegal activities. The major hurdle to overcome in the treatment of cocaine-related disorders is the user's intense craving for the drug. Although animal studies have shown that cocaine is a powerful inducer of self-administration, these studies have also shown that animals limit their use of cocaine when negative reinforcers are experimentally linked to the cocaine intake. In humans, negative reinforcers may take the form of work and family-related problems brought on by cocaine use. Therefore, clinicians must take a broad treatment approach and include social, psychological, and perhaps biological strategies in the treatment program.

Attaining abstinence from cocaine in patients may require complete or partial hospitalization to remove them from the usual social settings in which they had obtained or used cocaine. Frequent, unscheduled urine testing is almost always necessary to monitor patients' continued abstinence, especially in the first weeks and months of treatment. Relapse prevention therapy (RPT) relies on cognitive and behavioral techniques in addition to hospitalization and outpatient therapy to achieve the goal of abstinence. Psychosocial Therapies. Psychological intervention usually involves individual, group, and family modalities. In individual therapy, therapists should focus on the dynamics leading to cocaine use, the perceived positive effects of the cocaine, and other ways to achieve these effects. Group therapy and support groups, such as Narcotics Anonymous, often focus on discussions with other persons who use cocaine and on sharing experiences and effective coping methods. Family therapy is often an essential component of the treatment strategy. Common issues discussed in family therapy are the ways the patient's past behavior has harmed the family and the responses of family members to these behaviors. Therapy should also focus, however, on the future and on changes in the family's activities that may help the patient stay off the drug and direct energies in different directions. This approach can be used on an outpatient basis. NETWORK THERAPY. Network therapy was developed as a specialized type of combined individual and group therapy to ensure greater success in the office-based treatment of addicted patients. Network therapy uses both psychodynamic and cognitive-behavioral approaches to individual therapy while engaging the patient in a group support network. The group, composed of the patient's family and peers, is used as a therapeutic network joining the patient and therapist at intervals in therapy sessions. The approach promotes group cohesiveness as a vehicle for engaging patients in this treatment. This network is managed by the therapist to provide cohesiveness and support and to promote compliance with treatment. Although network therapy has not received systematic controlled evaluation, it is frequently applied in the psychiatric practice because it is one of the few manualized approaches that has been designed for use by individual practitioners in an office setting. Pharmacological Adjuncts. Presently, no pharmacological treatments produce decreases in cocaine use comparable to the decreases in opioid use seen when heroin users are treated with methadone, levomethadyl acetate (ORLAAM) (commonly called La-acetylmethadol [LAAM]), or buprenorphine (Buprenex). A variety of pharmacological agents, most of which are

approved for other uses, have been, and are being, tested clinically for the treatment of cocaine dependence and relapse. Cocaine users presumed to have preexisting ADHD or mood disorders have been treated with methylphenidate (Ritalin) and lithium (Eskalith), respectively. Those drugs are of little or no benefit in patients without the disorders, and clinicians should adhere strictly to maximal diagnostic criteria before using either of them in the treatment of

cocaine dependence. In patients with ADHD, slow-release forms of methylphenidate may be less likely to trigger cocaine craving, but the impact of such pharmacotherapy on cocaine use remains to be demonstrated. Many pharmacological agents have been explored on the premise that chronic cocaine use alters the function of multiple neurotransmitter systems, especially the dopaminergic and serotonergic transmitters regulating hedonic tone, and that cocaine induces a state of relative dopaminergic deficiency. Although the evidence for such alterations in dopaminergic function has been growing, it has been difficult to demonstrate that agents theoretically capable of modifying dopamine function can alter the course of treatment. Tricyclic antidepressant drugs yielded some positive results when used early in treatment with minimally drugdependent patients; however, they are of little or no use inducing abstinence in moderate or severe cases. Also tried but not confirmed effective in controlled studies are other antidepressants, such as bupropion, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), antipsychotics, lithium, several different calcium channel inhibitors, and anticonvulsants. One study found that 300 mg a day of phenytoin (Dilantin) reduced cocaine use; this study requires further replication. Several agents are being developed that have not been tried in human studies. These include agents that would selectively block or stimulate dopamine receptor subtypes (e.g., selective D1 agonists) and drugs that can selectively block the access of cocaine to the dopamine transporters but still permit the transporters to remove cocaine from the synapse. Another approach is aimed at preventing cocaine from reaching the brain by using antibodies to bind cocaine in the bloodstream (a so-called “cocaine vaccine”). Such cocaine-binding antibodies do reduce the reinforcing effects of cocaine in animal models. Also under study are catalytic antibodies that accelerate the hydrolysis of cocaine, and butyrylcholinesterase (pseudocholinesterase), which appears to hydrolyze cocaine selectively and is normally present in the body. Vigabatrin is a drug that has been used as a treatment for refractory pediatric epilepsy, which appears to function by significantly elevating brain γ-aminobutyric acid (GABA) levels. In animals, vigabatrin was also noted to attenuate cocaine, nicotine, heroin, alcohol, and methamphetamine-induced increases in extracellular nucleus accumbens dopamine as well as drug-seeking behaviors associated with these biochemical changes. Preliminary clinical studies suggest efficacy for the treatment of cocaine and methamphetamine dependence. Large scale clinical trials for this indication are needed, however. REFERENCES Barceloux DG. Amphetamines and phenethylamine derivatives. In: Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants. Hoboken: John Wiley & Sons; 2012:3. Bhargava S, Arora RR. Cocaine and cardiovascular complications. Am J Ther. 2011;18(4):e95. Callaghan RC, Cunningham JK, Sajeev G, Kish SJ. Incidence of Parkinson’s disease among hospital patients with methamphetamine-use disorders. Mov Disord. 2010;25(14):2333. Gunderson EW, Kirkpatrick MG, Willing LM, Holstege CP. Substituted cathinone products: A new trend in “bath salts” and other designer stimulant drug use. J Addict Med. 2013;7(3):153–162. Haney M. Neurobiology of stimulants. In: Galantar M, Kleber HD, eds. Textbook of Substance Abuse Treatment. 3rd ed. Washington, DC: American Psychiatric Publishing; 2008:143. Kosten TR, Newton TF, De La Garza II R, Haile CN, eds. Cocaine and Methamphetamine Dependence: Advances in Treatment. Arlington: American Psychiatric Association; 2012. Lee NK, Pohlman S, Baker A, Ferris J,

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10 - 20.10 Tobacco Related Disorders

20.10 Tobacco-Related Disorders

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ways. Tobacco does not cause behavioral problems; therefore, few tobacco-dependent persons seek or are referred for psychiatric treatment. Tobacco is a legal drug and most persons who stop tobacco use have done so without treatment. Thus a common, but erroneous, view is that, unlike alcohol and other illicit drugs, most smokers do not need treatment. Several recent events may reverse the reluctance of psychiatrists to play a role in treating tobacco dependence: (1) the growing recognition that most psychiatric patients smoke and many die from tobacco dependence; (2) remaining smokers will be more and more likely to have psychiatric problems, which suggests that many need more intensive treatments; and (3) the development of multiple pharmacological agents to aid smokers

in quitting. EPIDEMIOLOGY The 2004 Monitoring the Future Survey concluded that, despite the demonstrated health risk associated with cigarette smoking, young Americans continue to smoke. However, 30-day smoking rates among high school students declined from peaks reached in 1996 for eighth-graders (21.0 percent) and tenth-graders (30.4 percent) and in 1997 for seniors (36.5 percent). In 2011, 30-day rates reached the lowest levels ever reported by Monitoring the Future surveys for eighth-graders (6.1 percent), tenth-graders (11.8 percent), and twelfth-graders (18.7 percent), with tenth-graders showing the most significant decline. Of high school seniors, 19 percent reported smoking during the month preceding their responses to the survey. The decrease in smoking rates among young Americans corresponds to several years in which increased proportions of teens said they believe a “great” health risk is associated with cigarette smoking and expressed disapproval of smoking one or more packs of cigarettes a day. Students’ personal disapproval of smoking had risen for some years. In 2011, 88 percent of eighth-graders, 85.8 percent of tenth-graders, and 83 percent of twelfth-graders stated that they “disapprove” or “strongly disapprove” of people smoking one or more packs of cigarettes per day. In addition, eighth-graders and tenth-graders reported significant increases in the perceived harmfulness of smoking one or more packs of cigarettes per day. The World Health Organization (WHO) estimates that there are 1 billion smokers worldwide, and they smoke 6 trillion cigarettes a year. The WHO also estimates that tobacco kills more than 3 million persons each year. Although the number of persons in the United States who smoke is decreasing, the number of persons smoking in developing countries is increasing. The rate of quitting smoking has been highest among well-educated white men and lowest among women, blacks, teenagers, and those with low levels of education. Tobacco is smoked most commonly in cigarettes, and then, in descending order, cigars, snuff, chewing tobacco, and in pipes. About 3 percent of all persons in the United States currently use snuff or chewing tobacco, and about 6 percent of young adults ages 18 to 25 use those forms of tobacco. Currently, about 19.3 percent of Americans smoke. The mean age of onset of smoking is 16 years, and few persons start smoking after 20. Dependence features appear to develop quickly. Classroom and other programs to prevent initiation are only mildly effective, but increased taxation does decrease initiation. More than 75 percent of smokers have tried to quit, and about 40 percent try to quit each year. On a given attempt, only 30 percent remain abstinent for even 2 days, and only 5 to 10 percent stop permanently. Most smokers make 5 to 10 attempts, however, so eventually 50 percent of “ever smokers” quit. In the past, 90 percent of successful attempts to quit involved no treatment. With the advent of over-the-counter (OTC) and non-nicotine medications in 1998, about one third of all attempts involved the use of

medication. In terms of the diagnosis of tobacco use disorder per se, about 20 percent of the population develops tobacco dependence at some point, making it one of the most prevalent

psychiatric disorders. Approximately 85 percent of current daily smokers are tobacco dependent. Tobacco withdrawal occurs in about 50 percent of smokers who try to quit. According to the Centers of Disease Control and Prevention (CDC), regional differences exist in smoking throughout the United States. The 13 states with the highest prevalence of current smoking are Kentucky, West Virginia, Oklahoma, Mississippi, Indiana, Missouri, Alabama, Louisiana, Nevada, Tennessee, Alaska, North Carolina, and Ohio. Those states with lowest prevalence are Utah, California, Washington, Massachusetts, Rhode Island, District of Columbia, Hawaii, Maryland, Connecticut, New Hampshire, New Jersey, and Arizona. Utah had the lowest prevalence for men (10.6 percent) and for women (7.9 percent). Education Level of education attainment correlated with tobacco use. Of adults who had not completed high school, 37 percent smoked cigarettes, whereas only 17 percent of college graduates smoked. Psychiatric Patients Psychiatrists must be particularly concerned and knowledgeable about tobacco dependence because of the high proportion of psychiatric patients who smoke. Approximately 50 percent of all psychiatric outpatients, 70 percent of outpatients with bipolar I disorder, almost 90 percent of outpatients with schizophrenia, and 70 percent of patients with substance use disorder smoke. Moreover, data indicate that patients with depressive disorders or anxiety disorders are less successful in their attempts to quit smoking than other persons; thus, a holistic health approach for these patients probably includes helping them address their smoking habits in addition to the primary mental disorder. The high percentage of patients with schizophrenia who smoke has been attributed to tobacco’s ability to reduce their extraordinary sensitivity to outside sensory stimuli and to increase their concentration. In that sense, such patients are selfmonitoring to relieve distress. Death Death is the primary adverse effect of cigarette smoking. Tobacco use is associated with approximately 400,000 premature deaths each year in the United States—25 percent of all deaths. The causes of death include chronic bronchitis and emphysema (51,000 deaths), bronchogenic cancer (106,000 deaths), 35 percent of fatal myocardial infarctions (115,000 deaths), cerebrovascular disease, cardiovascular disease, and almost all cases of chronic obstructive pulmonary disease and lung cancer. The

increased use of chewing tobacco and snuff (smokeless tobacco) has been associated with the development of oropharyngeal cancer, and the resurgence of cigar smoking is likely to lead to an increase in the occurrence of this type of cancer. Researchers have found that 30 percent of cancer deaths in the United States are caused by tobacco smoke, the single most lethal carcinogen in the United States. Smoking (mainly cigarette smoking) causes cancer of the lung, upper respiratory tract, esophagus, bladder, and pancreas and probably of the stomach, liver, and kidney. Smokers are eight times more likely than nonsmokers to develop lung cancer, and lung cancer has surpassed breast cancer as the leading cause of cancer-related deaths in women. Even secondhand smoke (discussed below) causes a few thousand cancer deaths each year in the United States, about the same number as are caused by radon exposure. Despite these staggering statistics, smokers can dramatically lower their chances of developing smoke-related cancers simply by quitting. NEUROPHARMACOLOGY The psychoactive component of tobacco is nicotine, which affects the central nervous system (CNS) by acting as an agonist at the nicotinic subtype of acetylcholine receptors. About 25 percent of the nicotine inhaled during smoking reaches the bloodstream, through which nicotine reaches the brain within 15 seconds. The half-life of nicotine is about 2 hours. Nicotine is believed to produce its positive reinforcing and addictive properties by activating the dopaminergic pathway projecting from the ventral tegmental area to the cerebral cortex and the limbic system. In addition to activating this dopamine reward system, nicotine

causes an increase in the concentrations of circulating norepinephrine and epinephrine and an increase in the release of vasopressin, β-endorphin, adrenocorticotropic hormone (ACTH), and cortisol. These hormones are thought to contribute to the basic stimulatory effects of nicotine on the CNS. DIAGNOSIS Tobacco Use Disorder The fifth edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) includes a diagnosis for tobacco use disorder characterized by craving, persistent and recurrent use, tolerance, and withdrawal if tobacco is stopped. Dependence on tobacco develops quickly, probably because nicotine activates the ventral tegmental area dopaminergic system, the same system affected by cocaine and amphetamine. The development of dependence is enhanced by strong social factors that encourage smoking in some settings and by the powerful effects of tobacco company advertising. Persons are likely to smoke if their parents or siblings smoke and serve as role models. Several recent studies have also suggested a genetic diathesis toward tobacco dependence. Most persons who smoke want to quit and have tried many times to quit but have been unsuccessful.

Tobacco Withdrawal The DSM-5 does not have a diagnostic category for tobacco intoxication, but it does have a diagnostic category for nicotine withdrawal. Withdrawal symptoms can develop within 2 hours of smoking the last cigarette; they generally peak in the first 24 to 48 hours and can last for weeks or months. The common symptoms include an intense craving for tobacco, tension, irritability, difficulty concentrating, drowsiness and paradoxical trouble sleeping, decreased heart rate and blood pressure, increased appetite and weight gain, decreased motor performance, and increased muscle tension. A mild syndrome of tobacco withdrawal can appear when a smoker switches from regular to low-nicotine cigarettes. CLINICAL FEATURES Behaviorally, the stimulatory effects of nicotine produce improved attention, learning, reaction time, and problem-solving ability. Tobacco users also report that cigarette smoking lifts their mood, decreases tension, and lessens depressive feelings. Results of studies of the effects of nicotine on cerebral blood flow (CBF) suggest that short-term nicotine exposure increases CBF without changing cerebral oxygen metabolism, but long-term nicotine exposure decreases CBF. In contrast to its stimulatory CNS effects, nicotine acts as a skeletal muscle relaxant. Adverse Effects Nicotine is a highly toxic alkaloid. Doses of 60 mg in an adult are fatal secondary to respiratory paralysis; doses of 0.5 mg are delivered by smoking an average cigarette. In low doses the signs and symptoms of nicotine toxicity include nausea, vomiting, salivation, pallor (caused by peripheral vasoconstriction), weakness, abdominal pain (caused by increased peristalsis), diarrhea, dizziness, headache, increased blood pressure, tachycardia, tremor, and cold sweats. Toxicity is also associated with an inability to concentrate, confusion, and sensory disturbances. Nicotine is further associated with a decrease in the user’s amount of rapid eye movement (REM) sleep. Tobacco use during pregnancy has been associated with an increased incidence of low birth weight babies and an increased incidence of newborns with persistent pulmonary hypertension. Health Benefits of Smoking Cessation Smoking cessation has major and immediate health benefits for persons of all ages and provides benefits for persons with and without smoking-related diseases. Former smokers live longer than those who continue to smoke. Smoking cessation decreases the risk for lung cancer and other cancers, myocardial infarction, cerebrovascular diseases, and chronic lung diseases. Women who stop smoking before pregnancy or during the first 3 to 4 months of pregnancy reduce their risk for having low birth weight infants to

that of women who never smoked. The health benefits of smoking cessation substantially exceed any risks from the average 5-pound (2.3 kg) weight gain or any adverse psychological effects after

quitting. TREATMENT Strategies to prevent tobacco use in children and adolescents are listed in Table 20.10-1. For those who already smoke, psychiatrists should advise them to quit smoking. For patients who are ready to stop smoking, it is best to set a “quit date.” Most clinicians and smokers prefer abrupt cessation, but because no good data indicate that abrupt cessation is better than gradual cessation, patient preference for gradual cessation should be respected. Brief advice should focus on the need for medication or group therapy, weight gain concerns, high-risk situations, making cigarettes unavailable, and so forth. Because relapse is often rapid, the first follow-up phone call or visit should be 2 to 3 days after the quit date. These strategies have been shown to double self-initiated quit rates (Table 20.10-2). Table 20.10-1 Primary Care Interventions to Prevent Tobacco Use in Children and Adolescents

Table 20.10-2 Typical Quit Rates of Common Therapies Ms. H was a 45-year-old patient with schizophrenia who smoked 35 cigarettes per day. She began her cigarette use at approximately 20 years of age during the prodromal stages of her first psychotic break. During the first 20 years of treatment, no psychiatrist or physician advised her to stop smoking. When the patient was 43 years of age, her primary physician recommended smoking cessation. Ms. H attempted to stop on her own but lasted only 48 hours, partly because her housemates and friends smoked. During a routine medication check, her psychiatrist recommended that she stop smoking, and Ms. H described her prior attempts. The psychiatrist and Ms. H discussed ways to avoid smokers and had the patient announce her intent to quit and request that her friends try not to smoke around her and to offer encouragement for her attempt to quit. The psychiatrist also noted that Ms. H became irritable, slightly depressed, and restless, and that she had insomnia during prior cessation attempts, and thus recommended medications. Ms. H chose to use a nicotine patch plus nicotine gum as needed. The psychiatrist had Ms. H call 2 days after her attempt to quit smoking. At this point, Ms. H stated that the patch and gum were helping. One week later, the patient returned after having relapsed back to smoking. The psychiatrist praised Ms. H for not smoking for 4 days. He suggested that Ms. H contact him again if she wished to try to stop again. Seven months later, during another medication check, the psychiatrist again asked Ms. H to consider cessation, but she was reluctant. Two months later, Ms. H called and said she wished to try again. This time, the psychiatrist and Ms. H listed several activities that she could do to avoid being around friends who smoked, phoned Ms. H’s boyfriend to ask him to assist her in stopping, asked the nurses on the inpatient ward to call Ms. H to encourage her, plus enrolled Ms. H in a support group for the next 4 weeks. This time the psychiatrist prescribed the non-nicotine medication varenicline (Chantix). Ms. H was followed with 15minute visits for each of the first 3 weeks. She had two “slips” but did not go back to smoking and remained an ex-smoker. (Adapted from John R. Hughes, M.D.) Psychosocial Therapies Behavior therapy is the most widely accepted and well-proved psychological therapy for

smoking. Skills training and relapse prevention identify high-risk situations and plan and practice behavioral or cognitive coping skills for those situations in which smoking occurs. Stimulus control involves eliminating cues for smoking in the environment. Aversive therapy has smokers smoke repeatedly and rapidly to the point of nausea, which associates smoking with unpleasant, rather than pleasant, sensations. Aversive therapy appears to be effective but requires a good therapeutic alliance and patient compliance. Hypnosis. Some patients benefit from a series of hypnotic sessions. Suggestions about the benefits of not smoking are offered and assimilated into the patient’s cognitive framework as a result. Posthypnotic suggestions that cause cigarettes to taste bad or to produce nausea when smoked are also used. Psychopharmacological Therapies Nicotine

Replacement Therapies. All nicotine replacement therapies double cessation rates, presumably because they reduce nicotine withdrawal. These therapies can also be used to reduce withdrawal in patients on smoke-free wards. Replacement therapies use a short period of maintenance of 6 to 12 weeks, often followed by a gradual reduction period of another 6 to 12 weeks. Nicotine polacrilex gum (Nicorette) is an OTC product that releases nicotine via chewing and buccal absorption. A 2 mg variety for those who smoke fewer than 25 cigarettes a day and a 4 mg variety for those who smoke more than 25 cigarettes a day are available. Smokers are to use one to two pieces of gum per hour up to a maximum of 24 pieces per day after abrupt cessation. Venous blood concentrations from the gum are one third to one half the between-cigarette levels. Acidic beverages (coffee, tea, soda, and juice) should not be used before, during, or after gum use because they decrease absorption. Compliance with the gum has often been a problem. Adverse effects are minor and include bad taste and sore jaws. About 20 percent of those who quit use the gum for long periods, but 2 percent use gum for longer than a year; longterm use does not appear to be harmful. The major advantage of nicotine gum is its ability to provide relief in high-risk situations. Nicotine lozenges (Commit) deliver nicotine and are also available in 2 mg and 4 mg forms; they are useful especially for patients who smoke a cigarette immediately on awakening. Generally, 9 to 20 lozenges a day are used during the first 6 weeks, with decrease in dosage thereafter. Lozenges offer the highest level of nicotine of all nicotine replacement products. Users must suck the lozenge until dissolved and not swallow it. Side effects include insomnia, nausea, heartburn, headache, and hiccups. Nicotine patches, also sold OTC, are available in a 16-hour, no-taper preparation (Nicotrol) and a 24- or 16-hour tapering preparation (Nicoderm CQ). Patches are administered each morning and produce blood concentrations about half those of smoking. Compliance is high, and the only major adverse effects are rashes and, with 24-hour wear, insomnia. Using gum and patches in high-risk situations increases quit

rates by another 5 to 10 percent. No studies have been done to determine the relative efficacies of 24- or 16-hour patches or of taper and no-taper patches. After 6 to 12 weeks, the patch is discontinued because it is not for long-term use. Nicotine nasal spray (Nicotrol), available only by prescription, produces nicotine concentrations in the blood that are more similar to those from smoking a cigarette, and it appears to be especially helpful for heavily dependent smokers. The spray, however, causes rhinitis, watering eyes, and coughing in more than 70 percent of patients. Although initial data suggested abuse liability, further trials have not found this. The nicotine inhaler, a prescription product, was designed to deliver nicotine to the lungs, but the nicotine is actually absorbed in the upper throat. It delivers 4 mg per cartridge and resultant nicotine levels are low. The major asset of the inhaler is that it provides a behavioral substitute for smoking. The inhaler doubles quit rates. These devices require frequent puffing—about 20 minutes to extract 4 mg of nicotine—and have minor adverse effects. Non-nicotine Medications. Non-nicotine therapy may help smokers who object philosophically to the notion of replacement therapy and smokers who fail replacement therapy. Bupropion (Zyban) (marketed as Wellbutrin for depression) is an antidepressant medication that has both dopaminergic and adrenergic actions. Bupropion is started at 150 mg per day for 3 days and increased to 150 mg twice a day for 6 to 12 weeks. Daily dosages of 300 mg double quit rates in smokers with and without a history of depression. In one study, combined bupropion and nicotine patch had higher quit rates than either alone. Adverse effects include insomnia and nausea, but these are rarely significant. Seizures have not occurred in smoking trials. Of interest, nortriptyline (Pamelor) appears to be effective for smoking cessation and is recommended as a second-line drug. Clonidine (Catapres) decreases sympathetic activity

from the locus ceruleus and, thus, is thought to abate withdrawal symptoms. Whether given as a patch or orally, 0.2 to 0.4 mg a day of clonidine appears to double quit rates; however, the scientific database for the efficacy of clonidine is neither as extensive nor as reliable as that for nicotine replacement; also, clonidine can cause drowsiness and hypotension. Some patients benefit from benzodiazepine therapy (10 to 30 mg per day) for the first 2 to 3 weeks of abstinence. A nicotine vaccine that produces nicotine-specific antibodies in the brain is under investigation at the National Institute on Drug Abuse (NIDA). Combined Psychosocial and Pharmacological Therapy Several studies have shown that combining nicotine replacement and behavior therapy increases quit rates over either therapy alone. Smoke-Free Environment Secondhand smoke can contribute to lung cancer death and coronary heart disease in

adult nonsmokers. Each year, an estimated 3,000 lung cancer deaths and 62,000 deaths from coronary artery disease in adult nonsmokers are attributed to secondhand smoke. Among children, secondhand smoke is implicated in sudden infant death syndrome, low birth weight, chronic middle ear infections, and respiratory illnesses (e.g., asthma, bronchitis, and pneumonia). Two national health objectives for 2010 are to reduce cigarette smoking among adults to 12 percent and the proportion of nonsmokers exposed to environment tobacco smoke to 45 percent. Involuntary exposure to secondhand smoke remains a common public health hazard that is preventable by appropriate regulatory policies. Bans on smoking in public places reduce exposure to secondhand smoke and the number of cigarettes smoked by smokers. Support is nearly universal for bans in schools and day-care centers and strong support for bans in indoor work areas and restaurants. Clean indoor air policies are one way to change social norms about smoking and reduce tobacco consumption. Bans on outdoor smoking in areas, such as public parks, are increasing and in 2006 one municipality in California banned smoking entirely within city limits except in one’s own home or car and windows had to remain closed. Currently over 600 municipalities have smoke-free park laws, including New York City, which banned smoking in all its public parks, including famed Central Park, in 2011. REFERENCES Arehart-Treichel J. Smoking high on list of suicide-risk factors. Psychiatr News. 2011;46:16. Benowitz NL. Neurobiology of nicotine addiction: Implications for smoking cessation treatment. Am J Med. 2008;121:S3. Blazer DG, Wu LT. Patterns of tobacco use and tobacco-related psychiatric morbidity and substance use among middle-aged and older adults in the United States. Aging Men Health. 2012;16:296. Dome P, Lazary J, Kalapos MP, Rihmer Z. Smoking, nicotine and neuropsychiatric disorders. Neurosci Biobehav Rev. 2010;34:295. Fiore M, Jean C, Baker T, Bailey W, Benowitz N: Treating Tobacco Use and Dependence: Clinical Practice Guideline. Washington, DC: US Public Health Service; 2008. Hatsukami DK, Benowitz NL, Donny E, Henningfield J, Zeller M. Nicotine reduction: Strategic research plan. Nicotine Tob Res. 2013;15(6):1003–1013. Hughes J. Nicotine-related disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1353. Husten CG, Deyton LR. Understanding the Tobacco Control Act: Efforts by the US Food and Drug Administration to make tobacco-related morbidity and mortality part of the USA’s past, not its future. Lancet. 2013;381(9877):1570–1580. Lakhan SE, Kirchgessner A. Anti-inflammatory effects of nicotine in obesity and ulcerative colitis. J Translation Med. 2011;9:129. Margerison-Zilko C, Cubbin C. Socioeconomic disparities in tobacco-related health outcomes across racial/ethnic groups in the United States: National Health Interview Survey 2010. Nicotine Tob Res. 2013;15(6):1161–1165. Mushtaq N, Beebe LA, Vesely SK, Neas BR. A multiple motive/multi-dimensional approach to measure smokeless tobacco dependence. Addictive Behaviors, 2014; 39(3): 622–629. Roman J. Nicotine-induced fibronectin expression might represent a common

mechanism by which tobacco promotes lung cancer progression and obstructive airway disease. Proc Am Thorac Soc. 2012;9:85. Warbrick T, Mobascher A, Brinkmeyer J, Musso F, Stoecker T, Shah NJ, Vossel S, Winterer G. Direction and magnitude of

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nicotine effects on the fMRI BOLD response are related to nicotine effects on behavioral performance. Psychopharmacology. 2011;215:333. Weinberger AH, Desai RA, McKee SA. Nicotine withdrawal in U.S. smokers with current mood, anxiety, alcohol use, and substance use disorders. Drug Alcohol Depend. 2010;108:7. Weinberger AH, Sofuoglu M. The impact of cigarette smoking on stimulant addiction. Am J Drug Abuse. 2009;35:12. 20.11 Anabolic-Androgenic Steroid Abuse The anabolic-androgenic steroids (AAS) are a family of hormones that includes testosterone, the natural male hormone, which together with numerous synthetic analogs of testosterone have been developed over the last 70 years (Table 20.11-1). These drugs exhibit various degrees of anabolic (muscle building) and androgenic (masculinizing) effects; none of these drugs display purely anabolic effects in the absence of androgenic effects. It is important not to confuse the anabolic-androgenic steroids (AAS) (testosterone-like hormones) with corticosteroids (cortisol-like hormones such as hydrocortisone and prednisone). Corticosteroids are hormones secreted by the adrenal gland, rather than by the testes. Corticosteroids have no muscle-building properties and, hence, little abuse potential; they are widely prescribed to treat numerous inflammatory conditions such as poison ivy or asthma. AAS, by contrast, have only limited legitimate medical applications, such as in the treatment of hypogonadal men, the wasting syndrome associated with human immunodeficiency virus (HIV) infection, and a few specific diseases such as hereditary angioedema and Fanconi’s anemia. AAS, however, are widely used illicitly, especially by boys and young men seeking to gain increased muscle mass and strength, either for athletic purposes or simply to improve personal appearance. Table 20.11-1 Examples of Commonly Used Anabolic Steroids

AAS does not have its own diagnostic category in the fifth edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-5); rather it is coded as one of the other or unknown substance related disorders. EPIDEMIOLOGY Use of AAS is widespread among men in the United States, but are much less frequently used by women. Approximately 890,000 American men and approximately 190,000 American women reported having used AAS at some time during their lives. Approximately 286,000 men and 26,000 women are estimated to use steroids each year. Among this number, nearly one third, or 98,000, were between 12 and 17 years of age. Various studies of high school students in the United States have produced even higher

estimates of the prevalence of anabolic steroid use among adolescents. Across studies of high school students, it is estimated that 3 to 12 percent of males and 0.5 to 2.0 percent of females have used AAS during their lifetimes. The current high rates of steroid use among younger individuals appear to represent an important shift in the epidemiology of steroid use. In the 1970s, use of these drugs was largely confined to competition bodybuilders, other elite weight-training athletes, and elite athletes in other sports. Since then, however, it appears that an increasing number of young men, and occasionally even young women, may be using these drugs purely to enhance personal appearance rather than for any athletic purpose. PHARMACOLOGY All steroid drugs—including AAS, estrogens, and corticosteroids—are synthesized in vivo

from cholesterol and resemble cholesterol in their chemical structure. Testosterone has a four-ring chemical structure containing 19 carbon atoms (Fig. 20.11-1). FIGURE 20.11-1 Molecular structure of testosterone. Normal testosterone plasma concentrations for men range from 300 to 1,000 ng/dL. Generally, 200 mg of testosterone cypionate taken every 2 weeks restores physiological testosterone concentrations in a hypogonadal male. A eugonadal male who initiates physiological dosages of testosterone has no net gain in testosterone concentrations because exogenously administered AAS shut down endogenous testosterone production via feedback inhibition of the hypothalamic-pituitary-gonadal axis. Consequently, illicit users take higher than therapeutic dosages to achieve supraphysiological effects. The dose–response curve for anabolic effects may be logarithmic, which could explain why illicit users generally take 10 to 100 times the therapeutic dosages. Doses in this range are most easily achieved by taking combinations of oral and injected AAS, which illicit AAS users often do. Transdermal testosterone, available by prescription for testosterone replacement therapy, may also be used. Therapeutic Indications The AAS are indicated primarily for testosterone deficiency (male hypogonadism), hereditary angioedema (a congenital skin disorder), and some uncommon forms of anemia caused by bone marrow or renal failure. In women, AAS are given, although not as first-choice agents, for metastatic breast cancer, osteoporosis, endometriosis, and adjunctive treatment of menopausal symptoms. In men, they have been used experimentally as a male contraceptive and for treating major depressive disorder and sexual disorders in eugonadal men. Recently, they have been used to treat wasting syndromes associated with acquired immunodeficiency syndrome (AIDS). Controlled studies have also suggested that testosterone has antidepressant effects in some men infected with HIV with major depressive disorder, and is also a supplementary (augmentation) treatment in some depressed men with low endogenous testosterone levels who are refractory to conventional antidepressants.

Adverse Reactions The most common adverse medical effects of AAS involve the cardiovascular, hepatic, reproductive, and dermatological systems. The AAS produce an adverse cholesterol profile by increasing levels of low-density lipoprotein cholesterol and decreasing levels of high-density lipoprotein cholesterol. High-dose use of AAS can also activate hemostasis and increase blood pressure. Isolated case reports of myocardial infarction, cardiomyopathy, left ventricular hypertrophy, and stroke among users of AAS, including fatalities, have appeared, Among the AAS-induced endocrine effects in men are testicular atrophy and sterility, both usually reversible after discontinuing AAS, and gynecomastia, which may persist until surgical removal. In women, shrinkage of breast tissue, irregular menses (diminution or cessation), and masculinization (clitoral hypertrophy, hirsutism, and deepened voice) can occur. Masculinizing effects in women may be irreversible. Androgens taken during pregnancy could cause masculinization of a female fetus. Dermatological effects include acne and male pattern baldness. Abuse of AAS by children has led

to concerns that AAS-induced premature closure of bony epiphyses could cause shortened stature. Other uncommon adverse effects include edema of the extremities caused by water retention, exacerbation of tic disorders, sleep apnea, and polycythemia. ETIOLOGY The major reason for taking illicit AAS is to enhance either athletic performance or physical appearance. Taking AAS is reinforced because they can produce the athletic and physical effects that users desire, especially when combined with proper diet and training. Further reinforcement derives from winning competitions and from social admiration for physical appearance. AAS users also perceive that they can train more intensively for longer durations with less fatigue and with decreased recovery times between workouts. The dramatic effects of AAS on muscle growth are illustrated in Figure 20.11-2, which compares a “natural” bodybuilder who has never used these drugs with a bodybuilder of identical height and body fat who has used AAS extensively.

FIGURE 20.11-2 Physical effects of anabolic steroid use. The photographs compare a “natural” bodybuilder who has never used anabolic steroids (left) with a man who has used large doses of anabolic steroids over several years (right). Both men are 67 inches tall and have 7 percent body fat. The man on the left weighs 170 lbs and represents approximately the maximum degree of muscularity obtainable without drugs. His fatfree mass index is 25.4 kg/m2 by the formula of Elana Kouri, et al. The man on the right weighs 213 lbs and has a fat-free mass index of 31.7 kg/m2. Note the muscle hypertrophy from steroid use is particularly marked in the upper body in the pectoralis, deltoid, trapezius, and biceps muscles. Any man significantly more muscular than the man on the left has almost certainly abused anabolic steroids. (Courtesy of H.G. Pope M.D.) Although the anabolic or muscle-building properties of AAS are clearly important to those seeking to enhance athletic performance and physical appearance, psychoactive effects may also be important in the persistent and dependent use of AAS. Anecdotally, some AAS users report feelings of power, aggressiveness, and euphoria, which become associated with, and can reinforce, AAS taking. In general, males are more likely to take AAS than females, and athletes are more likely to take AAS than nonathletes. Some male and female weight lifters may have muscle dysmorphia, a form of body dysmorphic disorder in which the individual feels that he or she is not sufficiently muscular and lean. DIAGNOSIS AND CLINICAL FEATURES Steroids may initially induce euphoria and hyperactivity. After relatively short periods, however, their use can become associated with increased anger, arousal, irritability, hostility, anxiety, somatization, and depression (especially during times when steroids

are not used). Several studies have demonstrated that 2 to 15 percent of anabolic steroid abusers experience hypomanic or manic episodes, and a smaller percentage may have clearly psychotic symptoms. Also disturbing is a correlation between steroid abuse and violence (“roid rage” in the parlance of users). Steroid abusers with no record of antisocial behavior or violence have committed murders and other violent crimes. Steroids are addictive substances. When abusers stop taking steroids, they can become depressed, anxious, and concerned about the physical state of their bodies. Some similarities have been noted between athletes’ views of their muscles and the views of patients with anorexia nervosa about their bodies; to an observer, both groups seem to distort realistic assessment of the body. Iatrogenic addiction is a consideration in view of the increasing number of geriatric patients who are receiving testosterone from their physicians in an attempt to increase libido and reverse some aspects of aging. Mr. A is a 26-year-old single man. He is 69 inches tall and presently weighs 204 pounds, with a body fat of 11 percent. He reports that he began lifting weights at age 17, at which time he weighed 155 pounds. About 2 years after

beginning his weight lifting, he began taking AAS, which he obtained through a friend at his gymnasium. His first “cycle” (course) of AAS, lasting for 9 weeks, involved methandienone (Methanabol), 30 mg a day, orally, and testosterone cypionate, 600 mg a week, intramuscularly. During these 9 weeks he gained 20 pounds of muscle mass. He was so pleased with these results that he took five further cycles of AAS over the course of the next 6 years. During his most ambitious cycle, approximately 1 year ago, he used testosterone cypionate, 600 mg per week; nandrolone decanoate, 400 mg a week; stanozolol (Winstrol), 12 mg a day; and oxandrolone (Anavar), 10 mg a day. During each of the cycles Mr. A has noted euphoria, irritability, and grandiose feelings. These symptoms were most prominent during his most recent cycle, when he felt “invincible.” During this cycle he also noted a decreased need for sleep, racing thoughts, and a tendency to spend excessive amounts of money. For example, he impulsively purchased a $2,700 stereo system when he realistically could not afford to spend more than $500. He also became uncharacteristically irritable with his girlfriend, and on one occasion put his fist through the side window of her car during an argument, an act inconsistent with his normally mild-mannered personality. After this cycle of AAS ended, he became mildly depressed for about 2 months. Mr. A has used a number of drugs to lose weight in preparation for bodybuilding contests. These include ephedrine, amphetamine, triiodothyronine, and thyroxin. Recently, he has also begun to use the opioid agonist–antagonist nalbuphine intravenously (IV) to treat muscle aches from weight lifting. He also used oral opioids, such as controlled-release oxycodone (OxyContin), at least once a week. He uses oral opioids sometimes to treat muscle aches, but often simply to get high. He reports that use of nalbuphine and other opioids is widespread among other AAS users of his acquaintance.

Mr. A exhibits characteristic features of muscle dysmorphia. He checks his appearance dozens of times a day in mirrors, or when he sees his reflection in a store window or even in the back of a spoon. He becomes anxious if he misses even one day of working out at the gym, and acknowledges that his preoccupation with weight lifting has cost him both social and occupational opportunities. Although he has a 48inch chest and 19-inch biceps, he has frequently declined invitations to go to the beach or a swimming pool for fear that he would look too small when seen in a bathing suit. He is anxious because he has lost some weight since the end of his previous cycle of AAS and is eager to resume another cycle of AAS in the near future. (Adapted from Harrison G. Pope, Jr., M.D., and Kirk J. Brower, M.D.) TREATMENT Abstinence is the treatment goal of choice for patients manifesting AAS abuse or dependence. To the extent that users of AAS abuse other addictive substances (including alcohol), traditional treatment approaches for substance-related disorders may be used. Nevertheless, AAS users may differ from other addicted patients in several ways that have implications for treatment. First, the euphorigenic and reinforcing effects of AAS may only become apparent after weeks or months of use in conjunction with intensive exercising. When compared with immediately and passively reinforcing drugs, such as cocaine, heroin, and alcohol, AAS use may entail more delayed gratification. Second, AAS users may manifest greater commitment to culturally endorsed values of physical fitness, success, victory, and goal directness than users of other illicit drugs. Finally, AAS users are often preoccupied with their physical attributes and may rely excessively on these attributes for self-esteem. Treatment therefore depends on a therapeutic alliance that is based on a thorough and nonjudgmental understanding of the patient’s values and motivations for using AAS. AAS Withdrawal Supportive therapy and monitoring are essential for treating AAS withdrawal because suicidal depressions can occur. Hospitalization may be required when suicidal ideation is severe. Patients should be educated about the possible course of withdrawal and reassured that symptoms are time-limited and

manageable. Antidepressant agents are best reserved for patients whose depressive symptomatology persists for several weeks after AAS discontinuation and who meet criteria for major depressive disorder. Selective serotonin reuptake inhibitors (SSRIs) are the preferred agents because of their favorable adverse effect profile and their effectiveness in the only reported case series of treated AAS users with major depressive disorder. Physical withdrawal symptoms are not lifethreatening and do not ordinarily require pharmacotherapy. Nonsteroidal antiinflammatory drugs (NSAIDs) may be useful to treat musculoskeletal pain and headaches.

ANABOLIC STEROID–INDUCED MOOD DISORDERS Irritability, aggressiveness, hypomania, and frank mania associated with anabolic steroid use probably represent one of the most important public health issues associated with these drugs. Although athletes using these drugs have long recognized that syndromes of anger and irritability could be associated with AAS use, these syndromes were little recognized in the scientific literature until the late 1980s and 1990s. Since then, a series of observational field studies of athletes has suggested that some AAS users develop prominent hypomanic or even manic symptoms during AAS use. A possible serious consequence of AAS-induced mood disorders may be violent or even homicidal behavior. Several published reports have anecdotally described individuals with no apparent history of psychiatric disorder, no criminal record, and no history of violence, who committed violent crimes, including murder, while under the influence of AAS. In a number of cases, AAS use has been cited in criminal trials as a possible mitigating factor in the defense of such individuals. Although a causal link is difficult to establish in these cases, evidence of AAS use has frequently been presented in forensic settings as a possible mitigating factor in criminal behavior. Depressive syndromes induced by AAS have occurred and suicide is a risk. A brief and self-limited syndrome of depression occurs on AAS withdrawal, probably as a result of the depression of the hypothalamic-pituitary-gonadal axis after exogenous AAS administration. ANABOLIC STEROID–INDUCED PSYCHOTIC DISORDER Psychotic symptoms are rare in association with anabolic steroid use, but they have been described in a few cases, primarily in individuals who were using the equivalent of more than 1,000 mg of testosterone a week. Usually, these symptoms have consisted of grandiose or paranoid delusions, generally occurring in the context of a manic episode, although occasionally occurring in the absence of a frank manic syndrome. In most cases reported, psychotic symptoms have disappeared promptly (within a few weeks) after the discontinuation of the offending agent, although temporary treatment with antipsychotic agents was sometimes required. OTHER ANABOLIC STEROID–RELATED DISORDERS Symptoms of anxiety disorders, such as panic disorder and social phobia can occur during AAS use. AAS use may serve as a “gateway to the use of opioid agonist or antagonists, such as nalbuphine, or to use of frank opioid agonists, such as heroin.” A study of men admitted for substance dependence treatment in Massachusetts produced similar findings. DEHYDROEPIANDROSTERONE AND ANDROSTENEDIONE Dehydroepiandrosterone (DHEA), a precursor hormone for both estrogens and

androgens, is available over the counter. Recent years have seen an interest in DHEA for improving cognition, depression, sex drive, and general well-being in elderly adults. Some reports suggest that DHEA in dosages of 50 to 100 mg per day increases the sense of physical and social well-being in women aged 40 to 70 years. Reports also exist of androgenic effects, including irreversible hirsutism, hair loss, voice deepening, and other undesirable sequelae. In addition, DHEA has at least a theoretical potential of enhancing tumor growth in persons with latent, hormone-sensitive malignancies, such as prostate, cervical, and breast cancer. Despite its significant popularity, few

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20.12 Other Substance Use and Addictive Disorders

Rodrigues R, Ramos S, Almeida N. Anabolic androgenic steroids in psychiatric practice. Eur Neuropsychopharmacol. 2012;22:S403. Sagoe D, Molde H, Andreassen CS, Torsheim T, Pallesen S. The global epidemiology of anabolic-androgenic steroid use: A meta-analysis and meta-regression analysis. Annals of Epidemiology. 2014;24(5):383–398. Santamarina RD, Besocke AG, Romano LM, Ioli PL, Gonorazky SE. Ischemic stroke related to anabolic abuse. Clin Neuropharmacol. 2008;31(2):80. 20.12 Other Substance Use and Addictive Disorders This section considers a diverse set of drugs not covered in the previous sections that are not easily categorized and grouped with other substances. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes a diagnostic category for these substances called unknown or unspecified substance-related disorders. Some of these are discussed in the following. γ-HYDROXYBUTYRATE γ-Hydroxybutyrate (GHB) is a naturally occurring neurotransmitter in the brain that is related to sleep regulation. GHB increases dopamine levels in the brain. In general, GHB is a central nervous system (CNS) depressant with effects through the endogenous opioid system. It is used to induce anesthesia and long-term sedation, but its unpredictable duration of action limits its use. GHB has been evaluated recently for the treatment of alcohol and opioid withdrawal and narcolepsy. Until 1990, GHB was sold in U.S. health food stores, and body builders used it as a steroid alternative. Reports indicate, however, that GHB is abused for its intoxicating effects and consciousness-altering properties. It is variously referred to as “GBH” and “liquid ecstasy,” and it is sold illicitly in various forms (e.g., powder and liquid). Similar chemicals, which the body converts to GBH, include γ-butyrolactone (GBL) and 1,4butanediol. Adverse effects include nausea, vomiting, respiratory problems, seizures, coma, and death. In some reports, GHB abuse has been linked to a syndrome similar to Wernicke-Korsakoff syndrome. NITRITE INHALANTS The nitrite inhalants include amyl, butyl, and isobutyl nitrites, all of which are called “poppers” in popular jargon. The intoxication syndromes seen with nitrites can differ markedly from the syndromes seen with the standard inhalant substances, such as lighter fluid and airplane glue. Nitrite inhalants are used by persons seeking the associated mild euphoria, altered sense of time, feeling of fullness in the head, and, possibly, increased sexual feelings. The nitrite compounds are used by some gay men and users of other drugs to heighten sexual stimulation during orgasm and, in some cases, to relax the anal sphincter for penile penetration. Under such circumstances, a person may use the substance for a

few or a dozen times within several hours.

Adverse reactions include a toxic syndrome characterized by nausea, vomiting, headache, hypotension, drowsiness, and irritation of the respiratory tract. Some evidence indicates that nitrite inhalants can adversely affect immune function. Because sildenafil (Viagra) and its congeners are lethal when combined with nitrite compounds, persons at risk should be cautioned never to use the two together. NITROUS OXIDE Nitrous oxide, commonly known as “laughing gas,” is a widely available anesthetic agent that is subject to abuse because of its ability to produce feelings of lightheadedness and of floating, sometimes experienced as pleasurable or specifically as sexual. With long-term abuse patterns, nitrous oxide use has been associated with delirium and paranoia. Female dental assistants exposed to high levels of nitrous oxide have reportedly experienced reduced fertility. A 35-year-old male dentist with no history of other substance problems complained of problems with nitrous oxide abuse for 10 years. This had begun as experimentation with what he had considered a harmless substance. His rate of use increased over several years, however, eventually becoming almost daily for months at a time. He felt a craving before sessions of use. Then, using the gas while alone in his office, he immediately felt numbness, a change in his temperature and heart rate, and alleviation of depressed feelings. “Things would go through my mind. Time was erased.” He sometimes fell asleep. Sessions might last a few minutes or up to 8 hours. They ended when the craving and euphoria ended. He had often tried to stop or cut down, sometimes consulting a professional about the problem. OTHER SUBSTANCES Nutmeg Nutmeg can be ingested in a number of preparations. When nutmeg is taken in sufficiently high doses, it can induce depersonalization, derealization, and a feeling of heaviness in the limbs. In sufficiently high doses, morning glory seeds can produce a syndrome resembling that seen with lysergic acid diethylamide (LSD), characterized by altered sensory perceptions and mild visual hallucinations. Catnip Catnip can produce cannabis-like intoxication in low doses and LSD-like intoxication in high doses. Betel Nuts

Betel nuts, when chewed, can produce a mild euphoria and a feeling of floating in space. Kava Kava, derived from a pepper plant native to the South Pacific, produces sedation and incoordination and is associated with hepatitis, lung abnormalities, and weight loss. Over-the-Counter Drugs Some persons abuse over-the-counter and prescription medications, such as cortisol, antiparkinsonian agents, and antihistamines. Ephedra Ephedra, a natural substance found in herbal tea, acts like epinephrine and, when abused, produces cardiac arrhythmia and fatalities. Chocolate A controversial possible substance of abuse is chocolate derived from the cacao bean. Anandamide, an ingredient in chocolate, stimulates the same receptors as marijuana. Other compounds in chocolate include tryptophan, the precursor of serotonin, and phenylalanine, an amphetamine-like substance, both of which improve mood. So-called chocoholics may be self-medicating because of a depressive diathesis. POLYSUBSTANCE-RELATED DISORDER Substance users often abuse more than one substance. A diagnosis of polysubstance dependence is appropriate if, for a period of at least 12 months, a person has repeatedly used substances from at least three categories (not including nicotine and caffeine), even if the diagnostic criteria for a substance-related disorder are not met for any single substance, as long as, during this period, the criteria for substance dependence have been met for the substances considered as a group. TREATMENT AND REHABILITATION Treatment approaches for the substances covered in this section vary according to substances, patterns of abuse, availability of psychosocial support systems, and patients’ individual features. Two major treatment goals for substance abuse have

been determined: the first is abstinence from the substance; and the second is the physical, psychiatric, and psychosocial well-being of the patient. Significant damage has often been done to a patient’s support systems during prolonged periods of substance abuse. For a patient to stop a pattern of substance abuse successfully, adequate psychosocial supports must be in place to foster the difficult change in behavior.

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In some rare cases, it may be necessary to initiate treatment on an inpatient unit. Although an outpatient setting is more desirable than an inpatient setting, the temptations available to an outpatient for repeated use may present too high a hurdle for the initiation of treatment. Inpatient treatment is also indicated in the case of severe medical or psychiatric symptoms, a history of failed outpatient treatments, a lack of psychosocial supports, or a particularly severe or long-term history of substance abuse. After an initial period of detoxification, patients need a sustained period of rehabilitation. Throughout treatment, individual, family, and group therapies can be effective. Education about substance abuse and support for patients' efforts are essential factors in treatment. REFERENCES Bonano JS, Glennon RA, De Felice LJ, Banks ML, Negus SS. Abuse-related and abuse-limiting effects of methcathinone and the synthetic "bath salts" cathinone analogs methylenedioxypyrovalerone (MDPV), methylone and mephedrone on intracranial self-stimulation in rats. I. 2014;231(1):199–207. Bryson EO, Hamza H. The drug seeking anesthesia care provider. Int Anesthesiol Clin. 2011;49:157. Frances RJ, Miller SI, Mack AH, eds. Clinical Textbook of Addictive Disorders. 3rd ed. New York: The Guildford Press; 2011. Sewell RA, Petrakis IL. Does gamma-hydroxybutyrate (GHB) have a role in the treatment of alcoholism? Alcohol Alcohol. 2011;46:1. Sinha R. The clinical neurobiology of drug craving. Curr Opin Neurobiol. 2013;23(4):649–654. Stein LAR, Lebeau R, Clair M, Martin R, Bryant M, Storti S, Monti P. A web-based study of gamma hydroxybutyrate (GHB): Patterns, experiences, and functions of use. Am J Addict. 2011;20:30. Strain EC, Anthony JC. Substance-related disorders: Introduction and overview. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Vol. 1. Philadelphia: Lippincott Williams & Wilkins; 2009:1237. Szerman N, Martinez-Raga J, Peris. Rethinking dual disorders/pathology. Addictive Disorders & Their Treatment. 2013;12(1):1–4. 20.13 Gambling Disorder Gambling disorder is characterized by persistent and recurrent maladaptive gambling that causes economic problems and significant disturbances in personal, social, or occupational functioning. Aspects of the maladaptive behavior include (1) a preoccupation with gambling; (2) the need to gamble with increasing amounts of money to achieve the desired excitement; (3) repeated unsuccessful efforts to control, cut back, or stop gambling; (4) gambling as a way to escape from problems; (5) gambling to recoup losses; (6) lying to conceal the extent of the involvement with gambling; (7) the commission of illegal acts to finance gambling; (8) jeopardizing or losing personal and vocational relationships because of gambling; and (9) a reliance on others for money to pay off debts. Previous editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) include pathological gambling

disorder in the impulse-control disorder category because of patient's preoccupation or compulsion to gamble. However, the criteria for the disorder are structured more like a substance-related or addiction disorder than an impulse-control disorder, with the need to gamble with increased amounts of money to achieve desired excitement (tolerance) and feelings of irritability and restlessness when attempting to reduce or stop gambling (withdrawal). Substance use is often a common comorbidity with gambling. Thus, in the fifth edition of the DSM (DSM-5), gambling disorder is included in the section on substance use and addictive disorders and is diagnosed as a non–substance-related disorder. EPIDEMIOLOGY Although comprehensive worldwide statistics have yet to be compiled, excellent local studies all point to a 3 to 5 percent rate of problem gamblers in the general population and an approximate 1 percent rate of individuals meeting the requirements for gambling disorder. Problem gambling is more common in men and young adults than in women and older adults; however, escalation has been noted in the poor, notably poor minorities; adolescents; elderly retirees; and women. One of three pathological gamblers is now female: it has been suggested that women are gambling more because of an increased presence in the workplace that provides them with more cash. These groups are still underserved with regard to research and treatment. The prevalence of gambling disorder in individuals who have a substance use disorder is higher, with various surveys showing rates of 10 to 18 percent of patients with substance abuse being pathological gamblers. As every type of gambling has become increasingly accessible over the last few decades, the rate of normal and pathological gambling has risen spectacularly, especially in locales with legalized gambling. The most popular types of gambling are numbers/lotto (62.2 percent), slot machines or bingo (48.9 percent), gambling at a casino (44.7 percent), and office sports pools (44.3 percent) (Table 20.13-1). The least popular are betting on sports with a bookie or parlay card, internet gambling, and speculating on high-risk investments. Table 20.13-1 Lifetime Prevalence of Gambling Types

Family histories of pathological gamblers show an increased rate of substance abuse (particularly alcoholism) and depressive disorders. A parent or influential relative of the patient often has been a problem or pathological gambler. The family circle is likely to be competitively and materialistically oriented, evincing intense admiration for money and associated symbols of success. In this respect, compulsive gambling has been called the dark side of the American dream. COMORBIDITY Significant comorbidity occurs between pathological gambling and mood disorders (especially, major depression and bipolarity) and other substance use and addictive disorders (notably, alcohol and stimulant abuse and caffeine and tobacco dependence). Comorbidity also exists with attention-deficit/hyperactivity disorder (ADHD) (particularly in childhood), various personality disorders (notably, narcissistic, antisocial, and borderline personality disorders), and disruptive, impulse control, and conduct disorders. Although many pathological gamblers have obsessive personality traits, full-blown obsessive-compulsive disorder (OCD) is uncommon in this group. ETIOLOGY Psychosocial Factors Several factors may predispose persons to develop the disorder: loss of a parent by death, separation, divorce, or desertion before a child is 15 years of age; inappropriate parental discipline (absence, inconsistency, or harshness); exposure to, and availability of, gambling activities for adolescents; a family emphasis on material and financial symbols; and a lack of family emphasis on saving, planning, and budgeting. Psychoanalytic theory has focused on a number of core character difficulties. Sigmund

Freud suggested that compulsive gamblers have an unconscious desire to lose, and gamble to relieve unconscious feelings of guilt. Another suggestion is that the gamblers are narcissists, whose

grandiose and omnipotent fantasies lead them to believe they can control events and even predict their outcome. Learning theorists view uncontrolled gambling as resulting from erroneous perceptions about control of impulses. Biological Factors Several studies have suggested that gamblers' risk-taking behavior may have an underlying neurobiological cause. These theories have centered on both serotonergic and noradrenergic receptor systems. Male pathological gamblers may have subnormal 3methoxy-4-hydroxyphenyl glycol (MHPG) concentrations in plasma, increased MHPG concentrations in the cerebrospinal fluid (CSF), and increased urinary output of norepinephrine. Evidence also implicates serotonergic regulatory dysfunction in the pathological gambler. Chronic gamblers have low platelet monoamine oxidase (MAO) activity, a marker of serotonin activity, also linked to difficulties with inhibition. Further studies are needed to confirm these findings. DIAGNOSIS AND CLINICAL FEATURES In addition to the features already described, pathological gamblers often appear overconfident, somewhat abrasive, energetic, and free spending. They often show obvious signs of personal stress, anxiety, and depression. They commonly have the attitude that money is both the cause of, and the solution to all their problems. As their gambling increases, they are usually forced to lie to obtain money and to continue gambling while hiding the extent of their gambling. They make no serious attempt to budget or save money. When their borrowing resources are strained, they are likely to engage in antisocial behavior to obtain money for gambling. Their criminal behavior is typically nonviolent, such as forgery, embezzlement, or fraud, and they consciously intend to return or repay the money. Complications include alienation from family members and acquaintances, the loss of life accomplishments, suicide attempts, and association with fringe and illegal groups. Arrest for nonviolent crimes may lead to imprisonment. Gerry was a 35-year-old former auto dealership owner. Two of his uncles were compulsive gamblers, and his paternal grandfather was hospitalized with major depressive illness. He played poker and had been a racecourse habitué since the age of 15 years. He had dropped out of college after a few months and become a car sales representative. Soon he was promoted to showroom manager and then went out on his own. By age 32 years, he was a multimillionaire owner of a dealership chain, happily married with two children. Gerry continued to gamble frequently. He was a successful weekend sports bettor, as well as a consistent winner at weekly gin rummy and poker games and occasional

jaunts to Las Vegas and Atlantic City. In the context of his wife giving birth to a stillborn child, Gerry started going to casinos more often, gradually increasing the size of bets at blackjack and craps. His sport wagers also escalated. His games at home gradually became boring—"there was zilch action." He began frequenting an illegal local poker parlor that featured highstake action. Over several years, Gerry slipped into a typical gambling spiral. He accumulated several million dollars in debts and lied to family and colleagues about his whereabouts. He raided business and personal accounts, including his children's college funds, maxed out credit cards, and borrowed from loan sharks at exorbitant rates. He grew profoundly depressed and seriously thought of killing himself in a car crash so that his insurance would "take care of my family after I am gone." Gerry's dire situation was unmasked when his Porsche was repossessed one Sunday morning. Initially his wife threatened to divorce him. However, a wealthy relative intervened and bailed him out. He swore never to gamble again, entered Gamblers Anonymous, and within 2 months resumed his frantic chasing. Over the next decade, Gerry underwent four more episodes of recovery and relapse. His wife divorced him, he lost his dealerships, and he had to declare bankruptcy. Gerry finally enrolled in a pilot dual-diagnostic recovery program, where he was diagnosed with atypical bipolar disorder. His treatment included Gamblers Anonymous meetings, individual and family

counseling, and pharmacotherapy with bupropion (Wellbutrin) and lamotrigine (Lamictal). Gerry eventually reconciled with his wife and family. He returned to selling cars, started living modestly, and continued to attend Gamblers Anonymous meetings regularly. However, he declared emphatically that he always considers himself always one step away from becoming a “degenerate gambler” again. (Courtesy of Harvey Roy Greenberg, M.D.) PSYCHOLOGICAL TESTING AND LABORATORY EXAMINATION Male patients with gambling disorders have shown abnormalities in platelet MAO activity. Patients with pathological gambling often display high levels of impulsivity on neuropsychological tests. German studies have demonstrated increased cortisol levels in the saliva of gamblers while they gamble, which can account for the euphoria that occurs during the experience and its addictive potential. DIFFERENTIAL DIAGNOSIS Social gambling is distinguished from pathological gambling in that the former occurs with friends, on special occasions, and with predetermined acceptable and tolerable losses. Gambling that is symptomatic of a manic episode can usually be distinguished from pathological gambling by the history of a marked mood change and the loss of judgment preceding the gambling.

Manic-like mood changes are common in pathological gambling, but they always follow winning and are usually succeeded by depressive episodes because of subsequent losses. Persons with antisocial personality disorder may have problems with gambling. When both disorders are present, both should be diagnosed. COURSE AND PROGNOSIS Pathological gambling usually begins in adolescence for men and late in life for women. The disorder waxes and wanes and tends to be chronic. Four phases are seen in pathological gambling:

1. The winning phase, ending with a big win, equal to about a year’s salary, which hooks patients. Women usually do not have a big win, but use gambling as an escape from problems.
2. The progressive-loss phase, in which patients structure their lives around gambling and then move from being excellent gamblers to being stupid ones who take considerable risks, cash in securities, borrow money, miss work, and lose jobs.
3. The desperate phase, with patients frenziedly gambling with large amounts of money, not paying debts, becoming involved with loan sharks, writing bad checks, and possibly embezzling.
4. The hopeless stage of accepting that losses can never be made up, but the gambling continues because of the associated arousal or excitement. The disorder may take up to 15 years to reach the last phase, but then, within a year or two, patients have totally deteriorated. TREATMENT Gamblers seldom come forward voluntarily to be treated. Legal difficulties, family pressures, or other psychiatric complaints bring gamblers to treatment. Gamblers Anonymous (GA) was founded in Los Angeles in 1957 and modeled on Alcoholics Anonymous (AA) (Table 20.13-2). It is accessible, at least in large cities, and is an effective treatment for gambling in some patients. GA is a method of inspirational group therapy that involves public confession, peer pressure, and the presence of reformed gamblers (as with sponsors in AA) available to help members resist the impulse to gamble. The dropout rate from GA is high, however. In some cases, hospitalization may help by removing patients from their environments. Insightoriented psychotherapy should not be sought until patients have been away from gambling for 3 months. At this point, patients who are pathological gamblers may become excellent candidates for this form of psychotherapy. Family therapy is often valuable. Cognitive-behavioral therapy (e.g.,

relaxation techniques combined with visualization of gambling avoidance) has had some success. Table 20.13-2 Twelve Steps of Gambler’s Anonymous

Psychopharmacological treatment, once largely unsuccessful, now plays a significant role in the management of pathological gamblers. Effective agents include antidepressants, notably selective serotonin reuptake inhibitors (SSRIs) and bupropion (Wellbutrin, Zyban); mood stabilizers, including sustained-release lithium (Eskalith) and antiepileptics such as topiramate (Topamax); atypical antipsychotics; and opioid agents such as naltrexone (ReVia). In many patients it is difficult to determine whether an antidepressant or mood stabilizer alleviates gambling cravings directly or via treatment of a comorbid condition, particularly depressive or bipolar disorders. REFERENCES

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