09 - 20.9 Stimulant Related Disorders

20.9 Stimulant-Related Disorders

2012;32:3887. Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. J Pharm Pract. 2014;27(1):5–16. Kohmura K, Iwamoto K, Aleksic B, Sasada K, Kawano N, Katayama H, Noda Y, Noda A, Iidaka T, Ozaki N. Effects of sedative antidepressants on prefrontal cortex activity during verbal fluency task in healthy subjects: A near-infrared spectroscopy study. Psychopharmacology. 2013;226(1):75–81. López-Muñoz F, Álamo C, García-García P. The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: Half a century of anxiolytic drugs. J Anxiety Disord. 2011;25(4):554. Spiegel D. Trance formations: Hypnosis in brain and body. Depress Anxiety. 2013;30(4):342–352. Vinkers CH, Klanker M, Groenink L, Korte SM, Cook JM, Van Linn ML, Hopkins SC, Olivier B. Dissociating anxiolytic and sedative effects of GABAAergic drugs using temperature and locomotor responses to acute stress. Psychopharamacology. 2009;204(2):299. Vogel M, Knopfli B, Schmid O, Prica M, Strasser J, Prieto L, Wiesbeck GA, Dursteler-Macfarland KM. Treatment or “high”: Benzodiazepine use in patients on injectable heroin or oral opioids. Addict Behav. 2013;38(10):2477. 20.9 Stimulant-Related Disorders AMPHETAMINES Amphetamines and amphetamine-like drugs are among the most widely used illicit substances, second only to cannabis, in the United States, Asia, Great Britain, Australia, and several other Western European countries. Methamphetamine, a congener of amphetamine, has become even more popular in recent years. The racemic amphetamine sulfate (Benzedrine) was first synthesized in 1887, and it was introduced to clinical practice in 1932 as an over-the-counter inhaler for the treatment of nasal congestion and asthma. In 1937, amphetamine sulfate tablets were introduced for the treatment of narcolepsy, postencephalitic parkinsonism, depression, and lethargy. In the 1970s, a variety of social and regulatory factors began to curb widespread amphetamine distribution. The current U.S. Food and Drug Administration (FDA)–approved indications for amphetamine are limited to attention-deficit/hyperactivity disorder (ADHD) and narcolepsy; however, amphetamines are also used in the treatment of obesity, depression, dysthymia, chronic fatigue syndrome, acquired immunodeficiency syndrome (AIDS), dementia, multiple sclerosis, fibromyalgia, and neurasthenia. Preparations The major amphetamines currently available and used in the United States are dextroamphetamine (Dexedrine), methamphetamine (Desoxyn), a mixed dextroamphetamine-

amphetamine salt (Adderall), and the amphetamine-like compound methylphenidate (Ritalin). 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, Kay-Lambkin F. It’s the thought that counts: Craving metacognitions and their role in abstinence

from methamphetamine use. J Subst Abuse Treat. 2010;38(3):245.

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