41 - 468 Cocaine, Other Psychostimulants, and Hallucinogens

468 Cocaine, Other Psychostimulants, and Hallucinogens

community of fellow drug users. These medication-free programs, as well as the pharmacotherapy programs, also include counseling and behavioral treatments designed to teach interpersonal and cognitive skills for coping with stress and for avoiding situations leading to easy access to drugs or to craving. Relapse is prevented by having the indi vidual very gradually reintroduced to greater responsibilities and to the working environment outside of the protected therapeutic community.

■ ■PREVENTION Preventing the development of opioid use disorder represents a criti cally important challenge for physicians. Opioid prescriptions are a common source of drugs accessed by adolescents who begin a pat tern of illicit drug use. The major sources of these drugs are family members, not drug dealers or the Internet. Pain management involves providing sufficient opioids to relieve the pain over as short a time as the pain warrants (Chap. 14). The patient then needs to dispose of any remaining opioids, not save them in the medicine cabinet, because this behavior leads to diversion by adolescents. Finally, physicians should never prescribe opioids for themselves. PART 13 Neurologic Disorders ■ ■FURTHER READING Blanco C, Volkow ND: Management of opioid use disorder in the USA: Present status and future directions. Lancet 393:1760, 2019. Bruneau J et al: Management of opioid use disorders: A national clini cal practice guideline. CMAJ 190:E247, 2018. Food and Drug Administration: Information about medica tions for opioid use disorder. Accessed May 24, 2024. Available at https://www.fda.gov/drugs/information-drug-class/information-

about-medications-opioid-use-disorder-moud. White House Office of National Drug Control Policy (ONDCP): White House announces over $276 million for law enforcement to help address the overdose epidemic and crack down on illicit drug trafficking. Accessed May 23, 2024. Available at https:// www.whitehouse.gov/ondcp/briefing-room/2024/05/23/white-houseannounces-over-276-million-for-law-enforcement-to-help-address-theoverdose-epidemic-and-crack-down-on-illicit-drug-trafficking/. Karran A. Phillips, Wilson M. Compton

Cocaine, Other Psychostimulants, and Hallucinogens The use of cocaine, methamphetamine, other psychostimulants, and hallucinogens reflects a complex interaction between the pharmacology of the drug, the personality and expectations of the individual using the drug, and the environmental context in which the drug is used. These substances cause significant harm, although they are less commonly used than other addictive substances such as alcohol (Chap. 464), nic otine (Chap. 465), cannabis (Chap. 466), and opioids (Chap. 467). It is also important to recognize that polydrug use, involving the concur rent use of several drugs with different pharmacologic effects, is com mon. Sometimes one drug is used to enhance the effects of another, as with the combined use of cocaine and nicotine, or cocaine and heroin in methadone-treated patients. Some forms of polydrug use, such as the combined use of intravenous (IV) heroin and cocaine, are espe cially dangerous and account for many hospital emergency department visits. Cocaine and psychostimulant use (especially chronic patterns of use) may cause adverse health consequences and exacerbate preexist ing disorders such as hypertension and cardiac disease. In addition, the combined use of two or more drugs may accentuate medical

complications associated with use of one drug. Chronic use is often associated with immune system dysfunction and increased vulner ability to infections, including risk for HIV infection. The concurrent use of cocaine and opiates (“speedball”) is frequently associated with needle sharing by people using drugs intravenously (IV). People who use IV drugs represent the largest single group of individuals with HIV infection in several major metropolitan areas in the United States as well as in many parts of Europe and Asia. Furthermore, several out breaks of HIV in the United States since 2015 in rural and suburban areas have been attributed to clusters of injection drug use. Psychostimulants and hallucinogens have been used for centuries to induce euphoria and alter consciousness. Hallucinogens have become popular recently, and new drugs are continually being developed. This chapter describes the subjective and adverse medical effects of cocaine, other psychostimulants including methamphetamine, 3,4-methylene dioxymethamphetamine (MDMA), and cathinones; hallucinogens such as phencyclidine (PCP), d-lysergic acid diethylamide (LSD), and Salvia divinorum; and emerging drugs. PSYCHOSTIMULANTS Psychostimulants include cocaine and methamphetamine, as well as drugs with stimulant-like properties such as MDMA and cathinones. In addition, prescribed psychostimulants such as methylphenidate, dextroamphetamine, and amphetamine are considered here. ■ ■COCAINE Cocaine is a powerful psychostimulant drug made from the cocoa plant. It has local anesthetic, vasoconstrictor, and stimulant properties. Cocaine is a Drug Enforcement Agency (DEA) Schedule II drug, which means that it has “high potential for abuse and the potential to create psychological and/or physical dependence” but can be administered by a physician for legitimate medical uses, such as local anesthesia for some eye, ear, and throat surgeries. Pharmacology Cocaine comes in a variety of forms, the most com monly used being the hydrochloride salt, sulfate, and a base. The salt is an acidic, water-soluble powder with a high melting point, used by snorting or sniffing intranasally or by dissolving it in water and inject ing it. When used intranasally, the bioavailability of cocaine is about 60%. Cocaine sulfate (“paste”) has a melting point of almost 200°C, so it has limited use, but it is sometimes smoked with tobacco. The base form can be freebase or crystallized as crack. Cocaine freebase is made by adding a strong base to an aqueous solution of cocaine and extract ing the alkaline freebase precipitate. It has a melting point of 98°C and can be vaporized and inhaled. Freebase cocaine can also be crystallized and sold as crack or rock, which is also smoked or inhaled. Street deal ers often dilute (or “cut”) cocaine with nonpsychoactive substances such as cornstarch, talcum powder, flour, or baking soda, or adulterate it with other substances with similar effects (like procaine or

amphet amine) to increase their profits. A recent concern has been the adul teration of cocaine (and other psychostimulants) with fentanyl-related opioids, resulting in overdose deaths due to opioid effects or polydrug use. Xylazine, a nonopioid sedative, analgesic, and muscle relaxant only approved for veterinary use in the United States, has also been found cut into cocaine and other psychostimulants, as described below under “Psychostimulant Clinical Manifestations”. Given the extensive pulmonary vasculature, smoked or vaporized cocaine reaches the brain very quickly, similar in speed of onset to injected cocaine. The result is a rapid, intense, transient high, which enhances its addictive potential. Cocaine binds to the dopamine (DA) transporter and blocks DA reuptake, which increases synaptic levels of the monoamine neurotransmitters DA, norepinephrine (NE), and serotonin (5HT), in both the central nervous system (CNS) and the peripheral nervous system (PNS). Use of cocaine, like other harmful drugs abuse, induces long-term changes in the brain. Animal studies have shown adaptations in neurons that release the excitatory neu rotransmitter glutamate after cocaine exposure. Epidemiology According to the National Survey on Drug Use and Health (NSDUH), in 2023 an estimated 5 million people aged 12 years

or older (1.8% of the population) were past-year consumers of cocaine, including crack. Among those, 470,000 used cocaine for the first time (1287 cocaine initiates/day) including 23,000 adolescents aged 12–17 years. About 1.3 million people aged 12 years or older (0.4% of the pop ulation) in 2023 had a cocaine use disorder. According to the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics, the age-adjusted rate of drug overdose deaths involving cocaine more than quintupled from 1.5 deaths per 100,000 standard population in 2011 to 8.2 in 2022. The rate of drug overdose deaths per 100,000 standard population involving both cocaine and opioids in 2021 (5.9) was 7.4 times the rate in 2011 (0.8) and was driven by the involvement of synthetic opioids including fentanyl and fentanyl ana logues. The rate involving cocaine without opioid co-involvement in 2021 (1.5) was 2.1 times the rate in 2011 (0.7). The data are concerning because they describe increases over time in cocaine-related overdose both with and without the co-ingestion of opioids. ■ ■METHAMPHETAMINE Methamphetamine is a psychostimulant drug usually used as a white, bitter-tasting powder or a pill. Crystal methamphetamine is a form of the drug that looks like glass fragments or shiny, bluish-white rocks. It can be inhaled/smoked, swallowed (pill), snorted, or injected (after being dissolved in water or alcohol). Pharmacology When smoked, methamphetamine exhibits 90.3% bioavailability, compared to 67.2% for oral ingestion. Methamphet amine exists in two stereoisomers, the l- and d-forms. d-Metham phetamine, or the dextrorotatory enantiomer, is a more powerful psychostimulant, with 3–5 times the CNS activity as compared with l-methamphetamine. Methamphetamine is a cationic lipophilic mol ecule, which stimulates the release, and partially blocks the reuptake, of newly synthesized catecholamines in the CNS. Methamphetamine has a similar structure to the DA, NE, 5HT, and vesicular monoamine transporters and reverses their endogenous function, resulting in release of monoamines from storage vesicles into the synapse. Meth amphetamine also attenuates the metabolism of monoamines by inhib iting monoamine oxidase. Methamphetamine is more potent than amphetamine, resulting in much higher concentrations of synaptic DA and more toxic effects on nerve terminals. Outside the medical context, methamphetamine’s pharmacokinetics and low cost often result in a chronic and continu ous, high-dose self-administered use pattern. Epidemiology According to the NSDUH, in 2023, 2.6 million people aged 12 years or older (0.9% of the population) used metham phetamine (not including use or misuse of prescription amphetamines or other stimulants) in the past year; of those, 78,000 used metham phetamine for the first time (213 people per day). In 2023, an estimated 1.8 million people aged 12 years or older

(0.6% of the population and 69% of those with past-year use) had a methamphetamine use disorder. High rates of co-occurring substance use and mental illness exist in adults who use methamphetamine, and only about one-third of adults with past-year methamphetamine use disorder received addiction treatment. Methamphetamine availability and methamphetaminerelated harms (e.g., overdose deaths, treatment admissions, infectious disease transmission) continue to increase in the United States. According to CDC data, psychostimulants (primarily methamphetamine) caused 36,251 overdose deaths in 2023. Stimulant-involved overdose deaths have risen markedly in recent years; with rates of psychostimulant overdose deaths increasing from 0.7 in 2011 to 10.4 in 2022. Further, while preliminary reports show overdose deaths involving opioids decreasing from an estimated 84,181 in 2022 to 81,083 in 2023, over dose deaths due to cocaine and psychostimulants (like methamphet amine) increased. ■ ■MDMA AND CATHINONES MDMA also known as Molly, ecstasy, or X, is an illegal synthetic drug that has stimulant and psychedelic effects. Khât is a plant found in East Africa and the Middle East; it has been used for centuries for its mild stimulant-like effect. Synthetic cathinones or “bath salts” are

manufactured psychostimulants that are chemically similar to the naturally occurring substance cathinone found in the khât plant and are discussed under “Emerging Drugs” below.

MDMA Molly, slang for “molecular,” refers to the crystalline pow der form of MDMA usually sold as powder or in capsules. The content of Molly varies and is often not MDMA at all but rather contains methylone or ethylone, which are synthetic substances commonly found in so-called bath salts and pose significant health risks. The cli nician should always consider the possibility that the drug reported by the individual may be unwittingly contaminated with other substances. With MDMA use, individuals experience increased physical and mental energy, distortions in time and perception, emotional warmth, empathy toward others, a general sense of well-being, decreased anxi ety, and an enhanced enjoyment of tactile experiences. MDMA is usu ally taken orally in a tablet, capsule, or liquid form with first effect at 45 min on average, peak effect at 1–2 h, and duration ~3–6 h. MDMA binds to serotonin transporters and increases the release of serotonin, NE, and DA. Research in animals has shown that MDMA in moder ate to high doses can cause loss of serotonin-containing nerve endings and permanent damage. MDMA is a Schedule I drug, along with other substances with no proven therapeutic value. MDMA has been given a breakthrough therapy designation by the U.S. Food and Drug Administration (FDA) as a possible treatment for posttraumatic stress disorder allowing for expedited clinical trials, but at present MDMA remains a Schedule I drug, along with other substances with no proven therapeutic value. CHAPTER 468 Cocaine, Other Psychostimulants, and Hallucinogens Adulteration of MDMA tablets with methamphetamine, ketamine, caffeine, the over-the-counter cough suppressant dextromethorphan (DXM), the diet drug ephedrine, and cocaine is common. MDMA is rarely used alone and is often mixed with other substances, such as alcohol and marijuana, making the specific impacts of its use difficult to ascertain. According to NSDUH 2023 data, among individuals aged 12 or older, 0.8% used MDMA in the past year and 507,000 people tried MDMA for the first time (>1300 per day). MDMA is predominantly used by men 18–25 years of age, with use typically beginning at age 21 years. There is evidence that gay or bisexual men and women are more likely than their heterosexual counterparts to have used MDMA in the last 30 days. Cathinone This is an alkaloid psychostimulant structurally similar to amphetamine found in the khât (Catha edulis) plant, which grows at high altitudes in East Africa and the Middle East and whose leaves are chewed for their

mild stimulant-like effect. The extraction of cathinone and other alkaloids from the leaves by chewing is very effective, leaving little as unabsorbed residue. The leaves and twigs can also be smoked, infused in tea, or sprinkled on food. Cathinone increases dopamine release and reduces dopamine reuptake. Originally limited to its area of cultivation, with advances in rapid transportation and postal delivery, khât is now available in several con tinents including Europe and North America. Worldwide it is estimated that 10 million people chew khât, including up to 80% of all adults in some areas where the evergreen shrub is indigenous. In regions where the plant is indigenous, there have also been reports of khât use as a study aid among university students. Cathinone is a Schedule I drug in the United States, making its possession and use illegal. ■ ■PRESCRIBED PSYCHOSTIMULANTS Methylphenidate, dextroamphetamine, and dextroamphetamine/ amphetamine combination products are psychostimulants approved in the United States for treatment of attention-deficit hyperactivity disorder (ADHD), weight control, and narcolepsy. Prescription psy chostimulants increase alertness, attention, and energy. Phenylpropa nolamine, a psychostimulant used primarily for weight control, was found to be related to hemorrhagic stroke in women and removed from the market in 2005. Nonprescribed amphetamines and methylpheni date are used quite frequently by college students and as energy and productivity boosters by others. According to the 2023 NSDUH, pastyear prescription stimulant misuse was reported by 3.9 million (1.4%) people aged 12 years or older. Of note, in 2023 among individuals aged

12 or older, 786,000 individuals misused prescription stimulants and cocaine; 190,000 misused prescription stimulants and methamphet amine; and 182,000 people misused or used all three. Past-year initiates of prescription stimulant misuse totaled 712,000, which averages to ~1950 people misusing prescription stimulants for the first time each day, including >1000 young adults aged 12–25 each day. Among people aged 12 years or older, 0.6% of the population in 2023 had a prescrip tion stimulant use disorder in the past year.

■ ■PSYCHOSTIMULANT CLINICAL MANIFESTATIONS Psychostimulants produce the same acute CNS effects: euphoria/ elevated mood, increased energy/decreased fatigue, reduced need for sleep, decreased appetite, heightened sense of alertness, decreased distractibility, dose-dependent effects on focus, attention, and curios ity, increased self-confidence, increased libido, and prolonged orgasm, independent of the specific psychostimulant or route of administra tion. Peripheral effects may include tremor, diaphoresis, hypertonia, tachypnea, hyperreflexia, and hyperthermia. Many of the effects are biphasic; for example, low doses improve psychomotor performance, while higher doses may cause tremors or convulsions. α-Adrenergically mediated cardiovascular effects are also biphasic, with low doses result ing in increased vagal tone and decreased heart rate and high doses causing increased heart rate and blood pressure. Psychostimulant use can result in restlessness, irritability, and insomnia and, at higher doses, suspiciousness, repetitive stereotyped behaviors, and bruxism. Endocrine effects resulting from chronic use may include impotence, gynecomastia, menstrual function disruptions, and persistent hyperp rolactinemia (Table 468-1). PART 13 Neurologic Disorders Overdose presents as sympathetic nervous system overactivity with psychomotor agitation, hypertension, tachycardia, headache, and mydriasis, and can lead to convulsions, cerebral hemorrhage or infarc tion, cardiac arrhythmias or ischemia, respiratory failure, or rhabdo myolysis. It is a medical emergency; treatment is largely symptomatic and should occur in an intensive care or telemetry unit. Inhalation of crack cocaine that is vaporized at high temperatures can cause airway burns,

bronchospasm, and other symptoms of pulmonary disease. MDMA has also been shown to raise body temperature and can occa sionally result in liver, kidney, or heart failure, or even death. Psychostimulants are often used with other drugs, including opi oids and alcohol, whose CNS-depressant effects tend to attenuate psychostimulant-induced CNS stimulation. These combinations often have additive deleterious effects, increasing the risk of morbidity and mortality. An example of this risk is the use of cocaine with alcohol, which results in the metabolite cocaethylene. Cocaethylene's effects on the cardiovascular system are additive to that of cocaine's effects, result ing in intensified pathophysiologic consequences. Adulteration of psychostimulants, particularly cocaine, with other drugs is common and can have additional health consequences. In addition to contamination with fentanyl-related compounds, poten tially resulting in fatal overdose, multiple other substances have been noted as contaminants of psychostimulants. Levamisole, an anthelminthic and immunomodulator used primarily in veterinary medicine, has been found in cocaine and can cause agranulocytosis, leukoencephalopathy, and cutaneous vasculitis, which has resulted in skin necrosis. Clenbuterol, a sympathomimetic amine used clinically as a bronchodilator, has also been found in cocaine and can result in tachycardia, hyperglycemia, palpitations, and hypokalemia. Xylazine, a nonopioid veterinary sedative, analgesic, and muscle relaxant, is most often described in the context of an opioid adulterant; however, it is also seen as an adulterant of cocaine, methamphetamine, and other stimulants. Effects associated with xylazine include dry mouth, drowsi ness, hypertension, and tachycardia followed by hypotension and bradycardia, hyperglycemia, hypothermia, coma, respiratory depres sion, and dysrhythmia. Xylazine injection has been associated with necrotic soft tissue lesions both at the site of injection and elsewhere on the body. There is some evidence that xylazine itself can result in withdrawal symptoms such as sharp chest pains and seizures and cause physical dependence. Studies in Europe have found that, in addition to levamisole, some of the most common adulterants in cocaine include

TABLE 468-1 Complications of Psychostimulant Use Cardiovascular Acute • Arterial vasoconstriction • Thrombosis • Tachycardia • Hypertension • Increased myocardial oxygen demand • Increased vascular shearing forces • Coronary vasoconstriction • Cardiac ischemia • Left ventricular dysfunction/heart failure (high blood concentrations) • Supraventricular and ventricular dysrhythmias • Aortic dissection/rupture Chronic • Accelerated atherogenesis • Left ventricular hypertrophy • Dilated cardiomyopathy Central and peripheral nervous systems • Hyperthermia • Psychomotor agitation • Tremor • Hyperreflexia • Hypertonia • Headache • Seizures • Coma • Intracranial hemorrhage • Focal neurologic symptoms Pulmonary • Angioedema (inhaled) • Pharyngeal burns (inhaled) • Pneumothorax • Pneumomediastinum • Pneumopericardium • Reversible airway disease exacerbations • Bronchospasm • Shortness of breath ("crack lung") • Tachypnea • Pulmonary infarction Gastrointestinal • Perforated ulcers • Ischemic colitis • Bowel infarction • Impaction (body packing) • Hepatic enzyme elevation Renal • Metabolic acidosis • Renal infarction • Rhabdomyolysis Endocrine • Impotence • Gynecomastia • Menstrual function disruptions • Hyperprolactinemia Other • Diaphoresis • Irritability • Insomnia • Bruxism • Stereotypy • Splenic infarction • Acute angle-closure glaucoma • Vasospasm of the retinal vessels (unilateral or bilateral vision loss) • Mydriasis • Madarosis • Abruptio placentae

phenacetin, lidocaine, caffeine, diltiazem, hydroxyzine, procaine, tetra caine, paracetamol, creatine, and benzocaine. Withdrawal from psychostimulants often includes hypersomnia, increased appetite, and depressed mood. Acute withdrawal typically lasts 7–10 days, but residual

symptoms, possibly associated with neuro toxicity, may persist for several months. Debate remains whether psy chostimulant withdrawal symptoms decline monotonically or occur in discrete phases, becoming worse before they improve. Psychostimulant withdrawal is not thought to be a major driver of ongoing use. Most current theories of psychostimulant addiction emphasize the primary role of conditioned craving, which can persist long after physiological withdrawal has abated. Conditioned craving includes the urge to use drugs in response to cues in the environment associated with drug use, such as associates who use drugs, drug paraphernalia, or drug-using locations. Injection of psychostimulants places people at increased risk of con tracting infectious diseases from exposure to HIV and hepatitis B or C in blood or other bodily fluids, as well as skin abscesses and endocardi tis. Psychostimulant use can also increase risk for infection by causing altered judgment and decision-making, leading to risky behaviors such as unprotected sex. There is some evidence that psychostimulant use may worsen the progression of HIV/AIDS via increased injury to nerve cells exacerbating cognitive problems. The actions and effects of khât are like those of other psychostimu lants. Short-term effects include euphoria, increased alertness and arousal, loss of appetite, insomnia, headaches, and tremors. Long-term use may result in gastrointestinal disorders such as constipation, ulcers, and stomach inflammation, as well as increased risk for acute myocar dial infarction and stroke due to inotropic and chronotropic effects on the heart, vasospasm of coronary arteries, and catecholamine-induced platelet aggregation. There is evidence that, rarely, heavy khât use may cause mild to moderate psychological dependence. Compulsive use has been described, with resulting grandiose delusions, paranoia, and hallucinations. A mild withdrawal syndrome from khât can include depression, nightmares, low blood pressure, and lack of energy. ■ ■DIAGNOSIS The Diagnostic and Statistical Manual of Psychiatric Disorders, 5th edi tion (DSM-5) defines a stimulant use disorder (SUD) as a pattern of use of amphetamine-type substances, cocaine, or other stimulants lead ing to clinically significant impairment or distress, as manifested by at least 2 of the following 11 problems within a 12-month period: taking larger amounts, or over a longer period of time, than intended; persis tent desire or unsuccessful efforts to reduce or control use; a great deal of time spent in activities necessary to obtain, use, or recover; craving; use resulting in failure to fulfill major role obligations; continued use, despite recurrent social or interpersonal problems; giving up social, occupational, or recreational activities; recurrent use in physically haz ardous situations; continued use despite persistent or recurrent physi cal or psychological problems; tolerance; and withdrawal symptoms, or avoidance of withdrawal symptoms, by continued use. The International Classification of Diseases (ICD) 10th Revision (ICD-10) recognizes “stimulant dependence syndrome” and “stimulant withdrawal state,” and the ICD 11th Revision (ICD-11) further speci fies the definition to “stimulant dependence including amphetamines, methamphetamines, or methcathinone.” TREATMENT Acute Intoxication As with all emergency situations, the first task is to check a patient’s circulation, airway, and breathing. With cocaine use, succinyl choline is relatively contraindicated in rapid-sequence intubation; consider rocuronium (1 mg/kg IV) or another nondepolarizing agent as an alternative. If psychomotor agitation occurs, rule out hypoglycemia and hypoxemia first, and then administer benzodi azepines (e.g., diazepam 10 mg IV and then 5–10 mg IV every 3–5 hours until agitation controlled). Benzodiazepines are usually

sufficient to address cardiovascular side effects. Severe or symptom atic hypertension can be treated with phentolamine, nitroglycerin, or nitroprusside. Hyperthermic patients should be cooled within ≤30 min with the goal to achieve a core body temperature of <39°C (102°F). Evaluation of chest pain in someone using cocaine should include an electrocardiogram, chest radiograph, and

biomarkers to exclude myocardial infarction. The treatment approach is similar to nonstimulant-induced chest pain; however, it is recommended that whenever possible beta blockers not be used in people who use cocaine. The concern arises from the potential unopposed alphaadrenergic stimulation that results from beta blockade possibly causing coronary arterial vasoconstriction, ischemia, and infarction and limited data supporting the benefit of beta blockers in cocainerelated cardiovascular complications. If beta blockers are to be given, it is suggested that mixed alpha/beta blockers, e.g., labetalol and carvedilol, be used rather than nonselective beta blockers, and only in situations where the benefits outweigh the risks. Because many instances of psychostimulant-related mortality have been associated with concurrent use of other illicit drugs (particularly opioids), the physician must be prepared to institute effective emer gency treatment for multiple drug toxicities.

CHAPTER 468 Cocaine, Other Psychostimulants, and Hallucinogens Psychostimulant Use Disorders Treatment of psychostimulant use disorders requires the combined efforts of primary care physicians, addiction medicine physicians, psychiatrists, and psychosocial care providers. Early abstinence from psychostimulant use is often complicated by symptoms of depression and guilt, insomnia, and anorexia, which may be as severe as those observed in major affective disorders and can last for months and even years after use has stopped. Behavioral therapies, including cognitive-behavioral therapy (CBT), the community reinforcement approach (CRA), con tingency management (CM; providing structured and specific incentives to patients who remain substance free), motivational enhancement therapy (MET), combinations of these, and others, remain the mainstay of treatment for SUDs and show modest benefit. These behavioral therapies are designed to help modify the patient’s thinking, expectancies, and behaviors, and to increase life-coping skills, with behavioral interventions to support longterm, drug-free recovery. There is robust evidence, including recent meta-analyses and systematic reviews, that contingency manage ment, when implemented with fidelity to the principles of operant conditioning, is a highly effective treatment for psychostimulant use disorder, the benefit of which continues for up to 2 years beyond treatment discontinuation. There are no FDA-approved medications for psychostimulant addiction. Current research includes several neurotransmitterbased strategies targeting DA, serotonin, γ-aminobutyric acid (GABA), and glutamate. Trials of agonist therapy with longeracting psychostimulant medications such as dexamphetamine and methylphenidate have not been conclusive. Studies with the anti depressants mirtazapine, bupropion, sertraline, imipramine, and atomoxetine have been equivocal, as have studies with the atypical antipsychotic aripiprazole and the anticonvulsant topiramate. Other therapies being studied for the treatment of psychostimulant use disorder include acamprosate (possibly via a role in modulating the NMDA receptor), galantamine (reversible acetylcholine esterase inhibitor, which may strengthen impulse control, as well as cogni tive and social abilities depleted by long-term psychostimulant use), naltrexone (opiate receptor antagonist), doxazosin (alpha-adrener gic antagonist), and varenicline (partial agonist of the α4β2 nico tinic acetylcholine receptor and DA neurotransmission enhancer). Overall, it is promising that some of the medications studied showed significant outcome improvements over placebo, but many were also underpowered due to issues of small sample size, sample bias, low participant retention, and low treatment adherence rates. Ongoing studies are investigating lisdexamfetamine (a dexamphet amine prodrug), a combination of extended-release naltrexone

with bupropion, pomaglumetad (a glutamate agonist), and sev eral monoclonal antibodies. Special attention needs to be paid to the inclusion of underrepresented populations including women in

future stimulant use disorder medication trials. Vaccines for cocaine and methamphetamine use disorders are also being devel oped. Finally, recent preliminary studies have brought attention to the potential use of brain stimulation techniques such as transcra nial magnetic stimulation (TMS), theta-burst stimulation (TBS), and transcranial direct current stimulation (tDCS) to treat psycho stimulant use disorders, although further studies will be required to determine their value, if any, in this situation.

HALLUCINOGENS Hallucinogens are a diverse group of drugs causing alteration of thoughts, feelings, sensations, and perceptions. Some hallucinogens are found naturally in plants and mushrooms, while others are syn thetic. They include ayahuasca (a tea made from Amazonian plants containing dimethyltryptamine [DMT], the primary mind-altering ingredient), DMT (aka Dimitri; can also be synthesized in a lab), LSD (clear or white odorless material made from lysergic acid found in rye and other grain fungus); peyote (mescaline, derived from a small, spineless cactus or made synthetically); and 4-phosphoryloxy-N,Ndimethyltryptamine (psilocybin, comes from certain South and North American mushrooms). PART 13 Neurologic Disorders A subgroup of hallucinogens produces the added sensation of feel ing out of control or disconnected from one’s body or surroundings. These dissociative drugs include DXM (an over-the-counter cough suppressant, when used in high doses), ketamine (an FDA-approved human and veterinary anesthetic and a nasal spray [esketamine] for treatment-resistant depression); phencyclidine (PCP; a cyclohexyl amine derivative and dissociative anesthetic); and S. divinorum (salvia, a Mexican, Central American, and South American plant). Dissociative drugs distort the way the user perceives time, motion, color, sound, and self, and their use can lead to bizarre and dangerous behavior and cause respiratory depression, heart rate abnormalities, and a withdrawal syndrome including drug craving, confusion, headache, and sweating. Use of hallucinogens in religious and spiritual rituals goes back centuries, and they are ingested in a wide variety of ways, including orally, by smoking, intranasally, and transmucosally. Especially when taken orally, the onset of action of hallucinogens is within 20–90 min and the duration of action can be as long as 6–12 h, except for salvia, whose effects generally last about 30 min. Hallucinogens specifically disrupt the neurotransmitters serotonin and glutamate. Effects on the serotonin system can disturb mood, sensory perception, sleep, appetite, body temperature, sexual behavior, and muscle control. Glutamate sys tem effects include perturbations in pain perception, responses to the environment, emotion, and learning and memory. According to the NSDUH, in 2023, 2.6 million adults reported pastmonth use of hallucinogens and 8.8 million (3.1% of the population) reported past-year use of hallucinogens. Of these, 1.5 million used hallucinogens for the first time. Of note, these statistics include ecstasy (MDMA or “Molly”) in the overall hallucinogen use category as well as LSD, PCP, peyote, mescaline, psilocybin mushrooms, ketamine, N,N-dimethyltryptamine (DMT)/Alpha-Methyltryptamine (AMT)/ “Foxy,” and S. divinorum. Past-year initiation numbers among people aged 12 years and older include 364,000 for LSD, 24,000 for PCP, and 507,000 for ecstasy. In 2023, 0.2% of people aged 12 or older had a hal lucinogen use disorder. Clinical manifestations of hallucinogen use include false sensory experiences (i.e., hallucinations), intensified feelings, heightened sen sory experiences, and time perturbations. Additional physiologic responses include nausea; increases in heart rate, blood pressure, respiratory rate, or body temperature; loss of appetite; xerostomia; sleep problems; synesthesia; impaired coordination; and hyperhidrosis. Extremely negative experiences with hallucinogen use (the “bad trip”) can include panic, paranoia, and psychosis, which may persist for up to 24 h. Such experiences are best treated with supportive reassur ance, but benzodiazepines (e.g., diazepam 10 mg or lorazepam if liver

damage is present) may be administered if agitation is severe. There is some evidence that chronic effects of hallucinogen use can occur, including persistent psychosis, memory loss, anxiety, depression, and flashbacks. Long-term effects of PCP and other dissociative drug use can include persistent speech difficulties, memory loss, depression, suicidal thoughts, anxiety, and social withdrawal that may persist for a year or more after chronic use stops. The FDA issued breakthrough therapy designation for MDMA to expedite research into treatment of posttraumatic stress disorder and additional breakthrough therapy designations for two formulations of psilocybin for treatment of depression. In addition, some hallucino gens are being studied as potential treatment for certain SUDs, includ ing psilocybin for alcohol and tobacco use disorders and ketamine for cocaine and methamphetamine use disorders. There is also some evi dence that psilocybin and LSD may relieve pain in certain chronic pain conditions such as cluster headache, lower back pain, cancer-related pain, and phantom limb pain; studies are ongoing. The DSM-5 defines hallucinogen use disorder as meeting 2 or more of the first 10 criteria (see above for SUD) in the past 12 months. The withdrawal criterion does not apply to hallucinogens, because hal lucinogen use disorder is atypical in that use patterns are generally not chronic. There are currently no FDA-approved medications for the treatment of hallucinogen addiction. Research on behavioral treat ments for hallucinogen addiction is underway. EMERGING DRUGS With the aid of the Internet and some basic over-the-counter (and other) ingredients, the rise of the “kitchen chemist” is upon us. The production of new psychoactive substances (NPS), such as recreation ally manufactured synthetic cathinones (bath salts) and synthetic cannabinoids (K2, spice), is on the rise and has resulted in the use of unregulated psychoactive substances that are intended to copy the effects of more expensive illegal drugs such as methamphetamine and cocaine. NPS also include recreationally manufactured synthetic opioids containing brorphine and U-47700 and recreationally manu factured synthetic benzodiazepines such as bromazepams, desalkylgid azepam, and flubromazepam. In addition to NPS, nitazines (a synthetic opioid that can be more powerful than fentanyl) and tianeptine (a non-U.S.-approved antidepressant with opioid-like effects at high doses) are emerging and reemerging in the drug supply both alone and mixed into other drugs. These emerging drugs can be found online or sold in drug markets or convenience stores. Depending on the type of substance, whether a new type of opioid, depressant, synthetic can nabinoid, psychedelic, or stimulant, the effects will differ and may be unpredictable and unwanted, especially if unwittingly ingested as an adulterant in another drug. In addition, emerging substances are often not included in emergency department drug tests and are not routinely tested for when determining the cause of death after a fatal overdose. Synthetic cathinones (bath salts) are human-made drugs chemi cally similar to cathinone found in khât and are often stronger and more dangerous than the natural product. They usually take the form of a white or brown crystal-like powder, packaged in small plastic or foil bundles labeled “not for human consumption,” or as “plant food,” “jewelry cleaner,” or “phone screen cleaner,” and sold online and in drug paraphernalia stores. The popular nickname Molly (slang for “molecular”) often refers to the purported “pure” crystalline powder form of MDMA, usually sold in capsules. However, people who pur chase powder or capsules sold as Molly often actually receive other drugs, such as synthetic cathinones. The uncertainty of what is actually in these synthetic products, whose components might change from batch to batch, makes them even more dangerous, as anyone using them is unaware of what the products actually contain and how they might respond. The three most common synthetic cathinones are mephedrone, methylone, and MDPV (3,4-methylenedioxypyrovalerone). With oral ingestion, these drugs have an onset of action from 15–45 min, and a duration that varies from 2–7 h. Studies have found that MDPV affects the brain in a

manner similar to cocaine but is at least 10 times more potent. MDPV is the most common synthetic cathinone found in the

blood and urine of patients admitted to emergency departments after taking “bath salts.” High doses, or chronic use, of synthetic cathinones can lead to dangerous medical consequences, including psychosis, vio lent behaviors, tachycardia, hyperthermia, and even death. The ability to synthesize addictive and dangerous drugs relatively simply and rapidly, changing just a few molecules, yet retaining the effects, has allowed many of these emerging drugs to outpace efforts to regulate them, resulting in a developing global public health concern. SUBSTANCE USE AND MENTAL HEALTH According to the NSDUH, in 2023, among adults aged 18 and older with no mental illness, 21% consumed illicit drugs, compared to 51.9% with severe mental illness and 42.4% with any mental illness. In 2023, among adults 18 years of age or older, 84.5 million people had either any mental illness or an SUD in the past year, 38.2 million had any mental illness in the absence of an SUD, 25.8 million had an SUD and no mental illness, and 20.4 million (7.2% of the population) had both. The percentage of adults aged 18 or older in 2023 who had both any mental illness and an SUD in the past year was highest among young adults aged 18 to 25 (14.1% or 4.8 million people). The percentage of adults aged 18 or older in 2023 who had both any mental illness and an SUD in the past year was higher among multiracial adults (13.3%) than among white (8.4%), black (7.8%), Hispanic (7.1%), or Asian adults (3.5%); the percentage could not be calculated with sufficient precision for Native Hawaiian or other Pacific Islander adults. Among the 20.4 million adults aged 18 or older in 2023 with cooccurring any mental illness and an SUD in the past year, 62.4% (or 12.8 million people) received either substance use treatment or mental health treatment in the past year, and 37.6% (or 7.7 million people) received neither type of treatment. This equates to about two in five adults aged 18 or older with co-occurring any mental illness and an SUD in the past year who did not receive treatment for either condi tion. Taken together, these data point to the significant overlap of substance-related and other mental health problems and highlight the prodigious treatment gap that exists for both. GLOBAL CONSIDERATIONS After nicotine, alcohol, and cannabis, stimulants are the next most used drugs globally, worldwide in 2021, an estimated 22 million people used cocaine and 36 million people used amphetamines. The global cocaine supply reached a record high in 2022 with >2700 tons of cocaine pro duced, 20% more than the previous year, with main trafficking from the Andean region to other countries in the Americas and to Western and Central Europe. The two largest emerging methamphetamine markets in recent years have been the Near and Middle East/Southwest Asia and Southeastern Europe. The trafficking and use of synthetic stimulants, mainly cathinones, has risen notably in Central Asia and Eastern Europe. Globally, psychostimulant use has been associated with elevated mortality, increased incidence of HIV and hepatitis C infection, poor mental health (suicidality, psychosis, depression, and violence), and increased risk of cardiovascular events. The World Health Organization estimates that in 2019 global deaths attributed to cocaine and amphetamine use were 26,082 and 46,661, respectively. Worldwide 7.4 million individuals have a stimulant use disorder, and the United Nations Office on Drugs and Crime (UNODC) esti mates that only one in seven people with SUDs receives treatment.

The number receiving treatment is much lower in individuals with stimulant use disorder despite the fact that cocaine treatment demand alone has risen almost 60% from 2011 to 2022 in subregions in Europe.

Globally, stigma and marginalization make treatment of drug use disorders difficult and hinder sustainable inclusive development incor porating gender and racial equity and the empowerment of women and underrepresented minorities. The existing treatment gap is further magnified when the intersectionality of gender, race, age, and ethnicity is considered, as is the treatment gap faced by populations with housing instability, low socioeconomic status, or low educational attainment, as well as LGBTQIA+, and veterans, among others. FUTURE DIRECTIONS Despite their prevalence and public health impact, psychostimulant and hallucinogen use disorders have no FDA-approved treatment medications. While behavioral therapies, such as contingency man agement and CBT, have been shown effective in psychostimulant use disorders, further research needs to be done regarding their utility for hallucinogen use disorders. Based on experience with opioid and alco hol use disorders, it is also likely that the most efficacious treatments will employ a combination of behavioral and pharmacologic therapy. Research on medications to treat psychostimulant use disorder is ongoing. Additionally, new approaches that utilize emerging technolo gies have considerable potential for future treatment of psychostimu lant use disorders. These include neurostimulation/neuromodulation (TMS, TBS, tDCS), wearable biosensors, and mobile technology, including ecologic and geographic momentary assessment (EMA/ GMA), as well as real-time interventions delivered via smartphone or other mobile devices. CHAPTER 468 Cocaine, Other Psychostimulants, and Hallucinogens ■ ■FURTHER READING Centers for Disease Control and Prevention: A stimulant guide: Answers to emerging questions about stimulants in the context of the overdose epidemic in the United States. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2022. Compton WM: Polysubstance use in the U.S. opioid crisis. Mol Psychiatry 26:41, 2021. Farrell M et al: Responding to global stimulant use: Challenges and opportunities. Lancet 394:1652, 2019. Substance Abuse and Mental Health Services Administration: Treatment for Stimulant Use Disorders. Treatment Improvement Protocol (TIP) Series 33. SAMHSA Publication No. PEP21-02-01 004. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2021. Trivedi MH et al: Bupropion and naltrexone in methamphetamine use disorder. N Engl J Med 384:140, 2021. ■ ■WEBSITES American Society of Addiction Medicine: https://www.asam.org/ public-resources National Institute on Drug Abuse: https://www.drugabuse.gov/ drugs-abuse Substance Abuse and Mental Health Services Administration: https://www.samhsa.gov World Health Organization: http://www.who.int/substance_abuse/en/

This page intentionally left blank

Revision #1
Created 2026-01-06 16:35:59 UTC by Omar Ayman
Updated 2026-01-06 16:35:59 UTC by Omar Ayman