

Chapter 3—Medical Aspects of Stimulant Use Disorders

KEY MESSAGES

- Healthcare service providers need to learn the medical signs, symptoms, and consequences of stimulant use to understand how best to medically manage patients with stimulant use disorders. Behavioral health service providers should also learn the medical aspects of stimulant use disorders so they can refer patients for medical intervention quickly and appropriately.
- The physical effects of stimulants will vary by the type of stimulant taken, route of administration, dose, purity of the substance, the individual's pattern of use, other substances the individual may be using, and any medical or psychiatric comorbidities the individual may have.
- Common medical complications of stimulant use disorders are cardiovascular conditions, respiratory problems, cerebrovascular events, muscular and renal dysfunction, gastrointestinal problems, infections including HIV/AIDS, and hepatitis C.
- Common psychological complications of stimulant use disorders include psychosis, depression, hypervigilance, and anxiety.
- People with stimulant use disorders often have co-occurring conditions that, if untreated, can exacerbate their substance use or otherwise make recovery more difficult. Co-occurring conditions of note are polysubstance use, co-occurring mental illness, medical conditions, and traumatic injury.

This chapter addresses the psychological symptoms and other medical consequences commonly seen in people using various forms of stimulants (e.g., powder cocaine, crack cocaine, methamphetamine [MA]) who appear at hospital emergency departments (EDs) and other medical settings or who need specialized medical care while participating in residential or outpatient substance use disorder (SUD) programs. The purpose of the chapter is to assist medical personnel in recognizing and treating problems in people with stimulant use that may arise secondary to acute/chronic intoxication, during withdrawal, or in various stages of recovery and in differentiating these problems from similar presentations of other medical and psychiatric conditions. The information in this chapter may also be useful to nonmedical treatment providers to help them recognize physical symptoms that would warrant medical attention and follow-up. Another emphasis is the need for establishing and ensuring linkages between medical facilities and appropriate, comprehensive SUD treatment/rehabilitation programs.

People who use psychostimulants typically present with acute medical problems such as cerebrovascular accidents (i.e., stroke), acute myocardial ischemia, heart failure, hyperthermia, or seizures. Other major symptoms manifest as altered mental status, including confusion, altered perceptions of reality (e.g., delusions), paranoid ideation, hallucinations, and suicidal ideation. Cardiovascular disease is the third leading cause of death, behind overdose and accidents, among people who use MA (Kevil et al., 2019).

Because this chapter discusses medical topics and concepts that may not be familiar to all readers, Exhibit 3.1 defines key terms that will be used.

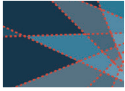


EXHIBIT 3.1. Key Terms

Altered perception of reality: A phenomenon in which the way that an individual understands or interprets external stimuli or internal sensations is distorted. The term is used in Chapter 3 specifically to refer to a **delusion**, which is a false belief based on an incorrect interpretation of reality, that is firmly believed despite evidence to the contrary, and that is not part of one's culture or religious beliefs (e.g., believing that a flickering light bulb is a sign that one is being spied on, believing that one is pregnant despite no medical indication that this is true) (Shahrokh et al., 2011). Hallucination, another altered perception of reality, is defined separately.

Alveolar rupture: A condition of the respiratory system in which pressure changes between the alveoli (air sacs) and the interstitium (a fluid filled space around the air sacs) cause a tear in the wall of the air sac that allows air to enter the interstitial space. Alveolar rupture can lead to breathing problems and lung damage.

Anticholinergic: A substance that inhibits the parasympathetic nervous system by interfering with the action of the neurotransmitter acetylcholine, which regulates neural impulses that control muscle movement. It is often used to describe the mechanism of action for a drug (e.g., anticholinergic medications).

Aortic dissection: An aortic dissection is a potentially life-threatening condition in which tears in the inner layer of the aorta, the large blood vessel that exits the heart and supplies blood to the rest of the body, lead to blood loss and separation of the layers of the aorta's wall, which can block blood flow, resulting in impaired perfusion throughout the body. Severe tears that extend all the way through to the outermost layer of the aorta are usually fatal (Mayo Clinic, 2017b).

Arrhythmia: A condition in which a person's heart rate or rhythm is abnormal due to malfunctions in electrical impulses. The heartbeat can be too fast, too slow, or irregular.

Barotrauma: An injury caused by a change in air or water pressure resulting in physical damage to body tissue, frequently affecting the ears or the lungs.

Bronchospasm: A tightening of the muscles that line a person's airway.

Bruxism: A condition in which people unconsciously or consciously grind or clench their teeth.

Catecholamine: A type of hormone that is produced by the adrenal glands or brain.

Choreoathetoid: Related to choreoathetosis, which is a movement disorder characterized by rapid or slow involuntary twitching or writhing of the body.

Conditioning: A learning process in which one stimulus signals the occurrence of a second stimulus either through pairing stimuli (classical conditioning) or applying a consequence after a behavior (operant conditioning).

Corticostriatal: Refers to the connection between the cortex and the striatum in the brain, which facilitates the flow of sensory, motor, and limbic information along a pathway to regulate motor control, action selection, and reward (W. Li & Pozzo-Miller, 2020).

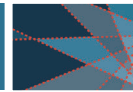
Depersonalization: A sense of experiencing one's own thoughts, feelings, and behaviors from a distance, as if observing or dreaming.

Derealization: A sense of feeling detached from one's surroundings, such that the environment appears distorted and not real.

End organ: Any organ fed by the circulatory system (e.g., heart, kidneys, brain, eyes) that can sustain temporary or permanent damage when circulation is disrupted.

Euphoria: A mental and emotional condition characterized by an intense feeling or state of pleasure, happiness, and excitement.

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GABA system: The network of brain receptors that respond to the inhibitory neurotransmitter gamma-aminobutyric acid.

Glomerular filtration: The process that takes place in the kidneys to filter the blood and eliminate excess fluid and waste from the body through the production of urine. The physiologic process is often expressed as a rate and used to determine the stage of kidney disease (if present).

Granulomatosis: A condition stemming from inflammatory processes that cause nodules made up of immune cells, known as granulomas, to form and affect various organs throughout the body.

Hallucination: A false sensory perception that occurs despite the fact that no sensory stimulus is present (Shahrokh et al., 2011). This could include experiences like seeing things that aren't really present (i.e., visual hallucinations), hearing voices that aren't really there (i.e., auditory hallucinations), or feeling tactile sensations that are not real (e.g., feeling like bugs are crawling under one's skin).

Hypertension: Blood pressure that is elevated above the normal range.

Hypomania: A state defined by abnormal elevations in mood, activity, or energy, typically lasting for at least 4 days. Hypomania is less extreme than mania and does not cause significant impairment in functioning.

Hyponatremia: A condition characterized by abnormally low levels of sodium in the blood, often caused by conditions such as kidney disease, liver disease, and heart failure.

Ideas of reference: The false belief that casual incidents and external events have a personal significance.

Ischemia: A condition in which blood flow to tissues and other organs is reduced, often resulting from damage to blood vessels caused by a blockage. Ischemia can occur anywhere in the body and can be classified as either partial or complete, leading to either reduction in oxygen transport or total impairment in oxygenation.

Kindling: A neurologic response, characterized by increased sensitivity to a substance, that worsens withdrawal symptoms following repeated attempts at cessation.

Metabolic acidosis: An imbalance of electrolytes that disrupts the acid-base pH balance and causes excess acid in body fluids. This condition can have severe consequences and become life threatening without medical intervention.

Myocardial infarction: Also known as a heart attack, myocardial infarction occurs when there is impaired blood flow to the heart, causing damage to the heart muscle and affecting its ability to pump blood efficiently and circulate oxygen throughout the body.

Necrosis: The premature death of cells due to external factors, such as infection or injury.

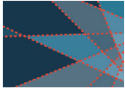
Perfusion: The movement of fluid through the circulatory system.

Perseveration: An uncontrollable persistence or repetition of a particular thought or behavior despite a clear reason for ceasing or absence of a stimulus.

Placental abruption: A sudden complication of pregnancy that occurs when the placenta partially or completely separates from the inner wall of the uterus prior to delivery, endangering the mother due to bleeding and the baby due to limited oxygen and nutrient transport (Mayo Clinic, 2020).

Pneumonitis: A condition affecting the lungs that is characterized by tissue irritation and inflammation that impairs oxygen exchange. Pneumonitis can be caused by infectious or noninfectious agents.

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Psychosis: A group of symptoms defined by diminished contact with reality. Individuals with psychosis can have positive symptoms characterized by odd or unusual thoughts, feelings, or behaviors, including the presence of hallucinations, altered perceptions of reality, and disorganized thoughts, speech, and behaviors. Alternatively, an individual with psychosis may experience negative symptoms defined by an absence or loss of normal behaviors and experiences, including impaired emotional responsiveness, poverty of speech, reduced motivation to complete tasks, lack of pleasure, apathy, flat affect, and social withdrawal. (See also the entries for “Altered perception of reality” and “Hallucination.”)

Rhabdomyolysis: The rapid breakdown of skeletal muscle due to injury. Rhabdomyolysis can cause permanent disability and become life threatening without medical intervention.

Sensorium: “The parts of the brain or the mind concerned with the reception and interpretation of sensory stimuli” (Merriam-Webster, n.d.-b). A clear sensorium suggests that an individual has a reasonably accurate memory and demonstrates appropriate orientation to person, place, and time.

Status epilepticus: A type of seizure with a specific duration (i.e., lasts longer than 5 minutes) or frequency (i.e., having more than one seizure within a 5-minute period, without returning to a normal level of consciousness between episodes; Johns Hopkins University, n.d.-a).

Stereotypy: Persistent, repetitive acts (e.g., body rocking, hand waving, or working through an elaborate process, such as disassembling and reassembling radios or other small gadgets) that seem to offer some relief from agitation and anxiety.

Tachycardia: An elevated resting heart rate, generally greater than 100 beats per minute for adults. In children and adolescents, the threshold for tachycardia varies with age.

Thrombotic microangiopathy: The formation of microscopic blood clots in the small blood vessels that can cause the breakdown of red blood cells, low platelet levels, and organ dysfunction, most commonly affecting the brain and the kidneys (Johns Hopkins University, n.d.-b).

Thyrotoxicosis: The presence of excessive concentrations of thyroid hormones in the body, which can increase metabolic function at the cellular level. Thyrotoxicosis is characterized by systematic alterations, including increased heart rate, sweating, anxiety, shakiness, weight loss, increased appetite, heart palpitations, heat intolerance, and difficulty relaxing (A. Sharma & Stan, 2019).

Tonic-clonic: A term used to refer to the type of seizure in which there is stiffening of the muscles (tonic) followed by rhythmic twitching or jerking of the muscles (clonic).

Urticaria: Also known as hives, urticaria is a skin reaction characterized by red, swollen, itchy bumps.

Valsalva maneuver: A breathing technique in which an individual tries to blow air (exhale as if one were inflating a balloon) while the airways are blocked (i.e., pinching the nose and closing the mouth). The technique is primarily used to restore heart rhythm when the heart is beating too fast or to diagnose a disorder of the autonomic nervous system. People who take cocaine sometimes perform this intentionally to increase the drug’s absorption and increase its effects.

Vasculature: The arrangement of blood vessels in organs within the body.

Vasoconstriction: A narrowing of blood vessels that reduces blood flow and causes increases in blood pressure.

Vasospasm: An acute or subacute contraction (spasm) of an artery that limits blood flow and reduces oxygen transport with the potential to cause ischemia and end-organ damage.

Toxicity, Addiction, and Other Adverse Reactions

Cocaine use impairs central and peripheral nervous system presynaptic nerve uptake of catecholamines, which increases catecholamine circulation (Bachi et al., 2017) and leads to impairment in the regulation of dopaminergic systems (Verma, 2015). The increased availability of extracellular dopamine as a result of cocaine exposure in the brain's reward centers is hypothesized to at least partially account for the drug's strong addiction potential and euphoric effects (Verma, 2015). This pattern is also seen in MA use, as MA both blocks dopamine reuptake and increases dopamine release (National Institute on Drug Abuse [NIDA], 2019b). Meta-analyses indicate a larger and more consistent dysregulation of dopaminergic systems with MA exposure than with cocaine (Ashok et al., 2017). The two common forms of prescription stimulants—methylphenidate and amphetamine—affect the dopamine system differently, but, like cocaine and MA, both increase extracellular dopamine. Methylphenidate primarily inhibits the reuptake of dopamine, whereas amphetamine both inhibits dopamine reuptake and also increases the amount of dopamine in the synapse (Yanofski, 2011).

The precise clinical effects of cocaine, MA, and prescription stimulants depend on a complex mixture of the pharmacologic properties and purity of the drug used; the dose, frequency of use, and route of drug administration; the person's state of intoxication or withdrawal and previous experience with the drug; the context in which the drug is used; and other concomitant medical and psychiatric factors, including simultaneous use of other substances, as well as personality attributes and expectations regarding drug reactions. All of these factors not only mediate drug effects, but also influence the person's susceptibility to an SUD and are an important part of screening and history taking (American Society of Addiction Medicine, 2015a).

Route of Administration

The method by which stimulants are taken—the route of administration—determines the dosage and the rapidity and intensity of effects. Route of administration also affects the potential for adverse reactions and the likelihood of developing an SUD. The principal routes for cocaine and MA use are oral ingestion, nasal insufflation (snorting), intravenous injection, and inhalation of smoke vapors (smoking/inhalation). These stimulants can also be taken vaginally, rectally, or sublingually. When taken as prescribed, prescription stimulants are taken orally. But when misused, they can be taken orally or by snorting, smoking, or injecting.

In general, smoking and intravenous use rapidly evoke similarly intense responses, whereas oral ingestion and intranasal administration are slower delivery mechanisms, causing lower and more gradually rising blood levels and less intense subjective responses. The fact that cocaine is seldom taken orally may be attributed to the reduced systemic bioavailability with this route of administration (Coe et al., 2018).

Smoking crack cocaine rapidly delivers a highly concentrated dose to the brain. As the efficiency of the delivery system increases, so does the intensity of both the pleasurable and the adverse effects. Subjective reports from people who smoke cocaine suggest that this route of administration delivers a more intense experience than do the intranasal or intravenous routes (Kiluk et al., 2013). Exhibit 3.2 depicts these general variations in response times according to the different routes of administration for cocaine, MA, and prescription stimulants.



EXHIBIT 3.2. Effects of Route of Use for Cocaine, Methamphetamine, and Prescription Stimulants

ROUTE OF USE*	FORM OF DRUG	ONSET OF ACTION FOR COCAINE, MA, AND PRESCRIPTION STIMULANTS	DURATION OF SUBSTANCE EFFECTS
Oral	Powder/ pill	Approximately 30 minutes for cocaine; 15 to 20 minutes for MA; 30 to 45 minutes for both amphetamine and methylphenidate	45 to 90 minutes for cocaine; 6 to 12 hours for MA, but can continue for up to 24 hours for large doses (peak concentration 3 to 6 hours); depending on brand, 4 to 6 hours for short-acting formulations of prescription amphetamine and 8 to 14 hours for long-acting [extended-release] formulations; depending on brand, 4 hours for short-acting prescription methylphenidate and 7 to 12 hours for long-acting formulations
Intranasal	Powder	Within 3 minutes for cocaine; 3 to 5 minutes for MA	15 to 30 minutes for cocaine; 5 to 15 minutes (peak concentration) for MA
Intravenous	Solution	Within 5 to 15 minutes for cocaine and MA	10 to 20 minutes for cocaine; 4 to 6 hours for MA
Inhalation	Crystalline solid	8 to 12 seconds for crack cocaine; within minutes for MA	2 to 20 minutes for crack cocaine; up to 8 to 12 hours for MA

**Limited information is available on the pharmacokinetics of methylphenidate and amphetamine when used intranasally or intravenously or when inhaled.*

Sources: Ballester et al. (2017); Cruickshank & Dyer (2009); Drug Enforcement Administration, Diversion Control Division (2019a); Hodgkins et al. (2012); National Center for Biotechnology Information (2021); NIDA (2016a, 2019b); Reddy et al. (2020); Steingard et al. (2019).

To some extent, the dangerous consequences and addictive potential of stimulants also reflect the route of drug administration. Routes that facilitate more rapid drug delivery are more strongly linked to addiction and worse severity of addiction (Allain et al., 2015). Inhalation and intravenous injection of cocaine or MA are more strongly linked to addiction than oral, intranasal, and transdermal routes and in some cases are also linked to other harms, such as increased risk of overdose and more frequent drug use (Allain et al., 2015).

Intravenous use produces the greatest effect with the greatest risk for negative side effects compared to intranasal or oral routes. Inhalation is generally perceived as a quick form of drug delivery, producing the highest peak blood levels and the most potent subjective impact without attendant hazards from syringe needle use (Cruickshank & Dyer, 2009; Kiluk et al., 2013; National Center for Biotechnology Information [NCBI], 2021; NIDA, 2019b; Reddy et al., 2020).

Different routes of drug use also produce different side effects. People who engage in intravenous drug use can develop illnesses associated with the preparation of drugs for use (i.e., mixing/making) and the use or sharing of unsterile needles, including HIV and hepatitis B and C, loss of vein functioning (venous sclerosis) and vein scarring, the formation of blood clots within veins, and skin and soft tissue infections (Allain et al., 2015; Al-Tayyib et al., 2017; Ciccarone & Harris, 2015; Hart et al., 2014; Raiker et al., 2016). Infections introduced into the bloodstream by contaminated needles can travel via the circulatory system to any end organ, including the kidneys, brain, liver, bone, and lungs. Nasal insufflation is associated with sinusitis, loss of sense of smell, congestion, atrophy of nasal mucosa, nosebleeds, perforation or necrosis of the nasal septum, hoarseness, and problems with swallowing (Center for Integrated Healthcare, 2013; Nassar & Ouanounou, 2020). Compared with inhalation, nasal insufflation of cocaine has also been linked to longer duration of outpatient treatment, better cocaine treatment-related outcomes, and less cocaine use posttreatment (Kiluk et al., 2013).

People who use MA may recognize these route-related effects in general and may vary the routes

of administration because of specific adverse effects. For example, someone may choose to insufflate or inject MA because of irritation that it potentially causes to the lungs, or people may choose to smoke to avoid the risks associated with injection use (McCarthy & McClain, 2019).

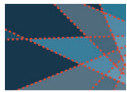
Differences Between Cocaine, Methamphetamine, and Prescription Stimulants

The major differences between cocaine, MA, and prescription stimulants pertain to the rapidity of responses and the duration of their effects (Exhibit 3.3). The sought-after effects of MA can persist for hours, whereas those from cocaine are over in minutes. Effects of prescription stimulants vary by formulation (i.e., short acting versus long acting). This has important consequences for the choice of drug and the patterns of administration adopted by individuals. The plasma concentration level refers to the amount of a drug in the plasma component of a sample of blood. Plasma concentration levels are an indicator of drug concentration (i.e., the concentration of the drug at a cell's receptor), which is important for understanding its pharmacologic effect or toxicity.

EXHIBIT 3.3. Differences Between Cocaine, Methamphetamine, and Prescription Stimulants

COCAINE	MA	PRESCRIPTION STIMULANTS
<ul style="list-style-type: none"> Plant derived Smoking produces a high that lasts up to 20 minutes; snorting produces a high that lasts 15 to 30 minutes 50 percent is eliminated from the body in 1 hour Limited medical use; used as a local anesthetic in some surgical procedures 	<ul style="list-style-type: none"> Synthetic Smoking produces a long-lasting high, about 8 to 12 hours Approximately 50 percent is excreted in the urine within 12 hours Limited medical use (e.g., attention deficit hyperactivity disorder [ADHD], narcolepsy, and weight loss) 	<ul style="list-style-type: none"> Synthetic Depending on brand, short-acting amphetamine produces an effect of about 4 to 6 hours and short-acting methylphenidate produces an effect of about 4 hours; depending on brand, long-acting amphetamine produces an effect of about 8 to 14 hours and long-acting methylphenidate produces an effect of about 7 to 12 hours 50 percent of short-acting methylphenidate is eliminated in about 3 hours, and 50 percent of short-acting amphetamine is eliminated in about 7 hours; elimination of amphetamines is highly dependent on urine pH Food and Drug Administration approved for medical use (e.g., ADHD, narcolepsy)

Sources: Courtney & Ray (2014); Hodgkins et al. (2012); NIDA (2019b, 2021b).



The plasma concentration levels of cocaine peak and decline rapidly, with a half-life of about 60 minutes (Coe et al., 2018). MA plasma concentration levels also peak rapidly but remain high for much longer, with a half-life of about 10 hours across routes of administration (Cruickshank & Dyer, 2009). Typically, the half-life of cocaine is about 60 minutes but can range from 40 to 90 minutes (ARUP Laboratories, 2019). The plasma concentration levels from smoked cocaine both peak and decline rapidly, whereas those from smoked MA also peak relatively rapidly but decline more slowly because metabolism takes longer. Regular repeated use may be more common among people who use cocaine in an attempt to sustain the drug's effects.

The half-lives and peak plasma concentrations of prescription stimulants vary by type (e.g., amphetamine and methylphenidate), brand, and formulation (e.g., short acting and long acting). Time to peak concentration for short-acting formulations of amphetamine ranges from about 2 to 3 hours; for long-acting formulations, it ranges from about 4 to 8 hours (Markowitz & Patrick, 2017). Time to peak concentration for methylphenidate is about 1 to 2 hours for short-acting formulations and about 3 to 6 hours for long-acting formulations (Mariotti et al., 2013). The misuse of long-acting methylphenidate by injecting or snorting can lead to a more rapid peak concentration level (Spiller et al., 2013).

Other factors in the preference for smokable forms of cocaine and MA include availability and price. Crack is generally less expensive and more available than powdered cocaine hydrochloride and produces, in the initial smoker, a very intense but brief rush (Drug Enforcement Administration, Diversion Control Division, 2019a). Because crystalline MA costs less per dose than other forms of MA and because the euphoria attained may persist for several hours, this form of MA delivery may be preferred. Because potential for addiction increases as time before onset of action decreases, concern about increased use of cocaine and MA pertains both to the smokable crystalline preparations and to continuing intravenous use of these drugs.

Dose

The incidence and severity of stimulant-induced side effects and overdose potential are also dose related. As the dose increases, the profile of side effects progresses from mild excitement to more intense reactions (NIDA, 2016a). Because tolerance develops rapidly to the desired euphoric effects, people using stimulants nearly always escalate dose size and frequency of drug use in pursuit of the vanishing rush. Compared with oral or intranasal routes, intravenous or inhalation use promises more rapid response rates and peak plasma concentration levels (Cruickshank & Dyer, 2009; NIDA, 2016a). People using stimulants may often change their route of use, dose, and frequency of use to achieve the desired effect (NIDA, 2019b).

Dosing patterns of MA vary by individual and pattern of use and can range broadly from 50 mg to 2,000 mg per day (Cunha-Oliveira et al., 2013). People with chronic MA use may binge in doses up to 5,000 mg per day (Cunha-Oliveira et al., 2013). Low-to-moderate doses of MA that range from 5 to 30 mg can induce arousal, euphoric mood, cardiac stimulation, and acute improvements in attention and psychomotor skills (Cruickshank & Dyer, 2009). High doses of MA (50 mg and up) can lead to psychosis (Cruickshank & Dyer, 2009).

A lethal dose of cocaine has been estimated to be around 50 mg, with documented cases of individuals having died after taking as little as 20 mg (NCBI, 2021). In low doses, cocaine can result in euphoria and agitation (NCBI, 2021). Large doses can lead to cardiovascular and respiratory dysfunctions, including hyperthermia, arrhythmias (irregular heartbeat), high blood pressure, and possibly death (NCBI, 2021; NIDA, 2016a). However, different routes of use may lead to higher concentrations in the blood, indicating a greater effect and greater potential for overdose.

Maximum doses of prescription stimulants depend on the age of the patient (i.e., child, adolescent, adult up to age 65, and older adult), the type of medication (methylphenidate or amphetamine), and the medication brand (PDR Network, n.d.). Severe tissue damage and necrosis can occur with intravascular injection, especially accidental

intra-arterial injection (Bruggisser et al., 2011). Ingestion of oral doses in mass quantities (e.g., approximately 3,000 mg) has been reported and can lead to death (Cantrell et al., 2014). Overdose of amphetamine is common and contributes to significant morbidity but is less fatal than other drugs (Spiller et al., 2013). The dosage leading to overdose depends on the patient's individual tolerance to amphetamine.

Purity of the Drug

The purity of the stimulant used also influences the rate and completeness of its absorption and effects. The purer the drug, the greater the effects. Illicit drugs, however, are seldom entirely pure. High drug purity is a public health and public policy concern that may be connected to overdose, overdose fatalities, and healthcare resource use (e.g., ED visits). In 2018, the average purity of wholesale cocaine analyzed by the Drug Enforcement Administration's (DEA) Cocaine Signature Program was 85 percent (DEA, 2019). That same year, the average purity of MA was 90 percent (DEA, 2019).

Adulterants are added to cocaine to increase its weight by cutting or substituting less expensive but similar-tasting and -acting products that will maximize profits for the seller while still satisfying the consumer. Of cocaine seized and tested by the DEA Cocaine Signature Program in 2018, 80 percent was unadulterated—an almost 36-percent increase from 2017 (DEA, 2019). Of the remainder, 17 percent was adulterated with levamisole (a veterinary drug that is not commercially available in the United States) and/or levamisole mixtures with dexamisole, and 3 percent was mixed with various other cutting agents (DEA, 2019).

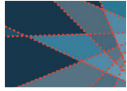
A growing trend has been documented in the United States of adulterating cocaine (and to an extent MA) with fentanyl and fentanyl derivatives (e.g., acetyl fentanyl, carfentanil, furanyl fentanyl, 4-fluoroisobutyrfentanyl). From 2016 to 2017, DEA found such substances in more than 180 seized cocaine exhibits from the State of Florida. The most common adulterant of these was carfentanil, which is 10,000 times stronger than morphine (DEA, 2018). MA–fentanyl mixtures have been on

the rise since 2015 and account for 2 percent of all reports on MA from DEA and the National Forensic Laboratory Information System (DEA, 2019).

From 2013 to 2018, the number of MA-positive urine drug tests also testing positive for fentanyl increased by 798 percent, and cocaine-positive urine drug screens that also tested positive for fentanyl increased by 1,850 percent (Han et al., 2019). These combinations increase the risk of opioid overdose, as patients may not be aware that the stimulant they are taking is laced with an opioid. From January to June 2019, 32 percent of all drug overdose deaths in 24 states and the District of Columbia involved an opioid–stimulant combination, and of those combination overdose deaths, 80 percent involved illegally manufactured fentanyl (O'Donnell et al., 2020). This underscores the importance of providing people who use stimulants access to and education about naloxone (the opioid overdose reversal drug).

The manufacturing processes for illicit MA can be crude and involve many impurities and contaminants that pose serious health consequences. Until recently, most of the MA in the United States was manufactured from phenyl-2-propanone (P2P), a method of synthesis in which lead acetate is used as a chemical reagent. Production using ephedrine or pseudoephedrine as the precursor became popular in the 1990s but has decreased in popularity somewhat as access to over-the-counter pseudoephedrine has become more tightly controlled under the Combat Methamphetamine Epidemic Act of 2005. The P2P method bypasses the use of ephedrine and pseudoephedrine and yields a highly potent form of MA; consequently, P2P has become the standard production approach. More than 98 percent of MA samples analyzed in the second half of 2018 by the DEA Methamphetamine Profiling Program were manufactured via P2P (DEA, 2019).

In 2014, an alternate P2P method was identified. Termed the nitrostyrene method, it uses benzaldehyde and nitroethane as precursors (DEA, 2019). In the second half of 2018, the older P2P method accounted for 48 percent of P2P production and the newer nitrostyrene method 12 percent (DEA, 2019). DEA has identified an even more recent production method using



phenyl-acetic acid, benzyl chloride, and sodium cyanide (which form an oil called benzylnitrile), but no forensic marker currently exists, and it is unclear currently how widespread these chemical precursors are (DEA, 2019).

Illicit MA is also likely to contain potentially toxic contaminants from unintended reaction byproducts and reagent residuals, as well as processing errors. Many clandestine laboratories are operated by untrained individuals who get instructions from unpublished handwritten sources or through the Internet. As with cocaine, most of the contaminants are intentional fillers used to dilute or cut the product. Some examples of fillers are lactose, lidocaine, procaine, caffeine, quinine, and sodium bicarbonate (Cole et al., 2010). Other impurities in illicit MA can cause dangerous toxic reactions.

Patterns of Use

The effects of stimulant use also reflect the temporal pattern of drug administration and the individual's experience history or chronicity of

use. Some people use stimulants only periodically, although most discover that tolerance builds rapidly to many of the desired effects, particularly euphoria, so increasing doses and increasing frequency are needed to achieve similar effects.

Although serious medical, psychological, and social consequences have followed experimental low-dose use of stimulants, two other patterns of self-administration are of greater concern. The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013) characterizes these as chronic or episodic, with binges occurring intermittently with brief periods of abstinence. An estimated 10 to 15 percent of people who use cocaine develop an SUD (Simon & Kreek, 2016).

Exhibit 3.4 lists the range of physiologic and behavioral symptoms often seen in stimulant intoxication (Paulus & Stewart, 2020; United Nations Office on Drugs and Crime [UNODC], 2019b).

EXHIBIT 3.4. Common Signs and Symptoms of Acute Stimulant Intoxication

PHYSIOLOGIC	PSYCHOLOGICAL/BEHAVIORAL
<ul style="list-style-type: none"> • Dilated pupils • Diaphoresis (profuse sweating)—often with chills • Hypertension • Tachycardia, with or without arrhythmia and chest pain • Decreased cardiac output • Hyperthermia (elevated temperature) • Suppressed appetite, weight loss • Nausea and vomiting • Abnormal body movements • Bruxism • Insomnia • Tremors • Headache (occasionally) 	<ul style="list-style-type: none"> • Euphoria, heightened sense of self • Increased vigor, giddiness, and sense of enhanced mental acuity and performance • Agitation, restlessness, irritability • Increased alertness • Decreased appetite • Increased sexual libido • Poor concentration, although some individuals may report improved concentration • Grandiosity, exaggerated self-esteem, egocentricity • Hypervigilance • Fearlessness • Suspiciousness, psychotic symptoms (e.g., paranoia) • Clear sensorium, not usually disoriented • Emotional lability with potential for violence, perceptions of persecution

Intoxication

The following paragraphs describe the sequence of phases that typically occur in a person as he or she moves from occasional or binge use to daily use and dependence as well as some of the accompanying side effects. Knowledge of these phases can help medical practitioners take a substance use history and understand what effects are likely to accompany a particular stage of acute intoxication, withdrawal, or more chronic use patterns.

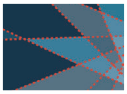
Stimulant use phases

- **Initiation, single-dose phase.** Early use of a single dose of stimulants results in euphoria and increased energy that correspond closely to stimulant plasma concentration levels. Higher levels of euphoria are achieved by inhalation (smoking) or injection routes of administration that evoke a rapid rise to peak drug concentrations. The rush experienced by people who inhale or inject stimulants is profoundly rewarding and reinforcing. Classical conditioning to the cues associated with drug use may occur during this initial phase.
- **Consolidation, dose-frequency escalation phase.** As tolerance develops to the euphoric effects, people tend to increase doses and frequency of stimulant administration in an attempt to recapture the original and most intense sensations. They may also switch the route of use to get a more rapid response. During this phase, intermittent consumption is prolonged with the discovery that higher doses produce greater effects and more frequent doses prolong those effects.
- **Maintenance phase with bingeing.** High-dose and high frequent-use patterns often lead to even more compulsive bingeing over a few hours to days that ceases only when the individual is totally exhausted or the stimulant supply runs out. Binges typically last 12 to 18 hours (but may last 2 to 3 days or longer) for people who use cocaine and much longer—from 3 to 15 days—for people who use MA. The high and sustained plasma concentration levels achieved during binges can have considerable pathological effects. The binge is characterized by frequent mood swings as plasma

concentration levels of the stimulant fluctuate. Stereotypic behaviors and thinking exclude other concerns so that the person focuses exclusively on internal sensations and withdraws from social activities in pursuit of direct pharmacologic effects. Almost all activity is directed to acquiring the drug and consuming it. Also, the settings in which the person consumes drugs become progressively restricted.

“Crash” and withdrawal syndrome phases

- **Acute withdrawal or “the crash” phase.** The timing of withdrawal phases will vary based on the type of stimulant used. Cocaine withdrawal will be shorter in duration than MA (Lerner & Klein, 2019). Withdrawal from MA use can be protracted, lasting several weeks (Courtney & Ray, 2014). Withdrawal syndromes should be thought of as a direct effect of a withdrawal from excessive dopaminergic activity throughout the body. A binge terminates with acute withdrawal, often called a “crash” (Lerner & Klein, 2019). Acute withdrawal is characterized by dysphoria, anxiety, and agitation and can begin a short time after cessation of stimulant use (Lerner & Klein, 2019). Intense cravings during the acute withdrawal phase frequently lead to recurrent substance use (Lerner & Klein, 2019). Individuals may exhibit a repetitive cycle of bingeing, with an intervening crash, over a period of several months. Anxiety and agitation are accompanied by a period of fatigue, increasing depression, and decreased mental and physical energy. An intense desire for sleep, often accompanied by insomnia, usually replaces the drug craving. During this part of the crash, individuals may use “landing gear,” such as alcohol, benzodiazepines, cannabis, or opioids, to induce and prolong sleep. During the acute withdrawal phase, patients may continue to experience psychotic symptoms related to sleeplessness or prolonged stimulant use. Additionally, in the first 1–2 weeks of withdrawal from stimulants, some patients may experience suicidality and should be monitored appropriately (Lerner & Klein, 2019).



- **Postacute withdrawal or “the wall.”** This period is characterized by a profound hypersomnolence, fatigue, mood lability, and increased appetite. People sometimes continue to have cravings during the postacute withdrawal period and return to recurrent use or a repeat binge during this period. The period of postacute withdrawal may extend to 2 weeks or more after the patient’s last use. During the immediate period after the initiation of abstinence, after psychosis subsides, patients often report anxiety or worry about painful memories lingering from the binge, and confusion about which are real and which are imagined. These disturbing events, whether real or imagined, can be traumatizing. Criminal or abusive behaviors that occur during acute intoxication, either real or imagined, can lead to feelings of remorse or dread and can contribute to impulsive self-harm behaviors.
- **Protracted withdrawal.** Following acute withdrawal, the person may experience symptoms that are opposite to those of stimulant intoxication: fatigue, loss of physical and mental energy, depression, anhedonia, and a limited interest in his or her surroundings (Lerner & Klein, 2019). Severity and duration of protracted withdrawal symptoms is often correlated with the duration and severity of stimulant use. As in previous phases of withdrawal, a severe and persisting depression in this phase can result in suicidal ideation or suicide attempts and is a major concern. Anhedonia and dysphoria can last for months in people who use MA (D. Hunt et al., 2006; Rawson, 2013). In the protracted withdrawal phase, periods of drug craving may reemerge or become stronger. These cravings are often triggered by conditioned environmental cues and can only be extinguished by sustained abstinence. Patients may also experience breakthrough psychotic episodes during the protracted withdrawal phase.
- **The post-crash euphoric phase or “the pink cloud.”** During the stage sometimes termed “the pink cloud,” patients enter a euphoric state. This often occurs around the 1-month mark following withdrawal and completion of detoxification, when the brain is overproducing dopamine. Patients may express a sense of positivity and self-confidence (“I am never

going to use drugs again!”). However, this period quickly subsides as the brain begins to underproduce dopamine, and patients typically fall into a depression at the 3- to 6-month mark, when they have a high likelihood of return to use.

Tolerance/Sensitization to Stimulant Effects

People with chronic stimulant use develop tolerance to many of the initial effects, often after only a few weeks of drug use. This means that a higher dose is required to achieve the same effects, or markedly diminished effects are attained if the same dose is continued (APA, 2013). (Note that this is not true of prescription stimulants when taken as prescribed.) Most notably, tolerance develops rapidly to the euphoric effects of stimulants and is the ostensible cause for most dose escalation by people who use stimulants, although dose increases may also stem from a desire to experience more intense effects. Tolerance also develops to the anorectic (appetite-reducing) effects of MA in humans because weight loss stops after several weeks. Tolerance also appears to develop to the cardiotoxic effects of large doses of MA that many people survive. In fact, many of the initial symptoms of stimulant intoxication disappear with chronic use: Blood pressure may be normal, and nausea and vomiting are seldom seen. This tolerance is not the result of increased MA metabolism (Cruickshank & Dyer, 2009).

Interestingly, people with chronic, high-dose stimulant use may also become sensitized to the drug, a unique phenomenon characteristic of psychomotor stimulants. Sensitization is essentially the reverse of tolerance and produces undesirable effects with lower doses of the drug than were required to yield these same reactions in an earlier phase of the addiction process. There appears to be some sensitization to the psychosis-inducing effects of stimulants in humans. After one psychotic episode is experienced following chronic, high-dose use, a lower minimal dose of cocaine or MA may induce another psychotic episode, with more rapid onset following drug intake and a longer duration than the initial psychosis. The sensitization process in stimulant use disorder is elaborated on in the “Stimulant-Induced Psychosis” section in this chapter.

Some researchers suggest that long-term use of stimulant medication may lead to tolerance in some patients and thus the need for patients with ADHD to increase their dosages over time; but it is unclear whether this tolerance and resulting need for more medication occur because of the chemical properties of the medication itself or because of other factors (Yanofski, 2011).

Clinical Manifestations and Medical Management

The intensity and duration of acute manifestations of stimulant intoxication correlate generally with the rate of rise and the height of peak blood levels reflected in brain concentrations. Acute intoxication with stimulants resembles hypomania or a manic state. In low doses, the libido (sexual drive) is stimulated; sexual desire and sexual response are enhanced (Ciccarone, 2011). Agitated states featuring increased paranoia, fear of persecution, or other psychotic symptoms may also occur with intoxication, particularly for MA (UNODC, 2019b). With increasing doses, impaired judgment, hypersexuality, and other atypical behaviors or mental alterations are more likely. Acute stimulant intoxication can result in seizures, confusion, respiratory depression, chest pain, or cardiac arrhythmias (UNODC, 2019b; see Exhibit 3.4).

Distinctive Characteristics of Methamphetamine Intoxication

- MA intoxication may be indicated by an odor of ammonia or stale urine, especially among people who smoke MA that has been crudely synthesized in illicit laboratories. Smoked MA is, however, essentially odorless.
- The person who uses MA may present with tachycardia, which may or may not be accompanied by arrhythmia (Richards & Laurin, 2020).
- People who use MA may present in the ED as a result of trauma from blunt force or penetrating injuries or from motor vehicle accidents (Richards et al., 2017).
- Given MA's longer lasting effects, its use may lead to more frequent mental impairment, more potent central nervous system (CNS) effects, and more overdoses. Chronic use of MA (beyond 2 weeks) is

more hazardous than chronic cocaine use because of MA's sustained effects. Moreover, drug-induced psychoses in people who use MA are likely to last longer than those of people who use cocaine and, in addition, may not respond as readily to available treatments.

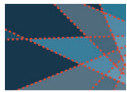
- Stereotyped activity—persistent, repetitive, and compulsive activity such as vacuuming the same part of the floor over and over again, popping knuckles repeatedly, picking at scabs, or taking apart and reassembling mechanical devices—may appear in people who use MA.
- People who chronically use MA will likely experience increased persecutory perceptions/suspiciousness (Alexander et al., 2017).
- Increased social avoidance and disorganization can occur.
- Dilated pupils and rapid eye movement can occur.

Distinctive Characteristics of Cocaine Intoxication

- People who have recently used cocaine may have increased issues with abstract concepts (as measured by problem solving in a card sorting task; Mangado & Madoz-Gúrpide, 2009).
- People who experience cardiovascular effects from cocaine are likely to return to baseline more readily than people using MA (Newton et al., 2005).

Distinctive Characteristics of Prescription Stimulant Intoxication

- Amphetamine intoxication may be less likely to produce cardiovascular problems and seizures than cocaine toxicity. Behavioral and psychiatric symptoms, such as hallucinations and psychosis, are common with amphetamine intoxication (Spiller et al., 2013).
- Rhabdomyolysis (a breakdown of muscle tissue that can release protein into the blood and damage kidneys) can occur with severe amphetamine toxicity and is often preceded by psychomotor agitation, hyperthermia, and seizures (Spiller et al., 2013).
- Distinctive signs of prescription stimulant misuse in college students can include poor psychosocial adjustment, lower academic performance (i.e., grade point average),



co-occurring use of alcohol and drugs (e.g., cannabis), and increased problems with attention (Munro et al., 2017; Rabiner, 2013).

- Behaviors indicative of prescription medication misuse in general that could appear in people with prescription stimulant misuse include stealing, forging (faking), or selling prescriptions; taking more doses than prescribed; repeatedly asking for early refills; continually claiming to have lost one's prescription (and thus needing another one); or "prescription shopping" (trying to obtain multiple prescriptions from multiple doctors; Mayo Clinic, 2018).

Management of Stimulant Intoxication

General measures to manage uncomplicated intoxication are monitoring vital signs for rising pulse rate, temperature, or blood pressure and providing a quiet and cool environment that helps to diminish agitation and overreaction to external stimuli. These measures are continued until symptoms subside, usually after several hours.

Physical exertion and an overheated room can increase the likelihood of adverse effects because stimulants affect the body's heat-regulating mechanism at the same time that blood vessel constriction conserves heat. Although verbal reassurance is usually sufficient for calming the patient, indications that agitation is escalating and moving toward paranoia and potential psychosis, with increasing risk for violence, may warrant talking with the patient about pharmacologic options (e.g., lorazepam or midazolam for severe cases in which rapid control over the patient is needed).

Background on Stimulant Overdose

Because of the rising trend of stimulants being combined with opioids, like fentanyl, risk of overdose should include the risk for both opioid overdose and stimulant overdose (Fleming et al., 2020). Variability in stimulant purity and an unpredictable and unknown relationship to body weight means overdose cannot always be predictable based on the substance used.

The symptoms of a sublethal stimulant overdose may include dizziness, tremor, irritability, confusion, mood lability, hallucinations, panic, headache, skin flushing, chest pain, palpitations, cardiac arrhythmias,

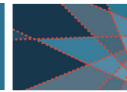
hypertension, vomiting, cramps, and excessive sweating (Richards & Laurin, 2020; Richards & Le, 2020; Vasan & Olango, 2020). High doses of stimulants may cause high fever, cardiac arrhythmias and arrest, irregular breathing, seizures, and stroke (Richards & Laurin, 2020; Richards & Le, 2020; Vasan & Olango, 2020). The development of hyperpyrexia (excessively high fever), severe hypertension, convulsions, and cardiovascular collapse signal a life-threatening situation (UNODC, 2019b). Prescription stimulant overdose is associated with pupil dilation, tremor, agitation, hyperreflexia, combativeness, confusion, hallucinations, delirium, anxiety, paranoia, movement disorders, and seizures (Spiller et al., 2013).

Lethal doses of stimulants produce a predictable sequence of events culminating in generalized convulsions and death. Heart rate, blood pressure, cardiac output, and body temperature rise rapidly, and a delirium is observed before generalized and terminal seizures begin (Mash, 2016; UNODC, 2019b). Overdose is more likely to occur when people have been abstinent for a time rather than when they have been actively and continuously using. They are at the highest risk for overdose when they enter treatment and stop using a substance.

Management of a Potentially Lethal Overdose

People who use stimulants and present with life-threatening medical conditions (e.g., arrhythmias, compromised airways, seizure) and lethal drug levels should be treated with standard life-saving techniques that respond to the presenting symptoms (NIDA, 2018b; Vasan & Olango, 2020). Acute neurologic symptoms, such as seizures or rapidly elevating vital signs, require immediate intervention. Non-drug-induced causes of any symptoms should be carefully ruled out, and the patient should also be evaluated for polysubstance use. Stimulant overdose—as well as acute intoxication and withdrawal—can be managed in hospital settings to help address medical complications and prevent symptoms from increasing in severity (UNODC, 2019b).

Management of prescription stimulant overdose should focus on providing supportive care, including the cautious use of benzodiazepines and—if



agitation, delirium, and movement disorders are unresponsive to benzodiazepines—the possible use of antipsychotics, central alpha-adrenoreceptor agonists, or propofol (Spiller et al., 2013).

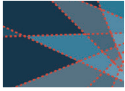
For a stimulant overdose in which opioid involvement is suspected (including fentanyl involvement), administration of the opioid reversal agent naloxone by emergency medical service personnel in the field or in the hospital setting is critical (Chou et al., 2017).

No specific antidotes or antagonists to stimulant overdose are available, unlike naloxone for opioids and the benzodiazepine antagonist flumazenil. However, the following procedures are suggested:

- Request specialist consultations as needed.
- Manage hyperthermia by rapidly cooling the patient with cooling devices or external cooling agents like water misting from convection cooling fans or ice (Richards & Le, 2020). Aggressive sedation and volume replacement may also be indicated.
- Provide adequate ventilation and oxygenation.
- Benzodiazepine therapy is generally sufficient to alleviate cardiovascular symptoms and signs. Otherwise, manage uncontrolled hypertension by administration of phentolamine. Non-dihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) may be used to reduce hypertension but not tachycardia (Richards & Le, 2020). The alpha-blocker phentolamine also may be used to manage hypertension but is not effective for tachycardia (Richards & Le, 2020). Labetalol, a mixed beta/alpha blocker, has demonstrated safety and effectiveness in cocaine-induced hypertension and tachycardia (Agrawal et al., 2015; Richards & Le, 2020) and is approved by an American Heart Association/American College of Cardiology guideline for patients with unstable angina/non-ST elevation myocardial infarction who have used cocaine or MA (J. L. Anderson et al., 2007). Beta-blockers are generally discouraged in the treatment of stimulant-induced hypertension (and particularly for cocaine), although this is an unresolved matter with some guidelines offering mixed advice on their use or avoidance.
- Treat seizures like status epilepticus with intravenous lorazepam or midazolam, preferably starting first with lorazepam (H.-Y. Chen, Albertson, & Olson, 2016). If intravenous access cannot be obtained, intramuscular midazolam can be administered (H.-Y. Chen, Albertson, & Olson, 2016). Barbiturates (typically phenobarbital) are recommended only if patients do not respond to benzodiazepines (H.-Y. Chen, Albertson, & Olson, 2016).
- Complaints of chest pain warrant evaluation for possible myocardial ischemia and infarction. Nitroglycerin is indicated for cocaine-induced myocardial ischemia to alleviate coronary vasoconstriction and for cocaine-induced chest pain (Agrawal et al., 2015). Beta-adrenergic blockers such as propranolol should not be used because they may enhance vasospasm. Aspirin should be administered, unless contraindicated, to reduce cocaine-mediated prothrombotic effects (Agrawal et al., 2015).

Correction of abnormal electrolytes, dehydration, and metabolic dysfunction should lower the risk of isolated arrhythmias. If arrhythmias occur, use standard treatments. Atrial arrhythmias (e.g., atrial fibrillation, atrial flutter) that do not respond to cooling, oxygen, volume resuscitation, and sedation may require the calcium-channel blocker diltiazem as frontline parenteral (i.e., administered by injection, such as intravenous or intramuscular injection) treatment; supplemental magnesium can also be helpful (Farkas, 2021). Cardioversion is unlikely to be successful during acute intoxication. Ventricular tachycardia should be treated with sodium bicarbonate to reverse antagonism of sodium channels; if the arrhythmia is resistant to this and electrical cardioversion, lidocaine is the next choice to terminate the arrhythmia (Farkas, 2021). Also, management of acute psychiatric manifestations of cocaine intoxication by sedation appears to have a beneficial effect on emerging cardiovascular complications.

In general, phenothiazines, especially chlorpromazine, are contraindicated because they may lower the seizure threshold (M. M. Dougherty & Marraffa, 2014). Haloperidol may precipitate or exacerbate acute dystonic reactions associated with recent cocaine use (K. Lewis & O'Day, 2020).



Manifestations of Stimulant Withdrawal/Abstinence

A characteristic withdrawal syndrome usually develops within hours to days after cessation of prolonged and heavy stimulant use. The symptoms can follow long-term use or much shorter binges (Exhibit 3.5).

Some clinicians distinguish between stimulant withdrawal symptoms following a several-day binge and complaints that characterize withdrawal after more chronic high-dose use. People who use stimulants who have binged for 2 to 3 days are dysphoric and exhausted, and they sleep excessively for 24 to 48 hours. To reduce irritability and induce sleep, people may commonly use alcohol, cannabis, benzodiazepines, or opioids with cocaine or MA (often called “landing gear”). Following more chronic and regular stimulant use, severe withdrawal symptoms last several days, with less severe symptoms (e.g., fatigue, depressed mood, anxiety, drug craving, concentration difficulties) lasting 1 to 3 weeks (UNODC, 2019b).

A substantial number of people with chronic cocaine use may have subclinical evidence of withdrawal symptoms. Some people who use cocaine report withdrawal symptoms beginning 1 to 2 days after the last dose, with the crash lasting several days and withdrawal persisting from 1 to 2 weeks, with waxing and waning of the drug

craving, although protracted withdrawal may last longer (Lerner & Klein, 2019). The mood state of the person may return to normal after several days to a month.

For MA, withdrawal symptoms seem to be most severe in the initial days following cessation of use (UNODC, 2019b). There may be some physical manifestations of a withdrawal syndrome when MA use is stopped (e.g., headache, increased or pounding heart rate, sweating, muscle or joint aches; Zorick et al., 2010). Symptoms begin 2 to 4 days after a person stops use and may persist for 2 to 4 weeks (Lerner & Klein, 2019). The patient initially feels depressed and anxious, with an intense craving for MA. This phase is followed by fatigue and sleepiness, possibly mixed with insomnia. Upon awakening after prolonged sleep, the patient may be very hungry and may have persistent anhedonia and dysphoria. Other symptoms include paranoia and agitation (Lerner & Klein, 2019).

Withdrawal from MA can mimic symptoms of depression, which complicates differentiating withdrawal from an independent depressive disorder (Hellem, Lundberg, & Renshaw, 2015).

Research on withdrawal from prescription stimulants is mostly concentrated on adults and suggests that vomiting, headache/migraine, and light sensitivity can occur with abrupt discontinuation or dose reduction

EXHIBIT 3.5. Common Signs and Symptoms of Stimulant Withdrawal/Abstinence Syndrome

PHYSIOLOGIC	PSYCHOLOGICAL/BEHAVIORAL
<ul style="list-style-type: none"> • Weight gain • Dehydration • Fatigue and lassitude, with lack of mental or physical energy • Dulled sensorium • Psychomotor lethargy and retardation—may be preceded by agitation • Hunger • Chills • Insomnia followed by hypersomnia 	<ul style="list-style-type: none"> • Dysphoric mood that may deepen into clinical depression and suicidal ideation • Persistent and intense drug craving • Anxiety and irritability • Impaired memory • Anhedonia (i.e., loss of interest in pleasurable activities) • Interpersonal withdrawal • Intense and vivid drug-related dreams

(Krakowski & Ickowicz, 2018). Other withdrawal symptoms in adults include depression, fatigue, appetite change, and sleep disturbance (Krakowski & Ickowicz, 2018). Symptoms of withdrawal in children are based mostly on case studies and can include symptoms like headache, depression, and a general feeling of malaise (Krakowski & Ickowicz, 2018).

Management of Stimulant Withdrawal

No consistent physiologic disruptions requiring gradual withdrawal have been observed, but some medications may attenuate symptoms and provide support and comfort throughout withdrawal.

The greatest risk during stimulant withdrawal is of doing harm to self. Because withdrawal-related dysphoria and depression can be particularly severe in people using stimulants, risk of suicide is intensified and sensitive management is essential (Lerner & Klein, 2019). Cocaine-induced depression usually dissipates fairly rapidly—in a matter of hours to days. The depression is agitated and often related to actual situations resulting from drug use (e.g., a patient is disturbed that he has spent all his savings on the cocaine binge or that his continuing SUD jeopardizes his interpersonal relationships).

Withdrawal-associated depression/suicidality following high-dose MA use is more prolonged. During the acute phase of withdrawal, the person using high-dose MA may exhibit agitated paranoia, extreme frustration, and the return of intense drug cravings. Suicidal ideation may be high. People in MA withdrawal have been known to become violent if they perceive that they are being persecuted.

Altered perceptions of reality after acute intoxication, particularly in a binge pattern of use, may result in patients perceiving caretakers' gestures and comments as persecutory. Stress reduction techniques and other approaches to prevent harm should be used; medical personnel can also use benzodiazepines (e.g., diazepam) to control agitation and tachycardia (see the section "Aggression and Violence" in this chapter).

For patients with preexisting diagnosed or unrecognized clinical depression, stimulant withdrawal worsens symptomatology. These individuals are most likely to experience deepening dysphoria and/or paranoia after use.

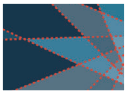
Medication management of withdrawal symptoms has not been well established in major clinical trials but might involve short-term use of sleep medications to manage insomnia or other sleep problems (Wilkerson et al., 2019). Antipsychotics are not recommended for MA withdrawal (Braunwarth et al., 2016).

Continuing agitation and persistent inability to fall asleep during the acute withdrawal stage may also be treated symptomatically by using the antidepressant trazodone, which can help to sedate the patient. Diphenhydramine is also used for its sedating properties and for its effects on the dermatologic problems that often accompany MA use (e.g., itching and hypersensitivity of the skin). However, caution should be exercised in using any medications with high potential for misuse.

During acute withdrawal, the "crash" results in patients who sleep several days at a time, depending on the dose and duration of the binge (Nishino, 2009). This hypersomnolence may interfere with assessment of mental status and physiologic functioning. Patients experiencing hypersomnolence will struggle to meaningfully engage in a treatment program and will need to be reassessed and referred during the postacute withdrawal phase, likely with additional supports.

Drug craving during stimulant withdrawal has been treated with a variety of medications (e.g., stimulant-replacement therapy [Stoops & Rush, 2013]). However, clinical evidence is limited. More research is needed in this area.

"Drug dreams" may occur during this period or as late as 6 months or more after termination of stimulant use during a protracted withdrawal phase (Jiménez-Correa et al., 2020). They usually entail vivid recall of actually using and experiencing the effects of the substance (Yee et al., 2004). The patient may actually sweat and experience other symptoms of intoxication while dreaming. These intense dreams, which may sometimes contain vignettes in which the person loses or drops a supply or refuses to smoke, can be used therapeutically to educate patients on their progress and identify potential triggers to recurrent use (Yee et al., 2004). The dreams may enhance



drug cravings and intensify a vulnerability for recurrent use. These dreams may be especially common in patients who have high ratings of drug craving and suicidality (Yee et al., 2004).

People who use stimulants will frequently self-medicate withdrawal symptoms with alcohol, benzodiazepines, or opioids. Patients may experience symptoms of withdrawal from these other substances if such use was regular or at high doses. These withdrawal symptoms require specific management and may potentially require a medication titration schedule to alleviate symptoms and prevent an acute medical event.

Withdrawal from prescription stimulants can also occur and result in fatigue, depressed mood, and sleep difficulties (NIDA, 2018b). Amphetamine withdrawal is associated with depression, fatigue, sleep problems, agitation, irritability, and concentration difficulties (Harro, 2015). There is limited research on methylphenidate withdrawal, but Food and Drug Administration (FDA)-approved labeling suggests withdrawal can include depressed mood, fatigue, vivid and unpleasant dreams, insomnia, hypersomnia, increased appetite, psychomotor retardation, or psychomotor agitation (see, for example, Novartis Pharmaceuticals, 2019).

SCREENING, BRIEF INTERVENTION, AND REFERRAL TO TREATMENT FOR SUDS: WHAT PRIMARY CARE PROVIDERS NEED TO KNOW

Screening, brief intervention, and referral to treatment (SBIRT) is a highly studied, widely used approach to ensure access to comprehensive care that has demonstrated effectiveness in identifying and treating SUDs (e.g., alcohol use disorder, tobacco use disorder) as well as depression and anxiety (Hargraves et al., 2017). Primary care providers need to be aware of SBIRT and how to implement it in their service settings, because people with stimulant use disorders and other SUDs often first present in primary care settings rather than SUD specialty treatment settings. Also, research suggests that primary care providers do not recognize and treat (or offer referral for) SUDs as often as needed (Pace & Uebelacker, 2018). Using SBIRT can help close these practice gaps.

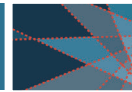
SBIRT for SUDs involves (Hargraves et al., 2017; Pace & Uebelacker, 2018):

- **Quick universal screening** (using validated measures, such as the NIDA Modified Alcohol, Smoking, and Substance Involvement Screening Test) to determine SUD presence. Quick screening often includes items to help **assess level of risk (i.e., low, moderate, or severe)** for patients who screen positive; answers to these items help determine treatment or service needs.
- **A brief motivational intervention** that educates patients about substance use and prescription stimulant misuse and helps increase their motivation for behavior change.
- **Referral to treatment and service providers** for individuals who need specialty services, a higher level of care, or both.

Best practices for primary care providers and clinics wanting to implement SBIRT for SUDs include the following (Hargraves et al., 2017; Pace & Uebelacker, 2018):

- Identify a practice champion or team lead to promote staff buy-in and increase accountability.
- Use a multidisciplinary team of professionals and nonprofessionals, such as administrative staff and information technology experts.
- Determine a screening strategy, such as which SUD screening measures will be used, who will administer them, and how the team will follow up on positive and negative screens. Nursing and intake staff can administer basic screening tools, saving time during the clinical encounter.
- Make sure the team understands the SBIRT components and their individual roles in making SBIRT a success.

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- Cultivate close relationships with referral partners and maintain lines of communication when patients are referred.
- Lay out a process for the brief intervention, such as identifying which team members will conduct the intervention and what key information needs to be conveyed to patients in the short amount of time allotted.
- Implement ongoing SBIRT training so all team members can stay up to date on policies and procedures. This includes providing staff education to reduce stigma associated with drug and alcohol addiction and to help the team understand the scientific evidence in support of SBIRT.
- Make sure SBIRT fits into the natural workflow of the office, and use visual diagrams to ensure that staff understand how and where each step of SBIRT is to take place.
- Leverage electronic health records to enhance the effectiveness of SBIRT; this will help ensure that appointments, billing, screening (e.g., reminders, flags for positive screens), and interventions are implemented, tracked, and monitored. Digital technology, such as tablets and mobile phones, can be used for screening before an appointment or while in the waiting room (Ramsey et al., 2019).
- Implement performance management tools and strategies to identify performance goals and benchmarks, barriers to implementation and positive outcomes, and potential solutions to these barriers. These efforts help organizations ensure continuous quality improvement.

Manifestations of Chronic Stimulant Use

Although fatalities from stimulant overdose or acute myocardial infarction following administration of cocaine by inexperienced people have been documented, and other medical and psychiatric complications have been observed at all dose levels and routes of administration among naïve individuals (i.e., people who previously have not been exposed to the drug), most serious stimulant-induced medical and psychological complications follow chronic, high-dose use. Potentially serious manifestations of chronic stimulant use may also be somewhat sensitive to the environment in which the person resides.

Long-term use can lead to stimulant use disorder, tolerance, and, upon cessation of use, withdrawal (UNODC, 2019b). This is also true for prescription stimulants, which are Schedule II drugs (DEA, Diversion Control Division, n.d.). A wide range of psychological and medical issues can arise with

chronic stimulant exposure, from psychosis to depressive and anxiety disorders to numerous (potentially life-threatening) cardiovascular and respiratory complications (Petit et al., 2012; UNODC, 2019b).

Although the medical consequences of chronic MA and cocaine use differ somewhat, the incidence of such side effects as chest pain, seizures, paranoid reactions, and suicidal thoughts is similar for both substances. Some studies indicate an increased risk of transient ischemic attack and sudden death/ventricular arrhythmia is associated with prescription stimulants, although more research is needed in this area (Westover & Halm, 2012). Exhibit 3.6 summarizes some of the more common symptoms and potentially serious complaints presented by chronic stimulant use or prescription stimulant misuse. Exhibit 3.7 shows the distinctive indicators of chronic MA use, cocaine use, and prescription stimulant misuse.

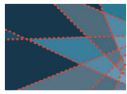
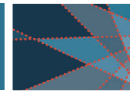


EXHIBIT 3.6. Common Symptoms of Chronic Stimulant Use or Prescription Stimulant Misuse

PHYSIOLOGIC	PSYCHOLOGICAL/ BEHAVIORAL
<ul style="list-style-type: none"> • Extreme fatigue—with physical exhaustion and disrupted sleep patterns • Nutritional disorders—extreme weight loss, anemia, anorexia, cachexia (body wasting) • Poor hygiene and self-care • Skin disorders and secondary skin infections—itching, lesions, hives, urticaria • Hair loss • Muscle pain/tenderness—may indicate rhabdomyolysis • Cardiovascular damage—from lethal doses of the drug and contaminants in MA production, with concomitant renal and hepatic problems • Hypertensive crises with renal damage from sustained hypertension • Difficulty breathing—may reflect pulmonary edema, pneumonitis, obstructive airway disease, barotrauma, and other complications • Myocarditis, infarcts • Headaches, strokes, seizures, vision loss • Choreoathetoid disorders • Impaired sexual performance and reproductive functioning • Cerebrovascular changes, including evidence of cerebral hemorrhages and atrophy with associated cognitive deficits • Ischemic bowel, gastrointestinal complaints 	<ul style="list-style-type: none"> • Paranoia with misinterpretation of environmental cues, psychosis with altered perceptions of reality, and hallucinations • Apprehension—with hopelessness and a fear of impending doom that resembles panic attacks • Depression—with suicidal thinking and behavior • Acute anxiety • Eating disorders • Mental exhaustion

EXHIBIT 3.7. Distinctive Indicators of Chronic Use of Cocaine and Methamphetamine, and Chronic Misuse of Prescription Stimulants

COCAINE	MA	PRESCRIPTION STIMULANTS
<ul style="list-style-type: none"> • Possible physical dependence and tolerance • Nasal perforations and nose bleeds among people who snort cocaine 	<ul style="list-style-type: none"> • Possible physical dependence and tolerance • In adults, increased risk of transient ischemic attack and sudden death due to ventricular arrhythmia • Dental problems, including missing teeth, bleeding and infected gums, cavities • Muscle cramping related to dehydration, with low magnesium and potassium levels • Dermatitis around the mouth from smoking hydrochloride salt • Stale urine smell due to ammonia constituents used in manufacturing MA • Various dermatologic conditions, including excoriated skin lesions 	<ul style="list-style-type: none"> • Possible physical dependence and tolerance • In adults, increased risk of transient ischemic attack and sudden death due to ventricular arrhythmia • Behaviors indicative of prescription drug misuse in general, like stealing, forging (faking), or selling prescriptions; taking more doses than prescribed; repeatedly asking for early refills; continually claiming to have lost one's prescription (and thus needing another one); or trying to obtain multiple prescriptions from multiple doctors (sometimes called "doctor shopping" or "prescription shopping")



Research on methylphenidate-specific misuse is lacking. However, knowing the signs of prescription stimulant misuse in general may be helpful in identifying long-term misuse in patients. Such signs and symptoms can include anxiety, loss of appetite, confusion, depression, irritability, memory problems, psychotic symptoms, and, in students, worsening academic performance (Greydanus, 2006). Additionally, behaviors consistent with prescription drug misuse in general could appear

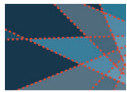
in people with chronic prescription stimulant misuse. These include stealing, forging (faking), or selling prescriptions; taking more doses than prescribed; repeatedly asking for early refills; continually claiming to have lost one's prescription (thus needing another one); or trying to obtain multiple prescriptions from multiple doctors (also sometimes called "doctor shopping" or "prescription shopping"; Mayo Clinic, 2018).

ROLE OF SOCIAL DETERMINANTS OF HEALTH IN MEDICAL COMPLICATIONS OF STIMULANT USE DISORDERS

Nonmedical influencers of health and well-being—termed "social determinants of health" (SDoH)—can play a role in the formation or exacerbation of medical conditions in people with stimulant use disorders. Common SDoH include income, housing status, employment status, education level, and adverse childhood events (like experiencing abuse or poverty as a child).

For instance, a person with cocaine use disorder who does not have access to stable housing and hygienic food preparation may be more vulnerable to contracting hepatitis A virus. Someone with MA use disorder with no job or health insurance who has developed a cardiac arrhythmia may not be able to afford (and thus adhere to) antiarrhythmic medication, which could lead to poorly controlled cardiac symptoms. When assessing patients with stimulant use disorders for possible medical conditions, clinicians should be sure to also assess for the presence of adverse SDoH. Where possible, link patients to professionals and resources that can help them address these challenges, such as mental health service providers, social workers, vocational rehabilitation services, child and family services, and financial assistance programs.

For more information, see the Chapter 6 text box "The Importance of Thinking About Social Determinants of Health" and visit the Centers for Disease Control and Prevention website Social Determinants of Health: Know What Affects Health (<https://www.cdc.gov/socialdeterminants/index.htm>).



Identification and Management of Medical Complications

The following sections briefly describe signs and symptoms of and treatments for common medical complications of stimulant use and prescription stimulant misuse. Certain populations of people with stimulant use disorders may be more likely than others to exhibit some of the medical complications described below (e.g., pregnant women exhibiting issues related to reproduction, pregnancy, childbirth, and the health of the fetus/newborn). Readers are encouraged to reference Chapter 6 for more detailed information about these special populations (i.e., people who engage in intravenous drug use, men who have sex with men, members of the transgender and gender nonconforming community, people in opioid treatment programs, individuals with co-occurring mental illness, people with medical illnesses [e.g., HIV, tuberculosis], people involved with the criminal justice system, racial/ethnic minorities, rural populations, women [including those who are pregnant], adolescents, and people experiencing homelessness/unstable housing) and consider their possible medical complications or other medical effects when developing patient-centered case conceptualizations and treatment plans.

Cardiovascular Effects

Cardiovascular complications are a leading cause of death among people who use MA. Hypertension, aortic dissection, acute coronary syndromes, pulmonary hypertension, and cardiomyopathy (heart muscle dysfunction) are frequently observed (Paratz et al., 2016; Paulus & Stewart, 2020). MA use damages the cardiovascular system via multiple mechanisms, including triggering surges in catecholamine (e.g., dopamine, norepinephrine) release, which cause vasoconstriction; direct toxicity to cardiac and vascular tissue; and inflammation of tissue and vessels (Kevil et al., 2019; Paratz et al., 2016). Hypertension and tachycardia are common and largely attributable to acute catecholamine release (Richards & Laurin, 2020). Vasoconstriction also triggered by catecholamine release can cause acute coronary syndromes and stroke. Damage to cardiac and vascular tissue, such as the endothelial

cells, by molecular mechanisms triggered by MA causes aortic dissection, dilated cardiomyopathy, arrhythmia, and pulmonary hypertension (Kevil et al., 2019). Inflammation triggered by MA contributes to functional and structural changes in the cardiovascular system, such as fibrosis and atherosclerotic plaque formation (Kevil et al., 2019; Paulus & Stewart, 2020).

Cocaine has been linked with many forms of heart disease, including different forms of arrhythmias, hypertension, coronary vasospasm, arteriosclerosis, myocardial infarction, hypertrophic cardiomyopathy, and sudden cardiac death (Kim & Park, 2019). Arteriosclerosis is seen in younger-age individuals who take cocaine, as well as in individuals with co-occurring cardiovascular risk factors (Kim & Park, 2019). Myocardial infarction can occur with both low-dose and high-dose cocaine use (Kim & Park, 2019). Studies on the association between cocaine use and cardiovascular mortality have produced conflicting results (Kim & Park, 2019). This may be due to variations in populations, as well as to study design issues, such as how studies control for other risk factors known to affect cardiovascular mortality, like cigarette smoking and depression. Some research suggests that individual factors may play a strong role in whether a person using cocaine experiences cardiovascular consequences (Kim & Park, 2019).

Life-threatening acute conditions like myocardial infarction and aortic dissection require emergency response to stabilize the patient. Treatment for these and other cardiac conditions, such as heart failure and stroke, should follow consensus-based guidelines from experts in cardiology (Havakuk et al., 2017). Sedation through benzodiazepines is a recommended treatment for cardiotoxicity and agitation (Richards & Le, 2020).

Prescription stimulants have been associated with increased resting heart rate and blood pressure (Torres-Acosta, 2020). In children and adolescents specifically, prescription amphetamine has been linked to increased diastolic and systolic blood pressure and heart rate, whereas methylphenidate in this population has been linked to increased systolic blood pressure (Hennissen et al., 2017). In some cases, prescription stimulants have

also been associated with cardiac arrhythmias, cardiomyopathy, and sudden death (Torres-Acosta, 2020). Adults with long-term use of prescription stimulants have increased risk of transient ischemic attack and sudden death due to ventricular arrhythmia, but children or adolescents with chronic use have not been observed to have increased risk (Westover & Halm, 2012).

Pulmonary Effects

Shortness of breath and chest pain can be either cardiac or pulmonary in origin. Wheezing, coughing, dark or discolored sputum, and hemoptysis (coughing up blood) can be symptoms of acute or chronic lung injury due to cocaine or MA use (Akwe, 2017; McCarthy & McClaine, 2019).

Barotrauma is a complication of cocaine use and also occurs with MA (Guck & Munyon, 2018; Restrepo et al., 2007). Barotrauma is caused by spasmodic or violent coughing following smoke inhalation, or increased airway pressure due to mouth-to-mouth drug delivery or Valsalva maneuver (Akwe, 2017; Kloss et al., 2010). Barotrauma can cause alveolar rupture and the release of air into the chest cavity, the area surrounding the heart, and even the subcutaneous tissues of the chest wall and neck. The amount of free air is usually small and resolves spontaneously under observation. Alveoli can be damaged without associated rupture and air leak. Alveoli can lose structural integrity, resulting in emphysema. Blood vessels can also be damaged causing affected patients to cough up blood and experience bleeding into the lungs (Akwe, 2017; Mégarbane & Chevillard, 2013).

The alveoli, blood vessels, and other lung tissue can be damaged in other ways as well. Mechanisms of injury to the lungs due to stimulant use include the introduction of foreign bodies or contaminants, triggering allergic or other inflammatory immune responses. Pulmonary granulomatosis, excessive bronchial reactivity or bronchospasm, and hypersensitivity pneumonitis are all possible manifestations of these types of lung injury (Akwe, 2017; Mégarbane & Chevillard, 2013). People with asthma are more likely to experience bronchospasm with stimulant use (Akwe, 2017).

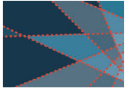
Bronchiolitis and pneumonia are common complications of cocaine use (Akwe, 2017; Restrepo et al., 2007). People who smoke cocaine can experience acute alveolitis (also known as “crack lung”), which presents with severe chest pain, difficulty breathing, and high fever but normal-appearing lung X-rays. Alveolitis requires supportive care and, in some cases, high-dose steroids. Recovery typically takes 2 weeks, but the patient may experience long-term respiratory effects (Mégarbane & Chevillard, 2013).

MA has been classified as a “likely” risk factor for pulmonary arterial hypertension—a potentially fatal condition—with the amphetamine derivatives fenfluramine and benfluorex classified as “definite” risk factors (Ramirez et al., 2018a). However, only certain subsets of people who use MA appear to develop the disease, raising questions about whether individual genetic factors confer additional risk (Ramirez et al., 2018a). One study of California hospital discharges from 2005 to 2011 showed an association with MA and both pneumonia and acute respiratory failure (H. Tsai et al., 2019). Use of amphetamine-containing diet pills has resulted in pulmonary arterial hypertension (Garg et al., 2017).

Research on amphetamine derivatives in prescription stimulants and their association with pulmonary arterial hypertension is not readily available, although at least one case report of methylphenidate-related pulmonary arterial hypertension (which subsided after treatment was ended) has been published (Ramirez et al., 2018b).

Cerebrovascular Effects

Medical consequences of stimulant use are produced in the cerebrovascular system through vascular, neuroexcitatory, and neurotoxic mechanisms. Neurologic effects of cocaine use are wide ranging and include seizures, cerebral ischemia, cerebral hemorrhages, infarction, cerebral atrophy, cognitive impairment, and mood and movement disorders (Cunha-Oliveira et al., 2014). Systemic hypertension can trigger stroke and hemorrhage within the brain tissue or between the brain and the protective layers around it. Two of the most catastrophic acute consequences of unhealthy stimulant use are damage to the blood vessels in the brain and vasospasm. MA



use has been linked to increased occurrence of hemorrhagic stroke in people younger than age 45 (Lappin et al., 2017). Damage to the heart can cause inadequate perfusion of the brain, resulting in hypoxic brain injury and subsequent edema, which can also cause lasting impairment after resolution of the acute injury (Ciccarone, 2011). Headache associated with cocaine use is also triggered by vasoconstriction or inflammation of cerebral vasculature (Farooque et al., 2020).

Seizures are a well-known complication of stimulant use (Klega & Keehbauch, 2018) triggered by neuroexcitation. Seizures triggered by cocaine tend to be short tonic-clonic events that stop without intervention and have no residual effects, but repeat seizures are typically managed with intravenous benzodiazepines. Seizures that don't stop on their own should be managed according to standard protocols for status epilepticus. Focal seizures should trigger an evaluation for stroke or hemorrhage (Zimmerman, 2012).

Neuroexcitation can also cause movement disorders and dystonia (Asser & Taba, 2015). Movement disorders consist of repetitive behaviors. Dystonia is the involuntary contraction of muscles in the face, neck, limbs, or other body parts. Dystonia can be painful and distressing (Ciccarone, 2011). Symptoms of these disorders typically resolve within a few days of discontinuation of stimulant use, but movement disorders or psychomotor disturbances, like tics and problems with gait and fine motor skills, have been seen in people who use MA and may persist even after a year or more of abstinence (Lappin et al., 2018). Benzodiazepines or neuroleptics may be used to manage acute, distressing, or persistent symptoms that impair function (Asser & Taba, 2015). More data are needed regarding the long-term management of patients with persistent movement disorders secondary to stimulant use.

Evidence from a small number of animal and human studies suggests that MA use may moderately increase the risk of developing Parkinson's disease or parkinsonism, including possibly causing premature onset of Parkinson's disease—especially when other risk factors are present (e.g., comorbid HIV infection, male gender;

Lappin et al., 2018). The potential increased risk of Parkinson's disease specifically has not been observed among people taking cocaine (Lappin et al., 2018).

Acquired brain injury is another mechanism contributing to the cerebrovascular consequences of stimulant use. Cocaine induces lesions and atrophy, mostly in the prefrontal cortex and basal ganglia (Cunha-Oliveira et al., 2014). MA is known to induce damage to dopamine and serotonin axon terminals in the striatum, prefrontal cortex, and hippocampus (Halpin et al., 2014). Cocaine and MA use have both been associated with deficits in executive functioning (decision making) and processing speed, often due to problems with perseveration, inattention, and working memory difficulties (Hall et al., 2018). Cocaine use has been linked to worse verbal working memory than MA, whereas MA has been associated with poorer delayed contextual verbal memory and delayed visual memory than cocaine (Hall et al., 2018). Cognitive deficits observed in cocaine and MA use are also seen in brain aging and dementia and may indicate premature brain aging, possibly due to cerebral atrophy resulting from direct effect of stimulants or hypoxic brain injury in people with stimulant use disorders.

Simultaneous alcohol and cocaine use produces cocaethylene, the ethyl ester of benzoylecgonine, and is also being researched further (A. W. Jones, 2019). (For more on the hazards of combining these two substances, see the "Polysubstance Use" section later in this chapter.) Another unresolved issue is whether stimulants are causal factors in CNS vasculitis; however, CNS vasculitis induced by MA or cocaine use is rare (Younger, 2019). People who have taken cocaine or MA and complain of sudden headache should be evaluated for possible intracranial hemorrhage (Farooque et al., 2020).

Case reports of current or past history of cocaine use have found an association with corneal or retinal nerve damage (Friedman et al., 2010; Stuard et al., 2017), and in some instances the damage may be similar to optic nerve damage found in people with diabetes (Stuard et al., 2017).

Although amphetamine-type substances have been hypothesized to increase the risk of stroke, a literature review of stroke incidence associated with prescription stimulant use found very little research on the subject and noted the need for additional, more robust research (Indave et al., 2018). Additionally, some studies have indicated long-term use of prescription stimulants might increase the risk of transient ischemic attack, but, again, more research is needed to reach firm conclusions (Westover & Halm, 2012).

People with ADHD are at an increased risk for seizures, but current evidence strongly suggests this is not due to stimulant medication (Wiggs et al., 2018). In an analysis of more than 800,000 insurance claims, ADHD medication use was associated with lower odds of seizure (Wiggs et al., 2018).

Muscular and Renal Toxicity

Cocaine and MA may directly cause muscle degradation, and acute rhabdomyolysis has been diagnosed in people who did not have any of the previously associated risk factors (i.e., hyperthermia, agitation, seizures, hypotension, toxic delirium or coma, acute renal failure [A.D.A.M. Medical Encyclopedia, 2021; Lannett, 2020]). Muscle necrosis may occur regardless of the route of drug administration, and the presence of rhabdomyolysis should be considered in patients with stimulant intoxication, particularly those presenting with myalgia, lower back pain, or muscle tenderness.

Cocaine is known to induce acute kidney injury, possibly through rhabdomyolysis, vasculitis, infarction, thrombotic microangiopathy, or severe hypertension (Goel et al., 2014; Pendergraft et al., 2014; Zimmerman, 2012). In the Healthy Aging in Neighborhoods of Diversity across the Life Span study (Novick et al., 2016), lifetime cocaine use was significantly associated with reduced renal functioning as measured by albumin-to-creatinine ratio (odds ratio = 1.8) and estimated glomerular filtration rate (odds ratio = 1.4). MA is associated with acute kidney injury, hyponatremia, and nontraumatic rhabdomyolysis (Pendergraft et al., 2014). Patients with stimulant use disorders should be encouraged to hydrate and take rest periods to minimize the risk of the development of renal toxicity/rhabdomyolysis.

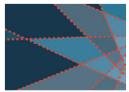
Gastrointestinal Effects

Some people who use stimulants experience abdominal pain, nausea, and vomiting, potentially indicating intestinal ischemia caused by vasospasm in the intestinal blood supply. Intestinal ischemia can lead to death of bowel tissue. Severe bowel infarction due to stimulant use has been reported (J. E. Anderson, Brown, et al., 2018; Attaran, 2017; Choi et al., 2019). Severe bowel infarction causes bleeding, elevated white blood cell counts, and metabolic acidosis, and can lead to shock and death. Even in the absence of infarction, intestinal ischemia associated with cocaine use may carry a higher risk of death compared with intestinal ischemia not caused by cocaine use. In one study, the prevalence of in-hospital death was 26 percent among people with cocaine-related intestinal ischemia versus 7.7 percent with non-cocaine-related intestinal ischemia (Elramah et al., 2012). Obstruction, perforation, and infarction are associated with cocaine use by any route of administration (Zimmerman, 2012). Although less common, gastrointestinal hemorrhage and pancreatitis can also occur from cocaine use (Carlin et al., 2014).

Reduced appetite is one of the most common adverse effects of prescription stimulants, with stomach ache, abdominal pain, dyspepsia, and weight loss also occurring (Cortese et al., 2015; Holmskov et al., 2017; Storebø et al., 2015).

Infections

As already noted, intravenous injection of cocaine or MA is associated with a variety of infectious diseases. Intravenous injection is not the most common method of misusing prescription stimulants, but it can and does occur. Individuals who inject prescription stimulants are at risk for the same injection-related infections as people who inject cocaine or MA. People engaging in injection drug use are at increased risk of infectious endocarditis, which accounts for 5 to 25 percent of hospitalizations for acute infection among people who inject drugs (Visconti et al., 2019). Increased HIV and hepatitis B and C transmission are likely consequences of stimulant use, particularly in individuals who inject intravenously and share equipment. HIV and other blood-borne pathogens may spread through communities of people



injecting drugs via shared injection equipment or unprotected sex. People who injected drugs accounted for 9 percent of all new cases of HIV diagnosed in 2017 (Centers for Disease Control and Prevention, 2021b). MA or cocaine use in the presence of HIV or hepatitis C virus can accelerate virus replication and impaired immunity, resulting in overall disease progression (NIDA, 2016c; Soontornniyomkij et al., 2016).

MA is also implicated in a host of infectious diseases, such as skin infections (cellulitis, skin abscesses), methicillin-resistant *Staphylococcus aureus* (MRSA), sexually transmitted infections, and opportunistic fungi (e.g., *Histoplasma capsulatum*; Salamanca et al., 2015). High-risk sexual behaviors, malnutrition, harmful effects of MA on immune system functioning, and inflammation likely contribute to infectious disease risk.

Cocaine use carries a significant increased risk of sexually transmitted infections such as syphilis, trichomoniasis, hepatitis C, HIV, and human papillomavirus and associated complications such as precancerous cervical abnormalities and pelvic inflammatory disease, and invasive pneumococcal disease. Tuberculosis, bronchitis, pneumonia, injection site infections, and MRSA infection are all also more common among people who use cocaine (Butler et al., 2017).

Improved access to treatment of HIV infection and prevention efforts can help address the elevated risk of HIV infection among people who use stimulants. Prevention of HIV infection may include screening and diagnosis of other bacterial or viral sexually transmitted infections, access to nonoccupational postexposure prophylaxis, and pre-exposure prophylaxis (PrEP; Nerlander et al., 2018; UNODC, 2019a; Workowski & Bolan, 2015). Given the multimodal risk factors for acquisition, including injection drug use and sexual transmission, the current recommendation for PrEP should be the use of tenofovir disoproxil fumarate with emtricitabine (Mayer et al., 2017). FDA also approved emtricitabine with tenofovir alafenamide for PrEP in individuals having nonvaginal sex (FDA, 2019). Multiple studies support the treatment of HIV as a prevention modality in patients using stimulants (Nerlander et al., 2018; UNODC, 2019a),

as even imperfect medication adherence may result in viral suppression and decrease the likelihood of transmission.

Reluctance to get tested for HIV and fear of being stigmatized by healthcare personnel may result in delays of HIV diagnosis (UNODC, 2019a). Patients with MA use in particular may have a lower CD4 nadir and may meet the criteria for an AIDS diagnosis within 6 months of HIV diagnosis. Frequent low-barrier testing and immediate access to antiretroviral therapy may improve overall outcomes for patients with co-occurring HIV and stimulant disorder (UNODC, 2019a).

Hypersexuality and lowered inhibitions for patients who use stimulants should warrant a comprehensive sexual health screen. Regardless of the patient's identified sexual orientation it may be prudent to offer multisite (i.e., vaginal, rectal, penile, pharyngeal) sexually transmitted infection testing to identify and treat bacterial infections early (UNODC, 2019a). Patients engaging in sexual activities with elevated risk for sexually transmitted infection should be screened for chlamydia, gonorrhea, and syphilis at least every 3 to 6 months or more frequently depending on their individual risk (Workowski & Bolan, 2015).

Harm reduction strategies related to skin and soft tissue infections should focus on the processes for injection that require sterile technique and should identify substances that may produce increased risks for infection (Saldana et al., 2020). Providing access to items to cleanse the skin prior to injection, safer injection techniques, and postinjection care are all important aspects of preventing skin and soft tissue infections (Hartnett et al., 2019; Saldana et al., 2020). Furthermore, for patients injecting crack cocaine who require an acid pairing to neutralize the base pair for injection, education should be provided regarding safer acid pairings, like ascorbic acid (British Columbia Center for Disease Control, 2011). Increased fungal infections, including endophthalmitis, have been well described in patients who have used natural acids like lemon juice to neutralize the base for injection (British Columbia Center for Disease Control, 2011).

For patients engaging in vaginal or anal consumption of stimulants, there is an elevated risk for toxicity and in some cases overdose or death (P. Jones et al., 2014). Patients using MA intravaginally or intrarectally should be educated on safety procedures to avoid tearing of rectal or vaginal tissues that may result in fissure or other microscopic tearing. Dissolution of the crystalline substrate is imperative to reduce the risk of microtears and associated acquisition of sexually transmitted infections.

Hepatotoxicity is a rare side effect of methylphenidate, but liver values should still be monitored throughout treatment (Tong et al., 2015). A review of the literature reveals few cases of methylphenidate-induced liver damage, and cases that do exist were generally mild in severity and resolved with discontinuation of methylphenidate (Tong et al., 2015).

Effects on Reproductive Function and on Fetus/Newborn

Chronic, high-dose stimulant use can affect reproductive and sexual functioning in both males and females. Men report gynecomastia (development of breasts), loss of sexual interest, impotence, and difficulty in maintaining an erection or ejaculating (Del Río et al., 2015; Longheu et al., 2016). Long-term stimulant use can lead to menstrual cycle irregularity (Shen et al., 2014). This may lead some women to believe they cannot become pregnant, which may not be true. Testing for pregnancy and regular use of birth control should be encouraged.

Cocaine effects on pregnant women include high blood pressure, heart attack, kidney failure, decreased platelets, and stroke. Pregnancy may increase the cardiovascular toxicity of cocaine, resulting in cardiac morbidity and mortality in otherwise healthy pregnant women (Smid et al., 2019). The constellation of cocaine effects—including high blood pressure, low platelets, swelling, protein in the urine, and seizure—can be mistaken for preeclampsia or eclampsia (Maagdenberg et al., 2006). Hypertension in pregnancy is often treated with labetalol or other beta blockers, but these drugs are associated with coronary vasoconstriction and end-organ ischemia when used concurrently with cocaine.

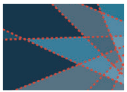
Preterm birth, low (less than 2,500 grams) birth weight, and newborns that are small for gestational age are all adverse perinatal outcomes associated with cocaine use (Gouin et al., 2011). Smoked cocaine specifically is associated with smaller head circumference (Dos Santos et al., 2018). There is a suggested association between increased risk of miscarriage, still birth, and placental abruption and cocaine use, with a somewhat more marked association between at least partial placental abruption and crack cocaine use specifically (Dos Santos et al., 2018).

There is uncertainty about the connection between cocaine use in fetal structural abnormalities, because of studies' poor control of common confounding variables such as maternal age, poverty, stress, co-occurring psychiatric conditions, and the use of other substances such as tobacco and alcohol. Concern persists about a possible link between cocaine use and defects in the genitourinary systems, limbs, and heart (Hetea et al., 2019).

Maternal cocaine use increases the risk of transmission of HIV and syphilis to the infant (J. A. Cook, 2011; Smullin et al., 2021). Problems of growth, cognition, language and motor skills, attention, affect, and neurophysiology have been described in children with prenatal exposure to cocaine (Smid et al., 2019). However, the evidence linking these findings to prenatal exposure to cocaine is less compelling than the evidence for association with gestational age; caregiver psychiatric illness; other prenatal exposures such as tobacco, cannabis, and alcohol; or the conditions of the postnatal environment.

Women who use MA are at substantially higher risk of death than those who do not (26 times higher rate of death) or men who use MA (9 times higher rate of death [Smid et al., 2019]). Reported lifetime use of MA is associated with pregnancy in adolescence (Smid et al., 2019). Pregnant women who use MA are more likely to be younger than 24 years old and are more likely to have significant psychiatric disorders (Smid et al., 2019), including ADHD (Marraccini et al., 2017).

Women who use MA during pregnancy are at higher risk of high blood pressure, heart attack, and cardiomyopathy (Smid et al., 2019). These



conditions produce more infant morbidity in pregnancies exposed to MA than in pregnancies exposed to cocaine. Cleft palate has a clear association with prenatal MA exposure, but the link with other birth defects is not yet established (Smid et al., 2019). Exposure to MA, a neurotoxin, may impact metabolism, chemical signaling such as with serotonin, and structure of the developing fetal brain (Smid et al., 2019). Gestational age and sex may be important considerations, whereas concurrent exposure to alcohol and tobacco are confounding variables (Smid et al., 2019).

MA use in pregnancy is associated with low birth weight, lower than expected gestational age at delivery, and smaller head circumference (Wright et al., 2015). Using MA throughout all trimesters has been linked to insufficient prenatal care, early delivery, and lower birth weight (Wright et al., 2015). Adverse perinatal outcomes including preterm birth, fetal growth restriction, and fetal death have been described, but studies have not been able to determine whether these outcomes are caused by MA or other factors such as contaminants, other drugs, cigarette smoking, or poverty.

At birth, infants exposed to stimulants may manifest symptoms suggestive of withdrawal. As with other newborns with substance exposure, implementation of the Eat Sleep Console model of caring for the mother and infant as a dyad, focusing on nonpharmacologic care and treatment of the newborn, has produced positive results (Dodds et al., 2019). The most common presenting symptoms are lethargy, sleepiness, and poor feeding. Stimulant-exposed infants may have difficulty being consoled (Anbalagan & Mendez, 2021); the action of consoling can increase crying because of damage to the infant's nervous system. The interaction between this and the stimulant-affected mother's low frustration tolerance (due to protracted withdrawal) can interfere with bonding and create negative feedback, psychologically and neurologically. Congenital malformations rarely occur because of stimulant exposure; those that do tend to affect the heart (Huybrechts et al., 2018). Risk of sudden infant death syndrome may be heightened slightly. Any reduction in stimulant use is correlated with improved outcomes for the baby.

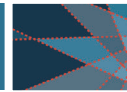
Few infants exposed to MA require intervention. For those that do, supportive feeding is often sufficient (Oei et al., 2012). A prospective study of MA-exposed mother–infant pairs matched with non-MA-exposed mother–infant pairs in New Zealand has provided valuable insights into infant and childhood development (L. M. Smith et al., 2015). Among MA-exposed pairs, this study has described increased anxiety, depression, and attention problems in children ages 3 to 5 and poorer cognitive outcomes at 7.5 years old. Imaging studies have identified sex-dependent structural brain changes, but the clinical and functional importance of these changes is not known. Of note, fetuses exposed to MA mixed with fentanyl may be at risk for opioid-related effects, such as poor fetal growth, preterm birth, stillbirth, specific birth defects, and neonatal abstinence syndrome (Centers for Disease Control and Prevention, n.d.-a).

Little is known about the impact of misuse of prescription stimulants on pregnancy, the fetus, or development. Existing knowledge is based on studies of therapeutic use of prescription stimulants. Exposure to prescription stimulants during the first trimester has not been shown to be associated with congenital defects (Andrade, 2018). Third-trimester exposure has been associated with some instances of intrauterine fetal death (Wright et al., 2015). However, a recent review of eight studies investigating the effects of ADHD medication use during pregnancy found no evidence linking this medication to negative effects on pregnant women or their children. The authors cautioned against drawing definitive conclusions given the small number of studies included in the review (L. Li, et al., 2020).

Dental Effects

Missing and filled teeth, cavities, and gum disease are all more common among people who use drugs (Yazdanian et al., 2020). Cavities are the most common dental problem among people who use drugs (Shetty et al., 2010).

People who use MA are 4 times as likely to have cavities and twice as likely to have untreated cavities compared with people who do not use drugs and have double the risk of decayed, missing, or filled teeth (Shetty et al., 2016). One



study of 552 people with MA use revealed that 96 percent had cavities, 58 percent had untreated cavities, 29 percent had severe periodontitis, almost 60 percent were missing one or more teeth, 7 percent were completely without their natural teeth, and only 23 percent still had all of their natural teeth (Shetty et al., 2015).

Fewer studies are available on the oral health of people who use cocaine, but gum disease and cavities are both positively associated with cocaine use (Bahdila et al., 2020). Cocaine is also associated with problems of the oral cavity, including oral ulcers, nasal necrosis, palate perforation, and oral candidiasis (Maloney, 2010), particularly with oral consumption and nasal insufflation (Fratto & Manzon, 2014). Oral or nasal administration of cocaine has been associated with oral lesions, receding gums, and dental erosion (Fratto & Manzon, 2014).

MA use was previously thought to have a direct chemical effect on the mouth and teeth that contributed to extensive dental disease. Comparison with National Health and Nutrition Examination Survey participants shows that elevated rates of dry mouth and regular consumption of one or more sugary beverages per day to compensate for it, along with poor dental hygiene and lack of preventive dental care over a prolonged period, underlie the problem (Clague et al., 2017). Longer history of substance use, polysubstance use, and concurrent tobacco use are all associated with worse oral health. Smoking MA was not more strongly associated with dry mouth or cavities than was snorting or injecting MA (Clague et al., 2017). Amphetamine use has been linked to broken or missing teeth, bruxism, gingival enlargement, cavities, and dry mouth (Fratto & Manzon, 2014).

People who use stimulants should receive education about preventive oral hygiene and the role of sugary drinks in the widely recognized dental problems affecting this population. Engagement, prevention, and treatment programs should provide the education and resources needed for people who use stimulants to maintain oral hygiene (Shekarchizadeh et al., 2013). Preventive dental care may be available under some Medicaid plans, at a dental school, or in a

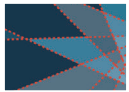
community clinic. Strategies to reduce the negative effects of dry mouth should also be considered by treatment programs. Use of hard candy or chewing gum by patients with dry mouth or bruxism may help to alleviate some of the symptoms.

A program should not make its efforts in this area contingent on someone with a stimulant use disorder deciding to enter treatment or achieving recovery. Poor dentition and oral health may also be associated with an increased risk for serious or life-threatening infections, including infective endocarditis or abscess. Prevention of periodontal disease should be viewed as a form of care for patients in active stimulant use.

Peripheral Vascular and Nerve Damage

Stimulants can damage the central nervous and cardiovascular systems regardless of the route of administration. Use of any substances by injection can be uniquely harmful to the peripheral nerves and vessels (Delaney et al., 2020; Raiker et al., 2016). Peripheral nerves control muscle use and sensation outside of the brain and spinal cord. They are fragile and can be easily damaged if struck by a needle during injection drug use. The peripheral vascular system comprises all the arteries and veins outside of the chest and abdomen. Use of any drug by injection can damage veins and arteries (Delaney et al., 2020; Raiker et al., 2016). All of the problems associated with use of drugs by injection described below are exacerbated by the chemical properties of all stimulants. Cocaine and MA cause vasoconstriction, especially near the injection site (Raiker et al., 2016). When blood flow is restricted, tissue dies, making damage to vessels and nerves as well as skin and muscle more pronounced among people who use stimulants by injection.

For patients who may use substances adulterated with levamisole, there is an elevated risk of levamisole-induced vasculitis (Abdul-Karim et al., 2013; George et al., 2019). Quick recognition of the signs and symptoms of levamisole-induced vasculitis may help in the evaluation of patients with severe presentations, including leukopenia or agranulocytosis. Most studies indicate resolution of symptoms with cessation of cocaine/levamisole consumption, but other studies have used oral steroids with unclear benefits over cessation of use alone.



The repeated puncturing of veins during injection drug use causes inflammation (phlebitis), scarring, and stiffening (Dunn & Gauthier, 2020). Injection drug use can also damage the function of veins (Delaney et al., 2020; Raiker et al., 2016). When valves in veins are damaged, blood pools in the surrounding tissues and in the venous system below the damaged area. Accumulated damage to the veins may cause venous insufficiency (Dunn & Gauthier, 2020). Venous insufficiency causes swelling of the extremities and discolored, thickening, scaling, and peeling skin. The affected extremity can be painful, hot, or itchy. The skin becomes fragile and heals poorly if at all and may result in chronic, weeping wounds. Both phlebitis and venous stasis increase the risk of formation of blood clots in the damaged veins. Clots in the arms or legs can break apart causing a thromboembolic event. If pieces of a clot travel to the lungs or heart, death may occur. A growing body of research has linked cocaine use to increased odds of developing venous insufficiency and venous thrombosis (Griffin & Cha, 2019; T. Sharma et al., 2019).

Arteries are deeper and harder to reach, but people who inject drugs may accidentally inject into arteries instead of veins (Lokoff & Maynes, 2019). Injecting into the artery is painful and can cause extensive bleeding. It also causes the drug to be delivered downstream into the extremities rather than to travel toward the lungs, heart, and brain. The extremities can become inflamed due to immune response provoked by the drug. Injection into the artery carries a high risk of clot formation (Lokoff & Maynes, 2019). The pressure in the arterial system pushes a clot until it lodges in a narrower artery; this is called a thromboembolism. Tissue past the clot no longer receives oxygen-rich arterial blood and begins to die in much the same way heart muscle dies during a heart attack. Like a heart attack, arterial blood clots are a medical emergency.

Like arteries, nerves are sometimes hit accidentally during injection drug use (Dunn & Gauthier, 2020). Hitting a nerve causes intense electric or burning pain both above and below the injection site (Dunn & Gauthier, 2020). After the injury, pain and abnormal sensations like burning or neuropathy (pins and needles) in the area served by the nerve can persist. Other forms of nerve damage also may occur with cocaine or MA use (e.g., nerve

compression; Dunn & Gauthier, 2020). In a sample of more than 900 people with injection drug use (Colledge et al., 2020), nerve damage was the most commonly reported injection-related injury and disease, occurring in 19 percent of the sample.

Injection drug use can lead to a loss of vein functioning (venous sclerosis) and vein scarring, which in turn can increase the risk of vascular disorders, like deep vein thrombosis (formation of a blood clot within the vein, which can then travel to other parts of the body, like the lungs) and skin and soft tissue infections (Ciccarone & Harris, 2015; Raiker et al., 2016). People at risk for injection drug use should have access to a sterile syringe for each use. Reusing a syringe—even one's own—increases the risk of infection. Dull or damaged needles tear and abrade delicate veins, increasing the risk for venous complications. Thorough, nonjudgmental education in phlebotomy techniques, including identifying appropriate sites for injection, rotating injection sites, and sterilizing injection equipment, should be provided. People who use injection drugs should be trained to recognize potentially life- or limb-threatening complications and apply first aid to common complications. Opportunities for wound assessment and care should be a standard part of outreach, prevention, and harm-reduction services for people who use drugs.

Identification and Management of Mental Complications

Stimulant-Induced Psychosis

Initially described by D. Young and Scoville in 1938, amphetamine-induced psychosis usually is a brief and spontaneously remitting paranoid state that is frequently accompanied by intense, fear-evoking altered perceptions of reality and hallucinations, but with clear consciousness and a relatively intact formal thought process (McKetin, 2018). Stimulant-induced psychosis occurs while the person is intoxicated, but may recur when a patient is in withdrawal or has been abstinent for many months (McKetin, 2018). The condition is not rare or idiosyncratic but typically follows chronic, high-dose use of amphetamines, MA, or cocaine and a lack of sleep. However, this drug-induced psychosis is seen more frequently with amphetamine and MA use than cocaine use

(Henning et al., 2019), probably because the short half-life of cocaine means that accumulating and sustaining high plasma concentration levels of that drug is difficult. Stimulant-induced psychosis has been reported after acute intoxication in relatively naïve people and occasionally after low doses. Original reports of the condition describe onset of psychosis following typically high doses (i.e., 100 to 300 mg of amphetamine; Henning et al., 2019).

The prevalence of stimulant-related psychosis is unclear, with studies on MA-induced psychosis reporting estimates ranging from 7 to 76 percent (Lecomte et al., 2018). A review of the literature suggests an overall rate of 36.5 percent among people using MA, with rates somewhat diverging based on whether MA use was lifetime (42.7%) versus current (22.1%; Lecomte et al., 2018). Fear regarding the stigma associated with psychotic symptoms and the persecutory nature of the altered perceptions of reality likely contribute to the inconsistent description of stimulant-induced psychosis.

The prevalence of psychosis induced by prescription stimulants is low. In adolescents and young adults taking prescription methylphenidate or amphetamine for ADHD, psychosis has been reported in approximately 1 in 660 patients, with amphetamine carrying a greater risk than methylphenidate (1.78 per 1,000 people per year versus 2.83 per 1,000 people per year; Moran et al., 2019). Although these rates are low, FDA added a warning label to these medications in 2007 that reads “stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history” (Moran et al., 2019, p. 1,129). This is especially true when prescription stimulants are injected or snorted.

The presence of stimulant-induced psychosis has implications for determining the appropriate level of care. Patients with stimulant-induced psychosis may require more acute psychiatric care, where there are staff to ensure patient safety. (Learn more about determining levels of care by reading Chapter 5.)

Development of stimulant-induced psychosis

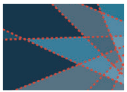
Some researchers and clinicians describe the development of stimulant-induced psychosis as an evolving process, dividing presentations of

stimulant-induced psychosis into three major categories: acute MA psychosis, chronic or persistent MA psychosis, and schizophrenia (Bramness et al., 2012; Deng et al., 2012). Acute stimulant-induced psychosis is directly related to the amount of substance used and lack of sleep of a specific binge. Persistent MA psychosis is related to the chronic use of MA, and patients tend to demonstrate more profound hallucinations, including visual, auditory, and tactile hallucinations.

Schizophrenia is a separate diagnosis from stimulant-induced psychosis, as the former is a substance-independent psychotic disorder. But a presentation of psychosis after stimulant use would warrant consideration of schizophrenia in the differential diagnosis to determine whether a stimulant use disorder–schizophrenia comorbidity exists. Use of stimulants in people with schizophrenia or schizoaffective disorder will likely exacerbate their psychosis; thus, patients may have a psychotic disorder like schizophrenia or schizoaffective disorder and stimulant use disorder simultaneously. Some patients may have co-occurring schizophrenia and present with positive and negative symptoms of schizophrenia after MA use, though this requires further study to determine the pattern of correlation.

Assessment of acute versus chronic stimulant-induced psychosis may be difficult and will likely require patients to engage in multiple treatment sessions. Patients should be evaluated after they have been able to sleep and regain some level of normal life functioning to differentiate between acute and chronic stimulant-induced psychosis. Patients who continue to experience hallucinations, altered perceptions of reality, and persecutory cues from their environment may be exhibiting chronic stimulant psychosis and may require longitudinal psychiatric intervention. Additionally, these patients may warrant diagnostic evaluation for a schizophrenia-spectrum illness. Persistent MA psychosis may occur with ongoing MA use, however, and requires medication treatment similar to that for schizophrenia (e.g., neuroleptics).

At first, people who use a moderately high amount of MA may experience intense curiosity about the world around them. This enthusiasm about “discoveries” changes, with time and increasing



doses, from “watching the world” to feelings of being watched. Behaviors become more fixed and stereotypic, culminating in intense suspiciousness and, in psychotic reactions, paranoid thinking and persecutory perceptions that misinterpret environmental cues. Visual hallucinations may be overreactions to barely glimpsed and recognizable objects in one’s peripheral vision or may be described as shadows of people or things. Auditory hallucinations similarly begin with hearing simple noises and usually progress to hearing others speak about oneself, typically derogatorily. In later stages of psychosis, the individual may have a persistently altered perception of reality and overwhelming feelings of being unsafe.

Manifestations of stimulant-induced psychosis

Although the symptoms of stimulant-induced psychosis mirror those of independent psychotic disorders (like schizophrenia), and heavy use of cocaine/amphetamines may precipitate schizophrenia, stimulant-induced psychosis and primary psychosis are distinct conditions (APA, 2013). DSM-5 criteria describe a substance-/medication-induced psychotic disorder as the presence of altered perceptions of reality (delusions) and/or hallucinations that occur during or soon after intoxication or withdrawal from a substance or shortly following exposure to a medication (APA, 2013). The symptoms cannot be part of a psychotic disorder and do not occur only during delirium. The substance must have the potential to cause altered perceptions of reality or hallucinations that result in clinically significant impairment. Per DSM-5, psychosis in the presence of substance use is considered a primary disorder when (APA, 2013):

- Symptoms substantially exceed what would be expected given the amount and type of substance taken.
- The individual has had previous non-substance-induced psychotic episodes.
- The onset of psychosis precedes the substance use.
- The psychosis lasts for at least 1 month after cessation of intoxication or withdrawal.

Presentation usually includes auditory and tactile hallucinations, paranoid thoughts, ideas of reference, and protective behaviors associated

with paranoia, all of which may lead to difficulties with social and occupational functioning (Glasner-Edwards & Mooney, 2014). Other often-reported psychotic symptoms include persecutory delusions, perceptions of jealousy, concerns of mind-reading, irritability, visual hallucinations, invasive thoughts, thought broadcasting, derealization, and depersonalization (Fluyau et al., 2019). Another common manifestation is stereotypy. As chronic, high-dose stimulant consumption continues, most people also withdraw from all social interactions and initiate other antisocial behaviors before intensive drug use culminates in paranoia or other symptoms of psychosis with limited insight.

Experimental studies in which participants received amphetamine or MA with variable doses/dosing schedules and with different routes of administration showed that, across all participants, only some people developed psychotic symptoms, the threshold dose was inconsistent, and the most common psychotic symptom was paranoia with ideas of reference (Glasner-Edwards & Mooney, 2014).

Risk factors for stimulant-induced psychosis include presence of ADHD, cognitive impairment, and certain neurobiologic factors (e.g., dysfunctions in the brain’s GABA systems; Bramness & Rognli, 2016). A family history of psychotic disorders (e.g., schizophrenia) may also be a risk factor.

The role of drug sensitization

Several issues pertaining to stimulant-induced psychosis are unresolved. There is some disagreement about the role of drug sensitization (kindling) in precipitating more frequent psychotic reactions at smaller doses than previously required and sooner after drug use is reinitiated following a period of abstinence (Rolland et al., 2011). There is also disagreement about the role of sensitization in deepening postwithdrawal depression. The mechanisms for this “reverse tolerance” are not fully understood.

Duration of stimulant-induced psychosis

Symptoms of acute stimulant-induced psychosis usually abate spontaneously with cessation of substance use. Symptoms of chronic or persistent psychosis may occur for 6 months or longer (Glasner-Edwards & Mooney, 2014), particularly among patients with a long history of severe MA

use. Hallucinations may stop within 24 to 48 hours of cessation of substance use, and paranoia and altered perceptions of reality decrease over the next week to 15 days. Clinicians also report that drug-induced psychosis dissipates more quickly for cocaine use—usually in 1 to 3 days—compared with up to 2 to 3 weeks for MA use. Resuming or continuing stimulant use, using other substances (including alcohol, when used heavily), and experiencing stress or lack of sleep can all trigger recurrence of psychosis after symptoms have resolved and after prolonged periods of abstinence (Glasner-Edwards & Mooney, 2014).

The duration of stimulant-induced psychosis is somewhat in dispute. Typically, uncomplicated psychosis induced by stimulants resolves rapidly unless more of the drug is taken. However, observational studies from Japan and Thailand suggest that MA-induced psychosis can persist well beyond the 1-month cutoff in DSM-5 and may become a more chronic condition, even in individuals without a previous psychiatric history (Glasner-Edwards & Mooney, 2014).

Treatment of stimulant-induced psychosis

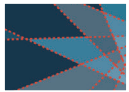
Treating a patient who presents with stimulant-induced psychosis entails rapid, systematic visual assessment, deescalation of agitated or paranoid

behavior, continued observation and monitoring, and symptom management. All unnecessary stimulation should be reduced, but complete sensory deprivation should be avoided. Ideally, the patient should be moved to a quiet hospital room with moderate lighting and sufficient space and staff should talk in a subdued manner and without rapid or unexpected movements. The clinician should try to calm the patient and provide reassurance that he or she is safe (Glasner-Edwards & Mooney, 2014; Holmwood & Gowing, 2019). Deescalation using the AGRO+ model may help engage the patient in a conversation, decreasing the patient's persecutory perceptions, and increasing the sense of safety and well-being (Holmwood & Gowing, 2019; Overdose Response Strategy, New England High Intensity Drug Trafficking Area, & Boston Medical Center Office Based Addiction Treatment Training and Technical Assistance, 2020). (See Exhibit 3.8.) It may be prudent to medicate patients who are nonresponsive to destimulation and deescalation using benzodiazepines and, if patients are unresponsive to initial benzodiazepine doses, antipsychotic medications. In rare instances, ketamine or similar medications may be appropriate in treating the patients' symptoms.

EXHIBIT 3.8. AGRO+ Method for Deescalation With Aggressive Patients

DEESCALATION				
A	G	R	O	+
Assess what triggered the agitation by calmly talking with the patient. Use a patient-centered focus.	Gauge your feelings about the situation. Be mindful that your verbal and nonverbal cues can escalate or deescalate the situation.	Respond calmly yet firmly to the patient. Stand at a safe distance in an open posture. Use open-ended questions and reflective listening.	Observe the patient's verbal and nonverbal cues. Are the deescalation techniques working?	Positive Reinforcement As the patient starts to deescalate, reinforce this desired behavior by offering something, like a glass of water or a snack.

Source: Adapted with permission from Hanieh et al. (2013).



Chronic/persistent stimulant-induced psychosis warrants referral for psychosocial intervention, like cognitive-behavioral therapy, SUD treatment to initiate abstinence and promote recovery, and the use of antipsychotic agents to treat the persistent symptoms of psychosis (Braunwarth et al., 2016; Glasner-Edwards & Mooney, 2014). Individuals with co-occurring stimulant use disorder and schizophrenia (or other psychotic disorder) may also benefit from case management and comprehensive care to address a broader range of potential service needs, like those pertaining to housing and vocational rehabilitation (Glasner-Edwards & Mooney, 2014).

The antipsychotics olanzapine, haloperidol, aripiprazole, risperidone, and quetiapine each may be useful in treating stimulant-induced positive and negative psychotic symptoms (Bramness & Rognli, 2016; Fluyau et al., 2019). Each medication carries unique side effects (e.g., metabolic syndrome caused by second-generation atypical antipsychotics, extrapyramidal symptoms [medication-induced movement disorders] caused by haloperidol). Prescribing decisions should be based on each patient's risk-benefit profile and reevaluated throughout the course of treatment (Fluyau et al., 2019).

Differential diagnosis of acute confusional states should include the possibility of head injury, intracranial hemorrhage, electrolyte imbalances, infection or medical comorbidity, acute trauma response, or thyrotoxicosis. Information from family and significant others is helpful, and toxicology testing may also help confirm a diagnosis (Glasner-Edwards & Mooney, 2014). Assessment tools like the Diagnostic Interview Schedule and the Composite International Diagnostic Interview can help differentiate between primary and stimulant-induced psychosis (Glasner-Edwards & Mooney, 2014).

Acute stimulant-induced psychosis should generally be managed in a hospital psychiatric department or similar facility. Minor psychotic episodes with low-grade symptoms that respond readily to neuroleptic medications may, on some occasions, be managed in a well-staffed, freestanding office-based addiction treatment program if sufficient

personnel with training and experience in treating co-occurring disorders are readily available. Urine testing is recommended to confirm a diagnosis of stimulant-induced psychosis because the syndrome can closely mimic other disorders that may have psychotic symptoms, such as medical comorbidities, schizophrenia, mania, depression, other substance intoxication states, or catatonia.

The criteria for placement should reflect the persistence of the condition, the competence and training of personnel, and the drug taken. People with MA use who have accumulated high plasma concentration levels from longer binges and larger doses of stimulants with longer half-lives may be more prone to protective behaviors during psychosis. This is especially likely if psychotic symptoms include paranoia about attempts to medicate them, which could lead to aggressive behavior and difficulty following medication instructions after release from the hospital.

Aggression and Violence

A potential problem associated with MA use is the risk of sudden and intense violence. Reports by law enforcement officials, psychiatrists, and people using these substances themselves link stimulants to aggression and unprovoked assaults. A causal link between aggression in humans and use of stimulants has yet to be consistently established (Kuypers et al., 2020). But research has shown a robust association between MA use and increased risk of violent behavior or being a victim of violence (Foulds et al., 2020; McKetin et al., 2020; Richards et al., 2019; Stoicescu et al., 2019). MA use and psychopathy traits and behaviors (e.g., aggression, violence, criminal acts) may be associated with corticostriatal abnormalities consistent with decision-making deficits, increased impulsivity, and addictive behavior (W. F. Hoffman et al., 2020).

Research suggests MA may be associated with aggression. Of individuals with MA use and with past violent behavior, 33 percent reported initiating MA use before first engaging in violent behaviors, and 12 percent first engaged in violent behavior during the same year they started using MA (Brecht & Herbeck, 2013). A study from New Zealand (Foulds et al., 2020) examined patients throughout

the life course and found an increased risk of both violence perpetration and violence victimization among people who used MA, suggesting that the population associated with violence is also a population that is disproportionately victimized.

Compared with MA, fewer studies have examined aggression and violence resulting from cocaine use (Kuypers et al., 2020). Cocaine may have some influence on impulsivity, but evidence for this is largely from animal studies, and human studies have been too inconsistently designed to yield firm conclusions (Kuypers et al., 2020). Among the small number of human studies reporting a link between aggression and cocaine use, acute cocaine use has been associated with violence resulting in injury (Chermack et al., 2010), youth violence (Stoddard et al., 2015), and—in women who inject drugs—violent criminal behavior (Butler et al., 2017).

Because drug-induced psychoses can increase the potential for violence in response to perceived persecution and resulting paranoia, sound behavioral management techniques to prevent this negative and dangerous response are essential.

For more information about how to manage violent behaviors in people with SUDs (with or without psychosis), see the Substance Abuse and Mental Health Services Administration's (SAMHSA) Treatment Improvement Protocol (TIP) 25, *Substance Abuse Treatment and Domestic Violence* (<https://store.samhsa.gov/product/TIP-25-Substance-Abuse-Treatment-and-Domestic-Violence/SMA12-3390>); TIP 36, *Substance Abuse Treatment for Persons with Child Abuse and Neglect Issues* (<https://store.samhsa.gov/product/tip-36-substance-abuse-treatment-for-persons-with-child-abuse-and-neglect-issues/SMA12-3923>); and TIP 44, *Substance Abuse Treatment for Adults in the Criminal Justice System* (<https://store.samhsa.gov/product/TIP-44-Substance-Abuse-Treatment-for-Adults-in-the-Criminal-Justice-System/SMA13-4056>).

Co-Occurring Disorders and Conditions

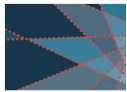
People with stimulant use disorders are likely to have one or more coexisting or preexisting disorders and conditions that can make differential diagnosis challenging or complicate treatment. Preclinical studies and some surveys seem to indicate that neurologic deficits associated with ADHD, neuroanatomical abnormalities, alcohol use disorder, posttraumatic brain lesions, and posttraumatic stress disorder (PTSD) may be correlated with increased vulnerability to stimulant use disorders.

People with MA use can experience co-occurring psychotic symptoms (e.g., paranoia, hallucinations), depressive disorders, anxiety disorders, polysubstance use (especially involving cannabis, benzodiazepines, and hypnotics), ADHD, gambling disorder, compulsive sex, sleep disorders, and eating disorders (Rawson, Ling, & Mooney, 2015). Cocaine use has been similarly linked to multiple psychiatric disorders, including ADHD, PTSD, bipolar disorder, antisocial personality disorder, eating disorders, insomnia disorder, and anxiety disorders (Butler et al., 2017; SAMHSA, 2020l).

The following sections describe some of the most common premorbid and co-occurring disorders and conditions among individuals who use stimulants, with some comments on treatment precautions.

Polysubstance Use

Concomitant use of a variety of other licit and illicit psychoactive substances is a common correlate of stimulant use. In a latent class analysis of more than 700 adults with past-month use of stimulants, four notable patterns of polysubstance use emerged: (1) high use of MA and cannabis but moderate use of alcohol and nonprescribed opioids; (2) high use of crack cocaine and alcohol but moderate use of cannabis; (3) high use of powder cocaine, alcohol, and cannabis but moderate use of crack cocaine; and (4) high use of crack cocaine, powder cocaine, nonprescribed opioids, alcohol, and cannabis but moderate use of MA, prescribed opioids, and



nonprescribed tranquilizers (Timko et al., 2018). Concomitant use of cocaine with benzodiazepines to blunt the dysphoric effects of the latter is also common.

Speedballing or goofballing—simultaneous use of an opioid and cocaine or other stimulant—is still prevalent in many places because the combination is perceived to smooth the effects of each drug. From 2011 to 2017, the number of people seeking opioid treatment who reported past-month MA use increased from nearly 19 percent in 2011 to 43 percent in 2017 (M. S. Ellis et al., 2018). From 2015 to 2017, the number of people with past-month heroin use who reported also using MA tripled from 9 to 30 percent, reflecting what some have termed a “twin epidemic” of opioid and MA addiction (Strickland et al., 2019).

In the 2009 to 2014 National Health and Nutrition Examination Survey, polysubstance use was common among people with current cocaine use (30 percent reported using one other substance, almost 31 percent reported using two, and 19 percent reported using three or more; Bahdila et al., 2020). Typically used substances were alcohol (almost 68%), tobacco (47%), cannabis (43%), prescription opioids (13%), MA (6%), and heroin (nearly 5%).

The combination of cocaine and alcohol is particularly dangerous. Researchers have established that cocaethylene, the ethyl ester of benzoylecgonine, forms in the liver when a person uses these two substances together. The person may experience more intense pleasure than if using either substance alone, but he or she is also exposed to the combined toxicities of cocaine and the even more potent cocaethylene (da Silva Maia et al., 2017; A. W. Jones, 2019; Liu et al., 2018).

Because cocaethylene has a longer half-life (2 hours) than cocaine (about an hour; A. W. Jones, 2019), the cumulative and additive effects found in the combination increase the incidence of lethal heart attacks and stroke (18 times higher risk of sudden death than with cocaine alone). Cocaethylene appears to prolong the duration of cocaine-related increases in blood pressure and, in turn, to increase the likelihood of small-vessel cerebral infarct or intracerebral hemorrhage.

Cocaethylene is particularly toxic to the liver and may be associated with increased risk of intensive care unit admission (Wiener et al., 2010). Cocaethylene has been detected in cases of cocaine-related sudden deaths that were attributed to drug toxicity as well as cocaine-related cases of violent death (i.e., gunshot wound, motor vehicle accident, suicide by hanging; Pilgrim et al., 2013). Fatalities involving cocaethylene may also be due to cerebral hemorrhage, stroke, other cardiovascular events, or hyperthermia (A. W. Jones, 2019). For people with chronic cocaine use, cocaethylene also increases the risk of experiencing panic and anxiety attacks, especially attacks that persist for some time.

The popularity of cannabis among people who use stimulants is explained by its pharmacologic properties. Because cannabis induces vasodilation of nasal mucosa, it attenuates the vasoconstriction of cocaine so that absorption is increased. Thus, co-use of cannabis and stimulants enhances their euphoric effects and, in MA use, decreases subjective dysphoric effects (Porcu & Castelli, 2017).

“Chemsex,” or the use of multiple substances to enhance sexual pleasure, is a potential health threat in polysubstance use with stimulant use (Giorgetti et al., 2017; Hammoud et al., 2018; Stevens et al., 2020; Torres et al., 2020). In particular, concomitant use of gamma-hydroxybutyric acid, alcohol, amyl nitrates, erectile dysfunction medications, and/or ketamine may be popular enhancements to the sexual experience, and each contributes differently to the potential for emergency intervention for patients.

Psychiatric Disorders

Research suggests that most people who use stimulants have concurrent mental disorders. Identified anxiety, phobias, ADHD, and antisocial personality disorder typically precede chronic cocaine use, whereas alcohol use disorder, depression, and paranoia generally follow stimulant use. For MA use, people appear more likely to have non-substance-induced, preexisting lifetime depressive, anxiety, or psychotic disorders than to have MA-induced depressive, anxiety, or psychotic disorders (Salo et al., 2011).

Differentiating co-occurring psychiatric disorders from stimulant-related disorders can be challenging. Acute or chronic stimulant intoxication can elicit symptoms of anxiety that are indistinguishable from phobias, obsessive compulsiveness, panic, and generalized anxiety. The parallels between symptoms of stimulant-induced psychosis and schizophrenia are discussed in the section “Stimulant-Induced Psychosis” earlier in this chapter. Withdrawal from stimulants can cause symptoms similar to major depression, resulting in symptoms like sad mood, fatigue, increased sleepiness, and thoughts of self-harm (UNODC, 2019b).

The prognosis for SUDs is worsened by the presence of other untreated psychiatric disorders (or polysubstance use). Patients with co-occurring SUDs and mental disorders need treatment for both; the psychiatric problems may or may not improve with reduction in use. Antidepressant and neuroleptic medications with low anticholinergic and sedative properties are preferred because of their low potential for addiction. Sedative–hypnotics and benzodiazepines must be used with caution in high-risk populations (e.g., older adults, people consuming alcohol, people with a history of prescription medication misuse; Guina & Merrill, 2018).

TREATING CO-OCCURRING MENTAL DISORDERS

People with stimulant use disorders also frequently experience other mental disorders or psychiatric symptoms, such as depression and anxiety. Patients with stimulant use disorder and any co-occurring psychiatric illness or symptoms should have both disorders treated concurrently rather than wait to address the mental health issue until after they are in recovery. Most mental disorders can be treated while the person is pursuing recovery. If clinicians delay in treating those co-occurring symptoms or disorders, it can put at risk the person's chances of achieving and staying in recovery from their stimulant use disorder.

Preexisting Medical Conditions

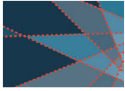
Any preexisting acute or chronic physical conditions are also likely to be complicated and exacerbated by the stress of stimulant intoxication and withdrawal. Particularly dangerous coexisting medical conditions include any history of seizures, coronary heart disease and other cardiac problems, thyroid problems, hypertension, or respiratory and pulmonary disease. Hypertension, renal failure, and possibly diabetes mellitus, which are risk factors for stroke, can be exacerbated by cocaine use (Goel et al., 2014).

Patients who are already taking medications for other medical conditions may be at heightened risk for serotonin syndrome when stimulants are combined with certain antidepressants or neuroleptics. Additional cardiovascular risk exists for patients prescribed beta-blockers who continue to use stimulants, particularly cocaine.

Traumatic Injury

People who use stimulants may be at an increased risk of traumatic injury. A review of studies looking at amphetamine-type substance use and associations with traumatic injury or death from motor vehicle accidents found a mixed association in terms of traumatic injury but a moderately positive association with death (Hayley et al., 2016). In one sample of more than 2,500 trauma patients admitted to a Level II trauma center between 2005 and 2015, 6.5 percent tested positive for MA and 5 percent for cocaine (Neeki et al., 2018). Traumatic brain injuries appear to be prevalent in people with cocaine and MA use disorder (Duong et al., 2018; Yeung et al., 2013) and should be managed with appropriate interventions based on the cognitive deficits identified in a neurologic evaluation (Ramesh et al., 2015).

Patients appearing in hospital EDs following mild to severe traumas may use stimulants and may have been involved in physical altercations or accidents. Among men reporting to the ED with traumatic injuries (Armenian et al., 2019), those who used stimulants had 2.9 increased odds of experiencing any violent injury and 3.3 increased odds of experiencing a penetrating injury (i.e., gunshot or stab wound).



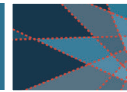
Stimulant use may be associated with not just an increased risk of traumatic injury but worse traumatic injury-related outcomes, such as mortality and healthcare resource use. A lifetime history of an SUD is associated with a significantly elevated mortality rate following inpatient discharge for traumatic injury (compared with people without lifetime SUDs); cocaine in particular has a 1.1 to 1.6 increased risk of all-cause mortality following discharge (Dezman et al., 2020). In individuals who sustain burn injuries, stimulant use is associated with longer hospital length of stay and a higher need for skin grafts, both of which suggest stimulant use may result in greater healthcare resource use (Hulsebos et al., 2020). In a survey of nurses, residents, and other faculty at a Level I trauma center, respondents largely agreed not only that patients who used MA tended to need more hospital resources and have a longer length of stay in the ED, but also that they required more effort on behalf of staff to treat and were perceived by staff to be more violent than patients who had not taken MA (Richards et al., 2019).

Sexual assault is also reported by an increasing number of both men and women who report stimulant use (Kittirattanapaiboon et al., 2017; Lutnick et al., 2015). Sexual assault while using stimulants is particularly problematic for women engaged in sex work for acquisition of the substance. Additionally, studies have examined the increased risk for intimate partner violence among both men and women who engage in regular stimulant use (Crane et al., 2014; Foulds et al., 2020; P. H. Smith et al., 2012). Clinicians should be familiar with appropriate places to which to refer patients to help them cope with trauma associated with sexual assault and intimate partner violence.

Linking Treatment Programs and Medical Facilities

Because the ED may be the first point of contact with the medical system and potential treatment for people with stimulant use disorders, hospitals need to give attention to establishing and supporting a continuum of care in which appropriate linkages among all necessary services and programs for these patients are present. The task of developing and encouraging these linkages among treatment components cannot fall to hospital staff alone; all providers and staff should be encouraged to cooperate in the effort. If not connected to the treatment system, people who use cocaine or MA will likely return repeatedly to the ED and other hospital departments for care of more and more serious health and mental health problems. Stimulant use disorders, like all SUDs, are lifelong, relapsing conditions that require ongoing management and support.

Hence, treatment programs should take primary responsibility for developing linkages with hospitals, using several approaches. The best approach is to have an SUD treatment practitioner or trained nurse/social worker visit the hospital and other medical facilities regularly to identify, screen, encourage, and follow up with patients who have stimulant-related and other substance use problems and need access to the ongoing treatment continuum. Peer recovery support specialists also can be found in hospital settings and can help link patients with acute SUD crisis to longer-term SUD services outside the hospital (see the text box “Connecting Patients to Peer Recovery Support Specialists”). A face-to-face visit by an outreach specialist or peer recovery support specialist is particularly effective in supporting the crisis-precipitated motivation to enter treatment, especially if the patient is hospitalized for some time. Because a crisis creates an intervention opportunity, the patient may be unusually receptive to considering lifestyle changes and the need for longer term treatment.



CONNECTING PATIENTS TO PEER RECOVERY SUPPORT SPECIALISTS

Medical providers can facilitate the recovery process for people taking stimulants by connecting them with a peer recovery support specialist. Also called a recovery coach, a peer recovery support specialist is an individual (or in the case of a family peer specialist, a close friend, family member, or other loved one of an individual) with lived experience with an SUD and recovery. These individuals carry out a wide range of recovery-related activities, such as mentoring or coaching people just entering recovery, facilitating and leading recovery groups, and connecting people just entering recovery to other recovery resources.

Research suggests that placing peer recovery support specialists in hospital settings is feasible and effective. For instance, Rhode Island's AnchorED program links patients presenting to the ED for opioid use disorder with peer recovery support specialists who provide naloxone kits and overdose education and who can connect these patients with more extensive community-based peer recovery support services as needed (Waye et al., 2019). Regardless of the type of setting in which a peer recovery support specialist works (e.g., hospitals, outpatient clinics, SUD treatment programs), use of peer recovery has been associated with improved outcomes, such as a greater likelihood of completing medically supervised withdrawal, reduced substance use, an increased likelihood of attending mutual-help programs (e.g., Narcotics Anonymous), reduced hospitalizations, fewer inpatient psychiatric or substance use-related readmissions, increased self-efficacy, and improved quality of life (Eddie et al., 2019).

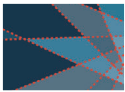
Not all medical facilities employ peer recovery support specialists. But if such individuals are available, medical personnel should become familiar with who they are, what they do, and how to connect them with patients.

It also may be realistic for hospital staff to provide patients with stimulant use a list of available treatment facilities for stimulant use disorders and/or other SUDs that is developed by the hospital's SUD treatment staff. However, patients in crisis may struggle to self-refer related to the fatigue, exhaustion, and depression associated with stimulant withdrawal and the persecutory perceptions of reality associated with acute stimulant use.

Some educational literature on stimulant use might also be helpful—particularly regarding withdrawal symptoms, stimulant-induced psychosis, and medical complications—if the patient or a significant other is willing to read it. Because hospital medical staff must know about the addiction process to understand patients whom they see every day, cross-training in the field of SUD treatment is vital for learning about and actively supporting the development and use of linkages and referral mechanisms. At least one-fourth of people treated in hospitals are thought to have some type of substance use-related problem.

Motivation for change is often difficult to determine in the individual. Health problems may, however, motivate an individual to move from contemplation to action (Prochaska et al., 1992). Healthcare personnel working with a patient hospitalized for an acute drug episode should emphasize strategies to keep the patient safe even when he or she is using substances. Motivational interviewing focuses on exploring and resolving ambivalence and centers on motivational processes within the individual that facilitate change. This evidence-based practice builds on the patient's strengths, which may be the most important component for patients to be able to initiate treatment for their stimulant use disorder (SAMHSA, 2020m).

Hospitals often deal with people with frequent, revolving use of hospital EDs or inpatient hospital beds because of medical or psychiatric complications resulting from their substance use. The financial burdens can be severe for these patients and, if the patients lack insurance, hospitals' costs of care may be unrecoverable. Collaborative arrangements between hospitals and local treatment facilities can allow for door-to-door SUD treatment.



Obtaining Consent for Treatment

In obtaining the patient's consent for treatment, gathering information from others about the patient's history of substance use, making referrals for continuing care, or seeking reimbursement from insurance carriers, hospital staff must be familiar with the provisions of special federal laws and regulations for protecting confidentiality of SUD patient records as set forth in 42 U.S.C. §290dd-2 and 42 C.F.R. Part 2, as well as any applicable state laws and regulations. Patients who are intoxicated or psychotic may have diminished capacity for providing informed consent to treatment. If consent is obtained, even temporarily, from a relative, this may be considered a "disclosure of identifying information" and be subject to federal guidelines. In referring a patient from a hospital to an outside treatment program and making an appointment, staff are also making a disclosure and will ordinarily need a written consent form from the patient containing specified information.

Special exceptions apply to disclosing information in SUD patient records when medical personnel need this information to treat a medical emergency. However, the Part 2 regulations require that the SUD treatment provider document in the patient's record the nature of the emergency, what information was released, the name of the

person making the disclosure, and the date and time. For additional information about consent and confidentiality, see <https://www.samhsa.gov/about-us/who-we-are/laws-regulations/confidentiality-regulations-faqs>.

Summary

Patients who use cocaine or MA or who misuse prescription stimulants are at risk for multiple medical complications—some of which can have severe, long-lasting, or possibly even fatal consequences. The various routes of administration and pharmacokinetics of stimulants also play a role in the development of medical complications, as well as in the intoxication and withdrawal processes. Even SUD treatment providers who do not have medical training can benefit from knowledge about the medical risks of and treatments for cocaine use, MA use, and prescription stimulant misuse. These clinicians can play an important part in identifying symptoms and helping to connect patients with healthcare providers in a timely manner. Further, educating patients about the health consequences of stimulants might also help increase their motivation for engaging in and completing SUD treatment. (Chapter 4 discusses options for the nonpharmacologic treatment of stimulant use disorders in further detail.)