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Stimulant-Based Drugs of Abuse in the Trauma Patient

Substance abuse is a major healthcare issue with effects on all aspects of patient care, including trauma. A large percentage of trauma patients have a positive drug screen, and acute and chronic abuse have impacts both on the acute and long-term management of these patients. This report is the first of a two-part series and focuses on stimulants and substances with sympathomimetic properties, with particular attention to the impact on the trauma patient.

—Ann M. Dietrich, MD, Editor

Substance abuse is an increasing problem in the United States and includes the use of controlled medications, such as opioids, amphetamines, and benzodiazepines, as well as illicit substances.[1] Major classes of drugs of abuse include stimulants, cannabinoids and synthetic cannabinoid receptor antagonists, hallucinogens, ethanol, sedative-hypnotics, opiates, and inhalants. Recently, high-potency synthetic analogs have been developed that combine features of many commonly abused substances.

Trauma patients have greater rates of substance abuse in comparison to non-trauma patients.[1-2] Studies have found that 40% to 80% of trauma patients have a drug screen that is positive for one or more substances.[2] Management of patients can be affected by both acute intoxication and chronic dependence. Normal physiology may be altered and vital signs may be unreliable markers of hemodynamic status.[2] In addition to effects of acute substance intoxication, individuals with chronic substance use are at higher risk for withdrawal syndromes.[2] Individuals may require greater doses of medications for sedation and anesthesia.[2] Certain substances also can affect drug metabolism.[2] Multiple studies have documented the increased requirement for mechanical ventilation in patients with positive drug screens.[2]

Providers often are faced with the challenge of determining whether a patient is intoxicated and, if so, with what substance. Agitation can be secondary to trauma or intoxication. Substance use may not be disclosed even in alert patients. First responders may assist by identifying substances found at the scene of a trauma. However, providers may rely on urine drug screens to assist with substance use history. Urine drug screens often are routine parts of a trauma workup, but they may have many false positives and false negatives.[3] Cross-reactivity with other substances, including therapeutic medications, can result in false-positive results. False-negative results also can occur due to poor cross-reactivity of antibodies used in assays, cutoff concentrations, or the time period between ingestion and specimen testing.[4]

Substance use may have a significant impact on patient care. A positive drug screen may result in delayed surgical management of non-life-threatening trauma complications due to concern that sympathomimetic properties could increase the risk of cardiovascular complications.[2-3] However, positive drug screens have not been

EXECUTIVE SUMMARY

- Trauma patients have greater rates of substance abuse in comparison to nontrauma patients. Studies have found that 40% to 80% of trauma patients have a drug screen that is positive for one or more substances. Management of patients can be affected by both acute intoxication and chronic dependence. Normal physiology may be altered, and vital signs may be unreliable markers of hemodynamic status.
- Amphetamine toxicity can present with anxiety, agitation, and hallucinations. Compared to other stimulants, such as cocaine, psychotic features are more prominent. Patients can have hypertension, tachycardia, mydriasis, diaphoresis, hyperthermia, and seizures.
- Amphetamines have high rates of false positives and false negatives. Over-the-counter cold preparations containing pseudoephedrine and bupropion can result in a false positive.
- Benzodiazepines are indicated first line for management of amphetamine-induced psychosis and seizures.
- Physiologic effects of cocaine are well established and are consistent with a sympathomimetic toxidrome. Hypertension, tachycardia, tachypnea, and hyperthermia are expected after use. Hyperthermia is the most critical finding. Typical sympathomimetic physical exam findings also include mydriasis, diaphoresis, and neuropsychiatric manifestations. Various neuropsychiatric manifestations of cocaine toxicity are common and include bizarre, erratic, and violent behavior. Stimulants, such as cocaine, can result in excited delirium.
- Cocaine also is used frequently with a potent opioid, such as heroin or fentanyl, a combination known as a "speedball." This is particularly dangerous since the stimulant effects of cocaine can mask the sedating opioid effects, resulting in a user taking a large opioid dose. Differences in drug half-life can lead to a fatal overdose. Severe agitation after naloxone administration should prompt consideration for the presence of a sympathomimetic agent, such as cocaine.
- If a patient requires endotracheal intubation, cocaine toxicity is a relative contraindication to the use of succinylcholine. Cocaine toxicity can result in rhabdomyolysis and hyperkalemia, which can be further exacerbated by succinylcholine administration and result in life-threatening dysrhythmias.
- Bath salts are structurally similar to amphetamines, with intended effects similar to cocaine and methamphetamines. They are manufactured and labeled so they can circumvent laws regulating sales of controlled substances set in place by the Drug Enforcement Administration and Food and Drug Administration.
- Given the broad presentations associated with cathinone toxicity, it is important to consider use in any patient presenting with agitation, anxiety, and psychosis in the setting of a negative urine drug screen.

shown to be associated with increased perioperative cardiac complications.[3] Trauma patients frequently require anesthesia and sedation. Patients with a history of chronic substance use may be at risk for undertreatment of pain. This is multifactorial and due to concerns for worsening respiratory depression, secondary gain, or increasing the risk of relapse.[5]

The goal of this article is to describe common drugs of abuse and how they may affect patient care in the trauma setting. This report is the first of a two-part series and focuses on stimulants and substances with sympathomimetic properties. Common mechanisms of intracorporeal drug smuggling and patient management also are characterized. A subsequent report will include substances with sedative and depressant characteristics, such as alcohol, sedative-hypnotics, and opioid medications.

Amphetamines, Methamphetamine, MDMA

Amphetamines are a broad class of drugs with stimulant and psychoactive properties.[6] Certain amphetamines have therapeutic use in conditions such as attention deficit hyperactivity disorder (ADHD). Others are synthesized in clandestine labs for recreational purposes.[7] Examples of amphetamines include methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA). General effects of amphetamines include psychomotor activation, euphoria, decreased appetite, and hyperthermia. The euphoric effects result in high abuse potential and may result in violent behaviors.[7]

Methamphetamine is a highly addictive and potent stimulant. Its use is widespread, and nearly 0.6% of Americans have used it in the last year.[8] It is found in the form of a white, odorless, bitter-tasting powder that can be dissolved in alcohol or water.[8] Crystal meth resembles glass fragments or shiny blue rocks.[9] Methamphetamine can be smoked, snorted, injected, or ingested.[8] Smoking or injecting methamphetamine results in an immediate "rush" that lasts several minutes. Individuals often will go on a "run," which involves binging on methamphetamine for several days without food or sleep.[8,9] Street names of methamphetamine include "chalk," "ice," and "speed."[8,10]

MDMA, also known as "ecstasy," is a semisynthetic drug with psychoactive properties between that of typical stimulants and hallucinogens.[11] MDMA results in distortion of sensory and time perception.[11,12] Desired effects include euphoria, increases in energy, and sexual arousal.[13] MDMA has "entactogenic" properties that result in emotional closeness and empathy toward others.[11,14] MDMA use is commonly associated with all-night dance parties with electronic music.[12,14] Its popularity is due to its low cost and misconceptions regarding low toxicity.[14] More than 17 million Americans report having used MDMA at least once in their lifetimes.[11] MDMA can be taken as a capsule, tablet, or powder. If ingested, the onset of action typically is within 30 to 60 minutes and lasts four to six hours.[11-14] Individuals can have different responses to the same dose due to differences in metabolism.[14] "Molly" is a form of MDMA that is crystallized into a powder and can be taken orally. Many individuals use Molly due to the erroneous belief that it is a purified form of MDMA without adulterants. However, Molly can contain any number

of compounds that result in similar adverse effect profiles to other amphetamines.[6]

Effects

Amphetamine toxicity can present with anxiety, agitation, and hallucinations. Compared to other stimulants, such as cocaine, psychotic features are more prominent.[6] Up to 40% of methamphetamine users display psychiatric symptoms.[10] Amphetamine psychosis can be clinically indistinguishable from schizophrenia.[15] Users can present with positive symptoms, such as delusions, hostility, or hallucinations. Negative symptoms also may occur. Psychiatric symptoms have been reported up to six months following amphetamine cessation.[10]

In addition to psychotic features, amphetamine toxicity can present with that of a sympathomimetic toxidrome.[16] Patients can have hypertension, tachycardia, mydriasis, diaphoresis, hyperthermia, and seizures.[6,8,10,11,16,17]

Amphetamine toxicity can result in death from several different mechanisms. Most commonly, fatal toxicity is secondary to hyperthermia, cardiovascular toxicity, or seizures.[10] Other causes can include pulmonary edema and respiratory distress, or cerebrovascular hemorrhage.[10] It is important to recognize that accidents, homicides, and suicides often are associated with amphetamine use and toxicity.[10] Methamphetamine increases the risk of violent criminal behavior.[8]

Cardiovascular complications are a prominent feature of amphetamine toxicity, and the presentation can be varied.[18] Cardiotoxicity is likely secondary to sympathomimetic activation, similar to that of cocaine toxicity.[14,16] A positive methamphetamine screen has been associated with increased heart rates both at the scene of trauma and on arrival to a trauma center.[19] A single dose can result in fatal cardiac complications.[8] Hypertension, tachycardia, and dysrhythmias are common.[6,14] Conversely, toxicity can trigger a vasovagal reflex that results in bradycardia and hypotension.[10,14] Dysrhythmias may include premature ventricular contractions or may progress to ventricular tachycardia and fibrillation that result in sudden cardiac death.[6,10] Myocardial ischemia and infarction can occur secondary to vasospasm in otherwise healthy individuals, or due to increased oxygen demand in those with preexisting disease.[14,18] Hypertension can result in aortic dissection or intracranial hemorrhage.[6]

Hyperthermia is one of the most dangerous complications of amphetamine toxicity.[8,10,11,16] This is due to both the vasoconstrictive properties of the drug as well as the settings in which amphetamines are taken.[11] For example, MDMA use often occurs in association with vigorous physical activity that occurs for extended periods and in warm environments.[11] Hyperthermia is associated with poor survival and can lead to liver damage, hyperammonemia, blood-brain barrier defects, and vascular edema.[10,14] Death also can occur secondary to pulmonary edema.[10] Hyperthermia in the setting of amphetamine use also can indicate the presence of serotonin syndrome. Serotonin syndrome is a potentially lethal condition characterized by hyperthermia, as well as hyperreflexia, agitation, tremors, and diarrhea.[10] Additionally, amphetamine toxicity can result in rhabdomyolysis secondary to agitation, seizures, hyperthermia, and excited delirium with physical restraint.[17]

MDMA toxicity has the unique toxicity of hyponatremia.[6,11,16,20] New users may be encouraged to drink plenty of fluids to avoid dehydration.[20] Additionally, MDMA results in secretion of vasopressin (antidiuretic hormone), resulting in reduced ability to excrete free water.[13,20] Severe hyponatremia can result in life-threatening cerebral edema.[11] Females may be at higher risk of MDMA-induced hyponatremia due to the effects of estrogen on vasopressin.[16]

It also is important to note that cheap, potent, synthetic opioids can be added to amphetamines without users' knowledge. Common adulterants can include synthetic cathinones, ketamine, and caffeine.[11-12] These adulterants can change the toxicity profile after a reported amphetamine overdose.[9] Additionally, MDMA often is intentionally combined with other substances, such as alcohol, marijuana, or caffeine.[11] These can increase the risk of adverse health effects associated with MDMA.[11]

Testing

Amphetamines typically are included in routine urine drug screens. However, these tests have high rates of false positives and false negatives.[6] Many substances, including those used therapeutically, are structurally similar sympathomimetics that can result in false positives.[21] For example, over-the-counter cold preparations containing pseudoephedrine or bupropion can result in a false-positive amphetamine result in a urine drug screen.[21] Even beta-blockers, such as esmolol and labetalol, can result in false-positive amphetamine screens.[21-22] Other substances, such as trazodone, amantadine, promethazine, and certain antihistamines, can result in false positives.[21] Derivatives of amphetamines, such as MDMA/ecstasy and cathinones, have greater variability in detection.[6,23] Given the high rates of false positives and false negatives, urine immunoassays should not guide clinical decision making in suspected acute amphetamine toxicity.[6]

Management

Initial management should emphasize supportive care. The workup could include complete blood count, complete metabolic profile, coagulation studies, and creatine phosphokinase.[6] An electrocardiogram (ECG) and continuous cardiac monitoring should be in place because of the increased risk of dysrhythmias.[6] The workup also may include a chest radiograph to evaluate for pulmonary edema. A computed tomography (CT) head and lumbar puncture can be considered for evaluation of suspected intracranial hemorrhage. A cardiac echocardiogram can assist in the evaluation of myocardial dysfunction.[6]

Acute amphetamine toxicity often presents with agitation and seizures. Benzodiazepines are the first-line management for amphetamine-induced psychosis and seizures.[6,15] Additionally, benzodiazepines are the drug of choice in many toxicities with similar presentations, such as cocaine overdose or ethanol and sedative-hypnotic withdrawal.[6] Benzodiazepines should be titrated to achieve control of agitation.

There are conflicting data regarding the use of antipsychotics in amphetamine psychosis.[15] Some studies have indicated that both olanzapine and haloperidol are effective in amphetamine-induced psychosis.[6,24] However, antipsychotics can increase the risk of hyperthermia and seizures, and should only be used for a patient with benzodiazepine-resistant psychomotor features or agitation in carefully selected patients.[6] Ketamine has been proposed for the

Table 1. Summary: Amphetamines, Methamphetamines, and MDMA	
Effects	• Stimulant • Psychoactive
Acute Toxicity Presentation	• Psychosis • Sympathomimetic toxidrome
Complications	• Cardiovascular, metabolic, renal, hepatic disorders • Death can occur from toxicity • MDMA can result in life-threatening hyponatremia
Management	• Supportive measures to address hyperthermia and cardiovascular and electrolyte abnormalities • Benzodiazepines may be needed for acute psychosis • Urine testing has limited role in acute setting because of high false-positive and false-negative rates

treatment of amphetamine agitation, but its use has not been validated.[25] Additionally, ketamine use may result in an emergence reaction or catecholamine surge that is problematic in patients with amphetamine toxicity.[25]

An accurate core body temperature should be measured, and significant hyperthermia requires aggressive interventions to achieve rapid cooling.[6] If not rapidly addressed, muscle breakdown and electrolyte imbalances can have life-threatening effects.[11] Temporary physical restraint may be needed to achieve adequate sedation, but it should be discontinued as soon as possible in the setting of hyperthermia and rhabdomyolysis.[6] Successful management of hyperthermia reduces the risk of rhabdomyolysis. If kidney injury is present, patients should be hydrated well with a goal urinary output of at least 1-2 mL/kg/h. Some patients with kidney injury, acidemia, and hyperkalemia have required urgent dialysis.[6] Dantrolene has been proposed for amphetamine-induced hyperthermia but has limited data and is not currently recommended for use.[6] (*See Table 1.*)

Cocaine

Cocaine is a commonly used stimulant drug with addictive properties. It is classified as a Schedule II drug due to high abuse potential.[26] Cocaine is purified from the coca plant and exists as a recreational drug in two different forms. One is a water-soluble salt that is a white powder that is often snorted or injected.[26] The insoluble form, known as "crack," is heated and smoked. Some street names of cocaine include "coke," "C," "snow," "powder," or "blow."[26]

Epidemiology

Cocaine is one of the most commonly used illicit drugs in the United States, with nearly 1.5 million current users ages 12 years and older. Use is highest in people ages 18 to 25 years.[26] In 2011, there were nearly 505,224 emergency department visits involving cocaine use.[26] One study found that trauma patients with positive cocaine screens had longer lengths of stay in intensive care units.[27]

Effects

Cocaine's popularity is due to its near immediate onset of stimulant effects within five to 10 minutes (longer if ingested).[26,28,29] Intended effects include increased energy, alertness, euphoria, and increased social interaction.[26,29] Anorexia and insomnia also occur.

Physiologic effects of cocaine are well-established and are consistent with a sympathomimetic toxidrome. Hypertension, tachycardia, tachypnea, and hyperthermia are expected after use.[28] Typical sympathomimetic physical exam findings also include mydriasis, diaphoresis, and neuropsychiatric manifestations.[28] Alternatively, patients also can present with apnea, hypotension, or bradycardia due to direct suppression of brainstem centers.[28]

Various neuropsychiatric manifestations of cocaine toxicity are common and include bizarre, erratic, and violent behavior.[26] Stimulants, such as cocaine, can result in excited delirium.[30,31] In this setting, lactate may be elevated and, therefore, may be an unreliable measure of shock.[30] Cocaine users also can experience anxiety and paranoia, leading to profound psychosis and auditory hallucinations.[26] In the setting of trauma, the combination of anesthetic properties and altered consciousness can mask occult fractures or injuries.[28] Headache, seizures, and stroke are associated neurologic effects. Cocaine use increases the risk of seizures and intracerebral hemorrhage.[26,28]

Musculoskeletal effects include mild twitching and muscle rigidity to acute dystonia.[28] "Crack dancing" is a name given to the commonly observed choreoathetoid movements.[28] Neuromuscular effects can be delayed and may occur even days after use.[32] Musculoskeletal injury also can occur secondary to vasospasm and direct muscle toxicity of cocaine.[28] Rhabdomyolysis may result in acute tubular necrosis even in the absence of trauma.[33]

Pulmonary toxicity has been well-established with cocaine use. Studies have shown that trauma patients who test positive for cocaine have increased rates of pneumonia.[34] Cocaine toxicity and thermal insult can result in bronchospasm and worsening of preexisting reactive airway disease.[28] Other forms of pulmonary injury can include pneumothorax, pneumomediastinum, and also pneumopericardium.[28,35-37] These injuries may relate to barotrauma from the mechanism of use. A user performs a Valsalva maneuver following insufflation or inhalation in an attempt to retain the drug, resulting in increased intrathoracic pressure.[28,35-37]

Another form of pulmonary toxicity secondary to cocaine use includes "crack lung." This term is given to the acute pulmonary syndrome that consists of fever, hemoptysis, hypoxia, acute respiratory distress, and, ultimately, respiratory failure.[28,38] Imaging can show diffuse alveolar and interstitial infiltrates.[28,38] This syndrome may be related to impurities mixed with cocaine, carbonaceous material from pyrolysis, or direct toxicity.[28] In summary, the pulmonary manifestations of cocaine use are broad but place patients at increased risk for respiratory failure.[38]

The mechanism of cardiovascular injury is likely multifactorial and related to increased oxygen demand and vasospasm.[28] Cocaine use can result in myocardial ischemia and infarction in the absence of atherosclerosis.[29] Hypertension and tachycardia can result in increased shear force, increasing the risk of aortic rupture or dissection.[26,28] Other forms of cardiovascular toxicity can include dysrhythmias

secondary to sodium or potassium channel blockade.[28] These can present with wide complex tachycardias on electrocardiogram.[28] Changes in pH and tachycardia can further exacerbate dysrhythmias.[28] Death associated with cocaine toxicity typically is related to cardiac arrest, seizure, or hypoxia.[26]

Cocaine can induce coagulation and impair thrombolysis, even in the absence of endothelial injury.[28] Cocaine activates platelets and stimulates a thrombotic cascade, impairing clot lysis.[28] Subsequent adverse ischemic effects are specific to the affected organ.[28]

Gastrointestinal complaints include abdominal pain, nausea, or vomiting. Clinicians also must consider body packing (drug smuggling) in a patient who has a history of cocaine use and gastrointestinal symptoms.[26]

Co-Ingestion

Cocaine is commonly ingested with other substances. Concurrent use with alcohol is common and particularly dangerous, since the compounds react to form cocaethylene.[26,39,40] This metabolite is dangerous because it increases the half-life and cardiotoxicity of cocaine.[26,39,41,42] Studies have shown that the presence of cocaethylene in urine increases the likelihood of requiring admission to an intensive care unit.[27,41]

Cocaine also is used frequently with a potent opioid, such as heroin or fentanyl, a combination known as a "speedball." This is particularly dangerous since the stimulant effects of cocaine can mask the sedating opioid effects, resulting in a user taking a large opioid dose. Differences in drug half-life can lead to fatal overdose.[26] Severe agitation after naloxone administration should prompt consideration for the presence of a sympathomimetic agent, such as cocaine.

Testing

Cocaine is metabolized rapidly in the body to form the metabolite benzoylecgonine (BE). BE is detected in urine for two to three days after the last use.[28,29] However, even very recent use of large quantities of cocaine can fail to result in a positive drug screen if there has not been substantial time for it to be converted to the metabolite.[43] Urine drug testing cannot address the specific time frame of use. Very few substances are structurally similar to BE, and false positives are unlikely in cocaine screens.[28,29,43] False negatives are possible, particularly if there is a large volume of urine in the bladder, or if urine has been diluted by fluid administration.[28]

Management

Initial management focuses on stabilization of the patient's airway, breathing, and circulation. Hypotension should be managed with fluid resuscitation. If a patient requires endotracheal intubation, cocaine toxicity is a relative contraindication to the use of succinylcholine. Cocaine toxicity can result in rhabdomyolysis and hyperkalemia, which can be further exacerbated by succinylcholine administration and result in life-threatening dysrhythmias.[28]

Elevated temperature is a marker of a poor prognosis and should be addressed promptly. Hyperthermia can be managed with external cooling measures, such as misting with convection cooling or ice water immersion.[28,44] Sedation and paralysis with intubation should be considered. Medications to prevent shivering should not be given due to ineffectiveness and the potential for adverse effects. Meperidine can further increase the risk of serotonergic toxicity.[28] Chlorpromazine can increase the risk of seizures.[28]

Agitation is common in cocaine toxicity and should be treated according to severity. Benzodiazepines are preferred over antipsychotics for management of altered mental status.[28,44] Midazolam and diazepam are preferred by some over lorazepam due to a delay in the time to peak effect.[28,45] Large doses of benzodiazepines with frequent redosing often are required due to cocaine-induced alterations in receptor function.[28] Propofol or rapidly acting barbiturates can be administered as last-line agents.[28] Insufficient evidence exists for routine use of ketamine in cocaine-induced agitation.[28] Clinicians also should consider hypoglycemia secondary to catecholamine discharge as an etiology of altered mental status. A point-of-care glucose level should be obtained, and hypoglycemia should be managed with prompt dextrose administration.[28]

Chest pain in cocaine toxicity can indicate cardiovascular pathology, such as myocardial ischemia or aortic injury. The workup should include appropriate vascular imaging, ECG, and cardiac markers. If there is concern for ischemia, an approach similar to the treatment of coronary artery disease should be pursued. Hypoxia should be treated aggressively with high-flow oxygen to overcome supply-demand mismatch.[28] Aspirin and heparin products are considered safe in cocaine toxicity with careful consideration of the risk-benefit ratio.[28] Chest pain secondary to vasospasm may improve with morphine, nitroglycerin, and benzodiazepines.[28]

Abnormal vital signs should be addressed. Sedation and management of agitation frequently result in resolution of hypertension and tachycardia. However, if vital sign instability persists, a direct-acting vasodilator, such as nitroglycerin or nicardipine, or a pure alpha-adrenergic antagonist (phentolamine) is the preferred agent.[28,29] No concrete blood pressure goals exist. However, hypertension can further exacerbate chest pain and also increases the risk of aortic injury or intracranial hemorrhage because of elevations in shear force.[28,29] In 2008, the American Heart Association released a scientific statement recommending against the use of pure beta-blocking medications in the management of cocaine-induced chest pain.[46] In theory, this could result in unopposed alpha agonism, resulting in life-threatening hypertension and vasospasm. Use of beta-antagonists remains contraindicated due to lack of an established safety profile and the availability of other therapies.[28] However, prior to attempting to treat tachycardia, clinicians should confirm it is not compensatory for low cardiac output.[28]

Other cardiovascular abnormalities in cocaine toxicity include dysrhythmias. Wide complex tachycardias can occur secondary to sodium channel blockade.[28,45] Wide complex tachycardias can be managed with sodium bicarbonate and, if this fails, lidocaine can be considered.[28,44,45] Other conduction abnormalities caused by cocaine toxicity include QT prolongation secondary to potassium channel blockade.[28] This can increase the risk of torsades de pointes. Cocaethylene, the metabolite of concurrent alcohol and ethanol use, is particularly noted for its dysrhythmic effects.[28]

It is important to note that cocaine often is adulterated with many substances that can change the toxicity profile. Levamisole is one agent that often is added to cocaine to increase bulk and weight. Levamisole is an antihelminth and immunomodulator that can result in hematologic changes,

Table 2. Summary: Cocaine	
Effects	• Stimulant • Used intranasally, intravenously, or smoked
Acute Toxicity Presentation	• Effects are increases in energy and euphoria • Sympathomimetic toxidrome: tachycardia, hypertension, chest pain, mydriasis
Complications	• Severe complications can involve multiple organ systems • Psychosis, ischemia, cardiac dysrhythmias, pulmonary toxicity
Management	• Respiratory and hemodynamic support • For management of agitation, benzodiazepines and sedation are first-line therapies • For ischemia and dysrhythmias, use standard practices • Monitor closely for pulmonary injury and evidence of respiratory distress • Maintain high index of suspicion for trauma because of cocaine's anesthetic properties

including neutropenia and agranulocytosis. Dermatologic effects of levamisole include vasculitis and purpura.[28] (*See Table 2.*)

Bath Salts/Cathinones

Synthetic cathinones have gained popularity during the past decade.[47-49] This class of psychoactive substances includes drugs with the street names "bath salts" and "flakka."[47-49] Bath salts include agents such as mephedrone, methylone, and methylenedioxypyrovalerone (MDPV).[48,50,52] The street drug "bath salts" resembles traditionally used Epsom salts or substances for dissolution in a bath tub by appearances only and do not share other pharmacologic properties.[48] These substances are an analog of a naturally occurring cathinone found in the khat plant.[51-53]

Bath salts are structurally similar to amphetamines, with effects similar to cocaine and methamphetamines.[47,54] They are manufactured and labeled so they can circumvent laws regulating sales of controlled substances set in place by the Drug Enforcement Administration (DEA) and Food and Drug Administration (FDA).[47,48,52,54] They are frequently labeled as "not for human consumption," "plant food," or "insecticides."[48,52,54] Street names include "bliss," "magic," "meow meow," and "zoom."[54] Their growing popularity is in part due to the ease of access, since these drugs can be purchased on the internet or in specialty tobacco and drug shops.[54] The only cathinone with medical use is bupropion, which is used for smoking cessation and other psychiatric indications.[51] All other synthetic cathinones are categorized as Schedule I by the DEA, which means they have high abuse potential with no accepted medical therapy use.[54]

Synthetic cathinones can be taken orally, rectally, intranasally, or used intravenously.[51,54,55] They are typically synthesized as a white or brown crystal-like powder.[51-55] The powder is then tableted, pilled, or adulterated prior to sale.[52] The composition is highly variable. There are limited data regarding the mechanism of action, pharmacokinetics, and toxicological profile. The duration of effect is highly variable; however, many are found to last two to four hours.[52]

Effects

Synthetic cathinones were designed as substitutes for MDMA and other stimulants.[52-53] Intended effects include increased sociability and libido.[55] At high doses, psychotic symptoms, such as hallucinations, paranoia, and agitation, can occur.[54] Intoxication can mimic acute psychosis. Psychiatric symptoms resolve in hours to days following use.[54] Self-mutilation and unusual, high-risk behavior can occur and are the second leading cause of death in cathinone toxicity. This behavior can occur without prior psychosis or depression.[52] Hangings are the most common fatal mechanism of self-harm, but gunshots, self-stabbings and lacerations, including slitting one's own throat, have been reported.[52]

Vital sign abnormalities are common in cathinone toxicity. Although bath salts do not cause one specific toxidrome, the presentation typically is consistent with that of a classic sympathomimetic toxicity.[51,52,54] In addition to psychosis, users will display agitation, tachycardia, hypertension, and hyperthermia.[47,51] Hyperthermia is the most critical vital sign abnormality.[47] Combative and violent behaviors often are present.[47,48,51] Co-ingestion with other psychoactive substances, particularly alcohol, is common.[48,51] Polysubstance use can further complicate toxicity profiles.

Serotonin toxicity can occur in cathinone toxicity.[51] This can present with increased tone and tremors, hyperreflexia, diaphoresis, and clonus. Clinical suspicion should be especially high in patients on other serotonergic medications, including monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), or tramadol.[56] Hyponatremia has been documented in cathinone toxicity. It is likely secondary to serotonin reuptake inhibition and related vasopressin release.[52] Rhabdomyolysis and acute kidney injury also have been reported.[51,53] Patients also must be evaluated closely for any evidence of compartment syndrome.[52]

Given the broad presentations associated with cathinone toxicity, it is important to consider use in any patient presenting with agitation, anxiety, and psychosis in the setting of a negative urine drug screen. Clinicians should be aware that cathinone toxicities can present with unusual findings, such as an unexplained acute kidney injury in an otherwise healthy patient.[54] Death has been documented secondary to cathinone toxicity and is frequently in association with metabolic acidosis, acute kidney or liver injury, disseminated intravascular coagulation, hyperthermia, cardiovascular abnormalities, or hyponatremia.[47,51,52,54,55] Sudden cardiac death has been reported.[51]

Testing

Many synthetic cathinones, including bath salts, are not detected on routine drug screens.[51,54,55,57] Recreational use of bath salts can result in a false-positive drug screen for phensyclidine (PCP).[50] Given the lack of testing available, clinicians must maintain a high index of suspicion for toxicity. Cathinone use should be considered in patients with evidence of psychiatric

symptoms or other unusual presentation in the setting of a negative urine drug screen. Advanced testing panels are available for some cathinones; however, testing does not typically inform acute management due to delays in obtaining results. Advanced testing is considered in some select cases, but it is not routinely recommended or necessary in all patients. Negative confirmatory testing may not fully exclude exposure to these agents because of the continuous development of new compounds.[58]

Management

There is no antidote for cathinone toxicity. Initial management should emphasize symptomatic and supportive care with airway stabilization, hydration, and sedation, if indicated. Patients must be monitored closely for arrhythmias, myocardial ischemia, rhabdomyolysis, compartment syndrome, and electrolyte abnormalities. Hyponatremia can occur and should be monitored closely and treated with fluid restriction and hypertonic saline if severe. Volume depletion, rhabdomyolysis, and acute kidney injury should be managed with isotonic fluids.[50]

Agitation and psychosis can be managed with benzodiazepines and sedation.[51] Benzodiazepines are preferred over antipsychotics. Antipsychotics may lower the seizure threshold. Additionally, antipsychotics can worsen the risk of muscle injury and rhabdomyolysis due to the risk of extrapyramidal symptoms and neuroleptic malignant syndrome.[51-53] If agitation is refractory to benzodiazepines, atypical antipsychotics can be considered with caution. Isolated dystonia can be treated with diphenhydramine.[54]

Hyperthermia is the most concerning finding in cathinone toxicity and can be life-threatening. Benzodiazepines can help manage hyperthermia. Refractory or severe hyperthermia should immediately prompt more aggressive cooling interventions. If all else fails, immediate paralysis with a nondepolarizing muscle relaxant and endotracheal intubation can be considered in cases with severe life-threatening hyperthermia. Antipyretics have no role in cathinone-induce hyperthermia.[56]

Clinicians also should maintain a high index of suspicion for polysubstance use. Drug screening should be performed to evaluate for other potentially ingested substances. (*See Table 3.*)

Table 3. Summary: Bath Salts/Cathinones

Effects	• Increased energy and euphoria
Acute Toxicity Presentation	• High doses can cause agitation and psychosis; propensity to engage in self-harm
Complications	• Severe: life-threatening hyperthermia, rhabdomyolysis, hyponatremia, serotonin toxicity
Management	• Benzodiazepines are first-line therapy for management of agitation and hyperthermia • Aggressive measures for hyperthermia

Cannabinoids/Synthetic Cannabinoids

Marijuana is the most commonly used illicit substance, with nearly 22 million active users ages 12 years and older.[59] Marijuana is considered a cannabinoid because it binds the cannabinoid receptors in the brain.[60] These receptors are CB1 and CB2. Marijuana contains many different types of cannabinoids, which are collectively referred to as "cannabis."[59] Of the many cannabinoids that are found in marijuana, the primary psychoactive ingredient is delta-9-tetrahydrocannabinol (Δ9 -THC).[59] Many other substances bind CB1 and CB2 receptors and are also considered cannabinoids. These include synthetic compounds designed in labs, as well as molecules that are found naturally in the brain.[59] Exposures to cannabis products are anticipated to increase dramatically with the loosening of regulations regarding use. This has already occurred in states with legalization of recreational use.[61]

Cannabis appears as a green mixture of dried plant material from *Cannabis sativa*. It can be rolled and smoked, inhaled from a bong or vaping device, or mixed with food or drinks and ingested.[59,60] If it is smoked, the effects are felt within minutes. Ingestion results in a delayed and unpredictable onset, which can be delayed one to three hours.[59,60] Street names of marijuana include "weed," "herb," "pot," "grass," "bud," "ganja," and "Mary Jane."[60]

Another class of illicit substance that binds cannabinoid receptors is the synthetic cannabinoids (SC). SCs were designed as research chemicals that bind the same CB1 and CB2 as cannabis, but they have no relation to the cannabis plant.[59] These substances are made in labs as liquids that then are sprayed on plants so that they have the same natural appearance as marijuana and can be smoked.[59,62] SC use is increasing, in part due to ease of access. SCs can be purchased online and in stores that sell tobacco and drug paraphernalia.[59,62]

SCs are much more dangerous than marijuana for several reasons. Although the active ingredient in marijuana is a partial agonist, SCs contain substances that are much more powerful and act as full agonists at the CB1 and CB2 receptors.[62,63] Additionally, the method by which SCs are sprayed on plants can result in unequal distribution and high concentrations of the substance.[64] Street names of SCs include "K2," "spice," and "kronic."[62] Agencies such as the DEA and FDA recognize the danger of these new substances. However, SCs are frequently labeled with "not for human consumption," and sold as incense, potpourri, or deodorizers as a "legal high."[62] Constantly changing formulations allows for evasion of enforcement agencies and detection methodology.[64]

Effects

Marijuana, SCs, and other cannabinoids by definition bind the cannabinoid receptor. This results in similar intended effects.[65,66] At lower doses, the effects of both marijuana and SCs include euphoria, relaxation, and heightened sensory perception.[59] Some individuals may experience anxiety, panic, or even acute psychosis, particularly at higher doses.[60] Cannabinoids can cause impaired thinking, balance, coordination, and delayed reaction time.[60] Studies have found associations between elevated blood THC and driving impairment.[67] These effects can increase the risk of trauma.

Cannabinoid use can result in vital sign abnormalities. Tachycardia is common, and an individual can have an increase in heart rate by up to 50 or more beats per minute. Users may be at increased risk of myocardial ischemia within the first hour after

use.[60] Effects on blood pressure can vary and include hypertension or orthostatic hypotension.[59,60] Postural hypotension can result in an increased risk of falls and subsequent trauma.[60] Cannabinoids cause the airways to relax and become enlarged.[59,60] There is a lack of cannabinoid receptors in the brainstem, which explains the lack of coma and respiratory depression with cannabinoid toxicity.[59] If these findings are present, this may indicate intentional concomitant ingestion of a central nervous system (CNS) depressant such as ethanol.[59] Additionally, synthetic cannabinoids can be adulterated with other substances, such as fentanyl, without the user knowing.[3] The physical exam also may reveal conjunctival injection.[60]

Clinical exam with SC toxicity is similar to that of marijuana toxicity but may present with more severe vital sign instability. A sympathomimetic toxidrome may be prominent, including mydriasis, slurred speech, and sweating, as well as nausea or vomiting.[68] Tachycardia and hypertension may be more severe and result in myocardial ischemia.[62,69] There are no consistent lab findings, but patients may have a mild leukocytosis (13,000-14,000) or hypokalemia.[68] Other reported adverse effects include renal failure requiring dialysis. Seizures have been documented in association.[59,68,69] There is a report that a single dose of SCs can induce acute psychosis.[64] Vomiting is more prominent with SC toxicity than with marijuana use.[64] Additionally, SCs are not subjected to any form of quality control and can have any number of chemicals with their own unique toxicity profiles.[59] These substances can include cathinones, methylxanthines, and long-acting beta agonists, such as clenbuterol.[59]

Reports suggest that SCs have an increased risk of cardiovascular complications compared to marijuana use. Both supraventricular and ventricular arrhythmias have been reported.[70] Tachycardia and life-threatening tachydysrhythmias requiring cardioversion have been reported.[59,71] An ECG may demonstrate QT prolongation, which can decompensate to torsades de pointes.[71]

While SCs were historically associated with a sympathomimetic toxidrome, more recent outbreaks resulted in users with bradycardia and hypotension with and without neurologic dysfunction.[59,69] This likely is due to a later generation of SC agents rather than drug contaminants. This varied presentation of SC has contributed to additional diagnostic uncertainty requiring a high clinical index of suspicion for use.[72] Patients were treated with IV hydration and resolved without complication.[69]

Cannabinoid hyperemesis syndrome (CHS) is a pattern of nausea, cyclical vomiting, and abdominal pain observed in chronic, high dose cannabis users.[73] The underlying pathophysiology in CHS is not well understood.[74] Improvement in symptoms after taking a hot shower or bath can be a diagnostic clue and is frequently reported in association.[73-75] CHS is a diagnosis of exclusion, since there is no confirmatory testing or widely accepted diagnostic criteria. Case reports have suggested that haloperidol may be effective in symptomatic management of CHS symptoms.[73,75] Ultimately, cannabinoid cessation is the most effective way to prevent recurrence of symptoms.[73-75]

Testing

There are many plasma and urine tests for marijuana and its metabolites. Urine tests frequently used in the emergency department can detect the presence of cannabinoids but not the degree of toxicity.[59] After discontinuation of use, metabolites can be detected in the urine of chronic users for weeks. These tests will not distinguish acute toxicity from prior use.[59,60] False positives for cannabis have been documented. Efavirenz, a medication used to treat human immunodeficiency virus, and several nonsteroidal anti-inflammatories have been documented to result in false-positive marijuana screens.[76]

SCs do not contain a specific cannabinoid that is detected by routine drug screening. Urine drug screening for cannabis (Δ9 -THC) will be negative. Sometimes SCs are used by those who desire negative urine drug screening and perceive it as a "legal high."[77]

Management

Early management should emphasize supportive care, including airway support and any necessary cardiovascular resuscitation. Patients may be acutely agitated, especially in the setting of SC use. Seizures and agitation should be treated with benzodiazepines as first-line therapy.[64] If there is clinical suspicion of SC toxicity, an ECG should be obtained.[71] This is particularly true in patients taking other QT-prolonging medications, such as methadone.[71] Medications that can prolong QT interval, such as antipsychotics, should be avoided.[71] (*See Table 4.*)

Table 4. Summary: Cannabinoids

Effects	• Cannabinoids include natural and synthetic substances that act on cannabinoid receptors, found in high concentrations in the brain • At low levels: euphoria and relaxation • At high levels: acute psychosis, cardiovascular complications, and seizures
Management	• Supportive care • Close monitoring for cardiovascular abnormalities

Body Packing and Stuffing

"Body packing" is the term used to describe the intracorporeal concealment of illicit substances for the purpose of smuggling.[78] Drugs are ingested or inserted into the rectum or vagina, then later evacuated with laxatives or enemas.[78] Body packing can conceal large amounts of drugs that are professionally packaged to ensure successful concealment.[79] Case reports have shown that about 1 kg of drugs can be divided into 50-100 smaller packets and smuggled this way.[80] Drugs commonly transported by body packing include heroin, cocaine, amphetamines, and ecstasy.[78]

Body packers may exhibit suspicious behavior, such as refusal to eat or drink anything or to use the toilet. They may sit motionless. Medical issues may arise because of the size and number of packets ingested or rupture of the packets.[78] If packets rupture, the toxidrome will depend on the contents of the concealed product.[78] Rupture is rare in body packing due to careful packaging. Medical complications typically arise from intestinal obstruction or perforation.[80]

"Body stuffing" refers to the unplanned spontaneous concealment of small quantities of drugs that have not been packaged with the intent of ingestion.[79,80] Often, these are smaller quantities than in body packing and typically are less than 1 g.[80] Unlike body packing, stuffing of drugs is not professional or planned out. Stuffing typically consists of several layers of cellophane that have poor resistance in the intestine. Body stuffers have a higher risk of rupture and leakage than body packers.[80]

General Management

The presentation of body packers and stuffers may vary and ranges from asymptomatic to fatal overdose. In the absence of rupture, leak, or intestinal obstruction, the physical exam often is normal.[80] Initial diagnosis of body packing often relies on imaging. Plain abdominal radiography often is the first screening test. Most studies report a sensitivity of 85% to 90% for detection of contraband, but other studies have reported lower sensitivities of 47%.[81] Plain radiography also can fail to visualize the full burden of contraband concealed in an abdomen.[81] Ultrasound has poor sensitivity.[81] Abdominal CT has a sensitivity approaching 100% and is the preferred imaging modality.[81] Urine drug screening may be more useful in body stuffing, given the increased likelihood of leak or rupture.[80]

Management of body packing and stuffing varies based on clinical presentation. Body packers without evidence of obstruction or intoxication can be given osmotic laxatives (such as lactulose) or polyethyleneglycol (PEG) and observed until complete expulsion of the packets.[80] If there is evidence of obstruction or perforation, immediate surgical intervention is required.[81] If body packers display evidence of drug toxicity, management varies based on the drug packed. Depending on severity, heroin and marijuana can be managed supportively. Opioid antagonists should be administered for opioid overdose. Cocaine or amphetamine intoxication can be fatal and requires surgical decontamination in addition to aggressive management of hypertension, seizures, and ventricular dysrhythmias.[81-82]

Management of body stuffers is not well documented, given the less predictable nature of packet rupture and leakage. Abdominal CT is the gold standard for diagnosis. Some reports suggest the use of activated charcoal.[80] Similar to body packing, evidence of a sympathomimetic toxidrome can be an indication for immediate surgical intervention.[80] Failure of packages to pass should be managed on a case-by-case basis, with a general preference for the most conservative approach.[80]

Conclusion

Drugs of abuse are frequently encountered in the trauma setting. Intoxication presentations can be variable and may be challenging to differentiate by clinical examination. Urine drug screens may not be reliable, since they can result in false positives and false negatives. In most cases, agitation can be managed with benzodiazepines. Emphasis should be placed on supportive care with close monitoring of respiratory and cardiovascular status.

The second part of this two-part series will characterize substances with sedative and depressant characteristics, such as alcohol, sedative-hypnotics, and opioid medications.

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CME/CE Questions

1. A 21-year-old female is brought to the emergency department (ED) by her friends after sustaining injuries to her right hand during a fight. The patient admits to using ecstasy at a dance club earlier in the night. What electrolyte disturbance can occur with ecstasy use and result in altered mental status?
   a. Hypokalemia
   b. Hypernatremia
   c. Hyponatremia
   d. Hypoglycemia

2. A 54-year-old male is being discharged from the hospital after an admission for minor injuries sustained in a motor vehicle collision. He is reviewing his lab work and becomes alarmed by the results of his urine drug screen (UDS) taken at the time of admission. His UDS was positive for amphetamines. The patient takes several home medications for depression and blood pressure but does not admit to any recreational substance use. What should this patient know about his positive results?
   a. No known therapeutic medications can result in false-positive amphetamine results on a UDS.
   b. Amphetamines can have many false-positive and false-negative results on a UDS.
   c. The results indicate that he is in denial of his substance use disorder.
   d. His positive UDS was likely the result of a lab error.

3. A 24-year-old male is brought to the ED by police after yelling at shoppers in a mall. He became aggressive with police and required physical restraint before being brought to the hospital. His chart notes a history of methamphetamine use. On arrival to ED, the patient is agitated and has a body temperature of 41°C. What medication is first-line in this patient?
   a. Beta-blocker therapy
   b. Benzodiazepines
   c. Dantrolene
   d. Diphenhydramine

4. A 35-year-old female is brought to the ED after a patio collapsed at a party. The patient fell 20 feet but does not have any obvious external injuries. She appears anxious and complains of sharp chest pain. She admits to cocaine use shortly before the fall. What physical exam findings might she have secondary to her substance use?
   a. Mydriasis, hypertension, tachycardia
   b. Mydriasis, bradycardia, hypothermia
   c. Clonus, hypothermia, mydriasis
   d. Miosis, clonus, hypothermia

5. Cocaine often is ingested with other substances that can complicate management. Cocaethylene is a compound that results in an increased half-life and toxicity of cocaine. Cocaethylene is formed by the use of cocaine with what other substance?
   a. Nicotine
   b. Heroin
   c. Ethanol
   d. Methamphetamines

6. An 18-year-old male is brought to the ED after attacking a neighbor's dog. The patient has injuries to his face and neck. He appears paranoid and agitated. He is tachycardic, hypertensive, and hyperthermic. His parents provide a photo of a substance labeled "insecticide" that was found in his room. The patient's urine drug screen is negative. What drug of abuse likely resulted in this patient's acute toxicity?
   a. Ecstasy
   b. Ethanol
   c. Cocaine
   d. Synthetic cathinone

7. Synthetic cannabinoids (SC) are man-made substances that bind the same CB-1 and CB-2 receptors as cannabis but are not derived from the cannabis plant. Effects of both SC and cannabis can include euphoria and relaxation at low doses. What is an important difference in toxicity of SCs compared to marijuana?
   a. SCs are more likely to have a positive urine drug screen than with cannabis use.
   b. SCs may result in a greater degree of vital sign abnormalities and cardiovascular complications than with cannabis use.
   c. SCs are synthetic substances that are subjected to strict quality control methods.
   d. SC toxicity can be treated with a Food and Drug Administration-approved antidote, whereas cannabis toxicity is managed supportively.

8. A sympathomimetic toxidrome can present with agitation, tachycardia, hypertension, and hyperthermia. Many drugs of abuse can result in this presentation, and it may be challenging to determine what substance has been ingested. What medication is recommended first-line for agitation in this setting?
   a. Benzodiazepines
   b. Ketamine
   c. Propofol
   d. Diphenhydramine

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