Substance Use, Intoxication, and Withdrawal in the Critical Care Setting

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KEYWORDS

• Critical care • Substance-related disorders • Opioid-related disorders
• Stimulant-related disorders • Synthetic cannabinoid • Synthetic cathinone
• Cocaine • MDMA

KEY POINTS

- Effects of substance use, including intoxication and withdrawal, are commonly encountered, although often difficult to detect in critically ill patients.
- Management is directed at the specific intoxication or withdrawal syndrome.
- Comprehensive management of patients with complications related to substance use includes engagement in longitudinal management of the underlying substance use disorder.

INTRODUCTION

Substance use disorders are common, although the prevalence in the inpatient setting is not well defined. In 2012, it was estimated that 11% of adult hospitalizations involved substance use disorders alone or in combination with mental health disorders, likely an underestimation given the frequency of underdiagnosis of substance use disorders.[1] The most common diagnoses were alcohol-related disorders, drug-induced mental disorders, opioid-related disorders, cocaine-related disorders, and hallucinogen-related disorders. The most common demographic was male Medicaid or Medicare recipients between the ages of 18 and 44 (drug-induced mental health, opioids, hallucinogens) or 45 and 64 (alcohol, cocaine). From a community sample,

Disclosure Statement: The authors have nothing to disclose.
This article is an update of an article previously published in *Critical Care Clinics*, Volume 24, Issue 4, October 2008.

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Crit Care Clin 33 (2017) 543–558
http://dx.doi.org/10.1016/j.ccc.2017.03.003 **criticalcare.theclinics.com**

approximately 19% of hospitalized patients had evidence of unhealthy substance use, of whom most were admitted to academic teaching service.[2] Recent trends point to increasing numbers of hospitalizations from overdose in persons with opioid use disorder (OUD), and intoxication with designer drugs such as synthetic cannabinoids (SCB), synthetic cathinones (bath salts), and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy).[3–6]

The epidemiology of substance use disorders in the critical care setting is largely unknown. Estimates from one community hospital noted 14% of intensive care unit (ICU) admissions were non–tobacco substance related.[7] Furthermore, substance use has been identified as a risk factor for hospitalization for diabetic ketoacidosis (DKA), with longer subsequent ICU stays compared with DKA unrelated to substance use.[8] In addition, substance use is associated with injury and trauma, including motor vehicle injuries, falls, drownings, thermal injury, homicide, and suicide.[9–12] In the United States, up to half of trauma beds are occupied by patients involved in alcohol-related traffic accidents.[10,13] Management of critically ill or injured patients who use illicit substances is complicated by both the intoxicating and the withdrawal effects of those substances. This review addresses the presenting features and management of non–alcohol-related intoxication and withdrawal syndromes of commonly used illicit substances likely to impact the care of a critically ill patient. Complications of alcohol intoxication and withdrawal are reviewed separately. Substances with mild intoxication and withdrawal syndromes unlikely to influence the care of critically ill patients, such as nicotine and natural cannabis, are not covered.

GENERAL CRITICAL CARE ISSUES RELATED TO SUBSTANCE USE

Overdose

Overdose may be suspected from history taken from patients or family, or the recognition of an overdose syndrome. Importantly, when caring for a person with altered mental status from suspected intoxication, HIPAA (Health Insurance Portability and Accountability Act) does not prevent providers from obtaining information from or giving information to close relations if such disclosure is thought to be important to the care of the patient.[14] General management principles include providing basic life support and airway management, obtaining intravenous (IV) access, vital sign monitoring, reviewing all potential medications the patient may have access to, a focused examination, including evaluation of pupils and a search for transdermal patches and signs of injection drug use, such as “track marks,” electrocardiogram, and basic laboratory work to review renal and liver function and to exclude other causes such as infection or myocardial infarction, as well as urine and serum toxicologies.[9]

Agitation

Agitation may result from intoxication or withdrawal, and management can depend on the specific substance or substances used. Management begins with providing a low stimulation environment. In terms of pharmacotherapy to manage agitation, benzodiazepines are often used. Antipsychotic medications can be used as second-line agents. Restraints should generally be avoided if possible and may worsen agitation and risk of sudden death, particularly in the setting of stimulant drug use.[15,16]

Withdrawal

Withdrawal syndromes are the response to abrupt discontinuation, decreased dosing, or altered metabolism of a substance to which there is physiologic dependence and are common to many substances. These syndromes commonly complicate the care of critically ill patients.[9,17,18] It may be especially challenging to treat patients with

substance withdrawal syndromes because of an unknown history of substance use, altered mental status, or complex physiologic responses resulting from the presenting illness, which can be confused with withdrawal.[19] In addition, patients may be withdrawing from several substances upon presentation. General principles regarding the management of substance withdrawal syndromes include use of a symptom-triggered approach, substitution of a long-acting replacement for the misused drug in gradual tapering doses, and establishing a plan for long-term management of the underlying substance use disorder.[20] When assessing for superimposed substance withdrawal, the critical care team must consider potential polysubstance use.

Iatrogenic Dependence

It is important to consider development of iatrogenic physiologic dependence on medications in patients (with or without a history of substance use disorder) who have extended hospitalizations. Patients with critical illness often require prolonged stays in the ICU as well as large cumulative doses of opioids and sedatives to facilitate pain control, anxiety, and sedation. Acute withdrawal syndromes may present in these patients as a result of rapid weaning for transitions to lower levels of care. Continuous infusions of opioids or benzodiazepines may place patients at higher risk for the development of acute withdrawal than would administration of these medications by bolus injection.[9] It is up to the critical care team, therefore, to consider implementation of weaning protocols, consisting of a 5% to 10% reduction per day, early on in the course of a patient's ICU stay.[21]

CRITICAL CARE ISSUES RELATED TO SPECIFIC SUBSTANCES

Opioids

In 2015, an estimated 2.6 million Americans over the age of 12 met criteria for OUD.[22] Opioids include substances that are derived directly from the opium poppy (such as morphine and codeine), the semisynthetic opioids (such as heroin and hydromorphone), and the purely synthetic opioids (such as methadone and fentanyl). Opioid medications primarily act as agonists at the μ-opioid receptor and may be prescribed or obtained illegally. Common means of administration include ingestion, nasal insufflation, inhalation, and injection via IV, intramuscular, or subcutaneous routes. In the course of managing critically ill patients with OUD, clinicians should be vigilant for associated comorbid medical conditions that can complicate care, such as acute bacterial infections, HIV, and hepatitis C (HCV) –related problems.[23,24]

Intoxication and overdose

Opioid intoxication leads to impaired judgment, psychomotor agitation or depression, and pupillary constriction (**Table 1**).[25] Opioid overdose should be suspected in patients with any combination of depressed mental status, decreased respiratory rate or chest wall rise, and miotic pupils.[26] Patients who are not protecting their airway, are hypoxemic or hypercarbic, or have a respiratory rate less than 10 to 12 breaths per minute should receive bag-valve mask ventilation and have IV naloxone administered.[26] Naloxone can also be administered intramuscularly, intranasally, or via endotracheal tube depending on the clinical scenario. Because the effects of naloxone only last 20 to 90 minutes, suspected overdoses involving long-acting opioids may require repeat dosing or IV infusion. Orotracheal intubation is required if the airway is difficult to maintain or respiratory rate does not improve after escalating doses of naloxone. Importantly, symptoms of opioid withdrawal should be expected after administration of naloxone in patients with physiologic opioid dependence.[9]

Table 1
Opioids intoxication and withdrawal in critically ill patients

Substance	Intoxication	Withdrawal	Associated Complications
Opiates • Morphine, codeine Semisynthetic opioids • Heroin, buprenorphine, hydromorphone Synthetic opioids • Fentanyl, methadone	Depressed mental status Impaired judgment Pupillary constriction Hypoventilation	Fever, tachycardia, hypotension Restlessness, irritability, insomnia Yawning, diaphoresis, piloerection Mydriasis, lacrimation, rhinorrhea Nausea, diarrhea, abdominal pain Myalgia, arthralgia	Overdose death Injection-related infection HIV HCV

Withdrawal

The severity of opioid withdrawal varies with the dose, duration of substance use, and route of administration.[27] The time to onset and duration of opioid withdrawal symptoms depend on the half-life of the drug being used. For example, withdrawal from heroin may begin 4 to 6 hours after the last use, may peak within 36 to 72 hours, and may last for 7 to 14 days, whereas withdrawal from methadone may not occur until 36 hours after the last use.[28,29] Symptoms include diarrhea and vomiting, thermoregulation disturbances, insomnia, muscle and joint pain, anxiety, and dysphoria. The severity of opioid withdrawal can be graded using instruments such as the Clinical Opioid Withdrawal Scale and Objective Opioid Withdrawal Scale, although neither scale has been validated in an ICU setting.[28] Although opioid withdrawal includes no life-threatening complications (unlike alcohol or benzodiazepine withdrawal syndrome), the acute opioid withdrawal syndrome causes marked discomfort, frequently leads to a relapse to drug use, complicates other medical and surgical conditions, and can strain patient-doctor relations.[28,29]

Management of opioid withdrawal begins by reassuring patients that their symptoms will be taken seriously, providing general supportive measures, and initiating specific pharmacologic treatment. Pharmacologic options include opioid agonist therapy (OAT, methadone, and buprenorphine), alpha-adrenergic agents, and other non–opioid medications that can provide symptom relief.[28] Studies indicate buprenorphine and methadone have similar effectiveness for managing withdrawal, and alpha 2 adrenergic agonists are more effective than placebo at preventing severe withdrawal.[30,31] The choice of pharmacotherapy, therefore, may be influenced by the presence and severity of patients' underlying medical comorbidities, patient preference, and medication interactions.[28,32] Methadone and buprenorphine not only have the advantage of stabilizing withdrawal but also can be continued for long-term management of OUD, depending on patient preference and provider availability. Whenever possible, hospitalized patients with OUD should be engaged in conversations about long-term management of their OUD.[28]

Careful initiation and titration of various medications can treat opioid withdrawal. Methadone initiated at 10 to 30 mg daily and slowly titrated to a total daily dose of 20 to 40 mg is usually sufficient to treat withdrawal symptoms.[28,33,34] Alternatively, buprenorphine can be initiated once moderate opioid withdrawal is evident using standard protocols.[35] Buprenorphine initiated too early can precipitate withdrawal. Limitations to the use of buprenorphine in the treatment of OUD in the ICU are its sublingual

administration and issues with regard to pain control and sedation. Typical doses of clonidine used to treat opioid withdrawal range between 0.1 and 0.2 mg every 6 hours with close monitoring of blood pressure. Side effects include sedation, dry mouth, orthostatic hypotension, and constipation.

Pain management in patients with opioid use disorder, including patients receiving opioid agonist therapy

Acute pain related to trauma and surgical procedures is common in critically ill patients. Issues unique to patients with OUD include provider misconceptions, opioid tolerance and decreased pain threshold, and concurrent OAT.[28,36] Provider misconceptions include the notions that the medication used for OUD should cover the acute painful condition, use of opioids for analgesia may result in relapse, addition of opioid analgesia to opioid maintenance is likely to result in central nervous system (CNS) and respiratory depression, and complaints of pain may constitute "drug-seeking" behavior. In general, patients should be maintained on medications to treat OUD (treatment programs should be contacted to verify dose and to ensure easy transition from inpatient hospital stay back to the community) and supplemented with short-acting opioids titrated to pain relief as well as use of non–opioid medications and techniques to treat pain. In ICU patients, physiologic responses such as heart rate and blood pressure may have to be used to monitor pain relief in patients maintained on sedation and mechanical ventilation. It should be recognized that patients with a history of OUD will likely exhibit tolerance to opioid medications and may require higher than usual doses to treat pain.[28,36]

Treatment of acute pain in patients maintained on buprenorphine for opioid dependence may be especially challenging because buprenorphine has a higher affinity for the μ-opioid receptor than do other opioids. Options for pain management in patients maintained on buprenorphine include discontinuation of buprenorphine treatment and transition to full agonist opioids for treatment of pain; transition to methadone for treatment of OUD with additional opioids to treat pain; division of daily dose of buprenorphine to 3 to 4 times daily to take advantage of analgesic properties of the medication; or continuation of buprenorphine with titration of short-acting opioids.[28,36]

Benzodiazepines

Benzodiazepines are one of the most widely prescribed psychotropic medications in the United States[37] (**Table 2**). Benzodiazepine medications act at the gamma-aminobutyric acid (GABA) receptor to amplify the effect of circulating GABA, thus leading to increased inhibitory tone and clinical sedation, muscle relaxation, and anxiolysis.[38] They are commonly prescribed for anxiety and sleep disorders, abortive therapy for seizure disorders, and management of alcohol withdrawal. Benzodiazepines

Table 2
Benzodiazepine intoxication and withdrawal in critically ill patients

Substance	Intoxication	Withdrawal	Associated Complications
Short acting • Alprazolam, midazolam Intermediate acting • Lorazepam, oxazepam Long acting • Diazepam, clonazepam	Depressed mental status Impaired judgment Decreased attention and memory Slurred speech Incoordination	Tachycardia, hypertension Agitation, hallucinations Tremor, seizure	Overdose death, especially with coingested opioids

are most commonly administered by oral ingestion, and more lipophilic (eg, diazepam) and short-acting (eg, alprazolam) formulations are most reinforcing.[38,39] It is important to note that illicit benzodiazepines are commonly coingested with other illicit substances, such as opioids, increasing the risk for overdose.[40]

Intoxication and overdose

Benzodiazepine intoxication is marked by impaired judgment and attention, depressed mental status, incoordination, slurred speech, and unsteady gait.[41] The risk of death resulting from benzodiazepines when used in isolation is relatively small; however, the risk of overdose and death increases substantially when benzodiazepines are coadministered with opioid medications, or other CNS-depressing agents.[42,43] Management of suspected benzodiazepine overdose is supportive. Flumazenil has a high-binding affinity for the GABA-A receptor but weak intrinsic action and thus can be used to reverse the intoxicating effects of other benzodiazepines. Its use, however, has fallen out of favor in the management of patients with depressed mental status who have known or suspected benzodiazepine ingestion due to the risk of precipitating seizures and arrhythmias.[43,44] In addition, intentional overdoses often involve coingestion of multiple medications, and benzodiazepines may actually have a stabilizing effect if the coingestants are prone to cause seizures, such as tricyclic antidepressants. Flumazenil may have a role, however, in reversing iatrogenic benzodiazepine overdose, for example, during procedural sedation, particularly when the chronicity of benzodiazepine use and other coadministered medications is known to the provider.[44]

Withdrawal

Benzodiazepine withdrawal is characterized by autonomic hyperactivity and can result in agitation, hallucinations, tremor, and seizures.[9,41] The severity and duration of withdrawal symptoms depend, in part, on the half-life of the medication being used. Inpatient management follows the same treatment protocol as for alcohol withdrawal. Treatment generally consists of use of a long-acting benzodiazepine in tapering doses over time. The symptom-triggered approach has been shown to be as effective as the fixed-dose approach for the acute treatment of benzodiazepine withdrawal.[45] For patients who have been taking benzodiazepines chronically for anxiety, either prescribed or illicitly, a prolonged tapering schedule with a long-acting benzodiazepine and appropriate management of the underlying anxiety disorder should be considered in order to reduce the chance of relapse to benzodiazepine use upon hospital discharge.[46,47] Careful coordination of care with outpatient providers is necessary to minimize relapse.

Stimulants: Cocaine and Methamphetamine

The stimulant effects of systemically administered cocaine, derived from the *Erythroxylum coca* plant, are due to the reuptake inhibition of catecholamines at the synaptic cleft (**Table 3**). In the United States in 2006, 1.7 million people reported cocaine abuse or dependence.[48] Illicit cocaine is either snorted or injected as cocaine hydrochloride, or smoked in its free base form.

Methamphetamine was the fourth most common illicit substance responsible for Emergency Department (ED) visits in 2011, and prevalence of use may be increasing.[49,50] Methamphetamine is a highly addictive synthetic stimulant that stimulates catecholamine release and partially blocks catecholamine reuptake at the synaptic cleft. It is distributed in either a powder, a pill, or a highly purified crystalline form, referred to as “crystal meth.” Methamphetamine is commonly smoked, injected, ingested, or nasally insufflated.

Table 3
Stimulant intoxication and withdrawal in critically ill patients

Substance	Intoxication	Withdrawal	Associated Complications
Cocaine • Cocaine hydrochloride • Crack (freebase cocaine) Methamphetamine • Powder D-methamphetamine hydrochloride • Crystal D-methamphetamine hydrochloride	Euphoria Increased attention Paranoia, anxiety, agitation Disorientation Hallucination	Depressed mood Fatigue Vivid dreams Insomnia Increased appetite Psychomotor retardation Agitation	Injection-related infection Rhabdomyolysis Hyperthermia Seizure Cardiovascular • Myocardial infarction, aortic dissection, myocarditis, cardiomyopathy, chest pain Cerebrovascular • Hemorrhagic and ischemic stroke Pulmonary • Pneumothorax, "crack lung," bronchospasm, diffuse alveolar hemorrhage, pulmonary edema, pulmonary hypertension, bronchiolitis obliterans, pulmonary infarction

Intoxication and overdose

Stimulant intoxication leads to euphoria, increased alertness, mydriasis, tachycardia and hypertension, and reduced appetite, with increasing doses causing anxiety and paranoia, aggressiveness, disorientation, and hallucinations.[41,50,51] Stimulants can lower the seizure threshold and cause hyperthermia and rhabdomyolysis.[52] Apart from the infectious-related complications from IV administration, the most clinically significant effects of stimulant use are on the cardiovascular, cerebrovascular, and pulmonary systems.

Catecholamine excess leads to potent vasoconstriction, tachycardia, and propensity for arrhythmia. Stimulant-related chest pain is a common symptom and can be caused by a myriad of effects, including myocardial infarction, aortic dissection, cardiomyopathy, myocarditis, pneumothorax, and pneumomediastinum.[50,53–55] Myocardial infarction occurs from the vasoconstrictive effects, increased myocardial oxygen demand, increased platelet aggregation, and accelerated atherosclerotic changes in chronic users.[53,55] Management of cocaine-induced myocardial ischemia is focused on decreasing platelet aggregation (aspirin), decreasing vasoconstriction and hypertension (nitrates, calcium channel blockers), decreasing overall sympathetic tone (benzodiazepines), and in the appropriate setting, early reperfusion therapy with a preference for percutaneous coronary intervention over thrombolysis due to a cocaine-mediated increased risk of intracerebral hemorrhage. Beta-blockers should generally be avoided because they can theoretically increase vasoconstriction.[53] Treatment of methamphetamine-related cardiovascular complications is less well described, although management should proceed in a similar fashion to cocaine-related complications.

Current and prior stimulant use are risk factors for both hemorrhagic and ischemic strokes. Hemorrhagic strokes are likely sequelae of elevations in blood pressure and

aneurysm formation, whereas ischemic strokes are due to accelerated atherosclerosis and vasoconstriction.[54,56–58] Stroke management in patients with current or prior stimulant use is similar to management in patients without stimulant use. As in patients with acute myocardial ischemia, beta-blockers should be avoided.[54]

The pulmonary effects of inhaled stimulant use are more widely described for cocaine and include bronchospasm, pneumothorax, diffuse alveolar hemorrhage, pulmonary edema, pulmonary hypertension, bronchiolitis obliterans, eosinophilic lung disease, pulmonary infarction, and exacerbation of underlying lung disease.[53,59] "Crack lung" is a syndrome of fever, shortness of breath, pleuritic chest pain, hemoptysis, and hypoxemic respiratory failure occurring within 48 hours of free base crack inhalation. Management is supportive, and improvement is expected within 24 hours of presentation.[60]

Withdrawal

Cocaine withdrawal is characterized by depressed mood and any 2 of the following: fatigue, vivid dreams, sleep disturbance, increased appetite, psychomotor retardation, or agitation.[61] Cocaine withdrawal is typically mild and treated supportively.

Frequent methamphetamine use results in significant psychiatric withdrawal symptoms and intense craving following abrupt cessation. Depressive symptoms are a prominent feature of withdrawal and can last for several weeks.[50]

3,4-Methylenedioxymethamphetamine

MDMA, or ecstasy, is a popular club drug with potentially life-threatening side effects[62] (**Table 4**). The prevalence of use is unknown, although available data highlight an increasing number of ED-related visits with 10,227 in 2004, 17,888 in 2008, and 22,498 in 2011.[49] Formulations contain varying and unknown quantities of MDMA and may contain other drugs, including amphetamines, ketamine, dextromethorphan, acetaminophen, and caffeine.[62,63] MDMA stimulates serotonin, dopamine, and norepinephrine synaptic release and may also inhibit the reuptake of serotonin in the synaptic cleft. The clinical effects of MDMA ingestion begin within 1 hour and can last up to 6 hours.[63]

Intoxication and overdose

MDMA has stimulant and hallucinogenic properties, and intoxication typically results in elevated mood, empathy, and increased energy. Minor effects may include trismus, bruxism, tachycardia, xerostomia, and ataxia. Acute toxicity can include sudden death presumably from arrhythmia, hyperthermia, rhabdomyolysis, renal failure, serotonin syndrome, liver failure, and hyponatremia.[62,63] The risk of significant toxicity likely relates to individual factors (eg, polymorphism influencing MDMA metabolism), environmental factors (eg, temperature at the event where MDMA was ingested), and chemical factors (eg, the amount of MDMA and other substances present in the ingested pill).[62,64]

Table 4
3,4-Methylenedioxymethamphetamine intoxication and withdrawal in critically ill patients

Street Names	Intoxication	Withdrawal	Associated Complications
Ecstasy	Euphoria	Depressed mood	Sudden death (arrhythmia)
Molly	Increased empathy	Fatigue	Hyperthermia
E, Vitamin E	Increased energy		Rhabdomyolysis
XTC	Trismus		Acute kidney injury
Skittles	Bruxism		Acute liver failure
Many more…	Xerostomia		Serotonin syndrome
	Tachycardia		Hyponatremia

The constellation of hyperthermia, rhabdomyolysis, and multiorgan failure is a well-described syndrome associated with acute MDMA intoxication. The cause may be secondary excessive exertion without adequate hydration to balance the associated hyperthermia. Prolonged extreme hyperthermia may predict subsequent morbidity and mortality.[62] Temperatures greater than 42°C have been reported, and rapid cooling is an essential component of care. Dantrolene has reported benefits for MDMA-induced hyperthermia, particularly when severe, although its use has not been subject to randomized study.[62,64] Rhabdomyolysis can be significant with creatinine kinase levels increasing to the tens to hundreds of thousands units per liter. Management includes addressing the hyperthermia and aggressive IV fluid resuscitation.[65]

MDMA can independently cause serotonin syndrome, although the risk is higher if multiple drugs associated with serotonin syndrome are ingested, including amphetamines, cocaine, antidepressants, and opioids. Serotonin syndrome is characterized by altered mental status, increased muscle tone, clonus, hyperreflexia, and hyperthermia. Management of severe cases may include sedation, mechanical ventilation, rapid cooling, and pharmacologic paralysis.[62,66]

Hyponatremia results from a combination of MDMA-induced antidiuretic hormone release, increased thirst resulting from xerostomia, and intentional overhydration by users attempting to minimize the known effects of hyperthermia and dehydration.[67] The degree of hyponatremia can be significant and lead to cerebral edema. The patient can present with confusion and seizures and can rapidly decompensate to coma and death. Management of severely symptomatic patients, marked by encephalopathy and seizure, includes careful administration of hypertonic saline.[67]

MDMA has also been associated with acute hepatitis and in one study was reported as second only to antituberculosis medications in causing drug-induced acute liver failure.[68] Patients may present with encephalopathy, jaundice, abdominal pain, and raised bilirubin and transaminases. Treatment is supportive.[68,69]

Withdrawal

Withdrawal syndrome from chronic MDMA use is related to serotonin depletion and does not play a major role in the management of critically ill patients. Symptoms, including depression and fatigue, typically occur the day following use and can last up to 5 days.

Synthetic Cannabinoids

SCB have become increasing popular because of perceived safety, ease of access, favorable cost and legal status, and lack of detectability on routine toxicology screening (**Table 5**). ED visits related to SCB increased from 11,406 in 2010 to 28,531 in 2011.[49] Preparation of SCB for consumption typically begins with taking

Table 5
Synthetic cannabinoid intoxication and withdrawal in critically ill patients

Street Names	Intoxication	Withdrawal	Associated Complications
Spice	Euphoria	Anxiety	Psychosis
K2	Relaxation	Tachycardia, hypertension	Catatonia
Bliss	Anxiety, agitation	Tremor, diaphoresis	Self-mutilation
Black Mamba	Tachycardia, hypertension	Nausea	Seizure
Genie	Hallucination, delusion	Nightmares	Myocardial infarction
Bombay Blue	Nausea		Acute kidney injury
Many more…			Serotonin syndrome

plant material, which may or may not have inherent psychoactive properties, and saturating it with SCB dissolved in a solvent. As the plant dries, the SCB remains on the plant material.[70] Administration may be via ingestion, insufflation, or inhalation. Similar to delta-9-tetrahydrocannabinol (THC), SCB bind the cannabinoid (CB) 1 and 2 receptors.[71] Stimulation of the CB1 receptors are thought to mediate the psychotropic effects. SCB and metabolites have higher affinity than THC for CB receptors, and SCBs have higher potency when compared with THC.[72,73]

Intoxication and overdose

The amount of SCB remaining on plant material after the preparation process varies, which in part accounts for its unpredictable potency. They are ingested primarily for the euphoric effects. Toxicity from SCBs includes tachycardia, agitation, drowsiness, hallucinations, delusions, hypertension, nausea, confusion, dizziness, and chest pain.[70,72] Less commonly, SCB toxicity can lead to severe psychiatric, nervous system, cardiovascular, renal, and gastrointestinal toxicity. Case reports of catatonia, seizure, self-mutilation, psychosis, cerebral ischemia, myocardial infarction, hyperemesis, acute kidney injury from tubular injury, and serotonin syndrome resulting from SCB use are noted in the literature.[4,70–72,74,75] Management of acute SCB intoxication is supportive with IV fluids for volume depletion and benzodiazepines, and less commonly, antipsychotics, for agitation or psychotic symptoms.[71]

Withdrawal

Discontinuation of SCB after chronic use has been associated with a withdrawal syndrome, including craving, anxiety, tachycardia, hypertension, nausea, tremor, diaphoresis, and nightmares.[70,73] Symptoms seem to appear soon after cessation, and the intensity correlates with the amount of daily SCB use.[71] The withdrawal syndrome is unlikely to be clinically significant in critically ill patients.

Synthetic Cathinones

Synthetic cathinones, commonly referred to as "bath salts" in the United States, are becoming increasingly more popular (**Table 6**). Adverse effects from their use are encountered more and more frequently in US hospitals with 6670 exposures reported in 2011.[5] Naturally occurring cathinones are derived from the *Catha edulis* (khat) plant, native to East Africa. Synthetic cathinones are derivatives of naturally occurring cathinones.[76,77] Pharmacologically, cathinones are thought to stimulate the presynaptic release of dopamine, norepinephrine, and serotonin and inhibit their reuptake.[77,78] Typical means of administration include nasal insufflation, inhalation, and oral ingestion, although IV, intramuscular, and intraocular administration have also been

Table 6
Synthetic cathinone (bath salts) intoxication and withdrawal in critically ill patients

Street Names	Intoxication	Withdrawal	Associated Complications
Cloud 9	Euphoria	Depressed mood	Psychosis
Vanilla Sky	Increased attention	Anxiety	Seizure, coma
Gold Rush	Sexual arousal	Sleep disorder	Hyperthermia
White Lightening	Anxiety, agitation	Paranoia	Blurred vision
Pure Ivory	Tachycardia, hypertension		Rhabdomyolysis
Ivory Wave	Hallucination, delusion		Respiratory failure
Stardust			Acute kidney injury
Wicked X			Hyponatremia
Many more…			Serotonin syndrome

described.[76,78] Similar to SCB, synthetic cathinones are not detected on routine toxicology testing; however, they may produce a false positive for methamphetamine and phencyclidine.

Intoxication and overdose

Clinically, the effects of synthetic cathinones are similar to other stimulants with euphoria, increased attention, sexual arousal, tachycardia, and hypertension.[76,78] After nasal insufflation and oral ingestion, effects are felt within 10 to 20 minutes and 15 to 45 minutes, respectively, and last 1 to 4 hours.[78] There is a spectrum of associated toxicities reported from synthetic cathinone use. Psychiatric manifestations account for a large portion of individuals seeking medical care and include mild agitation to severe psychosis. Anxiety, paranoia, and suicidal ideation have also been reported. Additional effects include seizure, coma, tachycardia, hypertension, hyperthermia, shortness of breath, chest pain, acute kidney injury, blurred vision, rhabdomyolysis, hyponatremia, respiratory failure, and serotonin syndrome among others.[5,76,78] Management is supportive, including IV fluids for dehydration, aggressive cooling for hyperthermia, and benzodiazepines for synthetic cathinone–induced agitation. Vigilance for other coingestions is important, because polysubstance use with synthetic cathinones is particularly common.[78]

Withdrawal

Chronic use of synthetic cathinones may lead to a withdrawal syndrome, including depression, anxiety, sleep disorder, paranoia, and cravings, although it is unlikely to play a significant role when managing critically ill patients.[76]

TRANSITIONS OF CARE FOR PATIENTS WITH SUBSTANCE USE DISORDERS

It is important not to lose sight of the underlying substance use disorder when caring for critically ill patients suffering from the effects of substance-induced intoxication, overdose, or withdrawal. The hospitalization, in fact, can be an important "engageable" moment for patients with substance use disorders. For example, hospital-initiated OAT paired with referral to outpatient addiction services can reduce discharges against medical advice and increase follow-up in postdischarge addiction treatment centers.[28,32] Appropriate referral sources include detoxification facilities, addiction recovery clinics, counseling services, and area 12-step programs.[79]

In addition, it is important to note that patients with substance use often have underlying psychiatric comorbidities, including mood disorders. Screening for and treatment of psychiatric disorders are essential parts of treatment of the underlying substance use and substance use disorders.[20]

SUMMARY

Intoxication and withdrawal from substance use is common among patients presenting to the ICU with critical illness and may complicate the treatment course. It is important for the critical care team to consider underlying substance use disorders and withdrawal syndromes in patients presenting for care. It may be difficult to obtain a history of these disorders as a result of altered mental status, and a patient's family should also be asked. In addition, it is important to consider polysubstance use in any patient presenting with intoxication or withdrawal.

General principles regarding the treatment of substance withdrawal include application of general resuscitative measures, including airway, breathing, and circulatory management. For specific withdrawal syndromes, substitution of a long-acting agent

(which acts on the same receptor pathway as the misused substance) in tapering doses is the general rule. In addition, use of a symptom-triggered approach to the treatment of substance withdrawal decreases length of stay and cumulative medication administered.

Of the utmost importance is long-term planning and referral for patients with underlying substance use disorders to allow for the best chance for successful treatment of these debilitating, chronic conditions. Consultation with an addiction specialist can be particularly helpful in this regard.

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