JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES
2020, VOL. 10, NO. 2, 117–126
https://doi.org/10.1080/20009666.2020.1742495

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REVIEW ARTICLE

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Substance use disorders: diagnosis and management for hospitalists

Ahmed K. Pasha[a], Arnab Chowdhury[a], Sanah Sadiq[a], Jeremiah Fairbanks[b] and Shirshendu Sinha[c]

[a]Division of Hospital Internal Medicine, Mayo Clinic Health System, Southwest Minnesota Region, Mankato, MN, USA; [b]Department of Family Medicine and Community Health, University of Minnesota, Mankato, MN, USA; [c]Department of Psychiatry and Psychology, Mayo Clinic Health System, Southwest Minnesota Region and Mayo Clinic College of Medicine and Science, Mankato, MN, USA

ABSTRACT

Substance use disorder is a significant health concern. Hospitalists manage patient with various forms of substance use disorder on a daily basis. In this review, we have tried to synthesize evidence together to give a brief, yet succinct, review of commonly encounters disorders; alcohol intoxication and withdrawal, opioid intoxication and withdrawal, cocaine intoxication and methamphetamine intoxication. We describe clinical features, diagnosis and management, which would serve as a great resource for hospitalist when managing these complicated patients.

ARTICLE HISTORY
Received 7 February 2020
Accepted 5 March 2020

KEYWORDS
Alcohol use disorder; alcohol withdrawal; cocaine; methamphetamines

1. Introduction

Substance use disorder is reckoned as an emerging national health concern [1]. It is expected that about 5.7 million older adults will have a substance abuse disorder by 2020 [2]. Substance abuse is often accompanied by non-adherence to medical therapy. This can lead to exacerbation of medical comorbidities which in turn lead to high readmission rates requiring a tremendous amount of hospital resources [3]. Given the magnitude of frequency and acuity of hospitalizations involving substance use, it is imperative that identification of the substance used and management of the patient's condition not be delayed as this pathology can be life-threatening. Four of the substances of abuse that result in many substance use-related hospitalizations include alcohol, opioids, cocaine and methamphetamine. The aim of this article is to introduce hospitalist providers to each of these substances as they relate to the identification of intoxication and management of acute overdose and withdrawal symptoms.

2. Alcohol use disorder

Alcohol use disorder (AUD) is a substantial public health constraint. AUD results in approximately 2.5 million deaths in the USA every year. Alcohol consumption is the third leading preventable cause of death in the USA [4]. Symptoms of alcohol use disorder include increased tolerance, withdrawal symptoms or drinking to prevent withdrawal, consumption over longer periods of time, persistent desire or inability to cut down, foregoing other important interests to consume and continued drinking despite known current harm [5]. Alcohol withdrawal syndrome (AWS) also causes a huge toll on the health care system of USA. Approximately 4 million people are affected by alcohol withdrawal per year, which can develop either when regular consumption is reduced or stopped altogether [6].

2.1. Alcohol intoxication

2.1.1. Clinical features

Health care professionals working in the hospital setting very frequently encounter alcohol intoxication so it is imperative that they are familiar with its signs and symptoms. Symptoms vary depending on tolerance to alcohol and the blood alcohol level, which is affected by the weight of the individual and type of beverage (percentage of alcohol) consumed. Symptoms range from impairment of simple tasks, to death at toxic levels of ingestion. Slurred speech, nausea, vomiting, lack of coordination, impaired judgment, mood and personality changes, hypothermia, somnolence, respiratory depression are few of the important clinical features seen during intoxication [7].

2.1.2. Diagnosis

Clinical presentation consistent with alcohol intoxication and a positive blood alcohol level is sufficient for diagnosis. In alcohol intoxication, calculation of the serum osmolality shows an osmolal gap which can aid in clinical diagnosis if a blood alcohol level is unavailable [8]. Clinical features of intoxication are similar to other important conditions known to cause altered sensorium; hence reasonable effort should be

CONTACT Shirshendu Sinha sinha.shirshendu@mayo.edu Department of Psychiatry and Psychology, Mayo Clinic Health System, Southwest Minnesota Region, 101 Martin Luther King Jr Dr, Mankato 56001, USA

made to rule these out. Differential diagnosis is presented in Table 1.

2.1.3. Management

Often times, the initial encounter of an acutely intoxicated person is in the emergency department. The patient should be assessed for adequate airway, breathing and circulation, and intravenous fluids should be initiated. Concurrently a 'banana bag' (dextrose, thiamine, folic acid, multivitamin) should be administered. Once the patient is stabilized, he/she may be admitted to the hospital for further observation if appropriate. Alcohol withdrawal severity scale (PAWSS) predicts the severity of withdrawal and helps in determining the level of care needed by the patient [9]. As an inpatient, patients are usually managed symptomatically with intravenous fluids, antiemetics as needed, thiamine, folic acid, multivitamins and use of restraints in agitated patients. Monitoring of the effects of alcohol on non-neurological organ systems is also an important task of the hospitalist. Attention should be paid to liver function tests (LFTs), electrolytes and blood glucose levels if patient is not eating well. Effort should be made to avoid letting a severely intoxicated patient to leave the hospital until their mentation improves as the patient is at high risk of self-harm in their altered state and physicians could be held responsible in case of harm to others or self- [8]. It is reasonable to put patients on a 72-h hold until the improvement of mentation. Intoxicated patients who have AUD have a high potential to undergo acute alcohol withdrawal as their blood alcohol level (BAL) decreases in the setting of abstinence. Severe alcohol withdrawal in the form of delirium tremens (DTs) could be life threatening and requires emergent treatment [10].

Table 1. Differential diagnosis of acutely intoxicated patients [7,8].

Substance abuse
intoxication of other alcohols-methanol/isopropyl alcohol
cocaine, amphetamine, cannabis, opiates
Metabolic
Electrolyte abnormality (hypo or hypernatremia)
Hypoglycemia
Hepatic encephalopathy
Hypertensive encephalopathy
Uremia
Diabetic ketoacidosis
Hyperosmolar non-ketotic coma
Infections
Sepsis
Meningitis
Encephalitis
Trauma
Subarachnoid hemorrhage
Subdural hematoma
Neurologic
Post ictal state
Cerebrovascular accident (ischemic or hemorrhagic)
Alcohol withdrawal

2.2. Alcohol Withdrawal Syndrome (AWS)

AWS is defined as cessation of alcohol or reduction in alcohol consumption that has been heavy and prolonged which is associated with two or more of the following; insomnia, nausea/vomiting, autonomic hyperactivity, tremors, agitation (psychomotor), transient visual, tactile or auditory hallucination, anxiety or generalized tonic-clonic seizures [11].

2.2.1. Clinical features

Symptoms vary depending upon the time since cessation. Within 6–12 h relatively minor symptoms like diaphoresis, nausea/vomiting, tachycardia, tachypnea, tremors may appear. From 12 to 24 hours, visual, tactile or auditory hallucinations may develop. During these hallucinations, the sensorium is clear, and this quality differentiates these hallucinations from DTs. Within 24–48 h generalized tonic-clonic withdrawal seizures may manifest. From 48 to 72 h, DTs can develop. DTs defining characteristics are hallucinations associated with disorientation and agitation [12].

2.2.2. Diagnosis

A comprehensive history, clinical exam and temporal relationship of symptom onset with alcohol cessation or reduction in alcohol consumption are important. No specific laboratory investigation is necessary to make this diagnosis. It is important to make sure there is no other medical or psychiatric cause for the symptoms. It is not uncommon for patients with AWS to not provide information regarding their alcohol use history. By the time patient presents, BAL may be undetectable. Laboratory tests could be obtained which help in confirming alcohol use in those you suspect alcohol withdrawal. These tests have variable sensitivity and specificity and have to be interpreted with caution. Three evidence-based test results that suggest recent alcohol use are elevated Gamma-glutamyl transferase (GGT) (blood), AST:ALT ratio>2 (blood) and elevated ethyl glucuronide (EtG)(urine) [13].

2.2.3. Management

Management begins with symptomatic care. Patients should be rehydrated, and nutritional support should be provided. Patientswho are dependent on alcohol are often times malnourished, hence multivitamin, thiamine and folic acid are administered. Thiamine should be administered before administration glucose-containing fluids in order to prevent acute onset or worsening of preexisting Wernicke encephalopathy. Severe electrolyte abnormalities that are often found in alcohol withdrawal should be treated to prevent cardiac arrhythmias [14].

Patients with alcohol withdrawal should be assessed periodically by the Revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) protocol [15]. In most of the hospitals, this protocol is nursing driven. Benzodiazepines are the first-line agent for withdrawal symptoms [10]. They significantly reduce the risk of seizure within first 2 days. Benzodiazepines are either used as symptom triggered therapy (STT) or fixed scheduled doses (FSD). In STT, benzodiazepine medications are administered per symptom-based CIWA-Ar protocol. This can not be used for non-verbal patients. Also, this approach is not considered safe for patients with history of alcohol withdrawal seizures. In FSD, the benzodiazepine is administered at scheduled intervals regardless of symptoms and then tapered. Both approaches are equally effective [16]. Various FDS dosing protocols exist.

The type of benzodiazepine used depends upon the age of patient and presence of liver disease or renal dysfunction. Lorazepam remains the most common benzodiazepine used for withdrawal because of its short half-life and lack of active metabolites [17]. Oxazepam is also short acting with no active metabolite, whereas diazepam and chlordiazepoxide are long-acting benzodiazepines and have long-acting metabolites [14].

Benzodiazepine sparing treatment with gabapentin has also been effective for mild alcohol withdrawal with no history of seizures. Gabapentin inhibits calcium channels and amplifies GABA synthesis. Gabapentin in alcohol withdrawal is used with a tapering protocol or fixed dosing [18]. A complete description of other drug treatments for alcohol withdrawal is out of scope of this review. Table 2 describes the dosing schedule for benzodiazepines and Gabapentin.

3. Opioids

3.1. Epidemiology

Opioids are a class of drugs used in a medical setting to treat acute and chronic pain. They include alkaloids from poppy seeds (codeine and morphine), semisynthetic opioids (oxycodone, hydromorphone and oxymorphone), synthetic phenylpiperidines (meperidine and fentanyl) and synthetic pseudopiperidines (methadone). It is estimated that up to 8 million Americans use opioid medications for chronic pain [20]. Lifetime self-reported misuse of opioid analgesics is 14% in persons 12 years and over [21]. These statistics help elucidate the magnitude of the current opioid crisis we are facing. Studies show that the opioid crisis has worsened over the past several decades, with mortality having quadrupled between 2000 and 2014 in opioid driven hospitalizations [22]. Most opioid-related hospitalizations are a direct result of opioid use such as intoxication, and others due to resulting traumatic injuries, injection site infections, and endocarditis. Unfortunately, these patients have been shown to be less compliant with follow up recommendations, resulting in recurrent ER visits and hospitalizations [3].

3.2. Types of opioids and their mechanism of action

The opioid receptors include μ, κ, δ subtypes. The effects of opioids are mostly a result of their actions on the μ opioid receptors. The role of κ and δ is not well defined. μ receptor stimulation cause euphoria and a sense of well-being. The clinically desired analgesia and cough suppressive effects of opioid medications, as well as the side effects of constipation, respiratory depression, tolerance and dependence are a result of opioid interaction with the μ receptor [23–25]. There are many subtypes of μ receptors and all μ opioids bind to all μ subtypes. The varying effects of different opioids result from their ability to activate receptor subtypes to a different degree [25]. Additional adverse effects of opioid medications may include nausea, vomiting, sedation, myoclonus or pruritus. The elderly population are at elevated risk for falls and delirium, however, withholding opioids for elderly patients in pain may also increase the risk of delirium [26].

The most commonly used opioids, which vary in potency, include heroin, morphine, codeine, hydrocodone, oxycodone, methadone, tramadol, fentanyl, buprenorphine. Morphine and heroin are equivalent in terms of potency as heroin is converted to morphine and monoacetylmorphine during metabolization. Codeine, hydrocodone and tramadol are considered the 'weak' opioids among the above. These differ from 'strong' opioids by a dose limit which results from the accumulation of side effects [26]. Codeine is a prodrug

Table 2. Symptom triggered benzodiazepine dosing and benzodiazepine sparing dosing in alcohol withdrawal syndrome.

Symptoms triggered dosing of lorazepam (Intravenous or Oral) [14]	
CIWA-Ar Score	Lorazepam dose
0-7	No medication required
8-10	1-2mg
11-15	2-3mg
16-19	3-4mg
20 or above consider transferring the patient to ICU	

*Gabapentin dosing schedule [18, 19]
300-400 TID for 3days, then 400 BID on day 4.

*Gabapentin has renal excretion requiring dose adjustment in renal failure

that is converted to morphine. Hydrocodone is a prodrug that is converted to dihydromorphine. Oxycodone has active metabolites which contributes to its euphoria thereby increasing its abuse potential. Methadone is a long-acting opioid. Tramadol is an opioid agonist that affects 5HT receptors in addition to opioid receptors. Buprenorphine is a partial opioid receptor agonist (activates receptors at a lower level) and is sometimes formulated with naloxone (a pure opioid antagonist) to decrease its abuse risk [26,27] Heroin, methadone, and oxycodone are highly reinforcing and the most abused opioid types.

3.3. Diagnosis

Diagnosis of opioid intoxication primarily includes the use of urine assays. In addition, there are tests available that utilize blood, saliva, sweat and hair. Interpretation of the test results can be complicated because most opioid urine immunoassays use morphine as the only calibrator to determine a positive result. As there are a variety of opioids available that differ in chemical structure, and metabolism may convert one to another, many opioids may escape detection. A prime example is oxycodone, where a 6-fold higher concentration is required to detect compared to other opioids. Fentanyl and buprenorphine require specific immunoassays as they are very distinct in structure. Assessing the accuracy of these urine tests is also difficult as they are used as the gold standard. In an urgent setting, these may be the only tests available and confirmatory testing may take over 24 h to obtain [28].

3.4. Intoxication/Poisoning

Symptoms of opioid intoxication include miosis, respiratory depression (usual cause of death) and depressed mental status. Management of acute opioid intoxication involves supportive measures and removal of offending agents such as transdermal patch. Vital signs should be frequently monitored including heart rate, respiratory rate, temperature. Patient should be treated for co-existing conditions if present such as infections and trauma. Patients should be evaluated for multi-drug intoxications by ordering other drug levels such as aspirin and acetaminophen [24]. Naloxone should only be given in respiratory depression/arrest as it may induce dysphoria, severe pain or ventricular arrhythmias. 0.4 mg naloxone diluted with 10 ml normal saline can be given at a rate of 0.5 ml every 2 min to maintain a respiratory rate over 8 respirations per minute. An alert mental status should not be used as a gauge of effectiveness and sedation should be tolerated. An intravenous infusion of naloxone may be necessary due to the short duration of action of naloxone once the effective dose is established. The infusion rate should be two-thirds of this dose every hour. A bolus should be available as needed of half the effective dose every 15 min. Delirium should be treated as usual with treatment of underlying contributory factors such as infections, metabolic abnormalities, medications and volume status. Haloperidol may be used if appropriate. A patient with opioid intoxication should preemptively be started on a bowel regimen. Nausea and vomiting should be treated symptomatically as usual. Pruritus can be treated with antihistamines [26].

Methadone causes dose-related QT prolongation which can result in torsades de pointes. This is treated with intravenous magnesium [27]. Tramadol and meperidine can cause seizures. Meperidine can cause serotonin syndrome [24].

3.5. Withdrawal

Cessation or reduced dose of opioids may result in withdrawal symptoms such as nausea, diarrhea, piloerection, diaphoresis, myalgias, arthralgias, restlessness, mydriasis, rhinorrhea, lacrimation, fever, hypotension or tachycardia. The severity of withdrawal symptoms depends on the type of opioid being used, dose, route of use and duration of use. Withdrawal from heroin may start at 4–6 h following last use, while withdrawal from methadone may not start until 36 h after last dose. Withdrawal from heroin peaks at 36 h and symptoms may last for up to 14 days. Treatment of withdrawal, as with intoxication, is supportive. There are objective tools available to determine the severity of withdrawal. These include the Clinical Opioid Withdrawal Scale [29] and the Objective Opioid Withdrawal Scale. Use of opioid agonists/partial agonists such as methadone or buprenorphine and non-opioid medications such as alpha-adrenergic and antiemetic agents can alleviate the symptoms of opioid withdrawal. Methadone is usually initiated at a dose between 10 and 30 mg and may be slowly titrated up to 20 mg to 40 mg daily. Both methadone and buprenorphine may be continued for long-term management of opioid withdrawal. Clonidine may be used at doses between 0.1 and 0.2 mg every 6 h. Blood pressure should be monitored with use of clonidine [30]. Please refer to table 3 for summary of opioid use disorder.

3.6. Use of opioids in pain management

There is good evidence of the efficacy of opioids in treatment of chronic cancer pain and acute pain. Physicians are often hesitant to prescribe opiates in the management of chronic noncancer pain due to the potential for abuse. Providers should be mindful of 'pseudo-addiction' which can present identical to addictive behavior except that it improves after adequate pain control is achieved. Patient-controlled analgesia pump is the appropriate way to treat

Table 3. Summary of opioid use disorder.

Mechanism of action	Act on opioid receptors including μ, κ, δ. [23–25]
Modes of use	Ingestion, inhalation, injection [32]
Diagnosis	Urine, blood, saliva, sweat, hair assays [28]
Symptoms of intoxication	Miosis, respiratory depression, depressed mental status [24]
Symptoms of withdrawal	Nausea, diarrhea, piloerection, diaphoresis, myalgias, arthralgias, restlessness, mydriasis, rhinorrhea, lacrimation fever, hypotension and tachycardia [30]
Treatment of intoxication	Supportive, opioid antagonist therapy when appropriate, management of comorbid conditions, intoxications [24,26]
Treatment of withdrawal	Supportive, use of opioid agonists or clonidine if indicated [30]

acute post-surgical pain or sickle cell vasoocclusive crises. Prescription of opioids should be limited upon discharge for patients treated for a reversible cause. Opioids should only be prescribed for the duration of recovery to maintain function. Elderly patients should begin with half the dose one would normally use in an otherwise healthy adult due to increased potential for side effects. A lower dose at initiation is also recommended for patients with renal disease. Fentanyl is best tolerated by patients with liver disease, however, limited preparations limit its efficacy [26]. Patients should be started on a bowel regimen prophylactically on initiation of opioid therapy. If constipation symptoms persist, the use of antagonist therapy with lubiprostone or methylnaltrexone may be necessary [31].

3.7. Opioid rotation

Opioid rotation plays a vital role in inpatient care. Scenarios in which this becomes necessary include a new organ failure/dysfunction, side effects from a particular opioid, inability to tolerate previous route of administration, or incomplete pain relief from previous regimen. Unavailability of a specific opioid may necessitate opioid rotation as well such as with the recent shortages of injectable opioids. In the absence of the above indications, it is best to avoid changing a patient's outpatient regimen. If the need arises to change to a different opioid, keeping incomplete cross-tolerance in mind, dose should be reduced by 25-50%. Follow up to evaluate analgesia and side effects should be 5–10 min after an intravenous test dose and 30–40 min after oral test dose [26].

4. Cocaine

4.1. Background

Cocaine is a powerful stimulant drug that is derived from the leaves of the Erythroxylum coca plant native to South America. Common street names of this drug include: Blow, Coke, Crack, Rock or Snow. Cocaine has also been combined with other psychoactive drugs that include opioids and stimulant amphetamines. Illicit cocaine is available in two forms: Cocaine salt and Cocaine base (crack, free base). Users can snort cocaine salt through the nose or rub it into their gums. Cocaine base can be heated to produce vapors that are inhaled into the lungs. The water-soluble form of cocaine can be injected intravenously as well. Cocaine's effect occurs almost immediately and dissipates quickly in a few minutes to an hour. As per the results of a national survey on drug use and health in 2016, there were an estimated 1.9 million people aged 12 or older (corresponding to 0.7% of the population older than 12 years) who currently used cocaine. This estimate was similar to the estimates of cocaine users between 2007 and 2015 but lower than the estimates from 2002 to 2006 [33,34].

4.2. Mechanism of action

Cocaine affects the monoamine neurotransmitter activity in the nervous system by blocking reuptake or recycling of these molecules, thereby causing increased concentrations extracellularly. Increased dopamine activity in the neurons of the mesocorticolimbic system leads to the behavioral and abuse-related effects of cocaine [35,36]. By increasing norepinephrine concentrations in the synaptic junctions, cocaine stimulates the sympathetic nervous system causing vasoconstriction, tachycardia, mydriasis, and hyperthermia. By blocking sodium channels in neuronal cells, it can also produce a local anesthetic effect [34].

4.3. Clinical features

Cocaine use is associated with significant cardiovascular complications. It causes increased sympathomimetic activity and inhibits transient inward flux of sodium across the cell membrane during depolarization, increasing myocardial oxygen demand while simultaneously decreasing myocardial oxygen supply through vasoconstriction. In addition, it can lead to endothelial dysfunction and platelet aggregation. This leads to a significant increase in risk of acute myocardial infarction in otherwise low-risk patients [37]. With long-term use, it can also accelerate atherosclerosis. Cocaine can cause decrease in left ventricular function and lead to development of cardiomyopathy in the absence of myocardial ischemia. It can also lead to prolonged corrected QTc interval and life-threatening ventricular arrhythmias [37]. Some studies have pointed toward sinus bradycardia in habitual cocaine users that possibly resulted from desensitization of beta-adrenergic receptors [38] Although the clinical significance of resulting sinus bradycardia is unclear. Neurologic complications of cocaine use can include seizures, headaches, transient loss of consciousness, focal neurologic complications that include intracranial hemorrhage and infarcts [39]. Psychiatric complications include transient

hallucinations, paranoia, suicidal ideation, aggression, agitation, stereotyped behavior, and anxiety [39,40]. Inhalation of crack cocaine can also lead to injury to the respiratory system. It can cause airway injury resulting in severe reactive airway disease. There have been reports of tracheal stenosis, pneumothorax, and pneumomediastinum. It can also exacerbate existing chronic lung diseases such as asthma [41]. 'Crack lung' has also been described in the literature to describe acute respiratory failure attributed to the use of crack cocaine and can include any combination of pulmonary hemorrhage, interstitial lung processes and pulmonary edema. In some reports, this syndrome was associated with eosinophilia indicating a possible immunologic mechanism [41–43]. Abuse of cocaine is associated with multiple gastrointestinal adverse effects as well. Multiple forms of intestinal disorders have been reported which include gastrointestinal bleeding, intestinal perforation, and ischemic colitis. Smuggling of cocaine by ingesting cocaine packets ('body packing') can lead to complications such as obstruction and perforation. If the wrapping deteriorates, release of cocaine can cause acute intoxication. In addition to damage to the gastrointestinal tract, cocaine use can also cause increased liver enzyme levels, the long-term significance of which is unclear [34]. Cocaine intoxication can lead to rhabdomyolysis that can lead to acute renal failure [34]. Other adverse effects of cocaine use include endocrine abnormalities, chronic rhinitis, erosion of dental enamel and nasal septum perforation [34].

4.4. Diagnosis

Diagnosis is generally made by testing urine specimens for cocaine metabolite, benzoylecgonine (BE), an inactive metabolite. Thin-layer chromatography (poor sensitivity) and enzyme-linked immunoassay technique are generally utilized as initial screening tools. Gas chromatography is the gold standard for detecting metabolites of cocaine. Cocaine metabolites can be detected for 5–6 days with gas chromatography with mass spectroscopy. Long-term use of cocaine can produce positive results for up to 10–22 days after cocaine use [44].

4.5. Management

Supportive treatment is recommended for cocaine intoxication-related complications as mentioned above. For acute agitation, benzodiazepines can be used. Haloperidol is not used as first-line as it can reduce the seizure threshold. For hyperthermic patients, aggressive cooling techniques can be used [45]. Please refer to table 4 for summary of cocaine use disorder.

Table 4. Summary of cocaine use disorder.

Cocaine
Common routes of administration
Smoking
Insufflation
Intravenous injection
Adverse effects
Cardiac
Myocardial ischemia
Cardiomyopathy
Prolonged QTc interval
Arrhythmias
Sinus bradycardia
Pulmonary
Reactive airway disease
Tracheal stenosis
Pneumothorax
Pneumomediastinum
Pulmonary edema
'Crack lung'
Neurologic
Seizures
Transient loss of consciousness
Stroke, ischemic and hemorrhagic
Renal
Rhabdomyolysis
Acute renal failure
Gastrointestinal
Gastrointestinal bleeding
Ischemic colitis
Obstruction and perforation in 'body packers'
Psychiatric
Transient hallucinations
Paranoia
Aggression
Agitation
Stereotyped behavior
Other
Chronic rhinitis
Erosion dental enamel
Perforated nasal septum
Management
Supportive
See Table 5 for cocaine-induced acute coronary syndrome
Withdrawal
Rarely medically serious
Depression
Anxiety
Inability to concentrate
Increased appetite

4.6. Management of cocaine-related acute coronary syndrome

American heart association guidelines recommend treatment of acute coronary syndrome (ACS) in patients with history of cocaine use in the same manner as patient's without cocaine use. It does recommend certain important exceptions in treatment of acute coronary syndrome, specifically in the acute intoxication phase. It is believed that because cocaine stimulates both alpha and beta-adrenergic receptors, beta-blocker usage can result in unopposed alpha-stimulation and worsen coronary spasm and should be avoided. In those patients, usage of benzodiazepines along with nitroglycerin can be useful in

Table 5. Management of cocaine-related acute coronary syndrome.

- Recommend against beta-blocker usage to avoid unopposed alpha-stimulation.
- Combination of nitroglycerin and benzodiazepines can be used for the management of hypertension and tachycardia.
- Other than above, management is same as in patients without cocaine use.
- Similar management recommended for methamphetamine-induced coronary events as well.

the management of hypertension and tachycardia. Above management is also applicable to patients with methamphetamine-induced acute coronary syndrome [46] (table 5).

4.7. Cocaine withdrawal

Cocaine withdrawal is rarely considered medically serious and should be treated based on symptoms. However, reported withdrawal symptoms of cocaine include depression, anxiety, trouble concentrating, irritability, fatigue, insomnia, increased appetite and rapid heart rate [47].

5. Methamphetamine

5.1. Background

Methamphetamine is a psychostimulant of the phenethylamine and amphetamine class of psychoactive drugs [48]. In the 1970s, methamphetamine was made using phenyl-2-propanone ('P2P') and methylamine. In 1980s, following P2P being classified as a scheduled substance, ephedrine, and pseudoephedrine became the main precursors to manufacturing methamphetamines. In the 2000s, restrictions placed on imports of pseudoephedrine and over-the-counter cold medicine containing pseudoephedrine did lead to a short-lived decrease in methamphetamine manufacturing. In the mid-2000s producers then shifted to using chemicals other than pseudoephedrine in methamphetamine production [49]. In 2016, an estimated 667,000 people aged 12 or older were current users of methamphetamine [33]. Methamphetamine is most commonly smoked although it can be injected, ingested, inhaled, or taken rectally as well [48].

5.2. Clinical features

Methamphetamine usage leads to arousal, decreased fatigue, tachycardia, hypertension, reduced appetite, behavioral disinhibition, and short-term improvement in cognitive function. At higher doses, psychosis can occur as well. Acute methamphetamine intoxication usually presents with tachycardia, hypertension, and altered mental status in the form of agitation and/or psychosis. Cardiovascular complications include ventricular fibrillation or acute cardiac failure. Acute coronary syndrome, acute aortic dissection, and sudden cardiac death can also occur due to methamphetamine-induced hypertension, coronary spasm, and arrhythmias. Prolonged corrected QTc is frequently observed in methamphetamine abusers. Intravenous use can be associated with bacterial endocarditis. Methamphetamine is also implicated as a cause of pulmonary arterial hypertension. Chronic users are at an increased risk for the development of cardiomyopathy and the left ventricular dysfunction is generally more severe compared to other causes of cardiomyopathy [50]. Pulmonary complications include the development of noncardiogenic pulmonary edema sometimes leading to respiratory failure [51]. Seizures, ischemic as well as hemorrhagic strokes have been reported in methamphetamine users. Methamphetamine usage is also linked to cognitive impairment which can persist for multiple months after abstinence. Psychiatric adverse effects include depressed mood, anxiety and associated anhedonia, irritability, and inactivity. Psychosis can occur in methamphetamine abusers as well [52]. In addition to above, accidents, suicide, and homicide remain an important cause of mortality associated with methamphetamine use [53]. Rhabdomyolysis and dehydration can occur sometimes leading to acute renal failure. Gastrointestinal adverse effects include development of acute liver injury, mesenteric infarction, and ischemic colitis. There are also reports of acute pancreatitis. Dermatologic complications often arise from skin-picking that predisposes methamphetamine users to skin and soft tissue infections. In addition, poor hygiene and malnutrition that are often related to chronic substance abuse can lead to skin diseases and dental decay. Dental decay is also possibly accelerated by bruxism and xerostomia [54] [51].

5.3. Diagnosis

Methamphetamine can be detected in the urine for approximately 48 h after use. It can also be detected by hair analysis. A positive methamphetamine screen should be confirmed as false-positive results can sometimes occur. Examples of medications that can cause false-positive results include bupropion, phenothiazines, trazodone, labetalol, and ranitidine [53].

5.4. Management

When managing patients with suspected acute intoxication of methamphetamine, a clinician should have a high degree of suspicion for concurrent abuse of other substances as well. Treatment of acute intoxication is largely supportive. For oral ingestions, use gastric lavage or activated charcoal. For agitation and psychosis, benzodiazepines and antipsychotic agents such as haloperidol and olanzapine can be utilized. For

hyperthermia, cooling measures may be required [53,55,56]. Management of Methamphetamine induced acute coronary syndrome is similar to management of cocaine-induced ACS noted previously in this review. Hypertension and tachycardia should be managed with medications other than beta-blockers. If malignant hypertension is present, sedation is generally recommended to assist with blood pressure control. Further investigations such as echocardiogram or coronary angiogram may be indicated based on the clinical picture [50]. Please refer to table 6 for summary of methamphetamine use disorder.

Table 6. Summary of methamphetamine use disorder.

Methamphetamine
Common routes of administration
Ingestion
Inhalation
Insufflation
Anal suppository
Adverse effects
General
Hypertension
Tachycardia
Hyperthermia
Cardiac
Arrhythmias
Acute heart failure
Pulmonary
Pulmonary edema
Pulmonary hypertension
Respiratory failure
Neurologic
Seizures
Ischemic/Hemorrhagic strokes
Cognitive impairment
Renal
Rhabdomyolysis
Acute renal failure
Gastrointestinal
Acute liver failure
Ischemic colitis
Mesenteric infarction
Dermatologic
Skin and soft tissue infection
Psychiatric
Anhedonia
Depressed mood
Anxiety
Psychosis
Agitation
Other
Suicide
Accidents
Management
Largely supportive
Benzodiazepines and anti-psychotics as needed for controlling agitation and psychosis
Avoid beta-blockers for hypertension, tachycardia or methamphetamine associated cardiac complications
Withdrawal
Depression
Inability to concentrate
Paranoia

5.5. Methamphetamine withdrawal

Withdrawal from methamphetamine generally causes depression, somnolence, anxiety, inability to concentrate, increased appetite, and paranoia. Seizures can occur as well. Depression associated with methamphetamine withdrawal can be more prolonged and severe when compared to cocaine withdrawal. Treatment should be symptomatic [53].

6. Conclusion

Substance use disorder is commonly encountered in hospital medicine practice and complicates patient presentations. Prompt recognition and management are crucial. Once patients with a substance use disorder are medically stabilized, hospitalists should encourage patients to obtain comprehensive evaluation by an addiction specialist to assess the patient's mental health status, need for detoxification as well as constitute an effective treatment plan to prevent relapse and promote sobriety.

Disclosure statement

The other authors report no competing interests.

Funding

Dr. Sinha has received grant funding from UCare Foundation.

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