The management of substance abuse in the critically ill

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Substance abuse continues to increase the burden on the health care system. In Diagnostic and Statistical Manual of Mental Health Disorders, 5th edition, text revision (DSM-IV-TR), substance abuse and dependence disorders are now combined into substance use disorders. Substance abuse refers to a maladaptive pattern of substance use leading to clinically significant impairment or distress manifested by at least 1 symptom that interferes with life functioning within a 12-month period. A diagnostic criterion for substance dependence requires at least 3 of the following within a 12-month period: development of tolerance to the substance, withdrawal symptoms, persistent desire/unsuccessful attempts to stop the substance, ingestion of larger amounts of substance than was intended, diminished life functioning, and persistent substance use with physical or psychological problems. Estimates regarding the management of substance intoxication and withdrawal are increasingly high, and many of the current interventions remain heavily weighted on science vs evidence-based practices. In addition, informed consent required for clinical studies would be difficult to obtain due to the nature of the disease state. Randomized-based controlled interventions to help guide clinicians on disease state management are desperately needed. The presentation of patients into the emergency department and the intensive care unit can be first-time users (naïve), social users, or chronic abusers. Individuals who are either social or chronic users of these intoxicants generally have an adapted tolerance to the substance, which results in the user requiring more drug over time to feel the same effects. Tolerance has a dual role, users develop a tolerance to the rewarding effect of these substances and they develop an adapted response and tolerance to the adverse effects. The synthesis of treatment care plans for patients admitted for substance intoxication or withdrawal requires an integration of drug/toxin, laboratory value(s), and clinical presentation. The integration of clinical information for an intoxication is critical, as the relationship is complex and dependent on multiple variables (e.g., treatment not based solely on a laboratory value(s)) (Fig. 1). Social, illicit, and prescription intoxicants (nicotine, alcohol, cocaine, marijuana, and opioids) are the focus of this review.

Alcohol

Clinical presentation

Alcohol is consumed during a variety of social gatherings, public establishments, and during sporting events. Alcohol screening tools are utilized upon admission for trauma in the ED and
elective surgery by anesthesia providers to aid in the screening process to prevent a prolonged post-operative recovery time. Chronic ingestion of alcohol results in decreased gamma-aminobutyric (GABA) activity and increased N-methyl-D-aspartate (NMDA) activity. After an abstinence period of 24 h, patients can experience additional symptoms of auditory, tactile, and visual hallucinations. If the withdrawal symptoms are left untreated, the patient progresses onto seizures and delirium tremens (48–96 h after last drink).

The selection of benzodiazepine is based upon the intended duration of activity, organ function, and availability. The benzodiazepines have distinct differences with respect to their liver metabolism (i.e., Phase I—chlordiazepoxide and diazepam vs Phase II—glucuronidation lorazepam). Lorazepam is available as an intravenous and oral preparation, possess an inactive metabolite, and has an intermediate duration of activity in comparison to the other agents. In addition, current clinical literature supports the initiation of lorazepam for the management of alcohol withdrawal based on its favorable pharmacokinetic properties. If the patient requires an intravenous infusion for alcohol management, lorazepam can be initiated; however, clinicians should monitor for propylene glycol exposure and toxicity (e.g., renal failure and metabolic acidosis) based on the patients daily dosage requirement. Another alternative for an infusion would be midazolam. Midazolam is extensively metabolized by the liver (Phase I—CYP 3A4 system) and possess an active metabolite (α-OH midazolam), which is eliminated renally; therefore, caution is advised with this therapy selection. Individuals with more severe agitation or hallucinations may require IM or IV medication. Chlordiazepoxide (25–100 mg orally) can be administered as an alternative to lorazepam. Phenobarbital (5 mg/kg IV or 15 mg of phenobarbital for each 30 mL “1 ounce” of 80–100 proof) may be used for resistant cases. Phenytoin is not useful in treating ethanol-withdrawal seizures. Patients requiring full respiratory support [i.e., mechanical ventilation (MV)] could be a candidate for a propofol infusion. Propofol infusion would start at 10 μg/kg/min and titrated upwards to a goal RASS score.

Sympathetic manifestations (e.g., blood pressure and heart rate) can be managed with β-antagonists and α2-agonists. Clinicians are cautioned against the sole use of β-antagonists until a confirmatory laboratory test can rule out the presence of cocaine in the patients’ system due to

![Integration of information](image-url)
concerns of unopposed α-activity that can be deleterious to the blood pressure.\textsuperscript{2,3} Initiation of analgesia for pain management is advised for patients with a suspected or confirmed co-ingestion of opioids and as an adjunct for patients on mechanical ventilation.

**Intoxication**

Individuals who abuse alcohol may present with alcohol intoxication characterized by behavioral changes, including expansive mood, social withdrawal, irritability, and/or aggression.

Nausea-Vomiting: Ask: Do you feel sick to your stomach? Have you vomited? (Observation)
0. No nausea-vomiting
1. Mild nausea, no vomiting
2. –
3. –
4. Intermittent nausea with dry heaves
5. –
6. –
7. Constant nausea, frequent dry heaves

Visual Disturbances: Ask: Does light appear too bright? Is color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know aren’t there?
0. Not present
1. Very mild sensitivity
2. Mild sensitivity
3. Moderate sensitivity
4. Moderately severe hallucinations
5. Severe hallucinations
6. Extremely severe hallucinations
7. Continuous hallucinations

Paroxysmal Sweats: (Observation)
0. No sweat observed
1. –
2. –
3. –
4. Beads of sweat on forehead
5. –
6. –
7. Drenching sweats

Tactile Disturbances: Ask: Have you any itching, pins-needles sensations, any burning, any numbness or do you feel bugs crawling on or under your skin? (Observation)
0. None
1. Very Mild itching, pins-needles, burning numbness
2. Mild itching, pins-needles, burning numbness
3. Moderate itching, pins-needles, burning numbness
4. Moderately severe hallucinations
5. Severe hallucinations
6. Extremely severe hallucinations
7. Continuous hallucinations

Agitation: (Observations)
0. Normal activity
1. Somewhat more than normal
2. –
3. –
4. Moderately fidgety, restless
5. –
6. –
7. Paces back-forth most of interview, constantly thrashes about

*Fig. 2.* Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar).
Physical/neurological symptoms, such as diminished concentration, attention, and coordination, may lead to falls and injury. Impulsivity and impairments in judgment and insight can be associated with violence or motor vehicle accidents. As alcohol is a short-acting sedative, in individuals with alcohol dependence, alcohol withdrawal begins 4–12 h after the last drink. Clinical presentation includes tremor, tachycardia, hypertension, anxiety, and diaphoresis. Patients that present to the hospital with suspected alcohol intoxication or trauma suspected to involve alcohol consumption should be tested via blood toxicology. Forensic lab testing involves whole blood measurements and hospital-based tests utilize serum/plasma samples. An

Auditory Disturbances: Ask: Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know aren’t there? (Observation)
0. Not present
1. Very mild harshness or ability to frighten
2. Mild harshness or ability to frighten
3. Moderate harshness or ability to frighten
4. Moderately severe hallucinations
5. Severe hallucinations
6. Extremely severe hallucinations
7. Continuous hallucinations

Headache, Fullness in Head: Ask: Does you head feel different? Does it feel like a band is around your head? (do not rate for dizziness or light-headedness)
0. Not present
1. Very mild
2. Mild
3. Moderate
4. Moderately severe
5. Severe
6. Very severe
7. Extremely severe

Orientation/Clouding of Sensorium: Ask: What day is today? What is this place?
0. Oriented and can do serial additions
1. Cannot do serial additions or uncertain regarding date
2. Disoriented for date by no more than 2 d
3. Disoriented for date by >2 calendar days
4. Disoriented for place and/or person

Anxiety: Ask: Do you feel nervous? (Observation)
0. None
1. Mildly anxious
2. –
3. –
4. Moderately anxious, guarded, so anxiety is inferred
5. –
6. –
7. Equivalent to acute panic states

Tremor: Extend arms, spread fingers apart (Observation)
0. None
1. Barely visible, but can feel
2. –
3. –
4. Moderate with arms extended
5. –
6. –
7. Severe, even with arms not extended

TOTAL CIWA-Ar SCORE: _____________

Fig. 2. (continued)
adjustment factor of 1.14 should be utilized in the final analysis when using hospital laboratory values for a true whole blood value. One area of focus when managing patients admitted for alcohol intoxication includes monitoring and replacement of electrolytes (e.g., K, Mg, and Phos). All of the electrolytes recommended for monitoring are concentrated intracellularly; therefore, aggressive replacement needs to be practiced to ensure appropriate clinical management. Another area of focus is on the prevention of Wernicke–Korsakoff syndrome. The main therapy for the prevention and treatment of Wernicke–Korsakoff syndrome is thiamine. Thiamine can be administered at doses of 100-mg IVP once daily for 5 days (prevention) or 500-mg IV infusion 3 times daily (treatment) for Wernicke–Korsakoff syndrome. The duration of therapy of thiamine for Wernicke–Korsakoff is typically for 1 week or resolution of clinical symptoms.

Patients who are admitted for alcohol intoxication can be managed with GABA-modulating therapy (e.g., benzodiazepines or BZDs), appropriate fluid, and electrolyte replacement. Patients are administered BZDs based on the Clinical Institute Withdrawal Assessment (CIWA) scale (Fig. 2). Antipsychotics are generally best avoided in alcohol withdrawal as they may lower seizure threshold. However, in cases of failure of benzodiazepines to control paranoid behavioral symptoms or hallucinations, judicious use of antipsychotic medication may be helpful.

Withdrawal

A significant portion of the population exhibits dependence on the substance and an abstinence time of 6–8 h can result in early symptoms of withdrawal. Early signs and symptoms of withdrawal include tremor, increased heart rate, and blood pressure, which are manifested from increased catecholamine release. Patients that present 96 h after their last alcohol consumption are at an increased risk for withdrawal behavior. Clinical findings include increased sympathetic activity (e.g., blood pressure and heart rate), hallucinations (e.g., visual, auditory, and tactile), and seizures secondary to depleted GABA activity and increased N-methyl-D-aspartate (NMDA) activity. Alcohol withdrawal patients are at an increased risk for aspiration pneumonia and secondary infection during the treatment phase as a result of impaired mental status.

One area of focus in addition to BZDs therapy for symptomatic withdrawal is antiadrenergic therapy targeting the α2-receptor. The 2 medications available and investigated for the management of alcohol withdrawal are clonidine and dexmedetomidine. Clonidine can be initiated at 0.1 mg orally 3 times daily. Dexmedetomidine is a more potent and approximately 8-fold more lipophilic than clonidine. Dexmedetomidine is an intravenous infusion that can be initiated in patients in whom significant amounts of BZDs are either anticipated or already being administered for the management of withdrawal. The infusion of dexmedetomidine allows the clinician to lower the requirement of BZDs and other mind-altering medication and spare any airway compromise during withdrawal management. A recent trial compared lorazepam vs lorazepam-plus-dexmedetomidine infusion; however, it did not demonstrate any clinical (e.g., mechanical ventilation days, ICU LOS, and ADEs) or statistical advantage over our current treatment modalities.

Titration of therapy (e.g., benzodiazepines and α-agonists) can be based upon 2 methods. The CIWA-Ar (Fig. 2) scale allows patient interaction and response to determine the dosage and frequency of drug administration. Selected patients may become significantly altered and may require mechanical ventilation for airway protection; therefore, utilizing the CIWA-Ar scale in this population would not be advised. A recommended strategy for patients in whom the CIWA-Ar scale is not possible to clinically use is the RASS method (Fig. 3). The RASS method for sedation titration (dose and frequency) allows clinicians to determine the patient's clinical medication requirements once the patient is either non-responsive or on mechanical ventilation. The utilization of a titration scale will allow the following: lowest requirement of a sedative, medication titration, and facilitate discharge/disposition from the medical center.

Specific therapeutic interventions that may be adjunctive in promoting alcohol abstinence are disulfiram, naltrexone, acamprosate, and some psychotropic drugs. Disulfiram competitively inhibits the enzyme aldehyde dehydrogenase, so that subsequent alcohol ingestion leads to serum acetaldehyde accumulation and resultant symptoms of flushing, feeling overheated,
nausea, and general malaise. Dizziness, palpitations, and hypotension may occur. Symptoms generally persist for 30–60 min and may be useful in motivated, healthy patients by assisting with abstinence. Disulfiram must be taken daily, generally in the morning, and is usually prescribed at a dosage of 125–250 mg/day. Although some individuals benefit from the addition of disulfiram to an alcohol treatment regimen, its use must be weighed against the medical risks (severe hypotension, hypocalcemia, and respiratory depression), which can present in individuals that continue to drink while on disulfiram therapy. Disulfiram should never be given to an individual without their knowledge. Naltrexone, a narcotic antagonist, can also be a useful adjunct as part of an alcohol treatment regimen. Naltrexone at doses of 50 mg/day may reduce drinking in recovering alcoholics. Adverse effects may include hypertension, GI disturbance, and sedation. Another medication that can be utilized is acamprosate for treating alcohol-dependent individuals seeking to continue to remain alcohol free after they have stopped drinking. Acamprosate may reduce alcohol craving and the amount that alcoholics drink when they do drink. The most common adverse effects are diarrhea, nausea, vomiting, and abdominal pain.

Caffeine

Intoxication

Caffeine is a methylxanthine that produces hyperadrenergic signs in overdoses (hypertension, tachycardia, seizures, hyperthermia, hypokalemia, and tremors). Caffeine has a relatively short half-life; however, when high doses are ingested (~500 mg), the metabolism is prolonged due to a transition of first-order to zero-order kinetics. Caffeine is different from theophylline owing to an additional methyl group on its chemical structure. Caffeine's systemic effects are secondary to its activity on phosphodiesterase (PDE) inhibition, adenosine receptor antagonism, and increased catecholamine secretion. More recently, a large governmental focus is surrounding the soft drink and energy drink industries and their effects on public health. Many of these substances contain caffeine amounts, which vary from 31 mg (Diet coke) up to 240 mg (Rock star). Treatment is focused on seizure control with benzodiazepines or phenobarbital. (Phenytoin should be avoided.) Multiple doses of activated charcoal can also aid in enhancing elimination of caffeine as can charcoal hemoperfusion.

Withdrawal

Physical dependency to caffeine does exist with withdrawal symptoms usually occurring within 12–24 h following cessation and peaks at 20–51 h that may last for 1 week. A daily dose over 235 mg (about 2.5 cups of coffee/day) can increase the risk for likelihood of withdrawal. While lethargy and weakness may occur, facial flushing and severe headaches predominate this
syndrome and may last as long as 9 days. Other symptoms include yawning, rhinorrhea, and irritability.\textsuperscript{15} Caffeine withdrawal symptoms correlate with the amount ingested prior to cessation. Treatment focuses on a gradual reduction of caffeine intake over several days. Caffeine tablets may be useful in headache treatment.

**Cocaine**

Cocaine intoxication generally presents with cardiovascular complications requiring medical intervention. The complications of cocaine ingestion include vascular vasospasm, myocardial ischemia, rhabdomyolysis, and stroke. Cocaine (benzolmethylecgonine) can be administered orally, intravenously, and intranasally.\textsuperscript{16,17} Cocaine manifests its pharmacologic activity via inhibition of re-uptake of norepinephrine, dopamine, and serotonin within the synaptic cleft. The end result of this activity is a powerful sympathomimetic response.\textsuperscript{7} The peak effect of cocaine is dependent on its route of ingestion. Cocaine is metabolized via plasma and liver esterases to benzolecgonine, which can be detected via urine and plasma analysis. Cocaine activity can peak within minutes of ingestion and the half-life is approximately 60 min.\textsuperscript{16,17} Cocaine also exhibits a degree of post-mortem metabolism and distribution.

**Intoxication**

Cocaine intoxication presents with signs and symptoms of sympathetic overdrive. Individuals become euphoric, talkative, and alert, possibly progressing to irritability, aggressiveness, agitation, and paranoia with frank psychotic symptoms. Physical symptoms of intoxication include hypertension, tachycardia, hyperthermia, and possibly cardiac arrhythmia, stroke, or seizures. As behavioral effects are generally short lived, individuals using cocaine often repeatedly self-administer the drug. Patients presenting with suspected or confirmed intoxication can have hyperthermia, agitation, significant euphoria, and delirium. Patients can also present with significant alterations in physical vital signs (e.g., increased heart rate and blood pressure) and electrophysiologic changes (e.g., QRS and QT intervals). Patients should be managed with supportive care for any of the cardiovascular manifestations (e.g., stroke or myocardial ischemia) and medication therapy includes benzodiazepines for agitation and antiadrenergic therapy for blood pressure elevation (e.g., calcium channel blockers). Since cocaine can inhibit the re-uptake of biogenic amines, it is important to stress that a single therapeutic plan utilizing $\beta$-blockers would not be advised, as there could be a risk of increased blood pressure with unopposed $\alpha$-activity. If rhabdomyolysis is suspected, elevations of creatine kinase (CK) are observed with acute kidney injury, resulting from myoglobinuria. Respiratory manifestations of cocaine intoxication include bronchoconstriction and may even progress to hemoptysis.\textsuperscript{16–19}

**Withdrawal**

Cocaine withdrawal is characterized by the 3 following phases: (1) an initial "cocaine crash" phase (fatigue, insomnia, and depression) lasting for 1–2 days; (2) withdrawal phase (dysphoria and anxiety); and (3) an extinction phase. An intense craving for cocaine can occur at any time. Cocaine withdrawal symptoms generally are managed supportively with no specific identified pharmacologic treatments. Intense cocaine cravings may lead individuals to self-medicate with cocaine or other illicit substances. Cocaine withdrawal symptoms are increased agitation, paranoia, and inability to sleep. The symptoms of cocaine withdrawal are a result of depleted biogenic amine stores (e.g., dopamine, serotonin, and norepinephrine).\textsuperscript{17} Clinical management includes supportive care with benzodiazepines and calcium channel blockers for agitation and blood pressure, respectively.
Marijuana

Marijuana, known as THC and delta-9-THC, results in euphoria, decreased inhibition, and elevated mood. Patients who have used marijuana describe an increased retention of memory and energy. Marijuana undergoes liver metabolism to form 11-hydroxy-THC. The metabolite, 11-hydroxy-THC, is more potent than the compound THC. The onset of action for THC, which is consumed via inhalation, is approximately 0.5–2 h. The half-life for THC and its metabolites is variable dependent on usage frequency (e.g., acute vs chronic use). Individuals who use THC acutely or for the first time will have a half-life of about 24–60 h. Individuals who are chronic users will have THC detectable in their system for up to 2–3 weeks due to the lipophilic redistribution of the compound and its metabolites.19–21

Marijuana intoxication and withdrawal are also managed in similar respects. Marijuana itself generally does not have significant toxicities. Tolerance generally does not develop to marijuana, although heavy daily users may experience withdrawal symptoms of insomnia, diaphoresis, dysphoria, irritability, tremor, and nausea. Symptoms peak at 48 h of abstinence and persist for 96 h. There is no recognized withdrawal regimen for THC ingestion. The major concern today is synthetic derivatives of THC, which are being obtained by users, that are significantly more potent and toxic. In some instances, the more synthetic forms of THC (e.g., K2 and Spice) have been reported to result in death after a single use. Patients presenting with THC ingestion can have acute psychotic episodes, but this is more characteristic of synthetic derivatives that are now infiltrating the drug market. Clinical management of marijuana intoxication includes benzodiazepines for agitation and airway observation if co-ingestion(s) are suspected. Marijuana withdrawal can manifest as aggression, anxiety, and insomnia.20,21

Opioids

Recent evidence indicates that the use of prescription opioids has increased; therefore, admissions and complications associated with opioid intoxication and withdrawal have as well. Patients who have been admitted for adverse events related to opioid therapy or illicit use are generally in 1 of 2 classifications based on exposure: naïve and non-naïve. Opioid-naïve patients are generally those who have been exposed daily for at least a 3-week period. Patients after being exposed to opioids for this approximate time period develop tolerance (or receptor desensitization) to the reward sensation of opioids, pain relief, and adverse events (e.g., respiratory depression) associated with increased exposure.22,23

Opioids have pharmacologic activity on the mu1 and mu2 receptors. Additional receptors that possess opioid activity include kappa and delta receptors. The mu receptors have the dominant pain relief (mu1) and adverse event (mu2) activity. Common adverse effects include gastrointestinal, respiratory, and mental status changes.23 The duration of the management of opioid withdrawal and intoxication should center on the ingested opioid(s) pharmacokinetics (pK). One scenario where the pharmacokinetics is not reliable is an overdose situation. In instances of an opioid overdose, the pharmacokinetics transition to toxicokinetics and population pK calculations become invalid as the metabolism transitions from first-order kinetics to zero-order kinetics.23 Often a clear patient history or description of the opioid in question is not obtainable; therefore, conservative management is advised to ensure patient safety.

Intoxication

Opioid overdose is not uncommon due to the variable tolerance of individuals, difficulty in determining street drug purity, and the fact that depression and suicide are often seen in opioid-abusing populations. Prescription opioids abuse/dependence has significantly increased over the last decade. The supply chain for these prescriptions originates and is driven by valid prescriptions from patients, the illegal market created for them on the street, and children/teens
now experimenting beyond alcohol. Physical symptoms of overdosage are respiratory depression, hypothermia, miosis, and coma. Opioid intoxication can manifest as mental status changes, respiratory compromise, and in severe cases cardiovascular collapse secondary to significant pulmonary edema.\textsuperscript{23,24} The core principle regarding the management of opioid intoxication centers on protecting the patient’s airway. Bag-mask ventilation strategies are appropriate management; however, intubation and mechanical ventilation are occasionally required until the opioid’s effects have dissipated. The pharmacologic management of opioid intoxication is naloxone, an opioid antagonist. Naloxone does possess a greater affinity for the opioid receptor (mu) than prescription opioids. Naloxone can be administered via inhalation, subcutaneously, or intravenously. Naloxone does have a relatively short half-life, and several prescription opioids possess sustained-release preparations; therefore, naloxone infusions may also need to be initiated in select cases for clinical management.\textsuperscript{3,23} Naloxone may be given at an adult dose of 0.4–2 mg IV and should reverse overdose symptoms within 2 min. Clinicians should be reminded that if a long-acting preparation (i.e., extended or sustained release) was ingested that the patient will require a continuous intravenous (IV) infusion of naloxone for the management of the opioid overdose.

Withdrawal

Opioid withdrawal can manifest just hours after the last exposure, but this is also dependent on the preparation as there are many on the market today. The clinical presentation of opioid withdrawal includes increased gastrointestinal activity (nausea, vomiting, and diarrhea) and mydriasis. General supportive measures (airway monitoring) are always recommended, and pharmacologic therapies include the following: alpha-adrenergic therapy (e.g., clonidine), gastrointestinal medications (e.g., dicyclomine and loperamide), and buprenorphine (a partial opioid agonist).\textsuperscript{23,24} For acute detoxification, clonidine 0.4–2 mg/day may be used. Due to its antihypertensive properties, pulse and blood pressure must be closely monitored. Some patients experience excessive sedation with clonidine, which may be moderated by dosage adjustments. Gastrointestinal cramps can be treated with dicyclomine (20 mg orally every 4–6 h as needed), while nausea can be safely treated with prochlorperazine (10 mg orally or IM every 6 h as needed). Loose stools may respond to loperamide (2 mg orally as needed, to a maximum daily dose of 6 mg). Trazodone (50–150 mg orally at night) can be given as a sleep aid. An alternative compound, buprenorphine, a partial opioid antagonist, may be useful in acute detoxification situations.\textsuperscript{25}

Buprenorphine was approved in 2002 by the FDA for the management of opioid dependence and is recommended to initiate low doses and to titrate conservatively. Buprenorphine also is available as a combination product with naloxone for the management of these patients, often those that enrolled in a detoxification program. Buprenorphine is a partial mu-opioid agonist and weak K-opioid antagonist. In typical doses used in clinical settings, buprenorphine acts similar to methadone. At higher doses, buprenorphine affects the pK plateau, acting as an opioid antagonist, thus resulting in a decreased ceiling effect, which translates into a lower overdose risk. Buprenorphine is FDA approved for treating opioid dependence. Buprenorphine is available as a sublingual tablet either alone or as a combination tablet containing buprenorphine and naloxone in a ratio of 4:1. Because of its partial agonist action, buprenorphine may precipitate withdrawal in opioid-dependent persons. Common daily dose range from 4 to 24 mg/day. Potential adverse effects include abdominal pain, constipation, nausea, vomiting, headache, and sweating. Careful titration and screening for drug interactions (CYP 3A4 and 2D6 systems) are advised with buprenorphine/naloxone therapy.\textsuperscript{22,25} Another medication that has become available for the management of opioid withdrawal and dependence is methadone. Methadone has a half-life of approximately 24 h; therefore, it takes 1 week to reach steady state. It is recommended that methadone therapy be initiated once daily administration has begun and that it be administered by certified and experienced providers
with appropriate patient monitoring secondary to the possible toxicity associated with its use. The main toxicities regarding methadone therapy are respiratory failure and cardiac electrophysiologic changes (e.g., QTc prolongation), both of which are dose dependent and fatal.\textsuperscript{3,22} Usual daily oral dose of methadone starts at 20–30 mg/day. Initial cardiac monitoring (e.g., EKG) can be utilized to screen and monitor for prolonged QTc during therapy. If patients have a QTc greater than 500 ms, then the patient should be advised to stop therapy by their physician and be transitioned to an alternative regimen. Clinicians that prescribe methadone should remember to initiate at low dosages and increase at a slow interval with periodic patient follow-up to monitor for central nervous system and cardiac side effects. Generally, patients must come to the clinic on a daily basis (usually morning) to receive methadone therapy. Other interventions involved in clinic treatment may include counseling, urine drug testing, vocational rehabilitation, etc. When used successfully, methadone maintenance reduces illegal drug use and reduces the medical, legal, and societal ramifications associated with the illicit drug culture.\textsuperscript{22}

An alternative strategy in managing long-term opioid abuse treatment is the use of opioid antagonists. Naltrexone, a long-acting (72 h) antagonist, blocks the euphoric effects of opioids and may be taken 3 times/week at dosages of 100–150 mg. Theoretically, the use of naltrexone discourages persons from opioid use as it eliminates the subsequent CNS effects. In clinical practice, poor adherence and high dropout rates limit the usefulness of naltrexone for maintenance treatment of opioid dependence. Naltrexone works best with highly motivated individuals with good psychosocial support as there are no physical incentives (withdrawal symptoms) to continue taking opioid antagonist on a long-term basis.

**Benzodiazepine**

**Intoxication**

Central nervous system depression with hypotension due to vasodilation and concomitant respiratory depression are the predominant sequelae. The mainstay of therapy is supportive with particular attention to ventilatory and circulatory support. Flumazenil (children 0.01 mg/kg; maximum dose of 0.05 mg/kg or 1 mg, whichever is lower; adults: up to 5 mg) is effective in reversing the sedative effects of benzodiazepines. Caution is advised with the utilization of flumazenil as seizures may be precipitated with administration secondary to GABA receptor antagonism from an abrupt reversal.\textsuperscript{26}

**Withdrawal**

Tolerance can develop rapidly in benzodiazepine therapy and from 15% to 44% of chronic users experience withdrawal symptoms, when their benzodiazepine dose is decreased. Patients who take benzodiazepines for greater than 3 months are at risk for withdrawal. The onset of symptoms may be as short as 1 day for the longer-acting benzodiazepines (i.e., diazepam). Symptoms may last for 6 weeks. Symptoms are due to neuronal excitation and may include anxiety, insomnia, fever, tremor, nausea, tinnitus, myalgias, seizures, vomiting, and diaphoresis. Treatment consists of reinstitution of a long-acting benzodiazepine with a gradual taper (over a period of 6–8 weeks). In cases of severe symptomatology, an intravenous infusion of diazepam (at 20 mg/h or more) in a monitored setting may be initially required. Phenobarbital 30-mg equivalency for benzodiazepines includes alprazolam 0.5 mg, clorazepate 7.5 mg, chlordiazepoxide 25 mg, diazepam 5 mg, flurazepam 30 mg, lorazepam 1 mg, oxazepam 15 mg, temazepam 60 mg, triazolam 0.5 mg, and clonazepam 0.25 mg. One-fourth of this calculated dose is administered and the dose is increased as necessary. The phenobarbital dose can be tapered after the patient is stabilized for 48 h at a rate of 10% of the dose daily. Propranolol (20 mg 3–4 times/day) can be instituted on day 5 and continued for 2 weeks as an adjunctive agent.
Inhalants

Intoxication

CNS effects of intoxication usually resolve within minutes to hours of inhalant use. Toxic effects depend on the solvent used and may require emergency treatment for arrhythmias or CNS hyperactivity (seizures). Exposure to some inhalants (i.e., toluene) can result in nephrotoxicity; therefore, renal function should be monitored. Overall inhalant intoxication management is generally supportive care.27

Withdrawal

Withdrawal reactions occur rarely as most inhalant use is relatively short lived. Symptoms that may occur are generally treated supportively with concurrent psychosocial interventions. In addition to supportive care, some literature supports the utilization of low doses of antipsychotics (e.g., risperidone 0.5 mg twice daily for 4 weeks. Other pharmacologic therapies include lamotrigine 100 mg daily (titrated up to) or vigabatrin (a selective GABA transaminase inhibitor) as treatment options during cessation.27 Psychotherapeutic interventions are generally most effective. Due to the young age of most patients, family therapy is often also indicated.

Nicotine

Intoxication/overdose

Nicotine intoxication from tobacco use is rare. Excess nicotine from nicotine replacement therapies used in smoking cessation (i.e., nicotine gum) may occasionally cause adverse effects, such as nausea, headaches, or cardiac abnormalities.2

Withdrawal

Withdrawal symptoms begin within 6–12 h and generally peak 24–72 h after smoking cessation. Most symptoms last for approximately 1 month, although craving can persist for 6 weeks or longer. Smoking cessation is associated with slowing on electroencephalogram and decline in metabolic rate, including mean heart rate decline of 8 beats/min. Blood levels of some antidepressants (e.g., clomipramine, desipramine, doxepin, imipramine, and nortriptyline) may increase as may some antipsychotic medications (e.g., clozapine, fluphenazine, haloperidol, and olanzapine) and some anxiolytics (e.g., oxazepam and diazepam) secondary to nicotine's effects on the cytochrome P450 metabolism.2

Nicotine replacement provides the nicotine-dependent patient with nicotine in a form that is not associated with the carcinogenic elements in tobacco. Nicotine gum, a nicotine lozenge, transdermal nicotine patches, nicotine nasal spray, and nicotine inhalers are available for smoking cessation. Nicotine gum, now available over the counter, consists of 2–4 mg of nicotine in a polacrilex resin, which is designed to be slowly chewed for 20–30 min. Nicotine absorption peaks 30 min after initiation of gum use. Most common adverse effects are GI complaints (nausea and anorexia) and headache. Although nicotine replacement has been used for relief of withdrawal symptoms, some patients utilize these therapies long term.

Nicotine patches consist of nicotine impregnated into an adhesive patch for transdermal application. Patches are applied daily each morning upon quitting smoking with starting dosages of 21–22 mg/24-h patch and 15 mg/16-h patch. Patients should not smoke cigarettes while on patches as nicotine toxicity may occur. Typical treatment duration is 6–8 weeks. The nicotine inhaler contains a replaceable component that delivers nicotine in inhaled air. Unlike
cigarettes, which deliver nicotine directly into the arterial blood in the lungs, the inhaler delivers nicotine into the buccal mucosa. Some clinicians advocate the use of combination therapy in the treatment of nicotine dependence.\textsuperscript{28,29}

One general approach is to combine a long-acting treatment, such as bupropion, with a shorter-acting treatment, such as nicotine gum. In addition to nicotine replacement, some antidepressants (bupropion, nortriptyline, doxepin, and desipramine) have been shown to improve the chances of nicotine abstinence. Sustained-release bupropion hydrochloride has been approved by the FDA for smoking cessation. In addition to reducing nicotine withdrawal symptoms, bupropion SR may diminish weight gain. Bupropion's mechanism of action is dual activity for inhibition of the re-uptake of dopamine and norepinephrine in mesolimbic and locus ceruleus in the brain. The therapy is focused to increase dopamine and norepinephrine to mimic the reward center in the brain, which nicotine is producing. Some clinicians utilize both bupropion and nicotine replacement concurrently. Some clinicians utilize clonidine at dosages of 0.1–0.4 mg/day for nicotine withdrawal in individuals who fail or are unable to tolerate other symptomatic treatment or nicotine replacement. However, use of clonidine for smoking cessation is often limited by adverse effects, including sedation, dizziness, and dry mouth.\textsuperscript{28–30}

Another pharmacologic option is varenicline. Varenicline is FDA approved for smoking cessation therapy and should be combined with behavioral interventions. Combination pharmacotherapy is advised for patients who have a high nicotine requirement, who have failed monotherapy, or those patients that have cravings throughout the day on treatment. Varenicline is a $\alpha_{4}\beta_{2}$ nicotinic receptor partial agonist. The drug was developed to target the mesolimbic reward center of the brain and decrease craving and withdrawal effects of nicotine. The FDA-approved indication recommends 0.5 mg daily for 3 days, then 0.5 mg twice daily for 4 days, and then 1 mg twice daily thereafter for 11 weeks. The patient should be instructed to stop smoking during week 2 of therapy.

The adverse events reported with varenicline include nausea (30%) and even higher percentage of patients reported abnormal dreams. In addition, varenicline could exacerbate co-morbid psychiatric disorders; therefore, careful screening is advised prior to initiation of therapy. In 2008, the FDA released a warning regarding varenicline and abnormal behavior.\textsuperscript{29,30}

**Summary**

Patients being treated for substance intoxication or withdrawal require intense monitoring and supportive therapy. The results of inappropriate monitoring and pharmacologic therapy can be catastrophic on a patient's outcome. The key factor in the management of substance intoxication or withdrawal is identification of the triggering substance(s). Specific therapies have been outlined above to address the clinical scenarios of nicotine, alcohol, cocaine, marijuana, and opioids. Supportive therapy should focus on prompt identification, pharmacologic management, and antidote administration (when applicable). Airway monitoring needs to be emphasized as patients often present with co-ingestions and are generally unable to provide an accurate medication/ingestion history.

**References**