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Drugs of Abuse in Trauma Patients Part II: Central Nervous System Depressants

Drugs of abuse are commonly encountered in the trauma setting. Patient care may be affected by acute intoxication and chronic use of these substances. Central nervous system depressants can result in coma and respiratory depression in severe toxicity. The authors discuss common presentations, potential complications, and management of central nervous system depressants in the context of a trauma patient.

—Ann M. Dietrich, MD, Editor

Introduction

Substance use is an increasingly important issue in the United States. Individuals with a substance use history present to the acute care setting for many reasons, including toxicity, withdrawal, or indirect complications, such as trauma and associated infections. Healthcare providers in these settings benefit from awareness of the acute and chronic effects of substance use and the impact on patient management. However, patients may not be forthcoming with substance use or they may be unable to provide a history. The challenge of determining if a clinical presentation is related to acute toxicity, withdrawal, or alternative etiology often is encountered.

This article is the second of a two-part series describing common drugs of abuse in the trauma patient. The first part of this series characterized stimulants and drugs with sympathomimetic properties as well as common mechanisms of intracorporeal drug smuggling. The goal of the second segment is to describe frequently encountered substances that can result in depressant effects. Substances may be legally obtained, such as purchased ethanol or benzodiazepines prescribed for therapeutic use by a physician. These substances also may be acquired illicitly for recreational use, such as gamma-hydroxybutyric acid (GHB) or synthetic opioid agonists produced in clandestine labs. The substances reviewed are those that can result in life-threatening respiratory depression and significant central nervous system (CNS) depression. This article characterizes these commonly used drugs with depressant effects as well as the testing and management in cases of toxicity.

Ethanol

Background

Ethanol is one of the most widely consumed substances in the world. Ethanol use is common in adults of all ages and socioeconomic groups.[1] In the United States, 15 million people ages 12 and older have an alcohol use disorder.[2] Ethanol's association with trauma, and specifically the increased risk of traumatic brain injury

EXECUTIVE SUMMARY

- Ethanol is one of the most widely consumed substances in the world. Ethanol use is common in adults of all ages and socioeconomic groups. Individuals under the influence of ethanol are more likely to be involved in a motor vehicle collision, and those with a positive blood alcohol level are more likely to be at fault in a collision.
- Initial management should emphasize supportive care, particularly with regard to airway management. Severe respiratory depression can occur in alcohol intoxication, and patients may require rapid sequence intubation and mechanical ventilation. Patients commonly present with evidence of central nervous system (CNS) depression but may have agitation, particularly in the setting of withdrawal. Agitated or combative patients may require sedation and restraint. Metrics commonly used in the setting of trauma, such as Glasgow Coma Scale, lactate, and base deficit, may be less reliable. Benzodiazepines or antipsychotics may be necessary to facilitate care. Recent literature suggests the use of droperidol may result in shorter lengths of stay in the emergency department compared to antipsychotics with longer half-lives, such as haloperidol and olanzapine.
- Sedative-hypnotics result in CNS depression, which can present with varying degrees of slurred speech, ataxia, or poor coordination. Deep coma with respiratory failure is rare with isolated sedative hypnotic toxicity, but it can occur at high doses or with the use of other CNS depressants, such as opioids or ethanol.
- Sedative-hypnotic overdose can present with varying degrees of CNS and respiratory depression. Initial management should emphasize airway, breathing, and circulation, with the provision of adequate supportive care. With proper supportive care and adequate respiratory support, most isolated sedative-hypnotic overdoses will recover without sequelae.
- The term opiates is used for opioids that are naturally extracted from the opium poppy, *Papaver somniferum*. Opiates include morphine and codeine. Other opioids, such as fentanyl and methadone, are synthetically manufactured in laboratories.
- In the setting of trauma, patients with chronic opioid use may exhibit hyperalgesia or heightened pain sensitivity. Individuals may require increasing doses of analgesics to mitigate pain. Medical consequences of chronic injection of intravenous drugs include scarring or collapsed veins, which may make obtaining intravenous access challenging in the trauma patient.
- Gamma-hydroxybutyric acid (GHB) is a drug with sedating effects. GHB has intense euphoria and is frequently used as a "club drug." Because of diminished availability of GHB, there has been a shift toward GHB analogues, such as gamma-butyrolactone (GBL) and other precursors that can be converted to GHB in the body.
- GHB toxicity presents with respiratory and CNS depression that may share similar features with other substances, such as ethanol and benzodiazepines. Initial management should emphasize supportive care.

(TBI), has been well documented.[3,4] Common mechanisms of trauma include motor vehicle collisions, altercations, and falls. Individuals under the influence of ethanol are more likely to be involved in a motor vehicle collision, and those with a positive blood alcohol level are more likely to be at fault in a collision.[5] Literature suggests that a blood ethanol level of 0.05% or higher results in an impaired ability to operate a motor vehicle.[6] Trauma studies have suggested that ethanol contributes to nearly 18.5% of all emergency department (ED) visits.[2]

Ethanol absorption occurs primarily in the stomach and intestines. Under optimal conditions, 80% to 90% of ethanol is absorbed within one hour and circulates through the body to the liver, where it is metabolized.[1,7] However, many factors affect absorption, such as food intake, the concentration of ethanol, and gender.[1,8]

Effects

The clinical effects of ethanol toxicity are well established. At low doses, ethanol selectively depresses the central nervous system. Users initially may experience a paradoxical stimulatory effect, leading to disinhibition, increased energy, and emotional lability. At higher doses, it acts as a general depressant, and users may become irritable, confused, and lethargic.[3] At critically high levels, users can become comatose and lose airway protective reflexes.[1] Coma can result at levels of 250 mg/dL in ethanol-naïve individuals.[1] Chronic users may tolerate higher blood serum levels than individuals with infrequent use.

Ethanol is a diuretic, which can result in volume depletion, with subsequent hypotension and tachycardia.[1,9] Acute ethanol toxicity has many effects on the heart and can further impair cardiac output in those with preexisting cardiac disease.[1] Even individuals with normal cardiac function can develop acute cardiac arrhythmias that can result in sudden cardiac death.[10] Acute ethanol withdrawal can result in increased sympathetic activity, resulting in arrhythmias.[1,10] Heavy ethanol use has been associated with the development of atrial fibrillation.[11] Other indirect injuries can occur due to ethanol toxicity. For example, hypothermia can result due to multiple mechanisms, such as environmental exposure, malnutrition leading to loss of energy substrates, or ethanol-induced vasodilation.[1]

The physical exam is relatively nonspecific in ethanol toxicity and may reveal flushed appearance, diaphoresis, mydriasis, or nystagmus.[1] Patients may have nausea, vomiting, dysarthria, poor muscle coordination, ataxia, or coma.[1] Seizures may occur in the setting of alcohol withdrawal and are more common in chronic users.[12]

Testing

Many tests exist for the quantitative evaluation of ethanol toxicity. These identify ethanol and its metabolites in biological fluids and exhaled air. Testing can identify recent use but does not provide any information regarding whether the level is rising, falling, or at a steady state. The rate of ethanol metabolism may not be evident.[13] If ethanol was consumed

immediately prior to presentation, ethanol levels could continue to rise as it is absorbed.[13] At high levels, ethanol exhibits zero-order metabolism, which means that it is eliminated at a constant rate regardless of the concentration of alcohol in the body. Metabolism is highly variable, but the average-size adult will have a decrease in their blood ethanol of approximately 15 mg/dL/h to 20 mg/dL/h.[1] Gender, the rate of gastric emptying, recent food ingestion, and total body water are several factors that can affect ethanol metabolism.[1,8,13] Chronic ethanol use induces hepatic enzymatic activity, resulting in faster rates of elimination in individuals with chronic abuse.[14]

Management

Initial management should emphasize supportive care, particularly with regard to airway management. Severe respiratory depression can occur in alcohol intoxication, and patients may require rapid sequence intubation and mechanical ventilation.[1] Patients commonly present with evidence of CNS depression but may have agitation, particularly in the setting of withdrawal. Agitated or combative patients may require sedation and restraint. Benzodiazepines or antipsychotics may be necessary to facilitate care.[15,16] Benzodiazepines may result in a synergistic effect on respiratory depression.[1] Recent literature suggests the use of droperidol may result in shorter lengths of stay in the ED compared to antipsychotics with longer half-lives, such as haloperidol and olanzapine.[17] Ketamine is used frequently in patients with undifferentiated agitation, but it has not been studied extensively in patients with ethanol intoxication.[18] Prior studies have identified both acute and chronic alcohol abuse as a risk factor for leaving against medical advice.[19,20] Decision-making capacity should be assessed and taken into consideration.

Patients with suspected ethanol toxicity can have many reasons for changes in mental status. Intoxication can directly result in altered mental status. Additionally, intoxication increases the risk of associated trauma, which also can result in mental status changes or seizures.[1] Ethanol inhibits gluconeogenesis and glycogenolysis, and acute intoxication may result in hypoglycemia that can be contributory.[21] Children with acute ethanol intoxication are at a particularly increased risk of hypoglycemia.[14] Ethanol withdrawal also can present with alterations in mental status, which include agitation and seizures. If the history and clinical presentation are not entirely consistent with isolated ethanol toxicity, clinicians should consider further workup for other medical etiologies.

Ethanol intoxication is associated with an increased likelihood of head injury. Intoxication may mask underlying injury, such as intracranial hemorrhage.[22] The Glasgow Coma Scale (GCS) is the standard scoring system of objectively assessing individuals with TBI. Many studies have sought to determine the relationship of GCS reliability in ethanol-intoxicated trauma patients.[23,24] GCS may guide clinical decision-making and triage in prehospital settings. It may affect decisions for imaging, airway management, or intracranial pressure monitoring in ED and trauma center settings.[25] However, GCS may be unreliable in individuals with elevated serum ethanol concentrations.[1,23,24] Some studies have suggested that ethanol intoxication can result in a lower calculation of GCS and overestimation of TBI.[23,24] Other studies have indicated that depressed levels of consciousness in patients with TBI may be improperly attributed to ethanol intoxication.[25] Occult trauma or pathology should be considered if there is clinical suspicion in the context of the patient's presentation.[9] Clinicians should have a lower threshold for emergent head CT due to the increased risk of traumatic head injuries.[1]

Ethanol intoxication and chronic use can result in metabolic and physiologic changes that further complicate the care of patients in hemorrhagic shock.[9] Ethanol has many known effects on hemodynamic, metabolic, and inflammatory homeostasis mechanisms in the setting of hemorrhage.[9] Ethanol blunts the natural catecholamine surge that typically occurs in trauma.[9] This catecholamine surge is involved in restoring mean arterial blood pressure after hemorrhagic shock.[26] In part this may be due to ethanol's effect as a diuretic, resulting in volume depletion.[9] Studies have found that patients with positive blood ethanol levels have lower systolic blood pressures on admission to the hospital.[9,27] Studies have indicated that alcohol intoxication can result in decreased responsiveness to initial fluid resuscitation.[9] Users with ethanol intoxication may have increased requirements for intravenous fluids and packed red blood cells compared to non-intoxicated individuals.[28]

Cardiovascular abnormalities can occur secondary to ethanol use. Ethanol has a depressive effect on the myocardium.[9] Ethanol-intoxicated patients should be assessed for cardiovascular complications.[9] Traumatic injury may result in metabolic and cardiovascular abnormalities that theoretically may place patients with hemorrhagic shock at a higher likelihood of cardiac arrest.[9] Patients presenting with myocardial injury, hypotension, or abnormal electrocardiograms may require monitoring for cardiovascular complications.[9]

Acute ethanol intoxication may affect laboratory parameters that often guide management in the setting of hemorrhagic shock. Lactate and base deficit frequently are used to guide resuscitation in the setting of hypoperfusion.[29-32] However, ethanol withdrawal can induce metabolic acidosis in the absence of shock.[1,29,33] Many studies have sought to determine if these laboratory values are reliable markers in an intoxicated patient, with varying results.[29-32] Given conflicting findings, clinicians may wish to consider the entire clinical picture rather than only using these metabolic markers for management of resuscitation in shock.[29-32] Individuals with chronic ethanol abuse also may have electrolyte disturbances, such as hyponatremia, or other derangements in phosphate, magnesium, or potassium that can affect resuscitation.[14,33]

Patients with acute and chronic ethanol use may have alterations in blood coagulation that result in hypercoagulability or hypocoagulability.[9] Patients with chronic ethanol use may have cirrhosis and subsequent liver dysfunction, which can increase bleeding risk. Ethanol use has an inhibitory effect on platelet function.[34] However, some studies have shown that acutely high blood ethanol levels (> 150 mg/dL) are associated with decreased fibrinolysis.[35] In the trauma setting, this may affect decisions to use antifibrinolytic therapy such as tranexamic acid.[35] Patients with chronic ethanol use are at high risk of thiamine deficiency,

which can progress to Wernicke encephalopathy. Ethanol users may have a high risk of thiamine deficiency, and a low threshold for supplementation should be considered. Parenteral thiamine 250-500 mg/day for three to five days, followed by oral thiamine 250-300 mg/day is a treatment regimen that has been described.[36,37]

Summary

Ethanol-intoxicated patients are at increased risk of trauma. Ethanol is a commonly used substance that results in disinhibition and increased energy and sociability at low doses. At high doses, users experience confusion, coma, and, occasionally, significant respiratory depression. Ethanol can result in metabolic and physiologic responses that increase the risk of complications and mortality in the setting of traumatic shock. Metrics commonly used in the setting of trauma, such as GCS, lactate, and base deficit, may be less reliable. Intoxicated patients may have many etiologies for changes in mentation, including trauma. Clinicians should have a low threshold for imaging patients to assess for trauma. Patients with ethanol intoxication should be managed with supportive care. (*See Table 1.*)

Table 1. Summary: Ethanol

Effects	• At lower doses, selective depression of central nervous system • At higher doses, acts as a general depressant, resulting in irritability, confusion, and lethargy • At critically high levels, can result in coma and loss of airway protective reflexes
Acute Toxicity Presentation	• Acute cardiac arrhythmias • Flushed appearance, diaphoresis, mydriasis, nystagmus • Nausea, vomiting, dysarthria, poor muscle coordination, ataxia, coma, seizures
Complications	• Electrolyte disturbances • Alterations in blood coagulation • Cirrhosis and liver dysfunction
Management	• Supportive care

Sedative-Hypnotics: Benzodiazepines and Nonbenzodiazepines

Background

Sedative-hypnotics are a class of prescription medications with anxiolytic, hypnotic, anticonvulsant, and muscle-relaxant effects.[38,39] Sedative-hypnotics produce CNS depression by interacting with the gamma-aminobutyric acid (GABA) receptors. They have many therapeutic uses, such as the management of anxiety and insomnia, but also have high abuse potential. Examples of sedative-hypnotics include benzodiazepines, nonbenzodiazepine sedative-hypnotics, such as zolpidem, and barbiturates. Benzodiazepines share a common chemical structure that results in varying durations of action and CNS penetration. Some benzodiazepines have active metabolites that can prolong duration of action.[38]

Benzodiazepines are among the most commonly prescribed psychiatric medications, with more than one in 20 people in the United States filling a prescription each year.[39] Examples include lorazepam (Ativan) and clonazepam (Klonopin).[38,39] The use of benzodiazepines is increasing in the United States.[40] In addition to the therapeutic use of benzodiazepines, medication diversion for illicit use is a concern. The use of "designer benzodiazepines" that produce strong sedation and amnesia has increased, and these agents are sold through online platforms that frequently bypass regulatory mechanisms. These medications have no approved medical uses in the United States.[41,42]

Benzodiazepine use may have implications for trauma care. Benzodiazepines can produce impairment that may increase the risk of motor vehicle accidents.[43-45] For example, benzodiazepine misuse is associated with suicidal ideation and self-harm attempts, as well as motor vehicle collisions and falls.[39,46,47] Benzodiazepines are associated with drug-facilitated sexual assault, which may relate in part to the amnestic properties.[48]

Effects

Sedative-hypnotics result in CNS depression, which can present with varying degrees of slurred speech, ataxia, or poor coordination.[38] Deep coma with respiratory failure is rare with isolated sedative hypnotic toxicity, but it can occur at high doses or with the use of other CNS depressants, such as opioids or ethanol.[38,49] Additionally, some individuals are at high risk for acute paradoxical reactions that present with delirium, psychosis, or transient global amnesia. Elderly individuals are at the highest risk of both toxicity and paradoxical reactions.[49]

The physical examination is relatively nonspecific. In addition to CNS and respiratory depression, patients may have a mild reduction in heart rate and blood pressure due to decreases in sympathetic tone.[38] Hypothermia is common but is most pronounced with barbiturate toxicity.[38] Skin manifestations can occur. These have been described as "barbiturate blisters" that are bullous lesions found at pressure points. These findings are nonspecific and are seen with many other CNS toxins.[38]

Testing

EDs frequently use urine assays that screen for benzodiazepines, but these urine studies have many limitations. These presumptively positive results do not specifically identify which benzodiazepine has been detected. Screening will not distinguish between therapeutic and recreational use.[50] Furthermore, positive results may demonstrate exposure to a drug but may not indicate the presence of toxicity.

Urine drug screens also are subject to many false-positive and false-negative results.[51] For example, sertraline is a commonly used antidepressant that has been associated with false-positive benzodiazepine assays.[51] False negatives can occur because screens do not detect certain commonly used benzodiazepines.[50] Additionally, newer "designer

benzodiazepines" have variable detection rates on urine drug screens.[41]

Management

Sedative-hypnotic overdose can present with varying degrees of CNS and respiratory depression. Initial management should emphasize airway, breathing, and circulation, with the provision of adequate supportive care.[1] With proper supportive care and adequate respiratory support, most isolated sedative-hypnotic overdoses will recover without sequelae.[38]

In the case of suspected intentional overdose, co-ingestion with other substances, such as opioids, ethanol, acetaminophen, and salicylates, should be considered.[38] Overdose can present as an undifferentiated comatose patient, and sedative-hypnotic toxicity may be challenging to distinguish from other causes of CNS and respiratory depression, such as opioid toxicity. Death in sedative-hypnotic toxicity typically occurs from cardiorespiratory collapse, often secondary to intoxication with multiple substances. Single-agent benzodiazepine use is rarely associated with high rates of morbidity and mortality. Fatal overdoses often occur with co-ingestion of other drugs, such as tricyclic antidepressants, ethanol, and opioid agonists.[52-57] Naloxone may be considered for empiric treatment in the undifferentiated comatose patient.

Flumazenil is a benzodiazepine antagonist, but its use is considered only with a high degree of caution and by experienced clinicians. Complication rates have been reported up to 23.4% after flumazenil administration and can include anxiety, agitation, seizures, and arrhythmias.[58] In patients with chronic benzodiazepine use, flumazenil can precipitate seizures that may be refractory to standard treatments (i.e., benzodiazepines).[38,59,60] In patients with co-ingestion, benzodiazepine toxicity may have a protective effect against seizures that may be lost if flumazenil is used.[53,59] When used appropriately, flumazenil has a short half-life of approximately 50 minutes and may require redosing.[59]

Summary

Sedative-hypnotic toxicity can present with sedation and respiratory depression. Examples include benzodiazepines, which have been associated with an increased risk of motor vehicle collision.

Table 2. Summary: Sedative-Hypnotics

Effects	• Central nervous system and respiratory depression • Mild reduction in heart rate and blood pressure • Skin manifestations • Hypothermia • Deep coma and respiratory failure can occur with severe toxicity
Acute Toxicity Presentation	• Varying degrees of central nervous system and respiratory depression
Complications	• In cases of suspected intentional overdose, consider possible co-ingestion of other substances such as opioids, ethanol, acetaminophen, or salicylates
Management	• Supportive care and airway management

The physical exam can be nonspecific and may include changes in mental status and respiratory drive, as well as mild bradycardia and hypotension. Commonly used immunoassays frequently do not test for all benzodiazepines and may result in false negatives. Management of toxicity should emphasize supportive care and airway management. Flumazenil is a benzodiazepine antagonist with limited use due to potentially serious adverse effects. Flumazenil is administered very carefully only in selected cases due to the risk of precipitating refractory seizures. (*See Table 2.*)

Opioids

Background

The term opiates is used for opioids that are naturally extracted from the opium poppy, *Papaver somniferum*. Opiates include morphine and codeine.[61] Other opioids, such as fentanyl and methadone, are synthetically manufactured in laboratories but target the same opioid receptors as opiates.[62] They are used therapeutically for their analgesic properties and have high abuse potential for their psychoactive effects.[61] Both naturally occurring and synthetic opioids result in euphoria due to the binding of the mu opioid receptors, which are found in high concentrations in the brain.[63] In general, the term opioid refers to the broad class of substances that bind to the opioid receptors.

Opioid use is found among a wide range of ages and demographics, with the average age of first opioid use being 22.9 years of age.[63] Some synthetic opioids used in pain management include oxycodone, hydrocodone, fentanyl, and hydromorphone.[61] Since 2013, the rate of drug overdose deaths has increased sharply, driven primarily by the illegal manufacturing of non-pharmaceutical fentanyl, fentanyl analogs, and novel opioid agonists.[61] In 2017, 47,600 drug overdose deaths involved an opioid.[64] Non-pharmaceutical analogs of fentanyl include acetyl fentanyl, butyryl fentanyl, furanyl fentanyl.[61] Carfentanil is a synthetic fentanyl analog with a potency of 10,000 times that of morphine, approved for veterinary use in large animals. However, it has been detected in the illicit drug supply and poses a risk of overdose to unsuspecting users.[65-67] Many other synthetic opioids are manufactured in illegal labs in China and Mexico.[61]

Morphine can be processed to form heroin, which is highly addictive. Heroin typically is sold as a white powder that can be snorted, smoked, or dissolved and injected into veins, muscles, or under the skin.[68] Heroin results in a pleasurable sensation experienced by users, known as a "rush," followed by warm flushing of the skin, dry mouth, and a heavy feeling in the extremities. Nausea, vomiting, and severe itching can occur.[62] Individuals can have drowsiness and depressed mental functioning for several hours.[62] CNS depression can progress to coma and respiratory depression.

Synthetic opioids include drugs such as fentanyl and fentanyl derivatives. Fentanyl is a synthetic opioid similar to morphine but it is 50 to 100 times more potent. It is used both therapeutically and illegally. Synthetic opioids are the most commonly implicated drugs in fatal

overdoses in the United States.[62] In 2017, nearly 60% of opioid deaths involved fentanyl.[62] Fentanyl can be injected, placed on the skin as a patch, or sucked on as a lozenge.[62] Illicitly manufactured fentanyl is more frequently synthesized as a powder or pill or diluted into a liquid.[62] Other drugs, such as heroin, cocaine, methamphetamines, or MDMA, may be adulterated by fentanyl because its strong potency results in euphoria at microgram doses. This can result in unintended fentanyl overdoses.[62]

Some commonly used medications, such as codeine and loperamide, act at the opioid receptors.[69-72] Codeine is an inactive opioid agonist that must be enzymatically activated by the body to morphine. Wide genetic variation exists in this enzyme, which is why some individuals experience no analgesia with codeine while others can have life-threatening opioid toxicity after use.[61,69,70] Loperamide is an opioid analog used as an antidiarrheal agent and can be purchased without a prescription. At therapeutic doses, it specifically targets mu-opioid receptors in the gastrointestinal tract. At high doses, this specificity is lost, and systemic effects such as euphoria can occur.[61,70] The effects of loperamide on potassium and sodium channels can result in QT prolongation and life-threatening dysrhythmias, such as torsades de pointes.[70-73]

Effects

Opioids target CNS opioid receptors as the primary mechanism of action. Binding to mu-opioid receptors in the brain results in euphoria with drugs such as morphine and heroin.[62] Adverse effects of opioid receptor binding include CNS depression that can result in coma and respiratory depression. Clinical exam may reveal mental status depression, hypoventilation, and hypoperistalsis. Although miosis is a common finding, it is not required for the diagnosis of opioid toxicity. Concurrent use of stimulant medications, such as cocaine, can produce pupils of any size. Patients with severe toxicity may have hypoxic brain injury that results in mydriasis. Additionally, some opioids such as meperidine have less pupillary constricting effects.[61]

Opioid fatalities typically are secondary to respiratory depression progressing to apnea.[62] Opioid toxicity decreases the response to hypercapnia and hypoxia, resulting in loss of stimulus to breathe and subsequent apnea. It is important to note that although chronic users can develop tolerance to other effects of opioids, complete tolerance to loss of hypoxic stimulation never develops.[61] Respiratory depression initially results in loss of tidal volume, but at higher toxicity results in reduction of respiratory rate.[61] The respiratory rate may not fully capture the degree of ventilatory depression.[61] Additionally, opioid toxicity and naloxone use have been associated with noncardiogenic pulmonary edema.[74]

Affected patients may have hypotension and bradycardia. Opioids result in both arteriolar and venous dilation. This rarely presents as overt hypotension in the supine patient, but patients can have orthostatic blood pressure and pulse changes.[61] Bradycardia is less common but can be secondary to CNS depression.[61] Many opioids, particularly morphine, can produce nausea and vomiting at therapeutic doses.[61] Morphine also is associated with increased histamine release in comparison to other opioids such as fentanyl.[75]

Certain opioid medications can result in unique effects. Some opioids can contribute to serotonin toxicity, which presents with diaphoresis, tremor, hyperreflexia, myoclonus, hyperthermia, agitation, and altered mental status.[61,76,77] Fentanyl, tramadol, and oxycodone have been implicated in serotonin toxicity.[76,77] Fentanyl has the rare but unique toxicity of chest wall rigidity with cases describing a "wooden chest syndrome" preventing adequate ventilation. Patients should be mechanically ventilated, and some case reports indicate that naloxone or other neuromuscular blocking agents may have a role in the management of fentanyl-induced chest wall rigidity.[61,78-80] Methadone is an opioid that can result in prolongation of QT interval.[61] Tramadol is a synthetic drug with both opioid and nonopioid mechanisms, which can lower the seizure threshold even at therapeutic doses.[81]

Certain medications with activity at opioid receptors are used in the management of opioid use disorder. Methadone is an opioid agonist used for the treatment of chronic pain and opioid dependence. Toxicity can result in fatal respiratory depression.[61] Buprenorphine is a partial opioid agonist with an improved safety profile in the adult population with less respiratory depression and no significant effects on QT interval.[61]

Testing

Opioid toxicity typically is diagnosed clinically by the classic exam findings of CNS depression, respiratory depression, and pinpoint pupils. There are many opiate immunoassays available on the market. Opiate assays often target morphine, which also is a metabolite of heroin and codeine.[82] Semisynthetic opiates have some similarities to morphine and may result in a positive drug screen.[83] Many marketed opiate assays are poorly sensitive to oxycodone, and detection may be concentration-dependent. Positive assays do not distinguish between recent and more remote use.[61]

Synthetic opioids, such as fentanyl analogs, represent a large proportion of overdoses. However, commercial urine drug screening assays, such as those specific for morphine (a metabolite of heroin), do not detect many semisynthetic and synthetic opioids. Drug screens have varying abilities to detect oxycodone, hydrocodone, and other morphine derivatives.[61] Tramadol, a commonly abused synthetic opioid medication, may not result in a positive drug screen.[61]

Management

Initial care should emphasize airway management and resuscitation, since respiratory depression is the leading cause of fatality in opioid overdose. A high priority should be placed on prompt administration of an opioid antagonist such as naloxone. Naloxone will rapidly reverse almost all adverse effects of opioid toxicity.[61] The goal of opioid antagonist administration should be restoration of spontaneous ventilation, not restoration of consciousness or precipitation of withdrawal. Naloxone can be administered by intranasal, intramuscular, or intravenous (IV) routes. One approach is to start at 0.04 mg IV and re-dose at three-minute intervals.[61,84] The onset of action of naloxone is slower at low doses, and patients may require prolonged ventilatory assistance such as bag-mask ventilation. If several doses do not achieve response, higher repeat doses up to 0.4 mg to 2 mg can be used.[84] Higher cumulative doses up to

10 mg have been required in some individuals with refractory effects, particularly in the setting of newer synthetic opioids.[85] Although some patients may require high doses of naloxone, lack of response at higher doses also should prompt clinicians to consider other toxicities that may result in CNS depression.

In the setting of trauma, patients with chronic opioid use may exhibit hyperalgesia or heightened pain sensitivity.[61] Individuals may require increasing doses of analgesics to mitigate pain.[61] Medical consequences of chronic injection of intravenous drugs include scarring or collapsed veins, which may make obtaining intravenous access challenging in the trauma patient.[68] Other modes of access in these patients may be required. Additionally, patients with a history of narcotic use may have more complex management and weaning of intravenous narcotic pain medications, which may result in increased length of hospital stay following trauma.[86] Alternatives for pain management, such as regional nerve blocks and non-narcotic medications, may be considered.

The use of certain opioids increases the risk of cardiotoxicity. Patients with suspected toxicity can be evaluated by electrocardiogram to assess for QRS or QT prolongation that may increase the risk of dysrhythmias. Wide-complex dysrhythmias may require treatment with sodium bicarbonate by intravenous bolus to overcome sodium channel blockade. Optimization of electrolytes, including potassium and magnesium, should be considered in the setting of significant QT prolongation.[61] Cardioversion and defibrillation can be considered for dysrhythmia as indicated.

Seizures are rare in opioid toxicity but can be due to decreased seizure threshold or hypoxia. Benzodiazepines are considered first-line agents.[61] Providers should also be aware that opioids very rarely can result in rigidity and myoclonus that may have an appearance similar to seizure activity.[61] In patients with noncardiogenic pulmonary edema, patients should be managed with supportive care.

Summary

Opioids include a diverse class of substances that bind to opioid receptors and are recognized for their analgesic properties. Many opioids also exhibit psychoactive properties, which has led to misuse of both naturally occurring opioids, such as morphine, as well as the illegal synthesis of structurally similar drugs, including fentanyl analogs. Opioid toxicity typically presents with mental status depression, hypoventilation, and hypoperistalsis. Management should emphasize respiratory support and prompt administration of naloxone at sufficient doses to reverse the respiratory depression. Other less common complications can include cardiotoxicity, noncardiogenic pulmonary edema, and seizures. (*See Table 3.*)

Table 3. Summary: Opioids

Effects	• Euphoria • Nausea, vomiting, and severe itching can occur with heroin • Drowsiness and depressed mental functioning can occur
Acute Toxicity Presentation	• Severe toxicity may have hypoxic brain injury
Complications	• Respiratory depression • Serotonin toxicity may occur with fentanyl, tramadol, or oxycodone
Management	• Emphasis on airway management and resuscitation • Prompt administration of opioid antagonist (naloxone)

Gamma-Hydroxybutyric Acid

Background

Gamma-hydroxybutyric acid (GHB) is a drug with sedating effects.[87,88] GHB has intense euphoria and is frequently used as a "club drug."[87,89] Because of diminished availability of GHB, there has been a shift toward GHB analogues such as gamma-butyrolactone (GBL) and other precursors that can be converted to GHB in the body.[90] Throughout its history, GHB also has been used as an anabolic supplement, antidepressant, anesthetic, and for sleep disorders, such as narcolepsy.[87,88] The potent sedative properties have been implicated in drug-facilitated sexual assault.[87,89] GHB is particularly dangerous when concurrently used with other sedative drugs, such as alcohol and benzodiazepines.[91,92] Additionally, it has a narrow safety margin between recreational and fatal doses.[91,93] When used recreationally, GHB often is found as a colorless, oily liquid or white powder that is ingested.[89] GHB is rapidly absorbed after oral ingestion, with peak intoxication and euphoria occurring within 15 to 20 minutes.[87,91]

Effects

GHB is an endogenous neurotransmitter that acts at GHB receptors. However, if taken exogenously, most of its effects are mediated through $GABA_B$ agonism.[88] GHB primarily affects the CNS, resulting in euphoria, memory loss, and drowsiness.[87] Intoxication with GHB can be clinically indistinguishable from intoxication by other CNS depressants, such as ethanol and benzodiazepines.[91] Coma and cardiovascular disturbances, such as hypotension, bradycardia, and respiratory failure, can occur with exposure to high doses.[87,91,94] The physical examination also may reveal miosis, poorly responsive pupils, and hypothermia.[87,92] The presence of myoclonus can resemble seizure activity.[87,92]

Laboratory tests, including complete blood counts and chemistry profiles, frequently are normal. Renal function tests and creatine kinase can demonstrate rhabdomyolysis. The electrocardiogram may reveal sinus bradycardia with prominent U waves.[87] In the case of suspected intentional overdose, other toxicities also should be considered.

GHB toxicity follows a predictable course, and full recovery typically occurs within six to eight hours.[87] One study found that in patients who presented with coma due to GHB intoxication, the average time to regain consciousness was 90 minutes. Activated charcoal and gastric lavage are of limited use because of the rapid absorption of GHB and may increase risk of aspiration.[91] Users

frequently extubate themselves due to the improvement secondary to rapid clearance of GHB.[87,91] Patients are at increased risk of complications secondary to aspiration.[91] However, without a history of prolonged hypoxia or aspiration, toxicity often resolves without complications.[87] Death secondary to GHB use typically is related to cardiorespiratory arrest or due to fatal accidents secondary to intoxication.[95]

Testing

Routine urine drug screens do not test for GHB. Testing is complicated by both the rapid metabolism of GHB as well endogenous production that can result in false-positive results at low cutoff levels.[91,93,96] If needed for forensic purposes, immunoassays that test urine and serum are available.[91,93,96]

Management

GHB toxicity presents with respiratory and CNS depression that may share similar features with other substances, such as ethanol and benzodiazepines. Initial management should emphasize supportive care. Hypotension can be addressed with intravenous fluid replacement. If affected patients have severe bradycardia resulting in hemodynamic compromise, atropine can be considered.[87] GHB use also can result in hypothermia, which can be managed with standard warming techniques.[87,92] Naloxone administration should be considered cautiously when opioid exposure may be contributory.[87] Blood glucose, ethanol concentrations, and an electrocardiogram may assist in the diagnosis of concurrent exposures and conditions.[87]

Respiratory depression typically is the most concerning and life-threatening finding in GHB toxicity and, therefore, the most common cause of death.[87,95] Prompt attention should be placed on airway assessment and management. Vomiting and salivation could result in aspiration and warrant attention and monitoring.[87] Supportive care and a nasal airway may be sufficient in somnolent patients with an appropriate gag reflex and respiratory function.[87] However, some users require intubation with mechanical ventilation.[87] Some patients may become combative when assessing the airway and require sedation and restraint.[87]

Table 4. Summary: Gamma-Hydroxybutyric Acid (GHB)

Effects	• Sedating effects • Euphoria, memory loss, drowsiness
Acute Toxicity Presentation	• Presents with respiratory and central nervous system depression
Complications	• Exposure to high doses can result in coma, hypotension, bradycardia, and respiratory failure
Management	• Supportive care • Improvement typically occurs within 6-8 hours • Hypotension treated with intravenous fluid replacement • Atropine can be considered in patients who have severe bradycardia resulting in hemodynamic compromise • Standard warming techniques for hypothermia

Most patients presenting with GHB toxicity will resolve clinical effects within six to eight hours.[87] If a patient does not follow this course, further workup may be required for observation and evaluation of other etiologies.[87] The subsequent development of severe, potentially life-threatening GHB withdrawal should be considered with the development of agitation, tremor, tachycardia, hypertension, nausea, vomiting, diaphoresis, hallucination, and seizure. High doses of benzodiazepines may be required for treatment in addition to supportive care. Other $GABA_B$ agonists such as baclofen have been used but require further investigation.[87]

Summary

GHB is a drug with amnestic, euphoric, and sedative properties. It is often used as a "club drug" but also as an anabolic supplement or for drug-facilitated sexual assault. Toxicity can result in CNS and respiratory depression that may require airway management. Symptoms typically are self-limited, and rapid improvement frequently occurs within six to eight hours. (*See Table 4.*)

Conclusion

Drugs of abuse are encountered commonly in the trauma setting. Patient care may be affected by acute intoxication and chronic use of these substances. CNS depressants can result in coma and respiratory depression in severe toxicity. Urine drug screens often are unreliable due to limitations, including high rates of false positives and false negatives. Emphasis should be placed on supportive care with close monitoring of respiratory and cardiovascular status. The judicious use of antidotes, such as naloxone, can be considered in the appropriate settings.

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CME/CE Questions

1. A 55-year-old male presents to the emergency department with agitation. He is alert and oriented to person, place, and time but appears restless and is quickly pacing the room. His electrocardiogram shows atrial fibrillation with a rate of 140 beats per minutes. He has a history of polysubstance use but has had a flu-like illness the last three days and not had anything to eat or drink. What substance-related issue could result in his presentation?
   a. Acute opioid toxicity
   b. Acute gamma-hydroxybutyric acid toxicity
   c. Ethanol withdrawal
   d. Naloxone withdrawal
2. Three young males are brought in by ambulance after being found unresponsive at a party. A friend who was at the party purchased an unknown drug from a dealer he had never met before. The males are unresponsive to painful stimuli, have constricted pupils, and have decreased respiratory rates. What medication should be administered?
   a. Flumazenil
   b. Naloxone
   c. Methadone
   d. Acamprosate
3. A 30-year-old male is brought in by ambulance for seizure-like activity. He is slightly lethargic but able to provide a history. He has had multiple emergency department visits in the past week for similar issues. The urine drug screen is positive for benzodiazepines and opiates. He adamantly denies any recreational substance use. Which of the following is true regarding these urine findings?
   a. These urine studies have few instances of false positives and likely represent recreational substance use.
   b. The patient likely received naloxone, which explains these urine findings.
   c. Urine studies are able to differentiate between medications administered for therapeutic and recreational use.
   d. Positive urine studies cannot differentiate between acute toxicity and recent use.
4. A 50-year-old male is brought to the emergency department after being found confused and wandering in a nearby park. He smells heavily of alcohol. He has no evidence of trauma. He is oriented to person only. Which important laboratory test should be obtained while performing an initial assessment?
   a. Complete blood count
   b. International normalized ratio
   c. Blood glucose
   d. Type and cross
5. A 33-year-old female is brought in by family after being found unresponsive in her bathroom. Her family brings an empty bottle, which was filled recently for lorazepam. The family reports that the patient has taken this medication regularly for years because of a history of anxiety. They ask about potential reversal agents for her mental status. Flumazenil use has many potential risks, which can include which of the following?
   a. No known adverse reactions
   b. False-positive benzodiazepine drug screen
   c. False-negative benzodiazepine drug screen
   d. Seizures, which may be refractory to commonly used therapies
6. An 18-year-old male is brought in by emergency medical services after being found unresponsive at a club. On arrival to the emergency department, he is minimally responsive to painful stimuli and has a depressed respiratory rate. Naloxone is administered without improvement, and the patient requires intubation. Four hours after intubation, he self-extubates and attempts to get out of bed to leave the department. What substance likely contributed to this patient's presentation?
   a. Gamma-hydroxybutyric acid
   b. Cocaine
   c. Opioids
   d. Ethanol
7. A 27-year-old male is brought to the emergency department following an unrestrained motor vehicle collision. He does not take prescription medications but states that he frequently ingests large amounts of loperamide to "get high" if he cannot access other opioids. For which complication of loperamide abuse should providers closely monitor this patient?
   a. Opioid-induced diarrhea
   b. Infective endocarditis
   c. Cardiac dysrhythmias secondary to sodium-channel or potassium-channel blockade
   d. Methemoglobinemia
8. A 62-year-old female presents as a trauma following a motor vehicle collision. While undergoing primary survey, she begins to have tonic-clonic activity concerning for a seizure. Her home medications include insulin, lisinopril, atorvastatin, and tramadol. Which medication has the known risk of lowering the seizure threshold?
   a. Melatonin
   b. Lisinopril
   c. Atorvastatin
   d. Tramadol
9. A 32-year-old male presents to the emergency department after a motorcycle crash. He is minimally responsive, has miotic pupils, and has a respiratory rate of six breaths per minute. His chart describes an extensive history of intravenous drug use. His urine drug screen (UDS) is negative for opiates. Which of the following is true about these results?
   a. Opiate drug screens are nearly 100% sensitive for all opioid medications.
   b. Opiate drug screens frequently fail to detect synthetic opioid medications.
   c. This is likely a laboratory error, and he should have his UDS repeated.
   d. The patient is likely on naloxone-buprenorphine, which can cause false-negative opiate results.

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