

Alternative Drugs of Abuse

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Abstract The incidence of drug abuse with alternative agents is increasing. The term “alternative drugs of abuse” is a catch-all term for abused chemicals that do not fit into one of the classic categories of drugs of abuse. The most common age group abusing these agents range from 17 to 25 years old and are often associated with group settings. Due to their diverse pharmacological nature, legislative efforts to classify these chemicals as a schedule I drug have lagged behind the development of new alternative agents. The potential reason for abuse of these agents is their hallucinogenic, dissociative, stimulant, anti-muscarinic, or sedative properties. Some of these drugs are easily obtainable such as *Datura stramonium* (Jimson Weed) or *Lophophora williamsii* (Peyote) because they are natural plants indigenous to certain regions. The diverse pharmacology and clinical effects of these agents are so broad that they do not produce a universal constellation of signs and symptoms. Detailed physical exams are essential for identifying clues leading one to suspect an alternative drug of abuse. Testing for the presence of these agents is often limited, and even when available, the results do not return in a timely fashion. Intoxications from these agents pose unique challenges for health care providers. Physician knowledge of the

physiological effects of these alternative agents and the local patterns of drug of abuse are important for the accurate diagnosis and optimal care of poisoned patients. This review summarizes the current knowledge of alternative drugs of abuse and highlights their clinical presentations.

Keywords Drug legislation · Epidemiology of drug abuse · Alternative drugs

Introduction

Drugs of abuse are traditionally classified as sympathomimetics such as cocaine or opioids, like heroin. However, over the past decade, novel and atypical drugs have emerged and become more prevalent [1, 2]. The term “alternative drugs of abuse” (ADA) is often used as a catch-all phrase for all non-traditional drugs. The alternative drug class includes the hallucinogens [lysergic acid diethylamide (LSD), peyote (mescaline), and mushrooms], dissociative agents [ketamine, phenylcyclidine (PCP)], the alternative stimulant (clenbuterol), the antimuscarinics (Jimson weed), and alternative sedatives [gamma-hydroxybutyrate (GHB) and its analogs].

Studies have shown that persons who use “natural products,” such as hallucinogenic mushrooms, do so because they believe these natural products are “safer” or “softer drugs of abuse” and because they carry less social stigma [3, 4]. The abuse of medications, such as ketamine, is rationalized because they are believed to be “pharmaceutical” agents [5, 6]. Combined with the widespread diverse availability of many of these alternative agents of abuse, public misconceptions have fueled a dramatic rise in the use and incidence of poisonings from these agents.

Health care providers face a number of challenges when evaluating patients who use ADAs. For example, clinical signs and symptoms are often not as predictable as those seen with traditional drugs of abuse [7]. Some alternative

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drugs, such as clenbuterol, are often abused by athletes who present with extreme tachycardia and agitation [8]. Other agents are potent sedatives. The agent GHB can cause both respiratory depression and decreased levels of consciousness that is so profound that the drug has been used to facilitate sexual assault [9–11]. Without knowing the specific history of the agent abused, the clinician is often left with trying to assimilate clinical findings that do not fit with traditional toxidromes [7].

Another reason why toxicity from these agents can be difficult to diagnose relates to challenges with drug testing [12]. Typically, the detection of traditional drugs of abuse is readily and inexpensively accomplished via routine immunoassays. ADAs often require specific send-out tests such as gas chromatography/mass spectroscopy and often do not return soon enough to help with clinical decisions. Hence, appropriate treatment may be delayed, and unnecessary diagnostic studies may be performed [13]. Moreover, there is no one test that will simultaneously detect all alternative agents of abuse. Collectively, these agents have an array of chemical structures, diverse hydro- and lipophilic properties, and distinct half-lives, so deciding which test(s) to order can be complicated and onerous. One example of such complexity is illustrated by GHB testing. GHB is rapidly metabolized to gamma-aminobutyric acid (GABA), so it is extremely difficult to distinguish ingested GHB from a patient's normal endogenous GABA if the parent compound is no longer present. Additionally, special handling of samples and only certain diagnostic laboratories are capable of GHB testing [10, 12]. Because of these diagnostic difficulties, clinicians must be astute and adept at recognizing possible alternative drug ingestions.

Legislation

One of the most difficult issues with regard to alternative agents of abuse is that regulatory legislation tends to lag behind the rapid development of new alternative agents. The legislative framework for drugs of abuse began with the Controlled Substances Act (CSA) of 1970 whereby the concept of “Schedules” for drugs was introduced [14, 15]. Specifically, Schedule I designated drugs with high abuse potential, but no accepted medical use, such as LSD. Schedule II was defined as drugs with high abuse potential, but with recognized therapeutic value, such as morphine [16]. Subsequent amendments to the CSA increased its scope and power. One amendment, the 1984 Comprehensive Crime Control Act, gave the attorney general, who was then the DEA administrator, the authority to place a substance in the Schedule I class while a formal review was conducted [17]. In 1985, this legislative authority was promptly executed to label 3,4-methylenedioxy-*N*-methamphetamine (MDMA, ecstasy)

a Schedule I drug [18]. More recent legislation has allowed for analogs of Schedule I drugs to be declared illegal without requiring specific laws for each analog. For example, in 2000, the “Hillory J. Farias and Samantha Reid Date-Rape Prohibition Act of 1999” was passed which designated GHB as a Schedule I controlled substance. Subsequently, under 21 U.S. Code § 813, GHB analogs are now also considered Schedule I substances [12, 19]. Of note, GHB is one of the few drugs that is listed under two different schedules, both schedule I and schedule III, for its use in treatment of narcolepsy. Another example of changing legislation occurred in 2012, where Senate Bill 3190 amended the CAS by including synthetic cannabinoid analogs (Spice, K2) in the Schedule I category [20]. The ability to declare new substances and analogs as Schedule I while further testing is performed is essential for appropriate regulation since new designer drugs of abuse are being swiftly developed.

Epidemiology

Alternative drugs are used by people of all ages. Most users of these drugs are between the ages of 17 and 25 years old [2, 21, 22]. Abuse of these drugs is often in group settings, such as raves, college events, and parties [22–24]. College age students who use MDMA are more likely to abuse other drugs, including alternative drugs, when compared to marijuana users alone [22]. The true magnitude of the abuse problem is difficult to quantify because the use of these agents is not required to be reported to public health agencies. Additionally, diagnostic testing or confirmation is often inadequate. Nonetheless, a targeted survey of lifetime drug use among college students found that 9 % had used MDMA and, of these, 98 % also abused marijuana and other alternative club drugs [22, 24].

It is suspected that alternative drug use is widespread among many demographic groups. Many epidemiological studies have often focused on the gay, lesbian, and bisexual community [25–32]. It is reported that gay and bisexual men who abuse methamphetamine are also more likely to abuse GHB and ketamine [27, 28]. Additionally, lesbian and bisexual women have higher lifetime rates of use of lysergic acid diethylamide (LSD) than heterosexual women [29]. Finally, a cross-sectional study of gay and bisexual men found that GHB and ketamine abuse was significantly associated with certain geographical, racial, and ethnic boundaries [28].

Certain ethnic communities may preferentially use certain alternative drugs. The hallucinogen, peyote, has been traditionally used in religious ceremonies in the Native American Church. Even though peyote is currently classified as a Schedule I drug, a federal exemption was passed in 1993 that allows for the use of peyote in bona fide religious ceremonies of the Native American Church [33].

Methods of Abuse

There are many routes of administration for ADA. Ingestion is the most common route of administration for hallucinogens. LSD is typically ingested on paper or placed on sugar cubes, whereas peyote is usually consumed as fleshy cactus buttons or in tea [7]. Hallucinogenic mushrooms may be eaten whole or as ground-up products [7]. The dissociative agents can cause intoxication via a variety of routes. PCP can be smoked (inhalation), snorted (insufflation), injected, or, less commonly, ingested. Ketamine, which shares structural similarities with PCP, is available in intravenous and intramuscular forms that are approved for pharmaceutical use in human and animal health care facilities [7]. Illicit ketamine is often acquired after it is stolen from veterinary offices or hospitals. Diverted injectable pharmaceutical ketamine is then converted to a powder or solid form which allows it to be ingested or insufflated [34]. The stimulant, clenbuterol, typically comes in a liquid or tablet form that can be ingested [35]. The antimuscarinic plant, Jimsonweed, is often brewed in tea or combined with toothpaste for ingestion; it is also inhaled [7]. Finally, the sedative agents, including GHB and its analogs, are typically abused by oral ingestion [12].

Hallucinogenics

Lysergic Acid Diethylamide

LSD is the most potent of all hallucinogens. Discovered in the 1940s, LSD became popular in the 1960s [36, 37]. While traditionally thought of as a drug of abuse, there are reports in the 1960s of lasting positive effects on attitude and personality when provided in a controlled setting [38]. Dr. Timothy Leary, an American psychologist and advocate for the therapeutic and emotional benefits of LSD, coined the popular phrase, “Turn on, tune in, drop out” [7, 39].

The pharmacologic mechanism of action of the hallucinogenic agents is complex and is related to basic tryptamines or monoamine alkaloids. As designer drugs emerged, “tryptamines” were sub-classified into “simple tryptamines” and “ergolines” [40]. LSD was the first ergoline developed, and it is thought that its complex and potent hallucinogenic properties are mediated through serotonin receptors (5HT_{1a} and 5HT_{2a}) agonism. Additionally, LSD seems to agonize the Vesicular Monoamine Transporter 2, which then increases the concentration of monoamines in the synaptic cleft [41, 42].

The combination of serotonin receptor agonism and increased monoamine concentration in the synaptic cleft is the primary biochemical basis for the clinical presentation of LSD intoxication (Table 1). The onset of clinical symptoms ranges from 15 to 30 min post-ingestion, and symptoms last for up to 12 h. Typically, the effects of LSD ingestion are

dominated by alterations in mental status and neurologic function. Hemodynamic instability or organ dysfunction is rare unless larger doses are ingested. There is no specific antidote for LSD ingestion [43]. Unless a massive ingestion occurs, the treatment of LSD intoxication is simply supportive care and waiting for the resolution of normal mental status [7]. Massive ingestions that lead to multi-organ involvement, hyperthermia, and bleeding may require more aggressive control of temperature, supportive care, and admission to the intensive care unit.

Toxicity

Respiratory System

Pulmonary effects are uncommon in LSD toxicity, but cases of respiratory depression have been reported with massive overdose [43]. One case of pulmonary edema has been described, though this was in the setting of a massive LSD overdose that led to cardiovascular toxicity (tachycardia), hyperthermia, platelet dysfunction, bleeding, and death [43]. No other reports of isolated pulmonary edema exist; therefore, the pulmonary edema in this case is likely related to secondary causes and not direct pulmonary toxicity.

Nervous System

Both acute and delayed neurologic effects occur in LSD toxicity. Acute ingestions of LSD often lead to impaired psychomotor function, specifically with coordination and reaction times [44–46]. LSD also impairs visual recognition, memory, time perception, and general cognitive processes [47–50]. Sensory misperceptions, such as “tasting colors,” “smelling sounds,” and vivid color perceptions, tend to dominate [37]. On examination, the most consistent objective neurologic findings are exaggerated patellar and other deep tendon reflexes [51]. Delayed neurological effects of LSD are uncommon, but can include “bad trips” or “flash-back” phenomena [52]. Beyond these uncommon flashbacks, other chronic neurocognitive effects or lasting impairments from LSD exposure do not seem to occur [53].

Hallucinogenic Mushrooms

Hallucinogenic or “magic” mushrooms belong to the *Psilocybe* species of fungi and are indigenous to the southern Gulf and western USA. They are also found in many other parts of the world, including Western Europe [54]. The active ingredient is psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine), a substituted indolealkylamine, which belongs to the tryptamine group of hallucinogenic compounds [55]. Historically, psilocybin-containing mushrooms were used in Mexico in religious sacraments during times

Table 1 Clinical signs and symptoms of hallucinogens

Organ system	LSD	Mushrooms	Peyote
Respiratory	Respiratory depression (rare)	Tachypnea Irregular respirations	
Nervous system	Impaired psychomotor function	Headaches	Headaches
	Altered perception	Mydriasis	Mydriasis
	Increased deep tendon reflexes	Altered perception	Paranoia
	Bad trips/flashbacks	Increased deep tendon	Altered perception
		Reflexes	Paresthesias
Cardiovascular		Paresthesias	Muscles spasms
			Botulism (rare)
		Tachycardia	Tachycardia
		Systolic hypertension Tako-tsubo cardiomyopathy	Systolic hypertension
Gastrointestinal and hepatobiliary		Nausea and vomiting	Vomiting
		Abdominal pain	Mallory-Weiss tears (rare)
Renal and metabolic		Decreased creatinine clearance	Decreased creatinine clearance
		Decreased clearance of inorganic phosphate	Decreased clearance of inorganic phosphate

that pre-date the Aztecs. These practices still persist within certain indigenous tribes today [54, 56]. Psilocybin was first isolated in the late 1950s [56] and since that time it has been used in medical research to simulate schizophrenia in otherwise healthy subjects [57–59]. As a recreational drug of abuse, psilocybin is used for its perception-altering effects.

Psilocybin is usually ingested in the form of whole mushroom caps, which can be eaten fresh or dried. The dried mushrooms can also be placed in hot water and then ingested as a tea [54]. An investigational pharmaceutical version was developed as an adjunct to psychotherapeutic procedures, and an intravenous formulation underwent clinical trials designed to evaluate the effects of psilocybin intoxication [60]. In the body, psilocybin is converted to its primary active substance, psilocin [60–62], which acts as a non-selective agonist of both the 5-HT_{1a} and 5-HT_{2a} serotonin receptors to cause the desired perception-altering effects [40, 55, 57]. These effects may also be partially mediated by dopamine, although psilocin itself does not directly act on the dopamine receptor [58].

Toxicity

Respiratory System

The primary respiratory effect of psilocybin is increased respiratory rate [59]. Although the exact mechanism of this tachypnea has not been described, it may be secondary to the anxiety and paranoia associated with psilocybin use [63]. One of the few reports of psilocybin-associated death described a patient who had irregular respirations prior to

his death; however, no clinical data such as respiratory rate or pCO₂ were available in this case [64]. Although no cases have been reported in the literature, there is a theoretical risk of aspiration as the ingestion of *Psilocybe* mushrooms is frequently associated with vomiting.

Nervous System

In the central nervous system (CNS), psilocin acts as a non-selective 5-HT receptor agonist. This is the primary mechanism of its perception-altering effects [65]. The indirect effects of psilocin on dopamine concentrations likely contribute to the hallucinations. Both visual and auditory hallucinations are reported by some users [56, 66]. Electroencephalography (EEG) patterns from psilocybin-intoxicated individuals show increased beta wave activity, along with decreases in both alpha and theta waves [67]. Headaches are frequently reported both during and after acute intoxication [65].

Psilocin demonstrates sympathomimetic autonomic nervous system properties [56, 66, 67]. This results in mydriatic pupils, facial flushing, and diaphoresis. Alterations in color and visuospatial perception, dizziness, and disequilibrium are frequently reported [56, 66–68]. Hyperreflexia is commonly present [56, 61]. Paresthesias, often involving a single extremity, may also occur [61, 67, 68].

Cardiovascular

Dose-related sympathomimetic induced tachycardia and systolic hypertension frequently occur with psilocin [56,

[59, 63, 67]. These effects are similar to other hallucinogens and are not usually associated with life-threatening dysrhythmias. Although the cardiovascular effects are rarely dangerous, there has been a reported case of tako-tsubo cardiomyopathy associated with psilocybin ingestion. This was associated with marked electrocardiogram changes resembling an ST-elevation myocardial infarction [69, 70].

Gastrointestinal and Hepatobiliary

Mild gastrointestinal effects are frequently reported with psilocybin ingestion. The most commonly reported symptoms include nausea with or without vomiting [56, 66, 67]. Abdominal pain, most often cramping in nature, is also described [56, 66, 69].

Misidentification of mushrooms can lead to serious hepatic consequences. The inadvertent ingestion of certain *Amanita* species of mushrooms can lead to fulminant hepatic failure requiring emergent transplantation [71]. To date, there have been no reported cases of hepatic failure from isolated psilocybin ingestion.

Renal and Metabolic

Early studies of psilocybin reported transient decreases in creatinine clearance after its ingestion, but this did not translate into overt renal failure. The decrease in creatinine clearance was associated with a more profound decrease in the clearance of inorganic phosphorous [72]. A few case reports of both acute and chronic renal failure have been reported, but these appear to be due to misidentification of mushrooms that were harvested in the wild [73, 74].

Peyote

Peyote (*Lophophora williamsii*) is a cactus that is indigenous to the southwestern USA and northern Mexico [54, 75]. It contains a chemical called mescaline [2-(3,4,5-trimethylphenyl) ethanamine], which provides its hallucinogenic properties [75]. Mescaline is also present in the San Pedro (*Trichocereus pachanoi*) and Peruvian torch (*Trichocereus peruvianus*) species of cacti [54]. Mescaline is a member of the phenylalkylamine class of hallucinogenic compounds. This class also contains novel synthetic hallucinogens, such as 2,5-dimethoxy-4-bromophenethylamine and high potency analogues [55].

The primary means of ingestion is by eating the flesh of the cactus itself. The top of the cactus is typically dried into "buttons" which are then eaten, or mixed with hot water to form a tea [54]. Purified mescaline is also available in the form of illicit tablets or powder which can be ingested or snorted [75]. In the central nervous system, mescaline acts as a selective agonist of 5-HT₂ serotonin receptor subtypes

(5-HT_{2a}, 5-HT_{2b}, and 5-HT_{2c}), which is thought to be the primary source of its hallucinogenic properties [55]. Hallucinations ensue 2–4 h after ingestion and typically last for several hours [54, 76].

Toxicity

Nervous System

In the CNS, mescaline acts as an agonist of the 5-HT₂ receptor subtypes a–c. It is highly selective for this receptor subtype, and its effect produces both desired hallucinatory effects as well as undesired psychotic effects [55]. Persons ingesting mescaline also have reported profound paranoia and un-witnessed seizure activity [75]. Paresthesias are frequently reported [68]. Mescaline has also been shown to result in alterations in color perception [68]. Persistent headaches, some lasting as long as 3 days, have also been described [65, 77].

In the peripheral nervous system, mescaline and other phenylalkylamines also produce a sympathomimetic toxidrome. Objective physical findings include mydriatic pupils, diaphoresis, and psychomotor agitation [66, 75]. Muscle spasms and tremors frequently occur. Improperly stored peyote has been reported to be the cause of at least one case of botulism [78].

Cardiovascular

The cardiovascular effects of mescaline stem from its sympathomimetic activity. The most frequently reported effects are tachycardia and hypertension [75]. There are no reported cases of life-threatening dysrhythmias occurring as a result of isolated mescaline ingestion.

Gastrointestinal

The primary gastrointestinal effect of peyote ingestion is emesis. In one reported case, it was forceful enough to cause a Mallory-Weiss esophageal tear [79]. The etiology of emesis with peyote ingestion is likely secondary to the bitter taste of the cactus flesh rather than to the direct effect of mescaline [75, 80]. In studies involving the isolated ingestion of mescaline powder or tablets, vomiting has not been reported [76].

Renal and Metabolic

Like psilocybin, mescaline ingestion has been associated with decreases in glomerular filtration rate and retention of inorganic phosphorous [72]. These changes tend to be small and do not result in long-term renal insufficiency.

Dissociatives

Phencyclidine

Phencyclidine (PCP) is a dissociative anesthetic which acts as an antagonist to the *N*-methyl-*D*-aspartate (NMDA) receptor in the CNS. It was initially discovered in 1926, but did not gain use as an anesthetic agent for surgery until 1963. This use was short-lived due to post-anesthetic dysphoria and psychosis [81, 82]. In 1978, PCP was added to the list of federally controlled schedule I substances, and its use was prohibited [83].

PCP gained prominence in the 1970s as a drug of abuse. It is available in a white powder, called “angel dust,” tablets, liquid, and crystals. The most common forms of ingestion are by smoking, either alone or in combination with tobacco or marijuana, snorting, or ingesting it in tablet form [83, 84]. It can also be injected, either subcutaneously or intravenously, although this route is less common. Phencyclidine ingestion leads to a dissociative state and also to a euphoria, which is the desired effect.

Toxicity

Respiratory System

The most common effect of PCP on respiration is tachypnea; rates as high as 88 breaths per minute have been reported [85, 86]. (Table 2) In some cases, Cheynes-Stokes respirations have been observed along with periods of apnea. Often these respiratory patterns coincide in the same patients, with periods of apnea followed by tachypnea. In rare cases, hypoventilation that requires assisted ventilation may occur [86].

There are a multitude of direct pulmonary effects noted with PCP intoxication. First, bronchorrhea and increase salivation can elevate the risk for obstruction and aspiration in the obtunded patient [86]. Pharyngeal and laryngeal reflexes are augmented, which can lead to laryngospasm [86]. Smoking and snorting PCP can result in local irritation and bronchospasm, particularly in asthmatics [86]. Finally, emesis combined with altered sensorium can increase the risk of aspiration of gastric contents leading to pneumonitis or pneumonia [84, 87].

Nervous System

The primary neurologic effects of PCP ingestion are mediated by its actions as an NMDA receptor antagonist. This antagonism leads to a dissociative state, which can be associated with marked psychomotor agitation [86, 88]. The agitation is likely secondary to the inhibition of GABA output, in combination with increased activity of norepinephrine and dopamine. Both

effects result from decreased re-uptake in the pre-synaptic neurons and increased synthesis. The increased synthesis is due to stimulation of the enzyme tyrosine hydroxylase [83].

PCP intoxication results in anesthesia and analgesia [83]. The combination of the dissociative effects, plus the drug-induced analgesia reduces pain perception. These actions have led users to believe that they possess superhuman strength. Anecdotal cases are often cited wherein PCP users have sustained multiple traumatic injuries, but without apparent effects on behavior [86, 88]. As a result, traumatic injury, both accidental and purposeful, is the most common cause of PCP-related death [81, 83, 86].

Seizures and rarely status epilepticus have been described in some users [86]. More frequently, ataxia, stereotypical movements, athetosis, and catalepsy have been described. Dystonic reactions may occur, including symptoms that mimic tardive dyskinesia, and these can be exacerbated by use of antipsychotic agents [86].

In the peripheral nervous system, PCP increases the synthesis of norepinephrine and also decreases its re-uptake in the pre-synaptic neurons [86]. The resulting sympathomimetic effects include diaphoresis, muscle rigidity, tremors, and hyperthermia [86]. Rotary, vertical, or horizontal nystagmus is often present [86, 88]. There is no consistent correlation between pupil diameter and PCP intoxication [86].

Cardiovascular System

The sympathomimetic actions of PCP on the heart result in tachycardia [86]. Hypertension also frequently occurs leading to cases of non-traumatic intracranial hemorrhage [86, 88]. Rare cases of hypotension have been reported, but most of these cases either had a co-ingestion noted or were associated with hypoglycemia [86].

Increased myocardial oxygen demand may lead to myocardial ischemia particularly in those with pre-existing coronary artery disease. Vasospasm may also occur, and this can further decrease oxygen delivery [83]. In addition to this, PCP has been shown to be a direct irritant to the myocardium leading to life-threatening dysrhythmias [82, 83].

Gastrointestinal and Hepatobiliary System

PCP has very few effects on the gastrointestinal system. Elevations in liver enzymes including serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase are reported [86]. Such elevations are usually associated with rhabdomyolysis. No instances of hyperbilirubinemia were found in a large case series of 1,000 patients with PCP intoxication [86]. A withdrawal syndrome has also been associated with diarrhea as one of its primary features [83].

Table 2 Clinical signs and symptoms of dissociatives

Organ system	PCP	Ketamine
Respiratory	Tachypnea	Respiratory depression
	Cheyne-Stokes respirations	Apnea (rare)
	Respiratory depression (rare)	Bronchodilation
	Bronchorrhea	Bronchorrhea
	Increased pharyngeal and laryngeal reflexes	Increased pharyngeal and laryngeal reflexes
	Aspiration	
Nervous system	Psychomotor agitation	Hallucinations
	Altered pain perception	Altered pain sensation
	Seizures	Seizures
	Ataxia	Increased ICP and IOP
	Athetosis	Nystagmus
	Muscle tremors and rigidity	Problems with balance and coordination
	Nystagmus	
Cardiovascular	Tachycardia	Tachycardia
	Hypertension	Hypertension
	Myocardial ischemia	Myocardial ischemia
	Dysrhythmias	Myocarditis
		Dysrhythmias
Gastrointestinal and hepatobiliary	Elevated liver enzymes	Nausea and vomiting
	Diarrhea (with withdrawal)	Abdominal pain
Renal and metabolic	Acute renal insufficiency	Renal Insufficiency
	Hypoglycemia	Rhabdomyolysis
		Ulcerative cystitis
		Altered detrusor muscle function

Renal and Metabolic

The primary renal effect of PCP use is acute renal insufficiency. This is most commonly secondary to rhabdomyolysis [86, 88, 89]. Urinary retention can also occur, but it is rarely severe or prolonged enough to result in renal injury [86]. The most common metabolic effect of PCP use is hypoglycemia. This can be profound, with glucose levels as low as 10 mg/dL [86]. Other electrolyte abnormalities have not been described.

Ketamine

Ketamine is a dissociative agent similar to PCP that acts primarily as a noncompetitive glutamate antagonist at the NMDA receptor in the central nervous system [90, 91]. Sympathomimetic effects have also been noted, along with inhibition of norepinephrine, serotonin, and dopamine reuptake [90, 92]. Ketamine was originally derived from phencyclidine molecule in the 1960s for medical use as a dissociative anesthetic [91]. It continues to be used both as an induction agent for general anesthesia, and as an anesthetic for short procedures [93]. In addition to its role as an

anesthetic, ketamine has also been used to treat severe depression that is refractory to traditional therapeutic agents and as an alternative to opiates for patients with chronic pain [93].

Because its dissociative properties are often accompanied by visual hallucinations, ketamine has gained popularity as a drug of abuse [34, 93]. Ketamine is referred to as "special K" and "cat valium" by recreational users [94]. It comes in the form of a liquid, which can be injected or taken orally, and as a powder, which can be smoked or snorted [91, 93]. The onset is rapid, and users achieve the desired dissociative state, called the "k-hole," within several minutes [93]. Its effects usually last 45–60 min, but prolonged effects can occur when ketamine is taken orally.

Toxicity

Respiratory System

Ketamine causes a dose-dependent drop in respiratory rate [95]. In a study performed by Bourke et al., it was noted that ketamine infusion results in a shift in the CO₂-response curve to the right, but the slope of the curve is not influenced

[96]. This phenomenon explains the relative sparing of respiratory drive that is seen with therapeutic ketamine administration. In higher doses, and in certain susceptible individuals, ketamine has been noted to cause apnea [97, 98].

Ketamine's direct effects on the lung are varied. It can cause bronchodilation, likely secondary to increases in circulating catecholamines [95]. Ketamine has been shown to result in hyper-salivation and bronchorrhea, which can lead to airway obstruction in rare instances [94, 95]. Like PCP, ketamine causes laryngeal hypersensitivity, and laryngospasm may ensue [97–99]. One unique effect of ketamine, noted in studies of respiratory mechanics, is the increased use of intercostal and accessory muscles [95].

Nervous System

The effect of ketamine on the NMDA receptor leads to a dissociative state in most users. In some cases, visual hallucinations occur [100, 101]. When used for medical purposes, patients often describe vivid, and sometimes frightening, dreams [94, 102]. A decreased pain sensation, combined with the dissociative state, can lead to secondary injuries. Like PCP, this is one of the primary causes of death associated with recreational ketamine use [103]. Lowered seizure threshold results in seizure activity in susceptible individuals [91, 94]. On EEG evaluation, ketamine is associated with decreased alpha wave activity with increases in beta, delta, and theta waves [95]. Ketamine has also been noted to cause increased intraocular and intracranial pressures [90, 94, 95]. Frequently, rotary nystagmus is reported in ketamine intoxication [94, 95, 101, 104]. Balance and coordination problems even with small doses of ketamine have been described [103].

Cardiovascular System

The primary cardiovascular effect associated with ketamine use is tachycardia [95, 101]. This is due to the fact that, in addition to acting as an NMDA antagonist, ketamine also acts as a re-uptake inhibitor of biogenic amines thus increasing the concentration of circulating catecholamines [90, 92]. In persons with cardiovascular disease, myocardial ischemia due to increased oxygen demand can occur [94, 95]. In rare cases, life-threatening dysrhythmias may arise [95]. Ketamine can sensitize the myocardium to the effects of epinephrine [105]. Transient increases in blood pressure also frequently occur with ketamine use [91, 94]. A case report of a patient who developed ST elevations on electrocardiogram with a Brugada pattern after ketamine insufflation has been published. This same patient subsequently developed myocarditis with congestive heart failure felt to be secondary to his ketamine use. Eventually, after a period of

abstinence, all of his cardiovascular signs and symptoms resolved [106].

Gastrointestinal and Hepatobiliary System

A large meta-analysis of ketamine sedation in children found that vomiting occurred in 8.4 % of patients [102]. Recreational users have reported nausea, vomiting, and generalized abdominal pain [91]. Elevations in liver enzymes and rare cases of biliary dysfunction have been described [107, 108].

Renal and Metabolic

Cases of renal insufficiency have been reported with ketamine use. Ketamine has been associated with elevated creatine kinase from muscle, and rare cases of rhabdomyolysis have led to renal insufficiency [91, 101]. An ulcerative cystitis has also been noted [109, 110]. This can result in detrusor muscle dysfunction, scarring of the bladder, and hydronephrosis [111].

Alternative Stimulants

Clenbuterol

Clenbuterol is a long-acting selective β_2 adrenergic receptor agonist, which is used for the treatment of asthma and chronic obstructive pulmonary disease. It is taken orally, twice daily, and is currently approved for human use in Europe [35, 94]. In the USA, it is not approved for human use and is primarily used for the treatment of reactive airways in horses and as a tocolytic in cows [35, 94]. At high doses, it loses its selectivity for the β_2 adrenergic receptor and also acts on the β_1 adrenergic receptor [94]. In addition to its treatment of obstructive airway disease in animals, clenbuterol has been used by ranchers to increase muscle mass and to decrease fat content. It achieves this by acting on β_3 adrenergic receptors to cause lipolysis and on β_2 receptors in the muscle to increase protein deposition in skeletal muscle [112, 113]. Its use in livestock was outlawed after it was noted that clenbuterol can build up in the tissues of animals, particularly in the liver, and cause toxicity in humans when ingested [114, 115].

These anabolic properties have led to the use of clenbuterol by athletes and bodybuilders. It is considered a performance-enhancing drug and is banned by most athletic associations [35]. Clenbuterol has been found as an adulterant in cocaine and heroin with intoxications of these mixtures having atypical presentations [113]. The primary modes of ingestion are as a tablet, powder, or syrup. It is also available in some parts of the world as an aerosol and in an intravenous formulation [35].

Toxicity

Respiratory System

At normal doses, clenbuterol results in β_2 adrenergic stimulation, and causes bronchodilation [35, 94]. (Table 3) Significant tachypnea can occur at higher doses. In rare instances, pulmonary edema and respiratory failure may occur [116].

Nervous System

The key effects of clenbuterol use on the CNS are vertigo and dizziness [114]. Agitation and muscle tremors may also occur, and in some cases, this may simulate tardive dyskinesia [117]. In massive ingestions, hallucinations, convulsions, and severe headaches have been reported [115].

Cardiovascular

The primary cardiovascular effect of clenbuterol ingestion is tachycardia [115, 118, 119]. The tachycardia may manifest as atrial fibrillation or other supraventricular tachydysrhythmias.

Table 3 Clinical signs and symptoms of alternative stimulants

Organ system	Clenbuterol
Respiratory	Bronchodilation
	Tachypnea
	Pulmonary edema (rare)
	Respiratory failure (rare)
Nervous system	Vertigo and dizziness
	Psychomotor agitation
	Muscle tremors
	Headaches
	Hallucinations
Cardiovascular	Tachycardia
	Atrial fibrillation
	Myocardial ischemia and infarction
	Hypertrophic cardiomyopathy
	Dysrhythmias
Gastrointestinal	Nausea and vomiting
	Abdominal pain
Musculoskeletal	Lipolysis
	Striated muscle hypertrophy
Renal and metabolic	Hypokalemia
	Hypophosphatemia
	Hypomagnesemia
	Hyperglycemia
	Lactic acidosis

Ventricular rates as high as 254 beats per minute have been reported [35]. This marked tachycardia, along with increased oxygen demand, can result in chest pain, myocardial ischemia, myocardial infarction, and cardiogenic pulmonary edema [113, 114, 116, 120]. The direct effect of clenbuterol on cardiac myocytes induces protein deposition. This can lead to hypertrophy and, eventually, hypertrophic cardiomyopathy [35, 119]. In addition to the structural changes, the induced ventricular hypertrophy can predispose clenbuterol users to cardiac dysrhythmias [35].

Gastrointestinal

The primary effect of clenbuterol ingestion on the gastrointestinal system is nausea with, or without, vomiting [115].

Musculoskeletal

Clenbuterol acts on adipocyte β_3 adrenergic receptors. The consequences include lipolysis and the release of free fatty acids. It also acts on striated muscle β_2 receptors to increase protein deposition which can lead to larger muscle fibers [112, 113].

Renal and Metabolic

Activation of the β_2 receptor incites shifts in intracellular potassium in skeletal muscle which can lead to profound hypokalemia [94, 118]. In addition to its effects on potassium, other consequences include the development of lactic acidosis and hyperglycemia [113, 116, 120]. The intracellular sequestration of phosphorous and magnesium is thought to drive the decrease in serum concentrations of these electrolytes [35, 116, 118]. In totality, these electrolyte disturbances increase the risk for cardiac dysrhythmias.

Antimuscarinics

Jimson Weed

Jimson weed (*Datura stramonium*) is an annual herb in the nightshade family. It grows in most parts of the USA along roads and in vacant fields and lots [121, 122]. It contains the belladonna alkaloids atropine and scopolamine (hyoscine) [122, 123]. These chemicals are present at varying concentrations in all parts of the plant and are responsible for both the desired hallucinogenic properties of Jimson weed as well as most of the toxicity associated with ingestion [123, 124]. (Table 4) Other members of the *Datura* family also contain belladonna alkaloids at varying concentrations [124–126].

Historically, Jimson weed was used for its medicinal properties. Pueblo Indians used it as an analgesic and in

Table 4 Clinical signs and symptoms of anti-cholinergics

Organ system	Jimson weed
Respiratory	Tachypnea
	Respiratory depression
	Apnea
	Aspiration
Nervous system	Hallucinations
	Delirium
	Psychomotor agitation
	Extensor posturing
	Dizziness and vertigo
	Seizures
	Dilated pupils
	Blurred vision, photophobia
	Hyperthermia
	Guillain–Barre (rare)
Cardiovascular	Tachycardia
	Dysrhythmias
	Peripheral vasodilation
Gastrointestinal and hepatobiliary	Vomiting
	Delayed gastric emptying
	Constipation
	Hepatic failure
Renal and metabolic	Renal failure
	Urinary retention
	Rhabdomyolysis

western medicine for the treatment of asthma [127]. One particular form, Asthmador™ (R. Schiffmann Co.), was available as a powder for inhalation and in the form of a cigarette which was smoked [127, 128]. Toxicity from Jimson weed was first described in relation to an event which occurred in 1676 after a group of British troops ingested a salad containing stramonium in the area around Jamestown. The resulting deleterious effects were described as lasting for several days [123, 129]. Its prominence as a recreational drug of abuse began in the 1960s after its hallucinogenic properties were discussed in a book by Carlos Castaneda [54, 127].

The most common form of ingestion is by eating the intact flowers or seeds [121]. This mode of ingestion explains the seasonal variation in rates of intoxication. Poisonings typically peak in the late summer and autumn [121, 130]. Other forms of ingestion include placing leaves or crushed seeds in boiled water and drinking the resulting tea and smoking dried flowers, seeds, or leaves [130]. The desired hallucinatory effects are achieved through the central anti-muscarinic effects of scopolamine [123]. Unlike the hallucinations seen with indoleamine or phenylalkylamine use, Jimson weed users are not aware that they are

Table 5 Clinical signs and symptoms of sedatives

Organ systems	GHB
Respiratory	Respiratory depress
	Apnea
	Aspiration
Nervous system	Depressed consciousness with periods of agitation
	Anterograde amnesia
	Headache
	Dysarthria
	Emotional lability
	Increased REM sleep
	Hypotension
Cardiovascular	Hypotension
Gastrointestinal	Vomiting
	Abdominal pain

hallucinating and typically do not remember their intoxication [131].

Toxicity

Cardiac and Respiratory System

Intoxication with Jimson weed initially manifests as tachypnea which is secondary to the anti-muscarinic effect on the vagus nerve, psychomotor agitation, and delirium. At higher doses, respiratory depression and respiratory arrest can occur [127, 130, 132]. When intoxication occurs, it results in seizures, aspiration, and hypoventilation [127, 131]. It is the anti-muscarinic effects resulting in bronchodilation and drying of the upper and lower airways.

Nervous System

The CNS effects of Jimson weed stem from the anti-muscarinic effects of scopolamine and atropine, which as tertiary amines readily cross the blood–brain barrier. These chemicals cause a profound delirium and hallucinations frequently associated with psychomotor agitation [130, 132–134]. At higher doses, CNS depression may occur [127, 132]. Extensor posturing, concerning for brainstem herniation is also reported [135, 136]. Cases of dizziness, vertigo, and rare seizures have been reported [127, 130, 131].

In the peripheral nervous system, anti-muscarinic effects cause dilated pupils with resultant blurred vision and photophobia [132, 137]. Direct ocular effects, without systemic effects, have also occurred in people during gardening and harvesting in fields containing Jimson weed [138]. Hyperthermia is not uncommon and is attributed to the

suppression of perspiration coupled with muscle tremors and spasms [130, 132, 137]. Dry mouth results from the suppression of salivation [132, 134]. A case of Guillain–Barré syndrome occurred in a 5-year-old boy who ingested *Datura suaveolens*, and required a brief period of mechanical ventilation because of respiratory failure [139].

Cardiovascular System

The effects of atropine and scopolamine on the cardiovascular system occur via blockade of parasympathetic actions of the vagus nerve on the sino-atrial node. This results in sinus tachycardia, the hallmark of anti-muscarinic intoxication [127, 129, 130, 134]. In the absence of structural heart disease, this tachycardia rarely leads to life-threatening dysrhythmias. Jimson weed intoxication also results in peripheral vasodilation. This is objectively seen in the form of facial flushing and warm, dry skin [127, 129, 130, 132, 133]. The vasodilation, combined with an absence of sweating, leads to decreased thermoregulatory ability.

Gastrointestinal and Hepatobiliary System

Vomiting is frequently described in Jimson weed ingestions [130]. The anti-muscarinic effects result in delayed gastric emptying and decreased gastrointestinal motility. These can be prolonged in massive ingestions [122, 129, 134] and can give rise to constipation [134, 137]. Rare cases of fulminant hepatic failure, one that required transplantation, have been reported in young children after accidental Jimson weed ingestion [140, 141]. The mechanism of liver toxicity is unknown, and co-ingestants may have played a role.

Renal and Metabolic

Direct renal injury from Jimson weed ingestion has not been reported. Prolonged urinary retention, however, is a relatively common effect of anti-muscarinic toxicity [130]. Relaxation of the detrusor muscle and resultant difficulties with bladder emptying is the mechanism [134]. A case of rhabdomyolysis after Jimson weed ingestion by an 8-year-old child has also been reported [141].

Alternative Sedatives

GHB and Its Analogues

GHB is a naturally occurring short-chain fatty acid that is produced in the nervous system and is a precursor to gamma-aminobutyric acid (GABA) [142, 143]. In the human body, it is thought to mediate sleep cycles, body temperature, glucose metabolism, and memory. It has been

developed as an approved therapeutic agent for treatment of narcolepsy and daytime somnolence in the form of sodium oxybate [144, 145].

As a recreational substance, it initially gained prominence as a body-building adjunct, being touted as a growth hormone booster [142, 146]. It is thought to result in release of growth hormone because of its effects on sleep cycles. However, this release is likely to be negligible since it has a short half-life [142]. In the 1990s, GHB was declared a Schedule III substance. Subsequently, it was re-classified as both a schedule I and schedule III in 2000 due to concerns that it was being used as a “date rape” drug [147]. GHB can still be easily manufactured from industrial chemicals [93]. In addition, it is produced in the body by the metabolism of the solvents 1,4-butanediol and gamma butyrolactone, both of which are frequently abused and often referred to as GHB analogs [145, 148–150].

GHB is usually ingested in the form of a powder that is often dissolved in a liquid or mixed with food. Typically, it is typically mixed with alcoholic beverages to mask the salty taste [93]. It can also be ingested in the form of a capsule or tablet. A liquid form, referred to as “liquid ecstasy,” is described [93, 151]. GHB is rapidly absorbed, and the effects appear within 15–30 min [152]. It acts on a multitude of receptors in the brain, but the primary mechanism of action is thought to be via binding to GABA-b receptors, and its own GHB receptor, to produce CNS depression [93]. This CNS depression can produce a euphoria, a more sociable experience, and amnesia [93, 148].

Toxicity

Respiratory System

GHB produces a dose-dependent suppression of respiratory drive, primarily through its effect on the GABA_b receptor [144]. (Table 5) At lower doses, GHB decreases the respiratory rate, but increases the tidal volume, thus minute ventilation is maintained. As doses get larger, the increase in tidal volume is lost and minute ventilation starts to decline [144], and Cheynes-Stokes respiration has been seen [152]. With higher doses, the central respiratory drive is lost, and cardiorespiratory collapse ensues [144]. This dose-dependent respiratory suppression is the cause of most fatal GHB-associated overdoses [145, 148]. Owing to the combined effects of depressed consciousness and frequent emesis, aspiration pneumonia or pneumonitis is also associated with GHB intoxication [153].

Nervous System

The primary effect of GHB on the nervous system is CNS depression through its actions on GABA receptors [154,

[155]. A secondary mechanism, whereby it decreases the release of dopamine from pre-synaptic neurons, has also been demonstrated in animal studies [143, 147]. The primary neurologic manifestation of GHB intoxication is a depressed level of consciousness, with unresponsiveness at high doses [151, 154]. Persons who experience this level of intoxication are typically amnesic to the events [145]. Periods of profound agitation in otherwise unresponsive individuals are the hallmark of GHB intoxication [156]. These periods are associated with rapid alternation from alpha wave to delta and theta wave activity on EEG [157]. The exact mechanism of this agitation has not yet been elucidated. In some cases, generalized tonic-clonic seizures have been reported [145, 152, 158].

In a large case study of GHB (liquid ecstasy) users, the primary neurologic complaints were headache, dysarthria, and disorientation [151]. Dizziness and hallucinations have also been reported [152]. Psychiatric effects, such as emotional lability and aggressiveness, can be present [151]. When taken at therapeutic doses, GHB causes rapid progression to rapid eye movement sleep and increases the period of time spent in this sleep stage. It is thought that this increases the release of growth hormone, giving GHB its presumed anabolic properties [142, 159].

Cardiovascular System

Episodes of bradycardia and hypotension are reported in up to one third of patients presenting to the hospital after a GHB overdose [151, 154]. These affects are dose dependent, and typically correlate well with the patient's level of consciousness.

Gastrointestinal System

Vomiting is commonly associated with GHB intoxication, and it contributes a significant degree of morbidity [145, 151, 154, 155]. This, in combination with depressed mental status, often leads to endotracheal intubation because such intoxicated people cannot protect their airways. Abdominal pain has also been reported [151].

Renal

GHB has no known renal toxicity, but it is actively re-absorbed in the renal tubules [144]. This re-absorption occurs in a saturable concentration-dependent manner via the monocarboxylate transporters [144, 160]. These transporters are inhibited by L-lactate and are a potential therapeutic target for enhanced elimination [144]. Due to its small size and similarity to other biologic chemicals, laboratory identification of GHB and its analogues is difficult using traditional assays. Multiple techniques, all using more advanced

processes such as gas or liquid chromatography and mass spectrometry, have been described and are currently in use in the clinical setting [161, 162].

Conclusion

The true magnitude of abuse of alternative drugs is difficult to quantify because of the lack of reliable testing and reporting. It is clear that abuse patterns are on the rise. Due to the fact that the clinical symptoms and examination findings in alternative drug intoxications are not predictable, physicians must keep this possibility in their differential diagnosis of patients who present with altered mental status or other nonspecific symptoms. Keeping abreast of local and regional trends of drug abuse is important, and should be emphasized to provide optimal medical care. New alternative drugs are continually being developed and abused; hence, healthcare providers must continually expand their knowledge in this area.

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