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MDMA ('ecstasy') and other 'club drugs': The new epidemic

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With the dawn of the new millennium, physicians saw encouraging trends in use of most illicit drugs. Overall drug use among adolescents has shown a gradual decrease [\[79\]](#). Abuse of the "club

drugs,” however, has become much more prevalent in the past 5 years.

The club drugs are so named because of their initial popularity in “raves,” all-night dance parties featuring loud and repetitive electronic music played by popular disc jockeys, attracting primarily adolescents and young adults aged 15 to 25 years. According to Weir [113], “Ravers seek sensory amplification and euphoric transcendence through a combination of marathon trance dancing, drug use and music.” Club drugs, most commonly methylenedioxymethamphetamine (MDMA; “ecstasy”), γ -hydroxybutyrate (GHB), and ketamine, are used to help maintain the energy levels for dancing or to enhance the altered state of consciousness.

Although these drugs became popular in the club scene, they are now widely available on college campuses and in high schools [80], and together now account for many drug-related deaths and emergency department visits [21] (Fig. 1). More concerning is the mounting evidence that these drugs, especially MDMA, have effects on memory and mood, as well as action as a neurotoxin that may have catastrophic effects on the CNS.

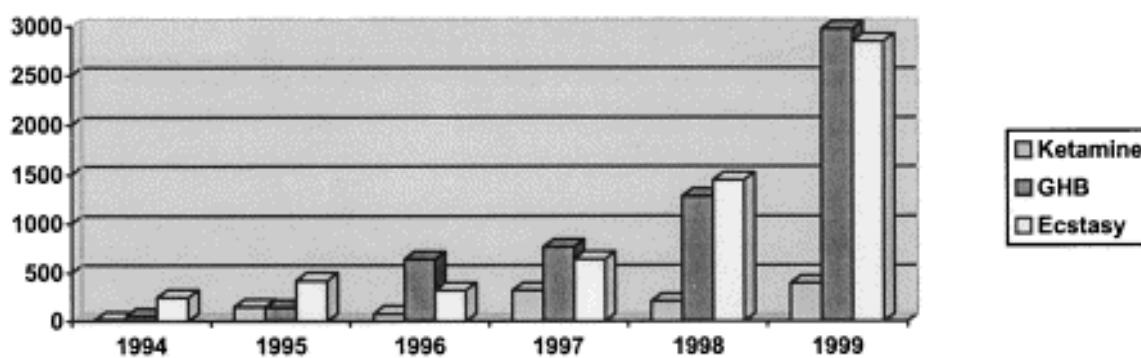


Fig. 1 Emergency department visits involving club drugs.

MDMA

Although ketamine, *Ma-Huang* of *Ephedra*, and GHB have been referred to or purchased as “ecstasy” at times [\[85\]](#), the predominant use refers to 3,4-methylenedioxymethamphetamine (MDMA).

Background

MDMA was first synthesized and patented in the early twentieth century but was never tested in humans [\[75\]](#). It received limited attention in the 1950s when secretly studied by the Central Intelligence Agency and the US army [\[50\]](#), but use did not become common until the 1970s, when therapists used MDMA to facilitate communication in therapy sessions. Soon it became available on the streets, known as “ecstasy,” and by the mid-1980s was becoming more widely abused. In 1985, the Drug Enforcement Agency classified MDMA a Schedule I drug, declaring it a substance with high abuse potential, no accepted medical uses, and illegal to possess. As a Schedule I drug, possession of MDMA is punishable by up to 20 years imprisonment and \$1 million fine [\[108\]](#).

Epidemiology

Initial popularity of MDMA faded in the mid 1980s when it was classified as a Schedule I drug. However, the Drug Abuse Warning Network (DAWN) [\[21\]](#) and Monitoring the Future [\[51\]](#) surveys documented patterns of increasing use and abuse in the latter half of the 1990s. MDMA has now passed cocaine in frequency of usage among teenagers [\[51\]](#).

Monitoring the Future surveys have shown a steady increase in MDMA use in eighth, tenth, and twelfth graders over the past 5 years and has now been used by more than 10% of twelfth grade

students surveyed (Fig. 2). At the same time, perceived availability of MDMA continues to increase, rising from 22% to 51% in the past decade [79]. Among college students, the past-year use of MDMA rose from 0.5% in 1994 to 5.5% in 1999. One recent European study found that 91% of those who had attended raves had used MDMA [72].

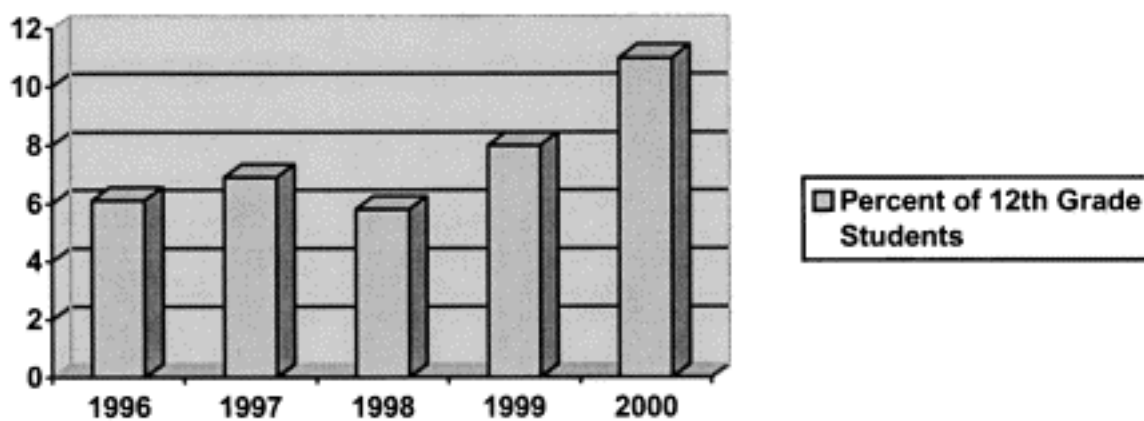


Fig. 2 Lifetime use of ecstasy.

MDMA use has been noted in a dramatically increasing number of emergency department visits (see Fig. 1) and was believed to have played a role in 27 deaths in the United States between 1994 and 1998 [21]. More than 50 MDMA-related deaths have been reported in the European literature [2]. The incidence of MDMA use is likely underestimated because most urine drug screens do not detect it [73], and the DAWN survey screens only a sample of emergency departments across the United States for drug-related visits.

Availability

MDMA is produced primarily in the Netherlands and Belgium [24]; it is made from chemicals restricted to research or industrial purposes in the United States [16]. Tablets are then smuggled into

the United States, where they are sold illegally. MDMA can be bought in Europe for as little as \$0.02 to \$0.50 and sells in the United States for \$15 to \$50 per tablet [75]. US Customs seized 9.3 million MDMA tablets in 2000, a twelvefold increase since 1998 [107]. The Drug Enforcement Agency also has reported an increase in seizures of this substance in recent years [24].

MDMA is known on the streets as “E,” “XTC,” “X,” and “Adam” [16]. Although it can be snorted, smoked, and, rarely, injected from its powder form, its predominant availability is as a tablet [27]. Typical doses contain 50 to 150 mg of MDMA, although actual concentrations in tablets available on the street vary widely. The tablets, produced by different clandestine laboratories, come in a variety of colors and are commonly imprinted with well-recognized emblems, such as automobile symbols, clover leaves, or cartoon characters, to differentiate the source.

Mechanism/metabolism

MDMA shares a chemical similarity to the stimulant amphetamine and the hallucinogen mescaline. It functions as an indirect sympathomimetic, acting at some adrenergic and dopaminergic receptors. MDMA also inhibits the reuptake of serotonin from the synaptic gap, which is thought to account for its mood-altering effects and possible psychomotor agitation [100].

Onset of action when taken orally is 20 to 40 minutes. Peak action occurs at 60 to 90 minutes and typically lasts 3 to 5 hours [50]. Metabolism of MDMA may be nonlinear, especially with higher-than-typical doses [22]. Approximately two thirds of MDMA is excreted unchanged in the urine [92], while MDMA is partially metabolized in the liver by the CYP2D6 isoenzyme of cytochrome P-450 [106]. Several genetic variants can affect an individual's ability to metabolize MDMA and may be responsible for the variable short- or long-term effects of MDMA [103].

Abuse potential

MDMA produces a profound euphoria, heightened feelings of empathy, emotional warmth, and self-acceptance, prompting its nicknames of “hug drug” or “love drug” [16]. Although MDMA does not appear to be as addictive as drugs such as heroin and cocaine, animal studies suggest a role for addiction [43]. Tolerance also appears to develop, with larger doses needed to achieve the desired effects and more side effects occurring with increasing use [103].

Effects

Effects after acute ingestion of MDMA have been described as occurring in three stages: (1) initial disorientation, (2) yielding to tingling and spasmodic jerking, and finally (3) “happy sociability” [78]. MDMA does appear to cause distortion and illusion but not overt hallucination in doses routinely ingested [14]. In addition to these properties, it causes a profound anxiolysis. Heart rate and blood pressure are increased by MDMA [57].

Adverse effects include trismus (tightening of jaw muscles) and bruxism (jaw-clenching), which prompt many MDMA users to suck pacifiers or lollipops to help alleviate this sensation [96]. Other unpleasant effects include nausea, diaphoresis, tremor, tics, nystagmus, and ataxia [50]. The mechanisms of these side effects are not well described. Despite its reputation as the “hug drug,” MDMA typically reduces libido and can cause sexual dysfunction [13]. Psychological effects include confusion, depression, insomnia, and drug craving [16].

MDMA also has been noted to cause rebound effects, including generalized fatigue, muscle aches, difficulty concentrating,

confusion, anxiety, insomnia, and depression lasting 1 to 2 days after ingestion [18], [78].

Dangers

Because it is manufactured in clandestine laboratories, there is no control over the content or purity of tablets sold on the street. Multiple studies have demonstrated that the concentration of MDMA can range from zero to several hundred milligrams. One study demonstrated that even tablets with the same emblem, denoting the same manufacturer, had a sevenfold range of MDMA content [98]. To further complicate matters, MDMA is frequently not the only substance present in the tablets (Table 1), and other dangerous drugs or combinations have been reported in tablets sold as “ecstasy” [19], [98].

Table 1 Drugs found in tablets sold as “ecstasy”

Illicit drugs	Commonly available medications
Methamphetamine	Dextromethorphan
Phencyclidine (PCP)	Acetaminophen
Ketamine	Caffeine
Methylenedioxyamphetamine (MDA)	Ephedrine/Pseudoephedrine
Methylenedioxyethylamphetamine (MDEA)	Aspirin

Data from Sherlock K, Wolff K, Hay AW, et al. Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department. *Emerg Med J* 1999;16:194–7; *and from* Current lab results. In: DanceSafe, Vol. 2001; *and from* Boyer EW, Quang L, Woolf A, et al. Dextromethorphan and ecstasy pills. *JAMA* 2001;285:409–10; with permission.

MDMA is rarely the first illicit drug used and is frequently used together with other drugs of abuse. DAWN data show that 78% of

emergency department cases reported involve at least one other illicit drug, while 47% were associated with alcohol use [21]. This can complicate the emergency care of critically ill patients and also makes it difficult to determine the pure effects of MDMA.

Ingesting multiple drugs, with unknown drug interactions, may have influenced the deaths that have been attributed to MDMA. Dextromethorphan, a common ingredient in cough preparations, is a common adulterant in “ecstasy” tablets. High doses of dextromethorphan may mimic physiologic effects of MDMA, including lethargy, hyperexcitability, tachycardia, ataxia, and nystagmus [11]. In addition, dextromethorphan appears to be metabolized by the same P-450 isoenzyme as MDMA [106], and co-ingestion raises the level of MDMA significantly. Other drugs utilizing the P-450 CYP2D6 isoenzyme include most selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, and some β -blockers [106].

MDMA has been associated with deaths related to malignant hyperthermia, severe dehydration, and disseminated intravascular coagulation (DIC), strokes, as well as some apparent idiopathic liver failure [6, 27, 40, 95]. Some rave promoters and education groups have advocated drinking plenty of water with MDMA use to prevent dehydration and overheating. This may accentuate electrolyte abnormalities, such as dilutional hyponatremia, which have led to some deaths [2]. The often overheated environment in raves likely exacerbates the sympathomimetic effects as well.

Neurotoxicity

Although acute effects of MDMA can have severe, even deadly effects, the drug appears to have long-term neurotoxicity. Studies in animal models have demonstrated that MDMA use decreases serotonin transporters [27]. This effect is reflected in lower levels of serotonin and its metabolite 5-HIAA in spinal fluid even 2 weeks

after MDMA use [87], as well as an anatomic loss of serotonin nerve endings [7]. In primates, this loss of nerve endings was apparent 7 years later [42], while animals who showed signs of recovery often demonstrated abnormal patterns of innervation [30]. Neurotoxic effects also appear to be exacerbated at higher ambient temperatures [71].

The mechanism of neurotoxicity is not clear, but a leading hypothesis suggests the following sequence. MDMA causes serotonin release from target neurons, with resultant depletion of intraneuronal serotonin. Dopamine synthesis and release also are stimulated by MDMA, and excessive dopamine enters the nerve terminals once serotonin is metabolized [104]. Dopamine is then deaminated by monoamine oxidase, resulting in free radical formation and selective oxidative damage to the neuron [7].

Human studies suffer from methodologic flaws; all studies have relied on patients to report both the extent and timing of MDMA use and are based on the assumption that the subjects of the studies would match controls before MDMA exposure. Other questions arise regarding the dosing in animal studies versus humans, and the possible confounding effects of other illicit drug use by humans [17].

Human studies of previous MDMA users have demonstrated decreased serotonin transporters as detected by positron emission tomography scans, which correlated with the extent of reported MDMA use [66]. Other studies have shown that serotonin metabolites are decreased in the spinal fluid and that these decreases correlated with detectable decreases in memory function [65]. Functional deficits related to these findings are discussed later.

Conclusions drawn about these data are unclear at best but are highly suggestive that MDMA induces neurologic changes. All animal species tested have shown susceptibility to neurotoxic

damage with as little as a single dose. Study doses, when adjusted for interspecies variations in metabolism, fall in the range of doses abused routinely by humans [88]. Furthermore, the findings of decreased transporters and metabolites in humans parallel those in animals with demonstrated evidence of neurotoxicity [64]. Some have proposed that the tolerance effect that MDMA users experience may actually be a result of neurotoxicity [69]. Finally, the possible amplification of effect by higher ambient temperatures could have significant implications for the most common site of use of this drug, raves [43].

Functional consequences

Measurable deficits have been reported in functions of brain areas rich in serotonergic innervation. The serotonergic system helps to modulate mood, impulse control, memory, and some cognitive aspects of behavior. Although overt effects may be few, more subtle changes in behavior might be the resultant effects [43], such as changes in sleep [1] or thermoregulation [20].

Previous users of MDMA score significantly higher on depressive scales compared with control patients [34] but do not appear to have an increased incidence in overt depression or psychosis [67]. The duration of these effects is not known. The presence of underlying depression before MDMA also is difficult to rule out but does not appear to be solely responsible for the results seen [43].

Most studies have shown that basic reaction times are normal compared with controls, as is concentration [89]. Decreases in word recall [109] and memory [74] and a heightened impulsivity [74] have been demonstrated. A nearly equal verbal memory deficit was demonstrated in both MDMA and cannabis users, but a second significant deficit in delayed (versus short-term) memory was unique to MDMA users [89].

The combined use of cannabis and MDMA resulted in impaired logical thinking and problem solving (Fig. 3), word recall (Fig. 4), and general knowledge compared with a cannabis-only group and drug-free controls [37]. Neither cannabis nor MDMA users perceived these deficits [89]. Some studies have shown that the amount of deficit correlated with the amount of reported MDMA use [7].

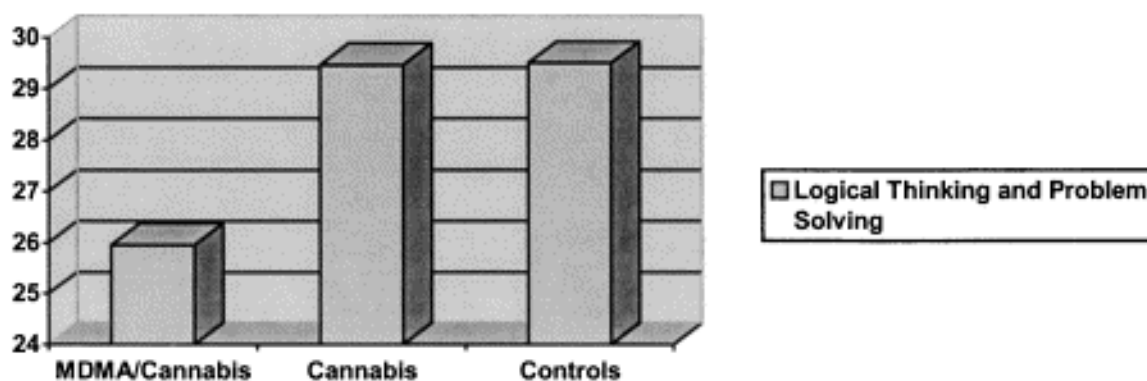


Fig. 3 Rating of problem solving ability.

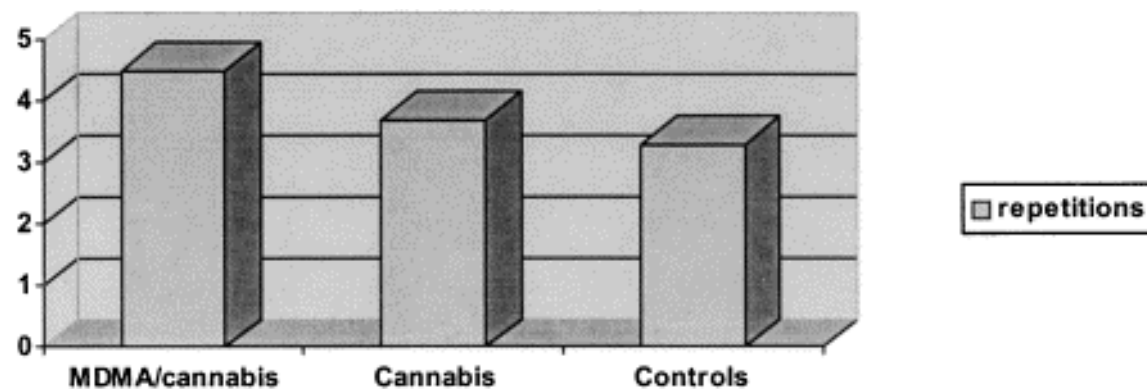


Fig. 4 Number of repetitions required to learn word list.

Although the effects have been relatively subtle, animal studies suggest that these effects may be persistent and may be cumulative. Because MDMA abuse is relatively new, long-term experience and delayed functional consequences that may come

with aging have not yet been reported or studied. Some speculate that diseases such as Alzheimer's or Parkinson's disease, in which a crucial level of neuronal depletion must occur before overt signs develop, could be accelerated in their course [\[52\]](#).

Detection and diagnosis of MDMA toxicity

High clinical suspicion and awareness of the effects of MDMA are important for all physicians who may encounter drug abusers. Signs such as tachycardia, agitation, tremor, mydriasis, and diaphoresis are common. Unfortunately, these signs are nonspecific and can be present with multiple other ingestions or illnesses. Elevated body temperatures have been observed in approximately one third of users and may simulate malignant hyperthermia when extreme [\[115\]](#). Other symptoms associated with MDMA use include muscle tension and jaw clenching [\[102\]](#). Some users may present with rhabdomyolysis or idiosyncratic reactions resulting in liver failure [\[92\]](#).

MDMA is not detected by as many as one third of current immunoassay urine screens [\[73\]](#), although some cross-reactivity with amphetamines may occur if concentrations of MDMA are high [\[96\]](#). MDMA can be detected reliably by gas chromatography and mass spectrometry (GC-MS), although not universally available. Effective confirmation may require a special request for detection of MDMA on the first urine specimen, as MDMA may be present in the urine for as little as 16 hours after ingestion [\[96\]](#). Even reliably reported MDMA use often is combined with other illegal (marijuana), legal (alcohol), and over-the-counter (dextromethorphan) drugs that can each cause toxicity. Dextromethorphan is not currently a part of the usual urine drug screen panel [\[68\]](#).

Treatment of MDMA intoxication

Approach to the patient with MDMA is well reviewed elsewhere [\[96\]](#) and briefly summarized here. Management is primarily supportive. Adequate vascular access and routine chemistries always should be obtained to treat dehydration and evaluate electrolyte abnormalities. Hyperthermia should be treated aggressively with cooling blankets, acetaminophen, and benzodiazepines. Paralysis with intubation to reduce muscular thermogenesis also should be considered in severe cases. Hypertension often responds to sedation, but medications such as nitroprusside and calcium channel blockers can be used if persistent. β -blockers are relatively contraindicated because of potential unopposed alpha effects that could exacerbate hypertension [\[96\]](#). Cardiac arrhythmias should be managed following standard Pediatric Advanced Life Support (PALS) or advanced cardiac life support protocol. Charcoal administration is indicated only if ingestion is suspected to have occurred recently. Urine acidification is not indicated because it may promote metabolic acidosis or myoglobin precipitation in renal tubules. Alkalinization also is not indicated because it reduces the rate of MDMA excretion [\[96\]](#).

Gamma hydroxybutyrate

Background

GHB, the current drug of choice for date rapes, was originally developed as a possible γ -aminobutyric acid (GABA) analogue; it was later found to naturally occur in specific areas of the brain [\[77\]](#). GHB became widely available in health food stores in early 1990, marketed for its anabolic and growth hormone stimulating effects. Both its use as a nutritional supplement and its abuse for its euphoric properties resulted in an outbreak of adverse events, prompting the US Food and Drug Administration to ban GHB by late 1990 [\[25\]](#).

GHB is currently used as a treatment of narcolepsy in Europe [\[63\]](#) and is under study for this indication in the United States. GHB also has been studied for its ability to reduce cravings for alcohol [\[32\]](#) and opiates [\[31\]](#) and is being studied for possible protective effects of GHB in intensive care medicine and surgery [\[4\]](#).

Epidemiology

Although GHB remains an uncommon cause of emergency department visits, its use has increased exponentially in recent years (see [Fig. 1](#)). GHB and its precursors have been involved in at least 12 deaths during this period [\[21\]](#). DAWN data do not include accidental or unintentional ingestions. Consequently, the use of GHB as a date rape drug would not be reported, and its prevalence may be much higher than data suggest. GHB use is highest among teens and young adults, who comprised 59% of GHB-related emergency department visits [\[21\]](#).

Availability

GHB is illicitly produced in Europe and Mexico, as well as in the United States. Its chemical precursors, γ -butyrolactone (GBL) and 1,4-butanediol (BD) also have been available as nutritional supplements (Blue Nitro, Renew Trient, Revivarant) and industrial chemicals (pine needle oil), respectively. Recipes detailing home synthesis of GHB also have been found on the Internet [\[44\]](#).

GHB is usually sold in a powder or liquid form. Its street names include “GHB,” “Georgia homeboy,” “liquid ecstasy,” “soap,” and “easy lay” [\[77\]](#). It is colorless, odorless, and tasteless. Purity of samples varies greatly. In one study, 40 mL of liquid contained from 3 to 20 g of GHB [\[15\]](#). Production of GHB can be quite lucrative, with an initial investment of \$800 of chemicals having an approximate street value of \$92,000 [\[90\]](#).

In 2000, the US government followed the preceding actions of 12 states and made GHB a Schedule I drug. Since then, GBL and BD have been declared a federal List I controlled substance and Class I health hazard, respectively. Unfortunately, BD is still marketed as a dietary supplement, which offers it protection from the Controlled Substances Analogue Enforcement Act [\[97\]](#).

Mechanism of action and pharmacokinetics

Although structurally similar to GABA, a neurotransmitter in the brain, GHB has limited activity at GABA receptors [\[116\]](#). GHB is known to alter the levels of dopamine in the brain in a biphasic manner, inhibiting release at low levels and stimulating release at higher levels [\[70\]](#). GHB does stimulate growth hormone secretion in humans [\[105\]](#), although the clinical significance of this remains debated. GHB readily crosses the blood–brain barrier [\[101\]](#) and functions primarily as a CNS depressant [\[94\]](#).

GHB usually is ingested orally, rapidly absorbed, and has an onset of action within 15 minutes [\[110\]](#). It reaches peak concentrations in 20 to 60 minutes, has a half-life of 27 minutes, and is metabolized almost completely to carbon dioxide, which is then exhaled [\[110\]](#). A small amount is excreted in the urine. Duration of effects is 6 to 8 hours. GHB also is produced by metabolism of its precursor, GBL, which can produce a similar clinical picture of toxicity [\[84\]](#). However, GBL undergoes less first-pass metabolism and has greater lipid solubility, resulting in higher levels and a longer duration of effects [\[58\]](#). BD also is metabolized to GHB, and its toxicity may be prolonged with co-ingestion of alcohol, which competitively inhibits enzymatic degradation of BD [\[83\]](#).

Abuse potential

GHB was initially used by bodybuilders for possible anabolic effects. Users of GHB reported experiencing euphoria, increased

libido, and feelings of relaxation [33]. GHB also is abused for its sedative properties, either as a sleep aid or as an adjunct to date rape [93]. Long-term users of GHB have noted tremor, insomnia, anxiety, muscle cramps, and feelings of “doom” on attempted withdrawal from use. The symptoms appear non–life-threatening and decrease in intensity in the first week [33].

Effects

GHB has a steep dose-response curve, and an individual's responses to even low doses remain unpredictable [47]. Actions of GHB include sedation and increased sleep REM-efficiency at doses of 25 mg/kg, arousable sleep at 40 to 50 mg/kg, and coma induction at approximately 60 mg/kg [26], [63], [94]. Because of its form as a powder or liquid, GHB also proves difficult to measure accurately, increasing the chances of accidental overdose. The most common drug used in combination with GHB is alcohol [21], which acts synergistically to cause respiratory depression [15] and can affect metabolism of the GHB precursor BD.

Side effects include drowsiness, nystagmus, vomiting, and ataxia [12]. Bradycardia has been noted in many patients, but cardiac output and blood pressure are generally maintained at normal levels [111], although hypotension has been reported in several cases with alcohol coingestion [15]. In higher doses, GHB results in coma, with or without respiratory failure. Despite clinical coma, intermittent combativeness has been noted by many [60], and an emergence phenomenon consisting of myoclonic jerking, combativeness, and confusion has been noted upon awakening from coma [15].

Diagnosis/detection

The most common presentation of GHB overdose is sudden onset of coma. Glasgow Coma Scale scores are frequently less than 8,

with as many as one fourth reported as 3 [15]. Pupils are typically miotic and unresponsive to light in a deep coma [45]. As mentioned earlier, bradycardia occurs in a significant proportion, especially with deep coma. Hypothermia has been noted in approximately one third of patients [15].

The diagnosis is generally a clinical one, and extensive laboratory studies generally are not indicated unless other drugs or physiologic processes are believed to be involved. Detection of GHB is difficult because it is metabolized quickly, and it is not detected on routine urine screens for drugs of abuse [62]. GHB and its precursors, GBL and BD, are reliably detected in urine by GC-MS [28], but a specific request often needs to be made to have GC-MS performed. A slight tendency toward hypokalemia has been noted, but this usually is not clinically significant; blood counts and other electrolytes are typically normal [3]. Blood gases typically are normal or show some degree of acute respiratory acidosis [15].

Treatment

Treatment is generally conservative and supportive, including pulse oximetry and aspiration precautions for patients with a decreased level of consciousness. Most patients are able to maintain their airway, and intubation is not usually necessary. If intubation is needed, additional sedation is generally not required because it may prolong duration of coma [59]. Because of the rapid gastrointestinal absorption of GHB, gastric lavage and charcoal administration are not indicated unless other drugs or toxins are suspected [97]. Blood pressures are usually normal, but symptomatic bradycardia has been effectively treated with atropine [15]. Neither naloxone nor flumazenil has demonstrated significant clinical reversal of GHB-induced coma [23], [35]. Some of the effects of GHB appear to be reversible by administration of 2 mg

of physostigmine intravenously [46], although results are somewhat controversial. Recovery is often complete in 2 to 6 hours [15].

Ketamine

Background

Thirty years ago, ketamine was found to be a potent analgesic and anesthetic, with sedative and amnestic properties. Initially used in adult surgical patients, its use was largely abandoned secondary to anesthesia emergence reactions that occurred in as many as 30% of adults [39]. There has been renewed interest in ketamine in the past decade because it provides excellent analgesia and sedation for brief and painful procedures [86]. Because it usually preserves airway and ventilatory reflexes, endotracheal intubation is rarely necessary [39]. In pediatric patients, emergence reactions are less common and tend to be mild [38], whereas in adults, most adverse reactions can be controlled with the administration of benzodiazepines [86].

Epidemiology

Although still relatively uncommon, the abuse of ketamine has continued to increase in recent years, with emergency department visits increasing by a factor of 20 over the past 6 years (Fig. 1). Forty-six deaths were associated with ketamine use during this time period [21]. Like the other club drugs, teens and young adults are the majority of abusers, with 58% of emergency department visits attributed to this age group.

Availability

Ketamine is relatively difficult to synthesize. The majority of ketamine used for illicit purposes in the past has largely been diverted from legitimate users, such as veterinary offices [99].

Mechanism of action

The mechanism of action of ketamine is not fully elucidated but appears to come from a combination of *N*-methyl-D-aspartate, cholinergic, and opiate receptor effects [54]. Ketamine also has been shown to raise cortisol and prolactin levels, although the physiologic significance of these changes is unclear [55].

Pharmacokinetics/metabolism

Ketamine is available as a powder, which usually is ingested orally or nasally, and as a liquid. Liquid ketamine may be smoked after application to cigarettes or may be administered intravenously, intramuscularly, or subcutaneously (“popping”) [112]. Oral doses tend to produce fewer effects secondary to significant first-pass metabolism [86]. It has short-acting CNS effects that resolve as the lipid-soluble drug undergoes redistribution [36]. Redistribution half-life is less than 5 minutes, whereas elimination half-life is a little over 2 hours [86]. Ketamine is metabolized in the hepatic cytochrome P-450 system to the active metabolite norketamine [8]. It is then conjugated and excreted in the urine [86]. Tolerance and hepatic enzyme induction have been reported with long-term use [86]. Although benzodiazepines often are used as an adjunct to ketamine anesthesia or to treat agitation and emergence, they have been shown to delay hepatic metabolism of ketamine [61].

Abuse potential

Ketamine is abused primarily for its dissociative effects. It causes hallucinations, perceived out-of-body experiences, slowed time perception, and changes in perception of environmental stimuli [55]. Doses used recreationally usually total 50 to 100 mg, less than the 2 to 10 mg/kg often used for anesthesia [49].

Effects

Ketamine causes sympathomimetic effects by inhibiting the reuptake of catecholamines, producing mild to moderate increases in heart rate, blood pressure, and overall cardiac output [86]. There are concerns that this may translate into coronary ischemia in predisposed adults. Other common effects include anxiety, altered mental status, hallucinations, nystagmus, and vomiting [55].

Rhabdomyolysis also has been reported [112]. Airway reflexes and patency are generally well maintained, but higher doses of ketamine can cause respiratory depression [10].

Other effects of ketamine appear to mimic both the positive and negative symptoms of schizophrenia. During ketamine use, otherwise healthy patients demonstrate increased unusual thought content and hallucinatory behavior, as well as increased emotional withdrawal and blunted affect [55]. Ketamine does cause pronounced psychic reactions rarely, especially in adults with a history of psychosis. These reactions appear to respond well to benzodiazepines [56]. Drug combinations were found in 81% of emergency department reportings. Alcohol and MDMA were each found in greater than 40% of ketamine users [21].

Long-term effects

Acute intoxication with ketamine impairs attention and learning [41], [55], but multiple cases of chronic abuse leading to impaired memory or attention have been reported [48]. No well-controlled studies are available to document these reports, however. Use of ketamine for anesthesia purposes does not appear to have any long-term adverse effects [91]. Like its analogue PCP, ketamine has been reported to cause flashbacks on occasion [29], [81], although these are typically much milder and less frequent than with PCP use.

Diagnosis

Diagnosis of ketamine abuse is largely a clinical one and should be included in the differential diagnosis of a patient presenting with tachycardia, hypertension, agitation, altered mental status or hallucinations, and nystagmus [112]. Although related to PCP, ketamine is not detected on routine urine drug screens. Ketamine can be detected reliably by high-performance liquid chromatography, but this test usually must be requested separately. The results generally are not returned quickly enough to impact initial care, however [8]. Because of the potential for rhabdomyolysis, basic laboratory testing, including electrolytes and creatinine levels, are recommended [5]. Careful interview for ketamine and other drug use should be performed if the patient is coherent or a reliable historian is present.

Treatment

Little treatment generally is required for patients with these symptoms if ketamine intoxication is strongly suspected. Allowing the patient to rest in a quiet, but monitored, environment may decrease the risk for significant agitation or emergence reactions [114]. Intravenous access and fluids are recommended until laboratory testing has ruled out rhabdomyolysis [112]. Emergence reactions or agitation respond well to benzodiazepines. Cardiovascular effects appear to be effectively reduced with only benzodiazepine treatment [39] but can be treated with α or β blockade or with calcium channel blockade if refractory [5]. Patients should be monitored until mental status and vital signs return to normal. Symptoms usually abate within 2 hours of presentation for medical evaluation, and patients usually can be released after observation in the emergency department. Prolonged symptoms should prompt evaluation for other drugs or disease processes [112].

Summary

Unfortunately, perceptions that the club drugs can be safe endure. Some groups, such as the Multidisciplinary Association for Psychedelic Study, continue to lobby for the legalization of MDMA for research purposes [76]. DanceSafe is an organization that seeks to educate the “nonaddicted” user to decrease the risks [82]. The DanceSafe Web site offers tips on the safe use of MDMA, such as attention to hydration status and ambient temperature. It also offers free testing of tablets submitted by mail and sells home testing kits to determine the content of pills sold as “ecstasy.”

Although much remains unknown about the long-term consequences of MDMA and the club drugs, there are clearly enough short-term dangers to prompt more aggressive education and surveillance for its use. Scare tactics and exaggerations often are ignored [53], while Web sites full of anecdotal or incomplete information may lead the unaware user to increased use [113]. Organizations such as DanceSafe imply that proper education decreases addiction and that only uneducated users or addicts suffer the life-altering consequences of drug use. The fallacy in the mission of educating “nonaddicted” users is evident. Peer-based education, with a focus on both the short-term dangers and long-term consequences, may be a more effective approach [9].

Both new and established drugs of abuse continue to plague teens and young adults. Pediatric and Med-Peds, family practice physicians, and pediatric pharmacologists need to remain vigilant about patterns and trends of drug abuse. MDMA and the other “club drugs” are not benign. Their effects target the brain, alter neurochemistry, and possibly cause irreversible structural damage. What may seem like a harmless drug in a weekend dance club has the potential for major public health problems in years to come [109]. Effective education and timely intervention may prevent

these addictive drugs from becoming a way of life, a lifestyle that may have a literal “dead end.”

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