

# Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and $\gamma$ -hydroxybutyrate

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Club drugs are chemical substances used recreationally in an attempt to enhance social experiences. They first gained popularity in Europe in the 1980s with the advent of “raves”—all-night dance parties with fast-paced, repetitive music often accompanied by elaborate light displays. Club drugs are now well established in the United States and are frequently mentioned in the popular media. Methylenedioxymethamphetamine (MDMA, “ecstasy”), flunitrazepam, ketamine hydrochloride, and  $\gamma$ -hydroxybutyrate (GHB) are the chemical substances most commonly referred to as club drugs. Such substances are consumed to heighten the user’s party experience, as by decreasing inhibitions and increasing the energy for dancing for long periods. Most users consider these agents to pose few if any safety risks, but the frequent arrests, serious reactions, and emergency department visits associated with their use

**Abstract:** The abuse of methylenedioxymethamphetamine (MDMA), flunitrazepam, ketamine hydrochloride, and  $\gamma$ -hydroxybutyrate (GHB) is discussed.

Club drugs are chemical substances used recreationally in social settings. Use is increasingly frequent among young people, especially during all-night dance parties. All four agents have been classified as controlled substances. MDMA (“ecstasy”) is available as a tablet, a capsule, and a powder; formulations may contain many adulterants. MDMA increases the release of neurotransmitters. The desired effects are euphoria, a feeling of intimacy, altered visual perception, enhanced libido, and increased energy. The most common adverse effects are agitation, anxiety, tachycardia, and hypertension. More serious adverse effects include arrhythmias, hyperthermia, and rhabdomyolysis. Flunitrazepam is a potent benzodiazepine. At higher doses, the drug can cause lack of muscle control and loss of consciousness. Other adverse effects are hypotension, dizziness, confusion, and occasional aggression. Ketamine is a dissociative anesthetic used primarily in veterinary practice. It may be injected,

swallowed, snorted, or smoked. Like phenylcyclidine, ketamine interacts with the *N*-methyl-*D*-aspartate channel. Analgesic effects occur at lower doses and amnestic effects at higher doses. Cardiovascular and respiratory toxicity may occur, as well as confusion, hostility, and delirium. GHB, a naturally occurring fatty acid derivative of  $\gamma$ -aminobutyric acid, was introduced as a dietary supplement. Increasing doses progressively produce amnesia, drowsiness, dizziness, euphoria, seizures, coma, and death. Flunitrazepam, ketamine, and GHB have been used to facilitate sexual assault. Supportive care is indicated for most cases of club drug intoxication.

The increasing abuse of MDMA, flunitrazepam, ketamine hydrochloride, and GHB, particularly by young people in social settings such as clubs, should put health care professionals on guard to recognize and manage serious reactions.

**Index terms:** Drug abuse; Flunitrazepam; 4-Hydroxybutanoic acid; Ketamine hydrochloride; MDMA; Toxicity

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suggest otherwise. Because the sources of many club drugs are clandestine laboratories, users may concomitantly ingest substances even more toxic than the purported drug or may consume doses far higher than "labeled." Older club drugs, such as lysergic acid diethylamide (LSD) and methamphetamine, continue to be used in social settings, yet their use has diminished. This review focuses on the abuse of MDMA, flunitrazepam, ketamine hydrochloride, and GHB.

### Epidemiology

The use of club drugs, particularly MDMA and GHB, continues to increase. Periodic reports from the Drug Enforcement Administration (DEA) and the U.S. Customs Service detail the growing importation of and trafficking in club drugs, while the Drug Abuse Warning Network (DAWN) implicates these agents in many emergency department visits. Other sources of information on the club drug trend are surveys conducted by the University of Michigan (Monitoring the Future) and the National Center on Addiction and Substance Abuse at Columbia University (the National Survey of American Attitudes on Substance Abuse) and reports from the Community Epidemiology Working Group (CEWG). These sources offer the best current estimates of club drug use. Most data focus on MDMA, particularly with respect to drug trafficking and patterns of use among teenagers.

The abuse of MDMA is growing faster than that of any other drug.<sup>1</sup> In 2000, 1.3 million high school seniors consumed MDMA, while approximately 450,000 admitted to being current users.<sup>2</sup> Lifetime and annual prevalence of MDMA use in 8th, 10th, and 12th-grade students increased substantially in 2001.<sup>3</sup> Recent data from CEWG document the spread of MDMA use to 17 of 21 metropolitan areas assessed, with use diffusing to a variety of settings, including house parties.<sup>4</sup> Of patients

ages 14–24 years who were enrolled in a drug-abuse recovery program in Seattle, 44% had used MDMA; 43% of those older than 25 years had also done so. MDMA has become the most common stimulant used in bars and clubs in many areas of the country. Street vending of MDMA and GHB and increasing sophistication of MDMA-trafficking organizations have been noted in the United States.<sup>4</sup> On the basis of trends identified by CEWG, the National Institute on Drug Abuse in 2000 launched a multimedia campaign to address trends in club drug abuse. The campaign included community drug alerts; flyers distributed in bars, record stores, and other popular venues; a public service campaign; and a club drug Web site ([www.clubdrugs.org](http://www.clubdrugs.org)).

Club drug use may be described as a youth movement. Since 1998, MDMA consumption among American teenagers has increased by nearly twofold, while teen use of many other illicit drugs has not changed.<sup>3</sup> In 2000, more than 50% of high school seniors stated that MDMA would be "fairly easy" or "very easy" to obtain, compared with 40% in 1999.<sup>2</sup> This figure rose to 62% in 2001.<sup>3</sup> The 2000 National Survey of American Attitudes on Substance Abuse found that 28% of the participants had a friend or classmate who had used MDMA and that 17% knew more than one user.<sup>5</sup> Raves had been attended by 10% of the respondents, and MDMA was available at 70% of the raves. A Massachusetts survey indicated that MDMA use among high school students increased from 6% in 1996 to 15% in 1999.<sup>6</sup> Questions on the use of GHB and ketamine were incorporated in the Monitoring the Future survey for the first time in 2000, so long-term patterns of use are not yet known. At least 80% of emergency room visits attributable to flunitrazepam and MDMA, 70% of those due to ketamine, and 60% of those related to GHB occur in patients 25 years of age or younger.<sup>6</sup>

MDMA trafficking has been likened to that of cocaine by the U.S. Customs Service, which described it as "ad hoc smuggling by small-time dealers" that grew into "organized trafficking by criminals."<sup>7</sup> MDMA seizures by U.S. Customs agents numbered 9 million tablets in 2000, up by nearly 2200% since 1997. DEA seizures increased to 3 million tablets in 2000.<sup>8</sup> The profit potential of MDMA trafficking is high. Production costs for a single MDMA tablet range from \$0.50 to \$1, with final retail prices reaching \$40. A total of 150 clandestine GHB laboratories have been discovered throughout the United States.<sup>9</sup>

Data from DAWN reveal a dramatic increase in GHB- and MDMA-related encounters at emergency departments across the country.<sup>6,10</sup> Far fewer visits were related to ketamine or flunitrazepam abuse. For the 1994–1999 period, more than 70% of emergency department episodes for any of the four agents involved more than one drug, with alcohol being the most common substance used in combination. In 2000, this figure rose to nearly 80% for each of the substances except flunitrazepam (60%). MDMA was combined with ketamine in 37% of cases and with GHB in 15%. A majority (69–80%) of these emergency department episodes occurred in white, non-Hispanic patients.<sup>6</sup> Hispanic patients accounted for 56% of the flunitrazepam-related episodes.

In 1999, FDA received 122 reports of GHB abuse from health care professionals. By January 2000, DEA had documented 60 deaths from GHB abuse, 60% of them in persons 20–29 years of age.<sup>9</sup> The Massachusetts Poison Control Center reported that calls regarding GHB (and one of its precursors,  $\gamma$ -butyrolactone) accounted for more requests than any other club drug and for 32% of all calls related to illicit drugs.<sup>11</sup> At least 30 sexual assaults have been associated with GHB and similar substances in 45 U.S. states since 1990.<sup>9</sup>

**Methylenedioxyamphetamine**

MDMA was first synthesized in Germany in 1914 and used as an appetite suppressant.<sup>12-15</sup> Although the drug was never marketed, it found a small niche in the 1970s as a communication enhancer during psychotherapy.<sup>14</sup> MDMA was classified as a Schedule I controlled substance in July 1985.

**Availability.** MDMA is manufactured in clandestine laboratories throughout Europe, as well as in a small number of locations in the United States.<sup>11</sup> Much of the product is imported from Amsterdam. Importation of MDMA tablets into the United States is said to be under the control of Israeli and Russian organized crime syndicates.<sup>13</sup> MDMA traffickers are often lured by the low cost of manufacturing, the reputation of MDMA as a “harmless” drug, and the large markup in retail price. The average age of federal offenders sentenced for MDMA trafficking in 2000 was 27 years, compared with 33 years for heroin and methamphetamine dealers.<sup>16</sup> The number of federal convictions for MDMA trafficking rose from 20 in 1998 to 169 in 2000. Pursuant to the Ecstasy Anti-Proliferation Act of 2000, federal sentencing guidelines provide for increased penalties for possession of MDMA and related substances.

Street names for MDMA include ecstasy, X, ADAM, XTC, roll, M, bean, clarity, lover’s speed, and hug drug. It is available as a tablet, a capsule, and a powder.<sup>11,15,17</sup> The tablets, typically containing 50 to 150 mg of drug,<sup>18</sup> are formulated in different colors and often imprinted with a popular icon, such as the Nike swoosh, the Motorola logo, smurfs, and a butterfly.

Many adulterants may be found in the tablets, including aspirin, caffeine, dextromethorphan, pseudoephedrine, ketamine, LSD, and paramethoxyamphetamine, a potent hallucinogen.<sup>11,17,19</sup> Other substances that may be sold as MDMA include

methylenedioxyamphetamine (MDA) and 4-bromo-2,5-dimethoxyamphetamine:(2-CB). Hyperthermia, a serious and sometimes fatal complication of MDMA exposure, has frequently been linked to adulterants. DanceSafe, an independent, nonprofit organization, will test MDMA tablets for adulterants and then return the tablets to the user.<sup>20</sup>

**Pharmacology.** MDMA is structurally similar to methamphetamine and mescaline; therefore, it shares both stimulant and hallucinogenic properties.<sup>14</sup> MDMA increases the release of serotonin, dopamine, and norepinephrine from presynaptic neurons and prevents their metabolism by inhibiting monoamine oxidase.<sup>12,21</sup> The end result is an excessive amount of neurotransmitters available at the synapse. The excess dopamine and serotonin are thought to be responsible for the hallucinogenic effects.<sup>12,21</sup> MDMA is metabolized by *N*-demethylation to MDA, an active metabolite, but may also be excreted unchanged in the urine.<sup>22</sup>

**Effects.** The effects of MDMA typically begin 30–60 minutes after oral administration; the duration of action is as long as eight hours.<sup>14,22</sup> MDMA powder may be snorted to achieve a more rapid onset of effect. The name “ecstasy” comes from the desired effects of the drug, which include euphoria, a feeling of intimacy, altered visual perception, enhanced libido, and increased energy; other effects are a distorted sense of time and diminished hunger and thirst.<sup>14,23</sup> The use of MDMA is commonly accompanied by characteristic paraphernalia, including pacifiers and candy suckers, which are used to avoid the bruxism commonly reported with the drug. Fluorescent necklaces, bracelets, and other accessories may be worn to augment visual hallucinations. Vicks inhalers and VapoRub are also often used to enhance the effects of the drug; the product may be directly inhaled, rubbed on the upper lip, or applied

to the inside of a painter’s or surgical mask for inhalation.<sup>24</sup>

MDMA can elevate body temperature.<sup>18</sup> The hyperthermia and dehydration may be exacerbated by hours of dancing. Large quantities of water and beverages containing vitamins and amino acids are consumed to combat dehydration.

Sympathetic stimulation by MDMA results in tachycardia, mydriasis, diaphoresis, tremor, hyperreflexia, palpitations, and hypertension.<sup>25-27</sup> Adverse neurologic effects include confusion, delirium, paranoia, headache, anorexia, depression, insomnia, irritability, and nystagmus, some of which may linger for weeks.<sup>14</sup> Severe reactions include seizures, cerebral edema, parkinsonism, and serotonin syndrome.<sup>28-31</sup> Hyperthermia produced as a result of serotonin syndrome can contribute to end-organ damage, such as acute renal and hepatic failure, adult respiratory distress syndrome, and coagulopathy.<sup>25,32</sup> Some serious adverse effects have been reported after the ingestion of single tablets.<sup>23</sup>

The cardiovascular effects of MDMA can progress to atrioventricular block, arrhythmias, cardiogenic collapse with pulmonary edema, and asystole.<sup>26,27,33</sup> Musculoskeletal effects, such as muscle tension or spasms, rigidity, muscle aches, and bruxism, have been reported.<sup>25</sup> The combination of high environmental temperature, elevated core body temperature, and increased muscular exertion associated with prolonged dancing may lead to rhabdomyolysis and subsequent renal failure.<sup>14,22,25,26</sup>

Metabolic effects, such as hyponatremia and syndrome of inappropriate antidiuretic hormone (SIADH), have been reported. SIADH has been noted after the ingestion of a single MDMA tablet and copious volumes of water.<sup>28,34</sup>

Cognitive impairment has been demonstrated in both animals and humans after long-term exposure to MDMA. This effect may occur sec-

ondary to decreases in the structural components of serotonergic neurons in the brain. There may be long-lasting and potentially permanent memory impairment.<sup>14,15,35</sup> Positron-emission tomography scans of the brains of MDMA users reveal reductions in the number of serotonin transporters, with greater loss associated with greater use of MDMA.<sup>35</sup> Animal studies indicate either complete neuronal regeneration or permanent damage seven years after exposure.<sup>36,37</sup> One group of researchers found impairment of long-term memory and learning in the offspring of rats exposed to MDMA, consequences that continued after adulthood.<sup>38</sup>

**Patient management.** Diagnosis of MDMA intoxication is based on a history of abuse and the symptoms of sympathetic stimulation. The most common symptoms patients display on coming to the emergency department are agitation, anxiety, tachycardia, and hypertension. Monitoring for the more serious adverse effects, including arrhythmias, hyperthermia, and rhabdomyolysis, should be conducted.<sup>25</sup> Because MDMA is most commonly ingested orally, gastrointestinal decontamination with activated charcoal and a cathartic can be helpful. However, a 60-minute delay after ingestion will leave very little drug available for removal by gastric lavage. Unless a massive dose is suspected or the individual is unwilling or unable to take activated charcoal, there is no need for gastric lavage. Inducing emesis is relatively ineffective and may potentiate psychological distress.

There is no antidote for MDMA intoxication, only supportive care. Agitation and anxiety can be controlled with benzodiazepines.<sup>18,22,25</sup> Treating agitation may, in turn, control the tachycardia and hypertension. If hypertension is severe, agents such as labetalol, phentolamine, and nitroprusside may be administered. Pure  $\beta$ -adrenergic-receptor-blocking agents

will cause unopposed  $\alpha$ -receptor stimulation and worsened hypertension and are therefore contraindicated in cases of MDMA intoxication.<sup>25</sup>

Hyperthermia should be assessed by measuring core body temperature.<sup>25,31</sup> Rapid cooling is a priority in the prevention of serious brain injury, hypotension, rhabdomyolysis, coagulopathy, and end-organ failure. During rapid external cooling with tepid water and fanning, shivering may occur, paradoxically leading to more heat generation. Neuromuscular blockade is the most effective means of controlling the shivering but requires intubation. Treatment of serotonin syndrome with dantrolene or cyproheptadine may be helpful, but aggressive supportive therapy with rapid-cooling measures is the mainstay of therapy.

Rhabdomyolysis, diagnosed by detecting myoglobinuria or increased serum creatine phosphokinase levels, requires the administration of alkalized intravenous fluids to maintain a urine output of 2–3 mL/kg/hr.<sup>25</sup> Acidic urine allows myoglobin deposition in the kidneys. To each liter of 5% dextrose injection, 100 meq of sodium bicarbonate should be added. Hemodialysis may be required in cases of acute renal failure.

**Detection.** MDMA and its chemical congeners (e.g., 2-CB) are detected in blood or urine samples by an immunologic assay for amphetamine and methamphetamine.<sup>39</sup> MDMA requires much larger concentrations than amphetamine and methamphetamine to be detected; the assay's sensitivity is only 50% of that for these other substances.<sup>22</sup>

The traditional toxicology screen with thin-layer chromatography can detect MDMA metabolites in the urine. Gas chromatography–mass spectrometry (GCMS) is used for confirmation when an immunoassay screening is positive. According to Verebey et al.,<sup>40</sup> a 50-mg dose of MDMA can be detected as unchanged

drug in the urine up to 72 hours after ingestion.

### Flunitrazepam

Flunitrazepam, a potent benzodiazepine, is available in over 60 countries in Europe and Latin America, where its legitimate use includes preoperative anesthesia or sedation and treatment of insomnia.<sup>15,41,42</sup> Flunitrazepam cannot be sold or prescribed in Canada, but limited quantities can be imported if prescribed by a foreign physician.<sup>43</sup> The same was true in the United States until March 1996, when legislation prohibiting importation was enacted.<sup>44</sup> Flunitrazepam is 10 times as potent as diazepam.<sup>43,45</sup> It is the only benzodiazepine that has been moved from controlled-substances Schedule IV to Schedule III in an attempt to improve the documentation of distribution.<sup>45</sup> Flunitrazepam is now being reviewed by DEA for possible assignment to Schedule I. Some of the concern over misuse of the product arises from its reported use during rape.<sup>41,43,46–48</sup> The drug has become increasingly popular among teenagers and young adults.

**Availability.** Street names for flunitrazepam include Mexican Valium, circles, roofies, la rocha, roche, R2, rope, and forget-me pill. Manufactured in Europe and Latin America by Roche, flunitrazepam is marketed as Rohypnol.<sup>45</sup> The product is available as 1- and 2-mg tablets and as an injection.<sup>42,45,49</sup> Roche has restricted distribution of the 2-mg tablets to inpatients.<sup>50</sup> Each flunitrazepam tablet costs \$0.50–\$5 on the street.<sup>41,43,51</sup> Because of the relatively low cost, many young people seek flunitrazepam as a “cheap high.”<sup>43,45</sup> Identifying characteristics include a single score, the imprint of “Roche,” and “1” or “2” to denote the tablet strength.<sup>42,43,50</sup> The shape and color of both legal and counterfeit products vary from country to country.

Illegal distribution and possession of flunitrazepam have been docu-

mented since 1985.<sup>46</sup> The drug often enters the United States in the mail.<sup>45</sup> Florida, Texas, and California have seen the most seizures. In Florida, flunitrazepam screening may be undertaken if an apparently impaired driver has a low blood alcohol level.

**Pharmacology.** The intravenous formulation of flunitrazepam is used for preoperative procedures and has an immediate onset of action. After oral administration of the tablet, bioavailability is approximately 85%.<sup>49</sup> Flunitrazepam is rapidly distributed from the plasma into the tissues and is extensively metabolized by the liver into two active compounds.<sup>48</sup> The area under the concentration-versus-time curve is described by a three-compartment open model.<sup>52</sup> The half-life of flunitrazepam is approximately 20 hours, and the metabolites are excreted renally. Despite the lengthy half-life, the clinical effects are short-lived because of the rapid distribution.

**Effects.** At low doses, flunitrazepam acts as an anxiolytic, muscle relaxant, and general sedative-hypnotic.<sup>15,51</sup> At higher doses, the drug can cause lack of muscle control and loss of consciousness.<sup>15</sup> The effects of flunitrazepam are potentiated by concurrent use of alcohol; there may be amnesia and loss of inhibitions.<sup>15,42,53</sup> Sedation occurs within 30 minutes after ingestion, with peak effects at two hours. As little as 1 mg can impair an individual for 8–12 hours.<sup>41</sup> The amnestic effect, which can occur within 30 minutes, may be dose related.<sup>54</sup> Flunitrazepam may often be ingested with other substances, such as cocaine and heroin.<sup>42,45,50</sup>

Adverse effects include hypotension, dizziness, confusion, visual disturbances, urinary retention, and, in some users, aggressive behavior.<sup>45,49</sup> Dependence on flunitrazepam can occur; abrupt withdrawal from the agent produces such symptoms as headache, tension, extreme anxiety, restlessness, muscle pain, photosensitivity, numbness and tingling of extremities, and even seizures.<sup>49</sup>

**Patient management.** Supportive care is generally sufficient for flunitrazepam intoxication.<sup>47,49</sup> The greatest concern arises when there has been concomitant ingestion of central-nervous-system (CNS) depressants. If the suspected ingestion occurred within the preceding 60 minutes, emesis can be induced in conscious patients.<sup>49,55</sup> Gastric lavage with a protected airway may be helpful for the unconscious patient. Otherwise, activated charcoal and a cathartic can be given to reduce absorption.

The antidote for benzodiazepine overdose is the antagonist flumazenil.<sup>49</sup> Initially, flumazenil is administered as 0.2 mg i.v., followed by 0.3 mg i.v. in one minute if there is no response.<sup>55</sup> The dose may be increased to up to 0.5 mg if necessary. The cumulative dose should not exceed 3 mg. Flumazenil should be administered with great caution, however. Seizures may be induced in patients receiving benzodiazepines for epilepsy, those experiencing acute withdrawal from flunitrazepam or other benzodiazepines, or those with a cyclic antidepressant overdose. Resedation can be expected rather rapidly, as the effects of flumazenil are short-lived. Vital-sign monitoring and support should be provided as needed.<sup>54</sup>

**Detection.** Testing for benzodiazepines is a standard component of most urine drug screens; however, flunitrazepam is administered in such small amounts and distributed so rapidly that detection methods commonly fail.<sup>47</sup> GCMS is the detection method of choice for both flunitrazepam and the active metabolite, 7-amino-flunitrazepam. GCMS can detect a flunitrazepam dose as low as 1 mg for up to 72 hours after ingestion.<sup>55</sup> If flunitrazepam is suspected in a case of rape, but the hospital laboratory is unable to analyze the sample, Roche can be contacted (800-608-6540) for assay recommendations.<sup>54</sup>

### Ketamine hydrochloride

Ketamine hydrochloride, a deriv-

ative of phencyclidine hydrochloride (PCP), was introduced in the 1960s as a dissociative anesthetic.<sup>56</sup> Its use in clinical practice has diminished with the introduction of safer and more effective products. It is still used on a limited basis in critical care settings, mainly because of its ability to maintain respiration and blood pressure. Veterinarians use ketamine to induce sedation in animals for surgery, travel, and euthanasia. Street names for ketamine include special K, K, kit-kat, keets, super acid, super K, and jet.<sup>57</sup>

**Availability.** In the clinical setting, ketamine is available as an injectable prescription formulation and is classified as a Schedule III controlled substance. Powder and tablet formulations are also available. Many states include ketamine in their controlled-substance legislation. The drug is difficult to manufacture; most abusers acquire it through diversion of the prescription product. Ketamine is believed to have entered the club scene in the 1980s. Originally, the drug may have been used as an adulterant of MDMA tablets.<sup>58</sup> As users became more familiar with the effects of ketamine, its use as a sole agent emerged.

The street cost of ketamine is approximately \$80 per gram. Users inject (intravenously or intramuscularly), ingest, smoke, or snort the product.<sup>a</sup>

**Pharmacology.** Ketamine is highly bioavailable after intravenous or intramuscular injection.<sup>59</sup> Oral doses are less well absorbed and undergo extensive first-pass metabolism. Like PCP, ketamine interacts with the *N*-methyl-D-aspartate (NMDA) channel.<sup>60</sup> In interacting with the NMDA channel, the drug binds noncompetitively to the PCP receptor and inhibits glutamate activation of the channel. Ketamine also interacts with a number of cellular receptors, including muscarinic, nicotinic, cholinergic, and opioid receptors. Ketamine has been found to inhibit the

neuronal uptake of norepinephrine, dopamine, and serotonin.<sup>56</sup>

**Effects.** In social settings, ketamine is most commonly snorted or ingested. The effects are rapid in onset and last approximately 30–45 minutes.<sup>58</sup> Analgesic effects are seen at lower doses, while higher doses are amnesic.<sup>54</sup> Patients often describe a dramatic feeling of dissociation from one's self—a sense of “floating over one's body.”<sup>61</sup> These out-of-body experiences usually last up to one hour. Visual hallucinations and a lack of coordination are also common.<sup>54,61</sup>

Cardiovascular toxicity may develop from reflex sympathetic activation and manifests as hypertension, tachycardia, and palpitations. Respiratory toxicity, including respiratory depression and apnea, may occur. Patients may also develop confusion, negativism, hostility, and delirium.<sup>60</sup> Users have reported that the effects of ketamine are somewhat dependent on the setting.<sup>62</sup> Noisy or rowdy surroundings have sometimes been correlated with negative effects, so some individuals prefer not to use the drug in club settings. Persons who continue to abuse ketamine may develop severe addiction and a withdrawal syndrome requiring detoxification.<sup>63</sup>

Because the drug is tasteless, odorless, and colorless, it can be surreptitiously added to beverages and used to facilitate sexual assault.<sup>64</sup> Along with reduced awareness or unconsciousness, the victim may develop anterograde amnesia as rapidly as 15 minutes after ingestion.<sup>54</sup> Vivid hallucinations, amnesia, and dreams make it difficult to discern drug-induced effects from reality, rendering the victim unreliable as a witness.

**Patient management.** No antidote exists for ketamine intoxication; as with MDMA and flunitrazepam intoxication, the cornerstone of management is supportive care with special attention to respiratory and cardiac function.<sup>54</sup> Clinicians can expect respiratory and cardiovascular

depression to be enhanced when ketamine is coingested with alcohol. Death from ketamine ingestion is rare.<sup>59</sup> Midazolam is considered the sedative of choice for patients requiring sedation. The hallucinatory effects of ketamine may be minimized by placing the patient in an area with reduced environmental stimuli.

**Detection.** Serum and urine levels of both ketamine and its active metabolite, norketamine, are generally not readily available to most clinicians.<sup>65</sup> When interpreting laboratory test results, clinicians should be aware that immunoassays for PCP may cross-react with ketamine assays.<sup>66</sup>

#### Gamma-hydroxybutyrate

GHB is a naturally occurring fatty acid derivative of the CNS neurotransmitter  $\gamma$ -aminobutyric acid (GABA).<sup>67</sup> In the United States, GHB was initially investigated as an anesthetic agent.<sup>68</sup> A lack of sufficient analgesia and an association with seizure-like activity and reflex autonomic activation halted most studies. In Europe and other foreign countries, GHB has been used in the medical management of narcolepsy.<sup>69</sup> Placebo-controlled trials examining the GHB analogue oxybate sodium for the management of narcolepsy-associated cataplexy are under way in the United States.<sup>70,71</sup>

GHB has also been tested or used for the promotion of muscle development, treatment of alcohol and opiate agonist dependence, management of weight control, induction of anesthesia, and management of schizophrenia.<sup>72-74</sup> Street names for GHB include G, liquid ecstasy, gib, liquid X, soap, salty water, scoop, and nitro.<sup>54</sup>

**Availability.** GHB was introduced in the United States in 1990 as a dietary supplement; manufacturers claimed that it could increase muscle mass and metabolize fat, as well as increase libido.<sup>75</sup> GHB quickly became popular among bodybuilders

and fitness proponents throughout the United States. As GHB's popularity increased, its ability to induce euphoria and to cause untoward effects also became evident. In late 1990, FDA banned all nonprescription sales of GHB, but the drug had already established itself as a club drug and “date-rape” drug.<sup>76</sup> In early 2000, GHB was reclassified as a Schedule I controlled substance.<sup>7</sup>

GHB is often imported from Europe, where it is classified similarly to a Schedule IV agent,<sup>72</sup> and it is manufactured in clandestine U.S. laboratories to various degrees of purity. Many Internet sites offer instructions for the home production of GHB or advertise the sale of kits that contain the ingredients necessary to produce it. Because GHB compounds most often exist as oral solutions, they are commonly available in small vials or are mixed into bottles of water. A typical dose is a capful of oral solution. GHB sells on the street for \$5–\$10 a dose.

Chemical precursors of GHB are  $\gamma$ -butyrolactone (GBL) and 1,4-butanediol (1,4-BD).<sup>77</sup> Since the reclassification of GHB to Schedule I, both GBL and 1,4-BD have become popular sources of the drug. GBL is widely used in the chemical industry and is available from chemical-supply companies.<sup>78</sup> After ingestion, GBL is rapidly converted to GHB by endogenous lactonases. Because GBL is more rapidly absorbed than GHB, it produces higher serum concentrations and has a longer duration of action.<sup>79</sup> GBL has been marketed by health stores under such names as Blue Nitro, Nitro, GH Revitalizer, and Gamma G.<sup>77</sup> In 1999, FDA warned the public of the dangers of GBL and asked manufacturers for a voluntary recall.<sup>80</sup> GBL is considered a List I chemical, requiring elaborate documentation and justification of all purchases and sales. If intended for human consumption, GBL and related substances are regarded as controlled-substance analogues.<sup>7</sup>

1,4-BD is also available in health stores under brand names including Weight Belt Cleaner, Serenity, Thunder Nectar, and Revitalize Plus.<sup>81</sup> Like GBL, 1,4-BD may be acquired through chemical-supply companies. Some street names for 1, 4-BD are lemon fx drops, cherry fx bombs, and orange fx rush. In 1999, a chiropractor was fined \$2000 and imprisoned after distributing liquids containing 1,4-BD that resulted in the intoxication of over 100 people at a party in Los Angeles.<sup>82</sup> Also in 1999, FDA issued a warning about the life-threatening potential of 1,4-BD.<sup>83</sup> 1,4-BD is metabolized in the body by alcohol dehydrogenase to  $\gamma$ -hydroxybutyraldehyde, which is in turn metabolized to GHB by aldehyde dehydrogenase. Prolonged toxicity occurs when 1,4-BD is coingested with alcohol.<sup>84</sup>

**Pharmacology.** GHB is a metabolite of GABA and is normally found in concentrations 1/1000 that of GABA.<sup>82</sup> Present endogenously in the CNS, GHB is thought to mediate sleep cycles, body temperature, cerebral glucose metabolism, and memory.<sup>85,86</sup> The chemical is also believed to influence endogenous dopamine levels—possibly increasing concentrations through interactions with GABA receptors.<sup>87</sup>

GHB's lipophilic properties lend to its rapid oral absorption and ability to effectively cross the blood-brain barrier.<sup>85</sup> Excretion is primarily through expired breath as carbon dioxide; 2–5% of a dose is renally eliminated.<sup>88</sup> Peak plasma concentrations occur 20–60 minutes after ingestion. The half-life is only 20 minutes.

The purported scientific basis for GHB's use by bodybuilders is an increase in the release of growth hormone.<sup>89</sup> GHB is believed to prolong slow-wave sleep, the period when the release of endogenous growth hormone is maximal. Although GHB has been associated with some short-term increases in growth hormone levels, these findings have never been

established in large, well-controlled, clinical trials.

**Effects.** Users often ingest GHB for its CNS depressant effects, specifically to counteract the stimulatory symptoms associated with other club drugs, such as MDMA. After oral ingestion of GHB, effects usually appear in 15–30 minutes.<sup>54</sup> The effects of ingestion are amplified by co-ingestion of alcohol or other CNS depressants, including opiate agonists, benzodiazepines, and neuroleptics.<sup>90,91</sup> Dose-related CNS depression is the most obvious manifestation. With increasing doses, CNS depression progresses from amnesia and hypotonia to drowsiness, dizziness, and euphoria.<sup>82,85</sup> Doses exceeding 50 mg/kg have been associated with Cheyne–Stokes respiration, seizures, coma, and death.<sup>68</sup> The margin separating the euphoric effects of GHB from life-threatening adverse effects appears to be slim.

Generalized tonic-clonic seizures have been reported in a number of cases of GHB intoxication in humans, and epileptiform electroencephalogram changes have been seen in animals.<sup>87,92,93</sup> In a series of 78 patients who had ingested GHB, 9% developed some form of seizure-like activity.<sup>94</sup> However, in another case series involving 88 patients, no patients had any reported seizure activity.<sup>95</sup> Often, random clonic muscular contractions caused by GHB are confused with epileptic manifestations. Some investigators have described an emergence phenomenon that may be misinterpreted as seizure-like activity.<sup>96</sup> Users are described as becoming highly agitated and flailing, like a drowning swimmer fighting for air.

Although most patients are able to maintain airway patency, some require intubation and mechanical ventilation.<sup>95</sup> Cardiovascular effects include bradycardia and hypotension. Bradycardia may occur in up to 36% of patients and seems to be correlated with the level of consciousness. Gastrointestinal effects include hypersali-

vation and vomiting.<sup>97</sup> Vomiting is more common when alcohol is co-ingested. Hypothermia (e.g., an initial body temperature of less than 35 °C) has been reported in up to 31% of patients.<sup>95</sup>

Severe dependence among chronic abusers has been reported.<sup>98–101</sup> Progressive dose escalation was described by Dyer et al.<sup>98</sup> in eight patients. Craving was indicated by excessively high doses, increased frequency of use, and continued use despite adverse effects. The investigators observed a withdrawal syndrome consisting of anxiety, insomnia, and tremor that progressed to severe delirium with autonomic instability in some patients.

Because GHB produces anterograde amnesia and can be easily poured into beverages, it has been used to facilitate sexual assault.<sup>54</sup> Victims often lose consciousness and may not be able to resist or recall a sexual assault. GHB is a powerful intoxicant and sexual stimulant, making it even more difficult for law enforcement personnel to successfully prosecute perpetrators of such assault.<sup>96</sup>

**Patient management.** No antidote exists for GHB intoxication.<sup>96</sup> With good supportive care, patients typically recover completely within about seven hours; there is usually no need for intubation and mechanical ventilation.<sup>95,96</sup> All patients in one series had complete recovery of mentation and respiratory function within six hours of arrival for treatment.<sup>96</sup> Clinicians should also strongly consider the possibility of 1,4-BD and alcohol coingestion, as these patients may develop prolonged toxicity requiring more treatment.

Cases of severe intoxication may require airway support, including intubation. Since GHB is a sedative amnesic, rapid-sequence intubation may be accomplished with neuromuscular blocking agents alone.<sup>82</sup> Aggressive suctioning may be necessary.

Because GHB can cause a rapid loss of consciousness, gastric lavage

and induction of emesis are contraindicated.<sup>96</sup> Gastric decontamination with charcoal may be effective, especially in cases of suspected co-ingestion. Symptomatic bradycardia can be managed with atropine, and seizures respond effectively to benzodiazepines. While GHB intoxication may resemble benzodiazepine overdose, flumazenil has not been found to reverse the toxic effects.<sup>85,96</sup> Stable patients who appear to be asymptomatic may be discharged from the emergency department after approximately six hours of observation, while patients with ventilatory or hemodynamic instability should be admitted to the hospital.<sup>96</sup> Similarly, patients who have consumed both 1,4-BD and alcohol should be admitted for more intensive monitoring.

**Detection.** Patients with unexplained or sudden coma who have no evidence of head trauma or elevated intracranial pressure should be suspected of GHB intoxication. In most cases, the diagnosis will be based on patient history. Unlike many other drugs associated with sexual assault, GHB is not odorless or tasteless. The drug has an unpleasant, salty taste that is often described as soapy.<sup>54,82</sup> However, this taste may be masked by strongly flavored beverages, such as alcoholic drinks.

GHB is not detected by routine urine or serum toxicology screens because of its rapid excretion as carbon dioxide through exhalation.<sup>100</sup> Only facilities equipped with GCMS equipment are able to detect GHB or its metabolites in urine or serum samples. The National Forensic Laboratory (National Medical Services, Willow Grove, PA; 800-522-6671) will perform urinalysis for GHB for a charge. (These assays do not have the ability to differentiate between GHB and its precursors, GBL and 1,4-BD.) The longer that collection is delayed after GHB ingestion, the lower the likelihood of detection.<sup>54,100</sup> GHB is virtually undetectable in the urine 12 hours after ingestion.

<sup>54</sup> Serum concentrations greater than 50 mg/mL are associated with loss of consciousness; concentrations greater than 260 mg/mL, with unresponsive coma.<sup>102</sup>

**Conclusion**

The increasing abuse of methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and  $\gamma$ -hydroxybutyrate, particularly by young people in social settings such as clubs, should put pharmacists and other health care professionals on guard to recognize and manage serious reactions.

<sup>a</sup>Ketamine abuse increasing. Drug Enforcement Administration news release. Washington, DC; 1997 Feb 4.

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