Club Drugs

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty
Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners
John M. Leonard, MD
Jane C. Norman, RN, MSN, CNE, PhD
Alice Yick Flanagan, PhD, MSW
James Trent, PhD

Director of Development and Academic Affairs
Sarah Campbell

Division Planners/Director Disclosure
The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use club drugs or whose past club drug use has resulted in untoward effects.

Accreditations & Approvals
In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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This course is considered self-study, as defined by the New York State Board for Social Work. Materials that are included in this course may include interventions and modalities that are beyond the authorized practice of licensed master social work and licensed clinical social work in New York. As a licensed professional, you are responsible for reviewing the scope of practice, including

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This course is considered self-study by the New York State Board of Mental Health Counseling.

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This course is considered self-study by the New York State Board of Marriage and Family Therapy.

This course has been approved by NetCE, as a NAADAC Approved Education Provider, for educational credits, NAADAC Provider #97847. NetCE is responsible for all aspects of their programming.

NetCE is approved as a provider of continuing education by the California Consortium of Addiction Programs and Professionals (CCAPP). Provider Number 5-08-151-0622.

NetCE is approved as a provider of continuing education by the California Association for Alcohol/Drug Educators. Provider Number CP40 889 H 0623.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 3 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

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Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 3 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

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Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

NetCE designates this continuing education activity for 3 ANCC contact hours.

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AACN Synergy CERP Category A.

Social Workers participating in this intermediate to advanced course will receive 3 Clinical continuing education clock hours.

NetCE designates this continuing education activity for 3 CE credits.

NetCE designates this continuing education activity for 1 NBCC clock hour.

NetCE designates this continuing education activity for 3 continuing education hours for addiction professionals.

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About the Sponsor
The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement
It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective
The purpose of this course is to enhance the ability of healthcare professionals to effectively identify, diagnose, treat, and provide appropriate referrals for patients who use club drugs.

Learning Objectives
Upon completion of this course, you should be able to:

1. Outline the history of club drug use.
2. Discuss the epidemiology of club drug use in the United States.
3. Outline the pharmacology, clinical effects, and treatment of MDMA abuse.
4. Describe the pharmacology, clinical effects, and treatment of GHB and ketamine abuse.
5. Discuss the pharmacology, clinical effects, and treatment of flunitrazepam abuse, including its association with the facilitation of sexual assault.
6. Describe the importance of utilizing an interpreter when assessing club drug use in non-English-proficient patients.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

The drugs methylenedioxymethamphetamine (MDMA), ketamine, flunitrazepam, and gamma-hydroxybutyrate (GHB) have become widely used by college students and by a segment of the youth population that attends all-night dance parties known as "raves." For this reason, this group of drugs has become known as "club drugs." Sporadic use seldom produces acute or lasting adverse effects in most persons, but heavy use can lead to psychologic and physical consequences of variable severity and duration, depending on the agent, the pattern of use, and individual factors. Individuals susceptible to addiction can become compulsive users of these drugs and develop psychologic dependence. Therefore, it is imperative that healthcare professionals in a variety of settings are knowledgeable in the availability and clinical effects of these drugs as well as approaches to treatment of toxicity and withdrawal.

BACKGROUND

Club drugs are generally consumed to heighten the user's party or social experience, decrease inhibitions, and to increase energy for long periods [1]. This may include stimulants, depressants, and hallucinogens if used for this purpose. Club drugs often appeal to younger drug users and present the possibility of significant toxicity that can be life-threatening or result in permanent morbidity [2].

Rave parties, or raves, began in England in the 1980s and spread to the United States in the early 1990s. These events are marathon dance parties held in clandestine locations, including warehouses, nightclubs, and farm fields, accompanied by extravagant light shows with themes emphasizing harmony, empathy, and a sense of belonging. Club drugs are used to increase feelings of closeness with others and to heighten the experience through sensory enhancement, visual distortion, and illusion [3]. Alcohol is generally not sold at raves, but designer and other drugs are obtainable

and affordable. Also, "power drinks" are often sold. These drinks consist of fruit juice mixed with amino acid powders and B vitamins to replenish fluids lost during strenuous marathon dancing [4].

Club drugs are also used at "circuit parties," which are weekend-long parties or raves with a homosexual orientation involving as many as 5,000 to 20,000 participants. The partygoers travel from event to event, with some parties being linked economically to fundraising or cultural events [4]. In underground dance and club culture today, electronic dance music (EDM) and EDM events have largely replaced rave culture, and with the exception of MDMA, use of the other club drugs discussed in this course has decreased. This may be the result of the influx of novel psychoactive substances and greater restriction placed on chemicals relevant to club drugs, such as precursor agents for GHB.

EPIDEMIOLOGY

Most epidemiologic data on club drug use focuses on MDMA. As noted, other drugs that are usually categorized as club drugs include ketamine, GHB, and flunitrazepam. Due to their effects, these drugs have come to be used in many drug-induced sexual assaults and may be referred to as "date rape drugs."

Club drug use may be described as a youth movement. While college is frequently the time of first MDMA use, use in high school students has become more common. The Youth Risk Behavior Survey 2019 reported that 3.6% of high school students nationwide had used MDMA at least once during their lifetimes [5; 41]. In 2020, a total of 1.8% of high school seniors had consumed MDMA during the previous year, and approximately 0.3% admitted to being current users [40].

In 2019, more than 24.3% of high school seniors stated that MDMA was "fairly easy" or "very easy" to obtain. In 2001, this figure was as high as 61.5% [40]. MDMA use peaked in 2001; in 2003, a sharp drop was noted, probably related to the increased perception of risk [7; 40]. The drop in past-year use of MDMA has continued through 2020. The combined past-year rates of students in grades 12, 10, and 8 showed lower rates in 2020 than in 1996, the first year MDMA use was measured [40].

A survey of 14,000 college students at 119 American colleges found a 69% increase in MDMA use between 1997 and 1999 (from 2.8% to 4.7%), with little change in cannabis use during the same period [8].

During the 1990s and 2000s, MDMA became one of the most common psychoactive drugs used in bars and clubs in many areas of the country. In one survey, 89% of young adults attending clubs reported lifetime MDMA use, compared with 18% of a sample of youthful offenders [9]. Of patients 14 to 24 years of age who were enrolled in a drug abuse recovery program in Seattle, 44% had used MDMA; 43% of those older than 25 years of age also reported past MDMA use [1]. Additionally, the Substance Abuse and Mental Health Services Administration (SAMHSA) reports that MDMA-related emergency department visits by patients younger than 21 years of age increased from 4,460 in 2005 to 10,176 in 2011 [10]. Each year, an average of 33% of visits involving MDMA also involve alcohol. As of 2016, MDMA is no longer considered exclusively a club drug.

The increasing popularity of MDMA is not just an American phenomenon but is also seen in Australia and Europe. In some countries, MDMA use is second in frequency only to cannabis use [11].

MDMA

MDMA is an amphetamine analog that is structurally similar to the endogenous catecholamines and chemically related to mescaline and methamphetamine. As such, it possesses both stimulant and hallucinogenic properties [12].

MDMA was first synthesized in Germany in 1914 as an appetite suppressant and as a parent compound to synthesize other pharmaceuticals. However, therapeutic use of MDMA in the United States did not begin until the 1970s. During the 1970s, MDMA was used as a psychotherapeutic tool by a limited number of psychiatrists, despite the fact that the drug was never subjected to clinical trials nor approved by the U.S. Food and Drug Administration (FDA) for use in humans. Nevertheless, the drug gained a small but enthusiastic following among psychiatrists in the late 1970s and early 1980s because it was perceived to enhance communication in patient sessions and reportedly allowed users to achieve insights about the nature of their problems. It was also during this period that illicit MDMA first started becoming available. In 1985, the U.S. Drug Enforcement Administration (DEA) banned MDMA by designating it a Schedule I substance, indicating a drug made entirely illegal with no proven therapeutic value. It was only in 2000 that the FDA approved the first small clinical trial for MDMA, for use in conjunction with psychotherapy under carefully monitored conditions to treat post-traumatic stress disorder [12; 13].

AVAILABILITY

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" [14]. The high profit potential of MDMA trafficking is reflected by the difference between the production cost for a single MDMA tablet, which is generally less than $1, and the final retail price of up to $50 [1; 6].

In the past, MDMA was mainly manufactured in clandestine laboratories throughout Europe, as well as in a small number of locations in the United States. Most MDMA manufactured in Europe was exported to the United States through Amsterdam. In the past 10 to 15 years, the trafficking pattern of MDMA has shifted, with most MDMA in the United States now being manufactured in Asia and shipped through Canada and the Netherlands [6; 39]. Tablets usually contain 50–150 mg of the drug; however, many adulterants are either found in MDMA tablets or are sold misrepresented as MDMA, including aspirin, caffeine, dextromethorphan, pseudoephedrine, ketamine, lysergic acid diethylamide (LSD), paramethoxyamphetamine (PMA), 3,4-methylenedioxyamphetamine (MDA), and 4-bromo-2,5-dimethoxyphenethylamine (2C-B) [1]. The street drug "Molly" has been sold as MDMA, but it often contains cathinones ("bath salts") alone or in combination with various other substances [15]. In 2014, the DEA placed 10 synthetic cathinones on Schedule I [15].

PHARMACOLOGY

MDMA is typically present in two optical isomers with the dextrorotatory form, S-(+)-MDMA having greater central nervous system (CNS) potency. MDMA is metabolized to MDA, 4-hydroxy-3-methoxymethamphetamine (HMMA), and 3,4-dihydroxymethamphetamine (HHMA) [8].

Many of the physiologic and psychoactive effects of MDMA stem from its serotonergic activity, by which it stimulates the release of serotonin and dopamine from nerve endings, and concomitant inhibition of serotonin reuptake [16]. MDMA also inhibits tryptophan hydroxylase, which decreases serotonin production. It has a very low affinity for post-synaptic serotonin receptors. Because MDMA depletes serotonin stores in neurons, subsequent doses produce diminished euphoria and increase adverse effects, such as depression and agitation. MDMA also has activity with noradrenergic and cholinergic neurotransmitter systems [2; 8].

MDMA reaches peak plasma concentration within two to four hours following oral ingestion. Its half-life is approximately eight hours, and metabolism occurs primarily through the hepatic enzyme CYP2D6 [17; 18].

CLINICAL EFFECTS

MDMA is almost always used in the company of other people, which provides the optimal setting for the manifestation of the empathogenic aspects of the drug. MDMA users often report several positive effects on mood and emotion, particularly in their relation to others, such as enhanced empathy, communication, and understanding [12]. Experienced and MDMA-naïve subjects also report euphoria, increased self-esteem, elevated physical and emotional energy, heightened sensual awareness, relaxation, and dissociation. One study showed that euphoria was greater with 125 mg MDMA compared to 40 mg amphetamine [8].

MDMA has been shown to increase energy and psychomotor drive, self-confidence and well-being, elevate mood, heighten sensory awareness, and produce derealization and depersonalization. The major reinforcing effects appear to be increased responsiveness to emotions and a sense of closeness to others [13].

The alteration of perception initiated by MDMA use may be experienced as dysphorogenic, and MDMA-naïve subjects have reported anxiety, mild depersonalization or derealization, moderate thought disorder, and poor coordination. MDMA ingestion can trigger psychiatric disturbances, including depression, panic attacks, and persisting perception disorder ("flashbacks"). It has been proposed that these disturbances are more likely to emerge in individuals with a vulnerability to mental illness [2]. Experienced MDMA users taking the drug under controlled conditions have frequently reported impaired decision-making ability, difficulty in concentrating, and decreased mathematics performance [8].

Cases of acute psychosis have been associated with MDMA use, but many of these cases are attributable to polysubstance use. Impulsive, aggressive, or irrational behaviors may result from MDMA use. These effects may be related to MDMA use, to associated factors that increase the likelihood of impulsive behaviors in MDMA users, or concomitant drug use [8].

Subjective Experience

Following the initial sensations of a "rush," which may last 15 to 30 minutes, MDMA users experience a sudden clarity and intensity of perceptions, reportedly seeing objects as "brighter and crisper" and feeling inner happiness. At this point, many users ingest an additional dose to prolong these feelings. However, booster doses increase the tolerance to the desired effects and increase the unwanted effects of coming down. Thirty minutes to three hours after the initial onset of effects, a plateau phase is reached of less-intense feelings. During the plateau, repetitive or trance-like movements become highly pleasurable, conducive to the long-lasting ecstatic states of "trance dancing" occurring at raves. The "coming-down" phase occurs three to six hours after initial ingestion, characterized by feelings of disappointment and other negative emotions. Residual effects, such as depression, anxiety, and sluggishness may last for several days. Ability to fall asleep may take up to six to seven hours after cessation of effects, despite extreme physical exhaustion [4].

Many of the accessories associated with raves have special significance for MDMA users. Pacifiers and candy suckers are often used to avoid the bruxism associated with the drug. Fluorescent necklaces, bracelets, and other jewelry or clothing may be worn to augment the visual effects. Camphor oil inhalers or rubs may be directly inhaled, rubbed on the upper lip, or applied to the inside of a painter's or surgical mask in order to further enhance the sensory effects [1].

One of the most common reasons given for MDMA use is enhanced sexual drive. In one survey, 90% of users reported increased sexual desire and satisfaction, with orgasm delayed but more intense. However, up to 40% of men using MDMA can experience erectile dysfunction [19].

Physiologic Effects

MDMA causes sympathomimetic stimulation and increases in heart rate, blood pressure, systemic vascular resistance, and myocardial oxygen consumption. Adverse cardiovascular effects have included arrhythmias and severe hypotension, possibly due to catecholamine depletion or MDMA-induced autonomic dysregulation. The environment of MDMA ingestion can potentially contribute to the development of toxicity. Users in clubs, raves, or EDM events often dance for extended periods (i.e., eight hours or longer). Together with the ambient heat from an indoor event and pharmacologic properties of the drug, the risk of hyperthermia is greatly elevated. Subarachnoid hemorrhage, cerebral infarction, and seizure activity have been reported after MDMA ingestion, with several case reports linking seizures to severe hyponatremia resulting from the profound sweating coupled with incredibly large amounts of water consumption (water intoxication). Increased neuromuscular activity associated with MDMA use is associated with jaw clenching, teeth grinding, and vigorous dancing. The frequently occurring trismus and bruxism are likely mediated by serotonin activation of the 5HT1B receptors of the trigeminal motor nuclei. Profound hyperthermia is one of the most common severe toxic effects of MDMA use, a result of MDMA activity on the serotonergic pathway that mediates thermoregulation. MDMA abuse can also result in hepatitis and accelerated hepatic fibrosis. Several deaths associated with fulminant liver failure after MDMA consumption have been documented. In addition, acute renal failure has been documented, due to rhabdomyolysis and disseminated intravascular coagulation [8; 12; 17; 20].

Many somatic toxic events have been associated with MDMA use, including thrombotic or hemorrhagic strokes, leukoencephalopathy, myocardial infarction, arrhythmias, and pneumothorax. These events are attributable to either idiosyncratic responses or impurities from the manufacturing process [8].

Neuropsychologic Impairment

Like other amphetamines, MDMA stimulates neurotransmitter activity. Unlike other amphetamine-derived drugs, such as methamphetamine, MDMA causes greater release of serotonin than dopamine. By releasing large amounts of serotonin, MDMA use may result in the brain becoming significantly depleted of this neurotransmitter [13]. MDMA has been found to be neurotoxic to serotonin neurons in lower mammals, and the results of several studies suggest the potential for neurotoxicity in humans. Cerebrospinal fluid 5-hydroxyindoleacetic acid levels have been found to be reduced in MDMA users. *N*-acetyl aspartate (NAA), a marker of cellular health measured with magnetic resonance spectroscopy, has been found to be significantly reduced in the frontal cortex of MDMA users, but not in the parietal or occipital cortex. The severity of frontal cortical neuronal loss is correlated with the extent of previous MDMA use. Magnetic resonance imaging has revealed significant reductions in cortical gray volume in MDMA users. MDMA use is associated with a reduction of binding of the serotonin transporter-specific radioligand, as evidenced by single photon emission computed tomography (SPECT) imaging. Evidence exists that some of these effects are reversible with long-term abstinence from MDMA [8].

Heavy use of MDMA is correlated with greater self-report of depression, obsessive-compulsive behavior, anxiety, somatization, and loss of libido. MDMA users can also develop impairments in memory, attention, reasoning, impulse control, and sleep abnormalities with long-term use. In one prospective study of MDMA users, there was a progressive decline of both immediate and delayed recall with ongoing use [8]. Long-term exposure to

MDMA has resulted in cognitive impairment in both animals and humans, possibly secondary to decreases in the structural components of serotonergic neurons in the brain. Memory dysfunction may persist for more than one year despite recovery of serotonergic abnormalities as measured by SPECT. Concerns have also been raised about the possibility of long-lasting and potentially permanent memory impairment. 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 [1; 12].

TREATMENT

Patients admitted to the emergency department for MDMA toxicity typically present with agitation, anxiety, tachycardia, hypertension, or hyperthermia. There is no antidote for MDMA toxicity; treatment is limited to supportive care [9; 20].

MDMA intoxication requires rapid cooling in individuals with severe hyperthermia. Hyperthermia should be assessed by measuring core body temperature. Rapid cooling is a priority to prevent serious brain injury, hypotension, rhabdomyolysis, coagulopathy, and organ failure [20]. Treatment with fluids is also imperative to maintain renal perfusion and prevent the development of rhabdomyolysis [1; 9].

Agitation and anxiety are best treated with benzodiazepines. Diazepam and lorazepam are the drugs of choice to control MDMA-induced seizures, reduce blood pressure, and treat arrhythmias. In addition to treatment with benzodiazepines, physical restraints may be necessary if severe agitation or disruptive behavior persists [20]. If hypertension is severe, agents such as phentolamine, nitroprusside, labetalol, and nitroglycerin may be administered [20]. Nitroprusside may be required if anxiolytics do not control the hypertension, and beta-blockers may be used if sedation is inadequate [9]. Treatment of serotonin syndrome with dantrolene or cyproheptadine may be helpful, but aggressive supportive therapy with rapid-cooling measures is the mainstay of therapy [1; 20].

It is uncommon for individuals to seek treatment for MDMA abuse or dependence. Consequently, there are no clear guidelines for treatment, and there are no specific treatment recommendations for either helping curb MDMA abuse or countering its consequences. Nevertheless, patient education is essential in communicating the short- and long-term risks of MDMA use [20]. Exploring the use of paroxetine and the atypical antipsychotic drugs olanzapine and clozapine in human MDMA toxicity is indicated [8].

GAMMA HYDROXYBUTYRATE (GHB)

GHB is frequently imported from Europe, where it is considered Class C, similar to a U.S. Schedule IV drug; however, as of 2021, steps are being taken to reclassify GHB as a Class B drug [42]. Many Internet sites offer instructions for the home production of GHB or advertise the sale of kits that contain the ingredients necessary to produce the drug. The chemical precursors of GHB are gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD). GBL is found in household solvents. Following ingestion, GBL is rapidly converted to GHB by endogenous lactonase, and 1,4-BD is metabolized in the body by alcohol dehydrogenase to gamma-hydroxybutyraldehyde, which is in turn metabolized to GHB by aldehyde dehydrogenase. Both precursors became popular sources of the drug, with 1,4-BD available in health stores and both available on the Internet [21; 22]. However, GBL and BD are now considered controlled substance analogues [38].

GHB is a naturally occurring, short-chain fatty acid metabolite of gamma-aminobutyric acid (GABA). It acts as a CNS depressant and induces rapid eye movement (REM) sleep within 15 minutes. GHB was originally developed as an anesthesia agent during the 1950s. Its effectiveness was limited by the tendency to induce substantial nausea, vomiting, and seizures, and its use was discontinued because of suboptimal analgesic properties and the development of new, more effective anesthetic agents [23].

Use of GHB has also been suggested for the treatment of opiate withdrawal and fibromyalgia, and data on its use in the treatment of alcoholism suggest possible efficacy in suppressing alcohol withdrawal syndrome, increasing abstinence, and reducing alcohol craving. In this context, GHB appears to act as a substitute for alcohol, similar to the relationship between methadone and heroin. GHB also stabilizes nocturnal REM sleep, significantly improving narcoleptic symptoms with only a few mild adverse effects. In 2002, the FDA approved GHB for the treatment of cataplexy associated with narcolepsy [24].

The non-medical use of GHB in the United States began in the 1990s, when GHB was introduced as a dietary supplement. Its manufacturers claimed that the drug could increase muscle mass, metabolize fat, and increase libido. It shortly began to be used in weight control management, and its purported anabolic properties and associated muscle growth made it a popular drug with body builders. GHB also began to be used recreationally to achieve euphoria, alleviate anxiety, increase relaxation, and enhance libido [2].

GHB is available as a clear liquid, white powder, tablet, or capsule and can be made in private residences with ingredients and recipes obtained on the Internet.

PHARMACOLOGY

GHB is present endogenously in the CNS in concentrations 1/1000th that of gamma-aminobutyric acid (GABA) and is believed to mediate sleep cycles, body temperature, cerebral glucose metabolism, and memory [1]. GHB is a metabolite of GABA, and although lacking an affinity to GABA-A receptors, it does bind noncompetitively to GABA-B when supraphysiologic amounts are ingested. There also exists high- and low-affinity GHB receptor sites that are highly specific for GHB and whose distribution differs from GABA receptors. These receptors are found in highest concentration in the hippocampus, cortex, and dopaminergic areas (striatum, olfactory tracts, and substantia nigra) [2].

GHB increases brain dopamine, serotonin, and acetylcholine and interacts with the opioid system. It is involved in the regulation of GABA, serotonin, and acetylcholine. GHB also disinhibits dopamine release and activates tyrosine hydroxylase, which together act to increase the central dopamine levels associated with the reinforcing effects of GHB [2].

PHARMACOKINETICS

GHB's lipophilic properties facilitate rapid oral, intravenous, and intraperitoneal absorption and effective penetration of the blood-brain barrier [1]. Peak plasma concentration of GHB occurs 20 to 60 minutes after ingestion. Effects of GHB occur within 10 to 30 minutes of ingestion and have a duration of three to six hours, depending on the dose [1]. GHB exhibits nonlinear elimination kinetics, with its half-life increasing with the dose. GHB is metabolized into carbon dioxide and water, without residue of toxic metabolites, making detection difficult. Most GHB is excreted during the first hours after ingestion. Urinalysis must be done within 12 hours to increase the likelihood of detection. There is no available blood toxicology screen for GHB. The toxic effects of GHB are potentiated by alcohol, opiates, barbiturates, and benzodiazepines. GHB use, alone and in combination with other substances, has resulted in fatalities [17].

CLINICAL EFFECTS

The desired effect of GHB is a euphoric, trance-like state that mimics physiologic sleep. It is also used to achieve an intoxicated state similar to alcohol intoxication. At toxic levels, memory impairment, confusion, loss of inhibition, seizures, dizziness, extreme drowsiness, stupor, nausea, and visual disturbances can occur. The CNS depressant effects of GHB are enhanced by alcohol, making the combination especially dangerous [17]. Other adverse effects related to GHB use include loss of consciousness or coma, tremors, agitation, seizure-like activity, amnesia, gastrointestinal symptoms

(vomiting, bladder and bowel incontinence), CNS and respiratory depression, vertigo/dizziness, confusion, hallucinations, bradycardia, and decreased respiration [2].

There can be a very small margin between the dose of GHB needed to achieve the desired effect and the amount that can induce coma. Bradycardia occurs in 30% to 35% of patients and seems to be correlated with the level of consciousness. With no known antidote for GHB overdose, treatment consists of nonspecific supportive care that may include airway maintenance with intubation and ventilation [25]. Failure to seek medical help contributes to the number of GHB-related deaths. Although overdose can occur quickly, most adverse symptoms resolve within a few hours [17].

Severe dependence can develop in chronic abusers. Addiction to GHB is characterized by progressive dose escalation and craving for the drug. Dependence is reflected by the use of excessively large doses, increased frequency of use, and continued use despite adverse effects [1].

TREATMENT

Treatment of Toxicity

As with MDMA, there is no antidote for GHB toxicity, and treatment is limited to supportive care. In patients with severe GHB intoxication, maintaining airway patency with intubation, if necessary, is the most important intervention. Because GHB can cause a rapid loss of consciousness, gastric lavage and induction of emesis are contraindicated. Symptomatic bradycardia can be managed with atropine, and seizures respond effectively to benzodiazepines [1; 25]. Withdrawal symptoms are best managed with anxiolytics [9].

Treatment of Withdrawal

Ingestion of high-dose GHB over extended periods of time can lead to withdrawal symptoms when the user abruptly stops taking the drug or tries to substantially cut back. Due to the pharmacokinetics of GHB, there is significant overlap in what appear to be adverse symptoms due to acute effects and withdrawal symptoms. Symptoms initially mistaken as adverse effects may actually be symptoms of withdrawal [2].

Withdrawal symptoms can last for several days and may require medical intervention [25]. Reports of GHB withdrawal indicate that the syndrome begins with milder symptoms, such as insomnia, tremor, anxiety, increased heart rate, confusion, nausea, and vomiting. Approximately two to three days following the last dose, symptoms become more severe and include mild autonomic instability, such as increased heart rate, hypertension, tremor, and profuse perspiration, as well as hallucinations, paranoia, anxiety, confusion, disorientation, and delirium with agitation. The duration of GHB withdrawal is 3 to 15 days, and at least one fatality has been reported [2; 25].

Treatment for GHB withdrawal is not well defined. Baclofen is being investigated for relapse prevention, and pharmaceutical GHB is being investigated for detoxification of patients with GHB dependence [26; 27]. For mild symptoms, management may consist of high doses of short-acting benzodiazepines such as lorazepam and trazodone to induce sleep. More severe symptoms may necessitate the addition of barbiturates and high-dose, short-acting benzodiazepines as well as a mood stabilizer, such as gabapentin, and a low-dose antipsychotic medication. Restraints may be necessary to protect the patient and medical staff [2].

KETAMINE

Ketamine is a phencyclidine (PCP) derivative with a combination of sedative, anesthetic, amnesiac, and analgesic properties. Ketamine has one-tenth the potency of PCP and a considerably briefer duration of action. This drug is used for medicinal and veterinary purposes when CNS dissociation is desired. Illicitly, it appears as a white powder that is snorted, taken orally, injected intravenously or intramuscularly, or smoked. Users of ketamine are attracted to the hallucinogenic effects, described as an "out-of-body experience" similar to that produced by LSD and PCP [28].

Ketamine is difficult to manufacture. Roughly 90% of legal ketamine use occurs in veterinary settings, and most illicit ketamine is acquired through diversion of the pharmaceutical product, usually of veterinary origin [2].

PHARMACOLOGY

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that binds to the same NMDA receptor site as PCP. Inhibition of excitatory amino acid neurotransmission mediated by NMDA receptors through calcium channel blockade is associated with the altered perception, memory, and cognition seen with this drug. NMDA blockade is also linked with increased dopamine release in the prefrontal cortex and midbrain. Additional pharmacologic action of ketamine-induced NMDA blockade includes activation of serotonin systems, particularly serotonin 1A receptors. Ketamine also inhibits the reuptake of serotonin, dopamine, and norepinephrine [2].

CLINICAL EFFECTS

Low doses of ketamine are associated with feelings of relaxation, while higher doses can produce dreamlike states, hallucinations, visual distortions, and unpleasant sensations of near-death experience. Some common effects of ketamine use are delirium, amnesia, and depression. Adverse effects include nausea, immobility, abnormally low body temperature, anxiety, dissociation, depression, recurrent flashbacks, impaired attention, learning disability, and symptoms of schizophrenia. Cognitive dysfunction related to attention, learning, and memory can result from chronic abuse [2].

PHYSIOLOGIC EFFECTS

Ketamine increases cerebral blood flow and intracranial pressure, heart rate, and blood pressure, impairs motor function, and depresses respiratory function. It can slightly enhance laryngeal reflexes, increase salivary and tracheobronchial secretions, increase muscle tone, and cause bronchodilation. At high doses, respiratory arrest can occur. Cardiovascular toxicity may develop from reflex sympathetic activation, manifesting as hypertension, tachycardia, and palpitations [17]. The effects of ketamine can be influenced by the setting. Noisy or rowdy surroundings have sometimes been correlated with negative effects [1].

TREATMENT

Because no antidote exists for ketamine intoxication, supportive care with special attention to respiratory and cardiac function forms the basis of management. Intramuscular diazepam or midazolam should be considered for patients requiring sedation [1; 29].

To date, no treatment modalities specifically tailored to ketamine abuse or dependence have been published in peer-reviewed literature.

FLUNITRAZEPAM

Flunitrazepam is a member of the benzodiazepine class of anxiolytics and hypnotics [30]. It has been a widely prescribed sleep aid throughout the world and is approved for therapeutic use in Latin America, Europe, Asia, and Australia for treating insomnia and as a presurgical anesthetic. Although not manufactured or approved for medical use in the United States, flunitrazepam is smuggled into the country from Mexico [17; 30].

Misuse of flunitrazepam began in Europe in the 1970s and in the United States in the 1990s [30]. Flunitrazepam is believed to have a higher abuse liability than other benzodiazepines, possibly due to its faster onset, longer duration of action, and stronger effects at lower doses [2].

Flunitrazepam acquired in the United States is usually purchased or imported from countries where it is legally sold, including Mexico [30]. It is often referred to by brand or slang names, such as Rohypnol or "roofies" [31].

PHARMACOLOGY

Similar to other benzodiazepines, flunitrazepam is a GABA agonist. Through binding to the GABA receptor, flunitrazepam opens neuronal chloride channels, leading to an influx of chloride and hyperpolarization of the cell, decreasing the excitability of the cell. The ensuing clinical effects include sedation, anticonvulsant activity, and anxiety reduction [2; 30].

Flunitrazepam is ingested orally. The effects are experienced within 30 minutes, peak within 1 to 2 hours, and continue for an average of 8 to 10 hours. The drug has a half-life of 19 to 23 hours [17].

CLINICAL EFFECTS

Flunitrazepam is used illicitly to achieve a feeling of relaxation similar to alcohol intoxication, reduce anxiety, increase comfort in social situations, and induce euphoria. It is sometimes combined with heroin to augment the opiate effect and to decrease opiate withdrawal symptoms. Flunitrazepam may also be used to enhance the effects of other substances, including alcohol and cannabis, and to lessen the adverse stimulant effects of cocaine [2; 30]. Other possible effects of flunitrazepam use include sedation, dizziness, memory impairment, impairment of cognitive and psychomotor tasks, decreased coordination, muscle relaxation, decreased blood pressure, slurred speech, impaired judgment, amnesia, loss of inhibitions, loss of consciousness, visual disturbances, nausea, gastrointestinal disturbances, and urinary retention [17; 30].

Prolonged use of flunitrazepam can result in physical dependence, and withdrawal symptoms can develop when the user stops or dramatically cuts back [30]. Withdrawal symptoms can include headache, tension, anxiety, restlessness, muscle pain, sensitivity to light, numbness, tingling of extremities, or seizures. Overdoses can lead to loss of consciousness and respiratory depression, which is potentially life threatening [30]. In cases of overdose or serious toxicity, flumazenil, a specific benzodiazepine antagonist, can be administered to reverse the effects [2].

TREATMENT

Flunitrazepam, as a benzodiazepine, is the only club drug with a known antidote. Flumazenil reverses the effects but must be used with caution in patients with polydrug ingestion because seizures and cardiac arrhythmias can be precipitated [9].

As previously noted, no recommendations or guidelines exist for the treatment of club drug dependence. However, participation in a 12-step program may be advocated for those dependent on the drug.

CLUB DRUGS AND FACILITATION OF SEXUAL ASSAULT

Several club drugs have been implicated for use in sexual assault because victims have difficulty resisting the attack due to the profoundly sedating and intoxicating drug effects. GHB has effects that are similar to alcohol, and a combination of alcohol and GHB puts a potential victim at heightened risk of loss of consciousness. Flunitrazepam causes similar symptoms. Due to its anterograde amnestic effects (inability to recall events taking place while under the influence of the drug), flunitrazepam is more commonly used in drug-induced sexual assault [2; 9]. The memory problems associated with both drugs and the fact that GHB clears from the body within 12 hours make detection difficult and increase the complexity of attempts to prosecute perpetrators utilizing these drugs [22]. In addition to GHB and flunitrazepam, ketamine is being used increasingly as a "date rape drug" due to its dissociative effect [17].

To combat its use in the facilitation of sexual assault, the manufacturer has reformulated flunitrazepam so that it releases blue dye when added to liquid [17; 30]. It is also recommended that facilities and law enforcement agencies establish guidelines for obtaining urinalysis samples for victims of sexual assault to determine if the act was club drug-mediated [32]. Other screening modalities for club drug exposure, including capillary electrophoresis, have been studied and may be useful [33]. Healthcare professionals should consider club drug-mediated assault whenever patients are amnestic regarding the details of the assault.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The British Association for Sexual Health and HIV recommends that clinicians be aware of the short detection times of substances that may be used in drug-facilitated sexual assaults. Blood and urine samples should be collected within three and four days, respectively.

(https://www.bashhguidelines.org/media/1079/4450.pdf. Last accessed December 16, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because specific details about the patient's history are crucial to diagnosing club drug toxicity, effective communication is required. Communicating effectively is more challenging when the patient's primary language differs from that of the practitioner. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

Depending upon the patient's language, an interpreter may be difficult to locate. Or, an organization may not have the funds to bring in an interpreter. Also, bringing in an interpreter creates a triangular relationship with a host of communication dynamics that must be negotiated [34]. Many view interpreters merely as neutral individuals who communicate information back and forth. However, another perspective is that the interpreter is an active agent, negotiating between two cultures and assisting in promoting culturally competent communication and practice [35]. In this more active role, the interpreter's behavior is also influenced by a host of cultural variables such as

gender, class, religion, educational differences, and power/authority perceptions of the patient [35]. Consequently, an intricate, triangular relationship develops between all three parties. Another factor affecting the communication process is that many interpreters are not adequately trained in the art of interpretation in mental health and general health settings, as there are many technical and unfamiliar terms. An ideal interpreter goes beyond being merely proficient in the needed language/dialect [36]. Interpreters who are professionally trained have covered aspects of ethics, impartiality, accuracy, and completeness [37]. They are also well-versed in interpreting both the overt and latent content of information without changing any meanings and without interjecting their own biases and opinions [37]. Furthermore, knowledge about cross-cultural communication and all the subtle nuances of the dynamics of communicating in a mental health or general health setting is vital [36].

Interpreters can be a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter.

CONCLUSION

Although club drugs are often used in party or social settings to enhance experiences of the environment, extended use can result in many untoward effects. Because the acute and long-term effects of club drug use may be similar to other medical or mental health conditions, obtaining an accurate patient history is vital to diagnosing and treating club drug-associated problems. In addition to their use recreationally, some club drugs have been used to facilitate sexual assault. Therefore, healthcare professionals in many practice settings will encounter patients who have, either willingly or unwillingly, ingested club drugs. It is vital that when confronted with these patients, healthcare professionals have a clear understanding of the clinical effects, available treatments, and available referral services.

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