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A Brief Overview of the Clinical Pharmacology of "Club Drugs"

GENA COVELL BRITT AND ELINORE F. McCANCE-KATZ

Division of Addiction Psychiatry, Virginia Commonwealth University, Richmond, Virginia, USA

Four different "c1uh drugs" are reviewed: MDMA (methylenedioxymethamphetamine, "Ecstasy"), GHB (gamma-hydroxyhutyrate), ketamine, and ROhypnol® (jiuni trazepam). The neurohiology, clinical pharmacology, and treatment issuesfor each are discussed.

Keywords club drugs; raves; MDMA; GHB; ketamine; Rohypnol®

Introduction

The term "club drugs" refers to a group of drugs used primarily by young adults often at all night dance parties called "raves" that take place in nightclubs. The U.S. Office of National Drug Control Policy (ONDCP, 2004a) identifies four specific club drugs: MDMA (methylenedioxymethamphetamine, "Ecstasy"), GHB (gamma-hydroxybutyrate), ketamine, and Rohypnol®(flunitrazepam). Although an argument could be made to include substances such as methamphetamine and LSD, these were not included for a couple of reasons. For one, they are inconsistently included in the category of club drugs. In addition, they have a longer history of misuse and a correspondingly larger literature, making them qualitatively different from the substances included in this review. This review will describe the clinical pharmacology of the stated club drugs including their origins, neurobiology, therapeutic and illicit uses, acute and chronic effects, and treatment for overdose and withdrawal.

Many published reports consist of case reports and retrospective investigations. Reported drug effects vary widely between subjects. Complete histories are not always available, including concomitant use of other substances that could interact with the substance of interest. Published reports on these drugs are generally not rigorous, well-controlled studies with control groups; differences reported could be due to pre-existing differences, making it difficult to draw strong conclusions.

These drugs differ in their dependence liability as well as in issues related to toxicity. Because of such differences, the treatments discussed for each substance differ in approach. For instance, MDMA and ketamine are not associated with a physical dependence, but there is an associated toxicity for each and the literature therefore focuses on treatments for the toxic effects. GHB, on the other hand, does produce dependence, and the treatment literature for it relate to treating withdrawal syndromes. Although Rohypnol® also produces

Address correspondence to Gena Covell Britt, Ph.D., Division of Addiction Psychiatry, Virginia Commonwealth University, Box 980109, Richmond, VA 23219, USA. E-mail: gcbritt@vcu.edu

Table 1
Summary of club drugs

	MDMA	GHB	Ketamine	Rohypnol®
Street names	Ecstasy, XTC, X, E, Adam, Clarity, and Lover's Speed	Liquid Ecstasy, Scoop, Easy Lay, Georgia Home Boy, Grievous Bodily Harm, Liquid X, and Goop	K, Special K, Cat Valium	Roofies, Rophies, Roche, Forget-me Pill, Circles, Mexican Valium, Rib, Roach-2, Roopies, Rope, Ropies, Ruffies, Roaches
Manner of use	Tablet or capsule; typically ingested orally; can also be crushed and snorted or dissolved and injected	Liquid; often mixed with alcohol, which amplifies its effects	Liquid—injected, added to items to be smoked. Powder—dissolved in drinks, smoked, snorted, or dissolved and injected	Tablet; typically ingested orally; can be crushed and snorted. Easily dissolved in beverages
Therapeutic uses	Therapeutic benefits not strongly supported	To treat cataplexy associated with narcolepsy	Veterinary anesthetic	To treat insomnia and as a presurgery anesthetic
Clinical effects	Depression, feelings of empathy, energy, psychomotor drive, self-confidence, well being, positive mood, heightened sensory awareness	Euphoria, anxiety reduction, increases relaxation, enhances libido, effects similar to alcohol	Relaxation, dream-like states, hallucinations, visual distortions, sensation of near-death experience	Euphoria, anxiety reduction, increased comfort in social situations
Toxic effects	Anxiety, thought disorder/psychosis, bruxism, difficulty concentrating, disturbance of balance, hypertension, hyperthermia, liver toxicity, neurological toxicity	Sleep induction, unconsciousness tremors, agitation, gastrointestinal symptoms, CNS and respiratory depression, dizziness, confusion, hallucinations, bradycardia	Increased heart rate, hypertension, cognitive and psychomotor impairment, respiratory depression, nausea, immobility, anxiety, dissociation, depression, recurrent flashbacks, delirium, schizophrenic symptoms	Decreased body temperature and blood pressure, sedation, cognitive and psychomotor impairment, visual disturbances, dizziness, confusion, gastrointestinal disturbances, urinary retention
Systems affected	Serotonin, noradrenergic, dopaminergic, cholinergic	Dopaminergic, cortical, hippocampal	Serotonin, dopamine, norepinephrine, calcium channels	Chloride channels
Dependence liability	No dependence syndrome	Can produce physical dependence	No dependence syndrome	Can produce physical dependence
Long-term sequelae	Possible: cognitive deficiencies, brain neurotoxicity	Unknown	Cognitive difficulties (attention, learning, memory)	Unknown. Likely similar to other benzodiazeines: depression, memory loss, mental confusion, stomach disorders, aggressive behavior

dependence, the literature focuses on treatment of toxicity. It is important to bear these differences in mind while reading the sections on treatment for each of these drugs.

This review will briefly summarize available up-to-date literature related to humans. Information is summarized in Table I.

MDMA

Commonly referred to as MDMA, the chemical compound 3,4-methylenedioxymethamphetamine is often referred to on the street with names such as "Ecstasy," "XTC," "X," "E," "Adam," "Clarity," and "Lover's Speed," and usually comes in tablet or capsule form (DEA, 2004a; NIDA, 2003). Most of the MDMA in the United States is trafficked from Europe.

Neurobiology

MDMA is typically ingested orally in tablet form, although it can also be crushed in order to snort or dissolved in order to inject (DEA, 2004a). MDMA has multiple effects on central neurotransmitter systems. However, its principle effects are on the serotonin system where it is an indirect serotonin agonist. MDMA inhibits tryptophan hydroxylase, which decreases serotonin production (Bialer, 2002). It induces the release of serotonin and also blocks serotonin re-uptake. These effects are thought to be related to the observed depression, anorexia, agitation, and marked feelings of empathy reported in association with use of the drug. Because MDMA depletes serotonin stores in neurons, subsequent doses produce diminished euphoria and increase adverse effects such as depression and agitation. In addition to its effects on serotonin neurotransmission, MDMA has also been shown to affect the noradrenergic, dopaminergic, and cholinergic neurotransmitter systems (DEA, 2004a; Koesters, Rogers, and Rajasingham, 2002; Smith, Larive, and Romanelli, 2002).

Clinical Pharmacology

In the 1970s and 1980s, MDMA was thought to be a useful adjunct to psychotherapy due to the altered state of consciousness it produced (Greer and Tolbert, 1998). The DEA performed emergency scheduling of MDMA as a Schedule I substance on July I, 1985, effectively making it illegal. After further considering the available evidence regarding MDMA, the DEA recommended on May 22, 1986 that it be placed in Schedule III (U.S. Dept. of Justice, 1986). It was then deleted from Schedule I on January 27, 1988 (U.S. Dept. of Justice, 1988a), and was then put back in Schedule I effective March 23,1988 (U.S. Dept. of Justice, 1988b). Although the scientific literature does not strongly support the therapeutic benefits of MDMA, the Multidisciplinary Association for Psychedelic Studies (MAPS), a nonprofit research and educational organization, is currently supporting the progression of research to investigate the effectiveness of MDMA as a therapeutic adjunct to psychotherapy (MAPS, 2004).

MDMA has been shown to increase energy and psychomotor drive, self-confidence, and well-being, and to produce a positive mood, heightened sensory awareness (such as intensified perceptions), derealization, depersonalization, and to increase responsiveness to emotions and sense of closeness to others (Liechti et aI., 2000; Vollenweider et aI., 1998).

Adverse effects include anxiety and thought disorder, jaw clenching (bruxism), lack of appetite, difficulty concentrating, disturbance of balance, and an increase in blood pressure. In a study of MDMA administration, some of these effects were still reported by some

subjects after 24 hours (Vollenweider et aI., 1998). In addition, Klitzman, Pope, and Hudson (2000) found a relationship between MDMA use (but not use of other drugs) and high-risk sexual behavior (unprotected anal intercourse) among homosexual and bisexual men attending New York City dance clubs. A stronger association was found between frequent (at least monthly) MDMA use and high-risk sexual behavior compared to less frequent use. Authors noted that pre-existing differences in risk taking might account for the finding.

More severe effects related to MDMA have also been reported (O'Connor, 1994). At least nine deaths related to hyperthermia have been noted, occurring after ingestion of MDMA along with extended episodes of heightened physical activity in the absence of adequate hydration and ventilation. These cases involved seizures, tachyarrhythmias, hypertension, diaphoresis, and pupillary dilation. In addition, body temperatures ranged from I04-1 10°F, which was associated with a variety of complications including kidney failure and death. Evidence of possible liver toxicity is also suggested as another severe outcome related to MDMA use, with reported cases of liver failure, as well as need for liver transplantation, although it cannot be determined if MDMA was the root cause or whether the outcome is the result of another associated factor or a combination of factors. Cases have also been reported of damage to the neurological system including cerebral infarctions and hemorrhage, accompanied by neurological impairment. MDMA ingestion has also been implicated in the experience of psychiatric disturbances such as depression, panic attacks, and flashbacks of hallucinations. It is likely that these disturbances emerge in individuals who are already "at-risk" for mental illness; however, it has been suggested that because MDMA has demonstrated neurotoxicity it might actually be able to induce chronic psychosis in the absence of such individual risk.

Long-term sequelae related to MDMA use have also been investigated. When individuals who used MDMA and cannabis were compared to cannabis-only users, the only differences that emerged were on two of the 18 tasks compared. However, when both drug-using groups were combined and compared to a group of nonusers, the nonusers performed better on eight of the 18 tasks. The fact that the MDMA/cannabis group did not perform more poorly than the cannabis group suggests that the cognitive deficiencies that have been reported among MDMA users are not due to MDMA use. Further analyses suggested that the observed cognitive deficits were more closely related to cannabis use than to MDMA use. It is notable that this study had a small sample size (31 nonusers, 30 users) and performed many statistical comparisons without correction for multiple comparisons. In addition, as the authors note, the differences could be due to naturally occurring differences between drug users and nonusers (Croft et aI., 2001). Long-term use of MDMA has been related to brain neurotoxicity (lower density of serotonin transporter sites) even after periods of abstinence, although the authors caution against conclusions regarding reversibility and permanence (McCann et aI., 1998; Ricaurte et aI., 2000).

Treatment

O'Connor (1994) discusses treatment of complications related to MDMA ingestion. Temperature reduction is one of the first procedures recommended, as extremely high temperatures have been implicated in several MDMA-related deaths. Other interventions related to hyperthermic syndrome include supportive care such as making certain the airway is clear, that there is adequate ventilation, and that cardiac output is maintained. Agitation and seizures can be treated with diazepam; chlorpromazine is not recommended since it might decrease the seizure threshold. Other supportive measures recommended include use

of activated charcoal to minimize absorption of the drug and emergent emptying of gastric contents. Referral to an intensive care unit may need to be considered for monitoring and ventilation.

GHB

GHB (gamma-hydroxybutyrate) 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 (DEA, 2004b; NIDA, 2003). Typically it is ingested in liquid form and often mixed with alcohol, which amplifies its effects (DEA, 2004a; NIDA, 2003). Street names include "Liquid Ecstasy," "Scoop," "Easy Lay," "Georgia Home Boy," "Grievous Bodily Harm," "Liquid X," and "Goop" (DEA, 2004a, b).

Neurobiology

GHB occurs naturally in the brain and has been suggested to possibly be a neurotransmitter. Structurally, it is related to GABA (gamma-amino butyric acid) and is a metabolite of GABA. Although it does not bind to $GABA_A$ receptors, it does bind noncompetitively to GABAsbut only when present in amounts larger than occur naturally. In addition, there are also high- and low-affinity GHB receptor sites that are highly specific for GHB and whose distribution differs from GABA receptors. The highest density of these receptors is in the hippocampus, cortex, and dopaminergic areas (striatum, olfactory tracts, and substantia nigra). GHB inhibits dopamine release and activates tyrosine hydroxylase, that together act to increase central dopamine levels (Galloway et aI., 2000), which could be associated with the reinforcing effects of GHB.

Clinical Pharmacology

GHB was suggested for medical use in anesthesia, obstetrics, and psychiatry (including possible use for alcohol and narcotic withdrawal symptoms) in the 1960s (Laborit, 1964). More recently, its use for the treatment of opiate withdrawal has continued (Gallimberti et aI., 1993), as well as investigations for the treatment of fibromyalgia (Scharf et aI., 1998). Research for its use in the treatment of alcoholism suggests possible efficacy to suppress alcohol withdrawal syndrome (Gallimberti et aI., 1989), increase the number of days of abstinence, reduce number of daily drinks, and reduce craving for alcohol. It appears to act as a substitute for alcohol, similar to the relationship between methadone and heroin. The dose typically used in these studies is 3.5 g per day, sometimes taken in divided doses throughout the day. Although the research results are thought to be encouraging, it has not been approved for use in the treatment of alcohol dependence (Addolorato et aI., 2000). Investigations as a treatment for narcolepsy found that it stabilized nocturnal sleep and thereby significantly improved narcoleptic symptoms with only a few, mild, adverse effects (Lammers et aI., 1993). In July 2002 the FDA approved it under the trade name Xyrem® as a Schedule III Controlled Substance to treat the cataplexy associated with narcolepsy (FDA, 2002). The manufacturers of Xyrem® recommend a starting dose of 2.25 g taken twice during the night (Orphan Medical, 2004). GHB is misused at doses ranging from 2.5-30 g (Addolorato et aI., 2000).

By the 1990s, GHB was being marketed for illicit use in weight control management [Bialer, 2002; Centers for Disease Control (CDC), 1990; Rome, 2001; Smith, Larive, and Romanelli, 2002] and its purported anabolic properties and associated muscle growth (DEA, 2004b) that made it a popular drug with body builders (DEA, 2004a; Dyer, 1991; Galloway

et aI., 1997; Steele and Watson, 1995). Aside from its use as a nutritional supplement and for bodybuilding use, it is misused to achieve euphoria (DEA, 2004b; Galloway et aI., 1997) as well as for effects similar to alcohol (Friedman, Westlake, and Furman, 1996; Galloway et aI., 1997; Steele and Watson, 1995), and to alleviate anxiety, increase relaxation, and enhance libido (Galloway et aI., 1997; NIDA, 2003). In addition, GHB has been implicated for its use in association with sexual assault because victims have difficulty resisting the assault due to the level of intoxication produced. The associated memory problems and the fact that it clears from the body quickly (within 12 hours) make detection difficult and increase the complexity of attempts to prosecute (U.S. Department of Justice, 2002; DEA, 2004a, b; NIDA, 2003).

Adverse effects related to GHB include drowsiness/sleep induction, loss of consciousness/coma, tremors, agitation, seizure-like activity, gastrointestinal symptoms (vomiting, bladder, and bowel incontinence), CNS and respiratory depression, vertigo/dizziness, confusion, hallucinations, bradycardia, and decreased respiration (CDC, 1990; Dyer, 1991; Friedman, Westlake, and Furman, 1996; Galloway et aI., 1997; Ingels et aI., 2000; Li Stokes and Woeckener, 1998; Sporer et aI., 2003; Steele and Watson, 1995). Due to its depressant effects, overdose can occur quickly and has been associated with deaths (NIDA, 2003). In fact, the DEA has documented at least 71 GHB-related deaths (2004a). However, generally most adverse symptoms resolved within a few hours (CDC, 1990; Craig et aI., 1999; Ingels et aI., 2000; Sporer et aI., 2003; Steele and Watson, 1995), although some report effects for 4 days (CDC, 1990; Friedman, Westlake, and Furman, 1996) and two reports note dizziness for up to 14 days (Dyer, 1991; Steele and Watson, 1995). It is important to note that most of these cases became known because of the need for emergency care related to toxicity.

Before discussing withdrawal from GHB, it is important to note that there is a fair amount of overlap in what appear to be adverse symptoms due to acute effects, and withdrawal symptoms (which are related to dependence and reportedly take longer to resolve). As such, it is possible that some of the symptoms reported to be adverse effects that take longer to resolve might actually be withdrawal symptoms. Dependence on GHB has been described as developing after regular use-every 2 hours around the clock-for 2 months to 4 years (McDaniel and Miotto, 2001).

In general, withdrawal symptoms include insomnia, muscular cramping, tremor, perspiration, anxiety, and feelings of doom (Craig et aI., 1999; Galloway et aI., 1997). Withdrawal from higher doses includes bowellbladder incontinence and blackouts (Galloway et aI., 1997). Withdrawal can last for several days, sometimes requiring medical intervention (discussed below). Some reports have characterized withdrawal as occurring in phases. The first few hours (2-12 hours after last dose) of withdrawal from GHB consists of milder symptoms such as insomnia, tremor, anxiety, increased heart rate, confusion, nausea, and vomiting. Beginning 2-3 days after the last dose, symptoms become more severe and include mild autonomic instability such as increased heart rate, hypertension, tremor, and profuse perspiration. In addition, hallucinations, paranoia, anxiety, confusion, disorientation, and delirium with agitation have been noted. Withdrawal purportedly lasts from 3-15 days, and one case resulting in death has been reported. In general, these cases included ingestion of high doses of GHB over extended periods of time (Dyer, Roth, and Hyma, 200 I; McDaniel and Miotto, 2001).

Treatment

Treatment for withdrawal from GHB is not well defined, and studies are needed to better describe the use of medications in treating GHB withdrawal (Freese, Miotto, and Reback,

2002). A variety of different approaches were tried in the reports documenting treatment of withdrawal syndromes as discussed above. McDaniel and Miotto (2001) provide a good summary of treatment suggestions, including high doses of short-acting benzodiazepines (such as lorazepam and trazadone) for mild symptoms to induce sleep. For more severe symptoms they suggest adding barbiturates and high-dose, short-acting benzodiazepines, along with a mood stabilizer (such as gabapentin) and low-dose antipsychotic medications. In addition, restraints can be used for protection of the patient and medical staff (Dyer et aI., 2001; Li, Stokes, and Woeckener, 1998; McDaniel and Miotto, 2001).

Ketamine

A liquid that can be injected, ketamine can also be added to items to be smoked. By allowing the liquid to evaporate, a powder is produced that can be dissolved in drinks, smoked, snorted, or dissolved and injected (DEA, 2004b; NIDA, 2003). Street names include "K," "Special K," and "Cat Valium" (DEA, 2004b).

Neurobiology

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist. It binds to the same NMDA receptor site as PCP located in the calcium channel leading to a blockade in calcium flow through these channels. Decreased excitatory amino acid neurotransmission mediated by NMDA receptors through calcium channel blockade has been associated with altered perception, memory, and cognition (Cotman and Monaghan, 1987). NMDA blockade is associated with increased dopamine release in prefrontal cortex and midbrain. NMDA blockade resulting from ketamine binding has also been linked to activation of serotonin systems, particularly serotonin IA receptors. It has also been suggested that ketamine, through its binding to the NMDA receptor, can inhibit the reuptake of serotonin, dopamine, and norepinephrine, although the mechanism underlying this action is not entirely clear (Smith, Larive, and Romanelli, 2002).

Clinical Pharmacology

Ketamine has been used as an approved anesthetic for both humans and animals since the 1970s, with most (90%) of legal ketamine use occurring in veterinary settings (NIDA, 2003; Rome, 2001). The nonmedical use of ketamine (ketamine hydrochloride) became popular in the 1980s (NIDA, 2003). Koesters, Rogers, and Rajasingham (2002) briefly reviewed reports of the uses of ketamine for human anesthesia, indicating that its use was associated with hallucinations after waking up, which led to discontinuation of ketamine as an anesthetic agent in humans. Recently there has been renewed interest in its use as an anesthetic agent in brief painful procedures. Ketamine has also been noted to cause few and milder adverse events in pediatric patients.

When misused, low doses are associated with feelings of relaxation called "K-Iand," while higher doses can produce dreamlike states, hallucinations, visual distortions, and sensation of near-death experience called a "K-hole" (DEA, 2004b; NIDA, 2003; Rome, 2001). Its use has also been associated with unintentional injuries that can occur because the user is insensitive to pain (Rome, 2001). In addition it has been associated with sexual assault because of its dissociative effect in humans (DEA, 2004b).

Acute adverse effects include increased heart rate, hypertension, impairment of motor functioning, respiratory depression, nausea, immobility that leads to abnormally low body

temperature, anxiety, dissociation, depression, recurrent flashbacks, delirium (confusion disordered speech, hallucinations), amnesia, impaired attention, learning disability, and symptoms of schizophrenia (Bourke, Malit, and Smith, 1987; DEA, 2004b; Harris et aI., 1975; Krystal et aI., 1994; NIDA, 2003; Perel and Davidson, 1976; Rome, 2001; Weiner et aI., 2000). Effects due to chronic misuse include cognitive difficulties in areas such as attention, learning, and memory (DEA, 2004b).

Treatment

Acute symptoms appear to often resolve without intervention. In half the cases seeking medical attention that were reviewed by Weiner et al. (2000), symptoms had resolved prior to arriving at the emergency department. Among those who were still symptomatic, tachycardia and agitation were the predominant findings. Treatment consisted of supportive care, benzodiazepines for agitation, and activated charcoal.

Rohypnol®

Rohypnol® comes in pill form and is typically taken orally, although reports of it being ground and snorted are also available (NIDA, 2003). Street names include "Roofies," "Rophies," "Roche," "Forget-me Pill," "Circles," "Mexican Valium," "Rib," "Roach-2," "Roopies," "Rope," "Ropies," "Ruffies," and "Roaches" (DEA, 2004b).

Neurobiology

Similar to other benzodiazepines, flunitrazepam is a GAB A (gamma-aminobutyric-acid) agonist. As such, it mediates inhibitory neurotransmission in the brain and spinal cord (Mattila and Larni, 1980). Benzodiazepines bind to the GABA receptor, opening the chloride channels of neurons and resulting in an influx of chloride and hyperpolarization of the cell. This decreases the excitability of the cell. The clinical effects of benzodiazepines include sedation, anticonvulsant activity, and anxiety reduction.

Clinical Pharmacology

Rohypnol® (flunitrazepam) is a sedative/hypnotic benzodiazepine that is approved for therapeutic use in Latin America, Europe, Asia, and Australia, but not legally available in the United States (Calhoun et aI., 1996). It is used for treating insomnia and as a presurgery anesthetic (George and Dundee, 1977; Mansikka, Kangas, and Kanto, 1980; Mattilla and Larni, 1980; NIDA, 2003). Misuse of Rohypnol® began in Europe in the 1970s and in the United States in the 1990s (ONDCP, 2004b). It is commonly associated with sexual assault due to the profound sedation it causes, along with its anterograde amnesic property in which an individual cannot recall events that took place while under the influence of the drug (DEA, 2004b; Schwartz and Weaver, 1998). It is odorless and tasteless and is easily dissolved in beverages (NIDA, 2003), allowing a perpetrator to add it to the beverage of a potential victim. The manufacturers, Hoffman-LaRoche, are now adding a blue dye to the pill that will be visible if added to a beverage (DEA, 2004b).

In addition to its association with sexual assault, high rates of misuse by individuals have been documented (Darke, Ross, and Hall, 1995; San et aI., 1993). It is reportedly used by teenagers and young adults at nightclubs and raves (DEA, 2004b). Indeed, it has been suggested to have a high abuse liability (Farre et aI., 1998; San et aI., 1993), higher, some say, than other benzodiazepines (Mintzer and Griffiths, 1998). Some research has

noted that Rohypnol®is preferred over other benzodiazepines (Barnas et aI., 1992; Darke, Ross, and Hall, 1995; San et aI., 1993). The potentially higher abuse liability, as well as its preference, might be due to its faster onset (15-20 minutes) and longer duration of action (12 or more hours), and its stronger effects at lower doses (Bond et aI., 1994; Mintzer and Griffiths, 1998; ONDCP, 2004b). Healthy volunteers have also reported liking the effects of flunitrazepam (Bond et aI., 1994; Farre, Teran, and Cami, 1996), and report sedation, but few side effects (Bond et aI., 1994).

Rohypnol® is used illicitly to achieve a feeling of relaxation similar to alcohol intoxication (Calhoun et aI., 1996; Schwartz and Weaver, 1998). It also may be taken together with heroin to enhance the effects of heroin, as well as to decrease the experience of opiate withdrawal symptoms (San et aI., 1993), and enhance the effects of other substances including alcohol and marijuana, and to lessen the adverse stimulant effects of cocaine (Calhoun et aI., 1996). It also reduces anxiety, increases an individual's comfort in social situations (Calhoun et aI., 1996; Schwartz and Weaver, 1998), and induces euphoria (Farre et aI., 1998).

Acute adverse effects associated with Rohypnol®ingestion include a decrease in body temperature, sedation (Farre et aI., 1998), impairment of cognitive and psychomotor tasks (Farre et aI., 1998; Mintzer and Griffiths, 1998), sleepiness (Schwartz and Weaver, 1998), decreased blood pressure, visual disturbances, dizziness, confusion, gastrointestinal disturbances, and urinary retention (NIDA, 2003).

Dependence on flunitrazepam can develop and withdrawal symptoms include headache, tension, anxiety, restlessness, muscle pain, sensitivity to light, numbness and tingling of extremities, and seizures (Schwartz and Weaver, 1998).

Treatment

Overdoses can lead to loss of consciousness and respiratory depression that can be life threatening (Schwartz, Milteer, and LeBeau, 2000). Supportive measures include use of activated charcoal to absorb drug in the gastrointestinal tract as well as respiratory support (Schwartz and Weaver, 1998). Flumazenil (Romazicon™) is a specific benzodiazepine antagonist that may be administered to reverse the effects of flunitrazepam toxicity (Schwartz, Milteer, and LeBeau, 2000; Schwartz and Weaver, 1998). Close medical attention is required since flumazenil has high affinity for GABA receptors and will displace GABA agonists such as flunitrazepam, which has the potential to induce seizures.

Conclusions

Club drugs encompass a variety of medications in several different drug classes. One of the challenges presented by club drugs is the changing face of the "club drug" environment. This environment is associated with the use of multiple drugs and new drugs that defy the development of specific interventions. Club drugs have appeal for younger drug users, but present opportunities for significant toxicity that can be life-threatening or result in permanent morbidity. Understanding the clinical pharmacological aspects of these drugs is important to recognition of their use and misuse, as well as a beginning to the development of effective educational outreach and treatments.

Many of the gaps in this literature are due to the nature of researching substance misuse. For instance, issues related to polysubtance use certainly span across virtually all illicit substance use, making it difficult to tease apart the effects of individual substances. Similarly, issues such as purity and dose of substances obtained illicitly hinder the conclusions that

can be drawn from research in this area. An issue that is somewhat unique to studying club drugs, at least at this point, is that although it is rightfully considered a significant problem, the population that misuses these drugs actually comprises a relatively small group of the population of substance misusers in general, providing a comparatively smaller population available for participation in research studies. Future research can continue to develop creative ways to investigate outcomes and treatments related to this important problem that disproportionately affects our youth.

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RESUME

Quatre "drogues de club" differentes sont passees en revue: Ie MDMA (le methylenedioxymethamphetamine, "d'extase"), Ie GHB (Ie gamma-hydroxybutyrate), la ketamine, et Ie Rohypnol® (Ie flunitrazepam). Pour chacune on discute la neurobiologie, la pharmacologie, et les issues de traitement.

RESUMEN

Cuatro diferente drogas de club son repasadas: la MDMA (extasis), el GHB (gammahidroxibutirato), el Ketamine, y el Rohipnol (nombre comercial del flunitracepam). La neurobiologia, la farmacologfa clfnica, y los tratamientos para cada droga son discutido.

THE AUTHORS

Elinore McCance-Katz, Ph.D., is Professor of Psychiatry at Virginia Commonwealth University. She specializes in the treatment of substance use disorders in those with infectious diseases, particularly HIV disease.

Gena Covell **Britt,** Ph.D., is Assistant Professor of Psychiatry at Virginia Commonwealth University. She has been doing research in the substance abuse field for the past 11 years.

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