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The effects and consequences of selected club drugs

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Abstract

Ecstasy (MDMA), gamma-hydroxybutyrate (GHB), ketamine, and methamphetamine are 4 examples of club drugs that are increasing in popularity. Although the pharmacological classifications of these drugs vary, MDMA has structural similarities to both amphetamine and the hallucinogen mescaline. Ketamine and GHB are anesthetic agents and methamphetamine is a long-acting psychostimulant. Medical visits for club drug-related toxicity have sharply increased across the country. This article provides a brief review of the literature on club drugs.

Keywords: Drug abuse; Club drugs; Ecstasy; MDMA; Methamphetamine; GHB; Ketamine

1. Introduction

Ketamine, MDMA (ecstasy), GHB (gamma-hydroxybutyrate), and methamphetamine are four examples of club drugs that are increasing in popularity. Although the pharmacological classifications of these drugs vary, MDMA has structural similarities both to amphetamine and the hallucinogen, mescaline. Ketamine and GHB are anesthetic agents and methamphetamine is a long-acting psychostimulant. Medical visits for club drug-related toxicity have sharply increased across the country. Examples of the increase in use of these drugs are reflected in the Drug Abuse Warning Network (DAWN), which collects data from emergency departments across the United States. Emergency rooms visits for MDMA increased from 250 in 1994 to 2,850 in 1999. A similar increase has been seen for GHB from 250 in 1994 to 2,850 in 1999. Mentions of ketamine rose from 19 in 1994 to 396 in 1999 (Drug Abuse Warning Network, 2000). Methamphetamine related episodes increased by 30% from 10,400 in 1999 to 13,500 in 2000 (Hanson, 2002). This paper provides a brief review of the literature on club drugs.

2. MDMA

MDMA (3,4-methylenedioxymethamphetamine), commonly referred to as "ecstasy," was developed by Merck in 1914 as a parent compound for the synthesis of other pharmaceuticals (Shulgin, 1986). In the 1960s and 1970s MDMA was used as part of the "New Age" movement for stimulating and enhancing sensory experience. In the 1970s, reports appeared that MDMA use could facilitate psychotherapy, by enhancing introspective states and increasing communication with others (Downing, 1986; Greer & Tolbert, 1998; McDowell & Kleber, 1994). However, in response to emerging reports of neurotoxicity, the DEA classified MDMA as a Schedule I substance in July 1985 and its use became illegal.

MDMA (also known as Ecstasy, XTC, E, X, Adam and Love Drug) is typically taken orally in tablets or capsules, but can also be used intranasally with acute effects that are reported to last 6–8 hr. MDMA tablets generally contain 50 to 150 mg of the drug and cost about $20–$40 each. However, the relative purity of the MDMA sold varies. In a recent report, only 63% of the analyzed tablets contained detectable amounts of MDMA or an analog. Common substitutes included dextromethorphan, caffeine, ephedrine, pseudoephedrine, and salicylates (Baggott et al., 2000).

Reported desired effects of MDMA include elevated mood, increased empathy and feelings of closeness, altered visual, sensual and emotional overtones, increased physical

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energy, extroversion, and self-confidence (Downing, 1986; Greer & Tolbert, 1998; Liecthi, Baumann, Gamma, & Vollenweider, 2000; Vollenweider, Gamma, Liechti, & Huber, 1998). Acute neuropsychiatric effects include moderate derealization and depersonalization, accelerated thinking, thought blocking, and impaired decision-making (Liecthi et al.; Vollenweider et al.). Other acute adverse effects include bruxism (teeth grinding), jaw clenching, decreased appetite, headaches, gait disturbance, and sweating (Downing; Liecthi et al.; McDowell & Kleber; 1994). The bruxism and jaw clenching may explain the use of pacifiers and lollipops commonly seen at raves.

MDMA is thought to cause increased release of serotonin as well as inhibition of its reuptake. Serotonin mediates elements of behavior including mood regulation, memory, cognitive function, impulse control, appetite control, and sleep. Alterations in serotonin are thought to be responsible for its psychotropic effects (Gudelsky & Nash, 1996; Liecthi et al., 2000; Steele, McCann, & Ricaurte, 1994). In addition to its psychotropic properties, the drug causes increased blood pressure and pulse (Downing, 1986; O'Connor, 1994; Vollenweider et al., 1998).

There is evidence of serotonergic neurotoxicity associated with MDMA use in animals and humans. The results of many animal studies suggest a dose-related reduction in serotonergic activity following repeated MDMA exposure. In addition, histological studies identify the destruction of serotonin axons and axon terminals (Ricaurte, Yuan & McCann, 2000). Less is known about the neurotoxicity in humans associated with MDMA use; however, recent evidence of neurotoxicity has been provided by neuroimaging studies. This damage to the serotonergic system may be responsible for the observed neuropsychiatric and cognitive impairments (Chang, Ernst, Grob & Poland, 1999; Chang et al., 2000; McCann, Szabo, Scheffel, Dannais, & Ricaurte, 1998; Obrocki et al., 1999).

Multiple reports of medical toxicity are associated with MDMA use include decreased sodium (hyponatremia) and case reports of MDMA-associated liver damage progressing to fulminant liver failure (Garbino, Henry, Mentha, & Romand, 2001). Cardiovascular problems include cardiac arrhythmia, hypertension and stroke have been identified, but the frequency of these symptoms is not known (O'Connor, 1994). In addition, there are most likely multiple mechanisms contributing to these complications. Drug interactions from other illicit drugs or adulterants in the MDMA preparations may interfere with the metabolism of MDMA (Baggott et al., 2000). Finally, non-linear pharmacokinetics have been reported for MDMA. This raises the possibility that small increases in the dose of MDMA may result in disproportionately large increases in blood concentrations, thereby increasing the risk of toxicity (de la Torre et al., 2000).

Some of the MDMA-associated deaths have involved a disturbance of body temperature. A hyperthermic syndrome resembling heat stroke may be due to an MDMA-associated disruption of the serotonin and dopamine pathways that regulate body temperature. High ambient temperatures, increased physical activity, and decreased water consumption may also contribute to the onset of these symptoms (Dafters, 1995; Vollenweider et al., 1998). Treatment of hyperthermia requires prompt medical attention, as it can lead to rhabdomyolysis (muscle breakdown) and this in turn can result in kidney failure. Promoters of raves attempt to combat these hyperthermic reactions by making water and misters available. Hyperthermia is also frequently mentioned on web sites discussing "safe raving" (see for example http://www.defenselink.mil/specials/drugawareness/usnnews00a.html).

Morgan (2000) and Parrott (2000) summarized long-term studies on cognitive changes in MDMA users, as it is clear that a considerable body of evidence supports an association between MDMA use and impaired memory. Interpreting these findings is somewhat complicated by the lack of control groups and the frequent use of other recreational drugs (e.g., cannabis and amphetamine) that are known to be associated with cognitive impairment (Croft, Mackay, Mills, & Gruzelier, 2001; Curran, 2000; Simon et al., 2000). Despite these limitations, the research supports an association of cognitive impairment with MDMA use.

There is evidence of an association between MDMA use and involvement in risky sexual behaviors in both heterosexual and homosexual populations. Research summarized in the NIDA (National Institute on Drug Abuse) Notes found that young women under the influence of MDMA in Ohio were more likely to have sex with men they had not intended to. Another study conducted among partygoers in Connecticut showed increase in unprotected sex and sexually transmitted diseases (Mathias, 2001). Among men who have sex with men, Klitzman and his colleagues found a strong association between ecstasy use and a recent history of unprotected anal intercourse even after controlling for age, ethnicity and the use of other substances (Klitzman, Greenberg, Pollack, & Dolezal, 2002; Klitzman, Pope, & Hudson, 2000).

3. GHB

Gamma-hydroxybutyrate (GHB) was initially developed by Laborit in 1960 as an anesthetic (Laborit, 1964). In early 1990, it was sold in health food stores and marketed for anxiety, insomnia, drug and alcohol abuse and for athletes and body builders. Recently, studies have been conducted showing it as a possible treatment for narcolepsy and cataplexy (Lammers et al., 1993), fibromyalgia (Scharf, Hauck, Stover, McDannold, & Berkowitz, 1986), and alcohol dependence and withdrawal (Addolorato, Caputo, Capristo, Stefanini, & Gasbarrini, 2000). It has also become a club drug and has begun to receive more attention due to emerging reports of toxicity (McDaniel & Miotto, 2001).

Many people began using GHB under the illusion of its safety. The FDA removed GHB from the market in 1990

due to reports of GHB-related coma and seizures (Centers for Disease Control and Prevention [CDC], 1998). Despite the known risks, multiple Internet sites continue to provide extensive pro-GHB information. GHB is easily made and continues to be sold illegally under multiple names such as Renutrient, liquid X, liquid ecstasy, scoop, soap, salty water and grievous bodily harm (Nicholson & Balster, 2001). In addition, GHB precursors, such as gamma-butyrolactone (GBL) and 1,4 butanediol are sold as substitutes (Galloway, Frederick-Osborne, Seymour, Contini, & Smith, 2000; Ingels, Rangan, Bellezzo, & Clark, 2000; Nicholson & Balster, 2001). Frequent name changes and analog preparations have contributed to the lack of awareness of the dangers associated with GHB.

Users of GHB describe effects similar to those of alcohol; however, episodes of loss of consciousness are more frequent and unpredictable after GHB use. Numerous articles have documented the acute adverse effects of GHB, including auto accidents, overdose and seizures (CDC, 1998; Dyer, 1991; Li, Stokes, & Woeckener, 1998; Steele & Watson, 1995).

On the street, GHB is often sold as a clear, salty liquid and is taken in capfuls or teaspoons. The teaspoon concentration of a street dose is unpredictable and varies from 500- mg to 5 g/dose, which can lead to unpredictable effects in users who change their GHB supply or preparation. (J Dyer, SF Poison Control, personal communication, October 15, 2001).

Some recreational GHB users report developing dependence rapidly. Often, GHB is used initially to enhance social activity and well being and as a sleep aid. Due to the rapid elimination of GHB from the body, GHB users describe a rebound insomnia or alertness, which occurs after two or three hours of sleep. Additional doses are then taken to return to sleep. Eventually, some GHB users escalate their use to every 2 to 4 hr in a pattern of "around-the-clock" dosing (Dyer, Roth, & Hyma, 2001; McDaniel & Miotto, 2001). GHB users who develop tolerance and dependence take multiple doses, and over time escalate their use to amounts in the range of 25–100 g per day (Dyer, Roth, & Hyma, 2001; Galloway et al., 2000).

Dependent users who abruptly stop taking GHB experience withdrawal. GHB withdrawal has features similar to alcohol and benzodiazepine withdrawal. The onset begins 1 to 6 hr after use (Dyer et al., 2001), and early symptoms include anxiety, tremor, insomnia, nausea and vomiting. Mild autonomic instability develops, as demonstrated by diaphoresis, hypertension, tremor and tachycardia. In severe cases of acute withdrawal, neuropsychiatric symptoms similar to delirium tremens occur during the first 24 hr and may last up to 15 days (Craig, Gomez, McManus & Bania, 2000; Dyer, Roth & Hyma, 2001). Supportive care is indicated, which may include use of physical restraints and high doses of sedatives for control of refractory agitation (Addolorato et al., 1999, Craig et al., 2000; Dyer et al., 2001, McDaniel & Miotto 2001; Zvosec et al., 2001). In addition, anticonvulsants have also been considered in the treatment of GHB withdrawal. Glutamate-induced excitatoxicity may contribute to the symptoms; therefore, inhibition of the production of glutamate by medications such as gabapentin may help reduce the severity of GHB withdrawal. However, controlled studies are necessary to develop medication guidelines to treat GHB withdrawal.

Beyond the potential medically dangerous syndrome of acute GHB withdrawal, a protracted withdrawal state lasting from three to six months has been observed that is characterized by dysphoria, anxiety, memory problems, and insomnia. The risk of relapse is very high due to these symptoms and users may turn to alcohol or benzodiazepine abuse in an effort to relieve persistent anxiety and insomnia (McDaniel & Miotto, 2001).

At a meeting about GHB conducted by the National Institute on Drug Abuse, GHB was identified as increasing the likelihood of date rape by causing a loss of muscle coordination, confusion, sedation, loss of consciousness, and amnesia (Schwartz, Milteer, & LeBeau, 2001; Whitten, 2001). Additionally, gay and bisexual men use GHB during circuit parties and there appears to be a link between use of GHB and increased risky sexual behaviors among men who attend these events (Mattison, Ross, Wolfson, & Franklin, 2001).

Treatment and prevention efforts for GHB users are often delayed due to the fact that many providers lack knowledge of symptoms of GHB intoxication and dependence. Information about GHB available through the Internet or other lay sources can be misleading, implying that GHB is non-addictive and has health benefits. Successful treatment requires knowledgeable treatment providers who are informed about GHB and its analogs as well as the stages of recovery. Advances in treatment will require further research that expands beyond case reports to controlled trials.

4. Ketamine

Similar to GHB, ketamine hydrochloride was originally developed as a human anesthetic agent. Ketamine is a phencyclidine hydrochloride (PCP) derivative introduced in the 1960s. It produces a state of sedation, immobility, amnesia, and analgesia. It is referred to as a "dissociative anesthetic" due to the intense feelings of dissociation from the environment experienced by patients using the drug. Ketamine is used in trauma and emergency surgical procedures, as well as in veterinary medicine (White, Way & Trevoe, 1982).

Ketamine is frequently available at dances and parties where GHB and ecstasy are used. Sources of ketamine include diverted shipments intended for other countries and stolen supplies from veterinary sources. Street names include K, Special K, Vitamin K, and Super Acid. Ketamine can be injected, taken orally, intranasally or smoked with marijuana or tobacco products. The elimination half-life is approximately 2 hr (Domino et al., 1984).

Ketamine acts at the excitatory amino acid receptor, the N-methyl-D-aspartate receptor (NMDA). The site of action

of ketamine and PCP is a unique modulatory binding site on the (NMDA) receptor complex. These receptors play a role in the neurochemistry of behavior and sensory information. They mediate the excitation of neurons by interactions with excitatory amino acid neurotransmitters such as glutamate. Ketamine is a potent noncompetitive NMDA antagonist (Haas & Harper, 1992). It is notable that NMDA receptor dysfunction has been implicated in the pathology of schizophrenia. Subanesthetic doses of ketamine have been shown to produce cognitive impairment, perceptual alterations and other symptoms resembling schizophrenia (Anand et al., 2000).

Most of the effects of ketamine are dose-dependent. The lower doses used by ketamine abusers produce mood elevation, psychiatric symptoms (e.g., derealization and depersonalization, and visual hallucinations) and pleasant or unpleasant dreams (Zacny & Galinkin, 1999). Attention, learning ability and memory are also impaired. At higher doses, ketamine can cause vomiting, slurred speech, amnesia, impaired motor function, tachycardia, palpitations, agitation, and delirium. High-dose users describe out-of-body or near-death experiences. Intense dissociative experiences are often referred to as being "stuck in a K-hole," "K-hold" or "K-land." Visual disturbances or "flashbacks" can recur days or weeks after exposure to ketamine. Reports of flashbacks appear greater with ketamine than with other hallucinogens. Possible long-term cognitive or neuropsychiatric effects have not been sufficiently studied in ketamine users.

Tolerance and dependence on ketamine have also been reported, generally through case reports involving medical personnel who administer the drug multiple times throughout the day (Dotson, Ackerman & West, 1995). Additional studies are needed to better understand the extent of ketamine abuse and dependence and to identify symptoms of withdrawal and effective treatments.

As with other club drugs, Mattison and colleagues identified a connection between ketamine use and risky sexual behaviors (Mattison et al., 2001). Studies have also shown that involvement in high-risk sex increased as the number of club drugs used (including ecstasy, ketamine, methamphetamine and GHB) increase among gay and bisexual men who attend circuit-party events (Mansergh et al., 2001).

5. Methamphetamine

Methamphetamine is a central nervous system stimulant that is structurally similar to but more potent than amphetamine. It can be taken intranasally, intravenous, orally or smoked. The half-life is in the range of 10 to 30 hr with its effects resulting from excitation of the dopamine and norepinephrine receptors in the brain (Anglin, Burke, Perrochet, Stamper, & Dawud-Noursi, 2000). Methamphetamine was originally synthesized from ephedrine in 1893, but it was not widely used until World War II when Japan, Germany, and the United States gave it to military personnel to increase endurance and performance (Suwaki, Fukui, & Konuma, 1997). Diversion and illicit use of methamphetamine has been a significant problem in the Western United States since the early 1960s (Miller, 1997). It is estimated that in 1998 4.7 million Americans (2.1% of the US population) had tried methamphetamine at some time in their lives (SAMHSA, 1999). Recognizing the spread of the problem of methamphetamine and the growing problems associated with its abuse, the Comprehensive Methamphetamine Control Act was enacted in 1996, which increased penalties for possession of precursor chemicals to methamphetamine and/or equipment used in its production and for trafficking or manufacturing methamphetamine or its precursor chemicals (Feinstein, 2002).

The desired acute effects include well-being, increased alertness, increased activity, excitement, and decreased appetite. Acute physical effects include elevation of blood pressure, pulse, respiration and body temperature. Medical problems associated with excessive dosages include cerebral hemorrhage, stroke, seizure, hyperthermia, arrhythmias, coma, and death. Psychological impairments associated with stimulant use include insomnia, psychosis, paranoia, suicidal tendencies, and cognitive impairment (CSAT, 1997; National Institute on Drug Abuse [NIDA],1998a). There are also there are indicators that structural changes to the brain may occur (NIDA, 1998b) as well as cognitive deficits in areas such as learning, memory and executive systems functioning (Kalechstein et al., 2000).

Methamphetamine use has been shown to lead to uncharacteristically risky sexual behaviors including involvement with prostitutes or HIV high-risk behaviors in heterosexual populations (Rawson, Washton, & Shoptaw, 1998). The connection between risky sexual behavior and methamphetamine use among gay and bisexual men has also been well documented (Frosch, Shoptaw, Huber, Rawson, & Ling (1996); Reback, 1997; Shoptaw, Reback, & Freese, 2002).

Stimulant withdrawal develops after cessation of regular use. It is characterized by depressive symptoms, increased appetite, fatigue, insomnia, agitation, and anergia (NIDA, 1998b). Paranoia and aggression may also occur. Suicidal ideation is a risk when the depressive symptoms are severe. In the absence of suicidal ideation stimulant withdrawal is not life threatening and is generally treated with symptomatic therapy (Anglin et al., 2000).

6. Discussion

Little is known about effective treatments for club drug use. Recent research identifies the neurobiology and toxicities of these drugs. However, more research is needed to develop effective prevention and treatment strategies for club-drug using populations. The increasing use by adolescents and young adults warrants a focus on the issues of comorbidity, polysubstance abuse, and education of providers in the signs and symptoms of abuse to facilitate early detection and quality care.

The unique social and cultural factors that support the use of these drugs in a given population must be taken into consideration in designing intervention and treatment strategies. Research is needed to determine which treatment elements are effective for which populations. Treatment providers who are working with club drug users have a unique perspective in understanding the role that these drugs play in social networks. Pairing clinicians with researchers may help to ensure that interventions are empirically validated and that effective treatments are disseminated as quickly as possible.

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