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Party Drugs: Properties, Prevalence, Patterns, and Problems

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This review summarizes the latest literature on "party" or "club" drugs, defined as MDMA, GHB, ketamine, and Rohypnol, as published from 2002 to early 2005. Club drugs have been categorized as being used at raves and dance parties. The literature shows that each drug has different properties, users, and settings. Each drug has different adverse effects and requires different acute care protocols. Although these drugs were identified early, scientific information about them, including the toxicological tests to identify them, is still evolving. Increasing numbers of studies on the short- and long-term effects of these drugs on humans are being published, but because of limitations on research using human subjects, they may not always be as rigorous as desired and can be cited by drug users to discredit findings of harm. The lack of research-based information on these drugs has led to the emergence of web sites that may or may not provide accurate data. Evaluated chemical dependency treatment protocols using the latest research for each of these different drugs are needed.

Keywords ecstasy; MDMA; GHB; ketamine; Rohypnol; "club drugs"; drug scene; "party drugs"

Introduction

The U.S. National Institute on Drug Abuse (NIDA) in its "Community Alert on Club Drugs," defined "club drugs" as ecstasy (MDMA), gamma-hydroxybutyrate (GHB), ketamine, Rohypnol, methamphetamine, and lysergic acid diethylamide (LSD), and described them as being used in all-night dance parties such as "raves" (National Institute on Drug Abuse, 1999). Because LSD and methamphetamine have been extensively described in the literature over the years, this article will concentrate on the "party drugs" or "club drugs" that are commonly (and sometimes incorrectly) called MDMA, GHB, Rohypnol, and ketamine. At the June, 2003, meeting of the National Institute on Drug Abuse's (NIDA) Community Epidemiology Work Group (CEWG), the appropriateness of the term "club drugs" was questioned, since use has diffused beyond the club culture to different populations (National Institute on Drug Abuse, 2003).

This article is an updated and expanded version of one originally published in *Current Opinion in Psychiatry* in 2003 (Maxwell, 2003a). As detailed within the text of this article, there have been some specific patterns that have emerged in the response to the "club drug" phenomenon:

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- Each drug has very different pharmacologic properties, physiological and psychological effects, and potential consequences.
- These drugs are often used in combination, particularly with marijuana or alcohol, although the combinations and patterns of use can be quite different.
- These drugs are being used in an expanding variety of venues by groups who differ in terms of age, gender, sexual orientation, and race/ethnicity.
- The problems with these drugs in the U.S. were identified early by members of CEWG, which is a group of researchers from 21 areas around the country who meet semi-annually to report on drug patterns, changing trends, and emerging drugs. MDA was reported as early as 1980 at a CEWG meeting, MDMA was reported in 1985, GHB was first reported in 1990, ketamine was first reported in 1991, and Rohypnol was first reported in 1993.
- Even with the early warnings about the emergence of these drugs, information on the pharmacology of these substances and their adverse effects has lagged, with the result that acute care health workers and substance abuse treatment professionals have been handicapped in responding to these drugs.
- The drug scene today is impacted by the Internet, where "underground" websites provide thousands of pages of information on how to obtain, synthesize, extract, identify, and ingest substances (Halpern and Pope, 2001a; Bogenschutz, 2001; Halpern and Pope, 2001b) that have not been medically evaluated for dose range, effect, risk, or abuse liability (Franken, 2001). At the same time, government websites have contained information that was later withdrawn as more current findings emerged. In 2002, the National Institute on Drug Abuse discontinued distribution of the ecstasy brain scan poster, flier, and art card, which was adapted from a positron emission tomography (PET) image in a 1998 paper by McCann et al. (1998). Since then, newer technologies that have greater precision, efficiency, and/or sensitivity have emerged. In another instance, a major study was retracted for errors (Ricaurte et al., 2003). Some antidrug sites used scare tactics and exaggerations that users ignored while prodrug sites contained anecdotal or incomplete information that could lead the unaware user to increased use (Koesters, Rogers, and Rajasingham, 2002). Recent ecstasy users rated, in order, friends, drug abuse treatment programs, physicians, non-government websites, and MTV/VH1 specials as "very accurate" sources of information on ecstasy, and younger and more educated users were more likely to use the Internet to obtain information on ecstasy (Falck et al., 2004).
- Scientific studies about the uses of these club drugs and their short-term and long-term effects on animals have shown MDMA damages specific neurons in the brain. Studies on humans are evolving but due to constraints in the use of these drugs on human subjects, conclusive evidence has not yet been established. And the complexity of research on the effects on the brain can discourage reception of the findings by users and potential users, since many of the studies are difficult for nonscientists to understand.
- Routine drug screens do not pick up various club drugs, and gas chromatography and mass spectrometry (GC-MS) testing must be requested to confirm the presence of the specific drug. Because of the short half-life of some of these drugs (27 minutes for GHB and 3.5 hours for Rohypnol), cases of sexual assault and driving under the influence have gone undetected. Improved procedures for identifying these drugs are now available.
- Evidence-based information on treating dependence on each of these club drugs is sparse, in that findings on the effects of these drugs on the brain have not been

translated into clinical practice. Treatment protocols that recognize the specific effects of these different drugs have not been trialed, and outcome studies that show the effectiveness of treatment for "club drug" clients have not yet been published.

- Groups such as DanceSafe and RaveSave have been organized to reduce harm at dance parties by distributing information about hydration status and ambient body temperature, health education, drug and safe sex information, and pill testing. The response by local government in terms of enforcing fire and safety codes has varied from supportive to shutting down such venues to ignoring them, often with the unintended problems with crowd control and traffic jams.
- Pro-Rave organizations and websites have implied that only uneducated users suffer life-threatening consequences of drug use and that proper education decreases the possibility of misuse or dependence. Given the scientific information that is emerging, peer-based education with a focus on both short-term dangers and long-term consequences may be a more effective approach to prevent major public health problems in the future (Koesters, Rogers, and Rajasingham, 2002). An online survey of over 900 drug users found 73% viewed ecstasy as carrying at least "some risk." However, the extent of ecstasy use was unrelated to its perceived dangerousness. Of all the factors driving drug use, perceived mood-related and social benefits and immediate negative effects as experienced personally or by friends were the most important. The presence or absence of actual problems had more weight than the awareness of potential risks in the future (Gamma et al., 2005).

Ecstasy (MDMA)

Ecstasy (3,4-methylenedioxymethamphetamine) (MDMA) (also called Adam, E, X, eccie) is a synthetic, psychoactive drug with both stimulant and hallucinogenic properties similar to methamphetamine and mescaline. It is classified as an empathogen or enactogen because the subjective experience has been described as intensely emotional and as creating the perception that one can experience the emotions of others (Nichols, 1985). E. Merck Pharmaceuticals filed a patent for the drug in Germany in 1912, but it remained unnoticed until a large toxicological study was done under a classified contract with the U.S. Army after World War II. In 1976 it was used as an adjunct to psychiatric treatment, and its use in psychotherapy increased at the same time that its recreational use was increasing (Pentney, 2001). It has been a Schedule I drug since 1985. Schedule I drugs are those with a high potential for abuse. They have no currently accepted medical use in treatment in the United States, and there is a lack of accepted safety for use of the drug or other substance under medical supervision. Heroin, LSD, cannabis, peyote, and psilocybin are other Schedule I drugs.

A similar compound, 3,4-methylenedioxyamphetamine (MDA), was synthesized in 1910 and was tested by the U.S. military as a truth serum after World War II. Its empathy-producing effects led to recommendations that it be used in psychiatry, but these same effects led to widespread abuse (Pentney, 2001). In 1970, it was classified as a Schedule I drug in the U.S.

The effects and pharmacological actions of 3,4-methylenedioxyethamphetamine (MDEA, Eve) are reported to be similar, but not identical to MDMA (Barrionuevo et al., 2000). MDEA has been found to induce effects probably indicative of neurotoxicity when given to rats at doses higher than MDMA. It is not known whether MDEA will produce the same serotonergic deficits seen for MDMA in studies of human users, although the high

percentage of MDEA occasionally found in "ecstasy" tablets is of concern (McCann et al., 1998).

Other drugs that appear in the ecstasy scene include p-methoxyamphetamine (paramethoxyamphetamine) (PMA), a drug packaged as ecstasy and mistakenly assumed to be a by-product in the synthesis of MDMA. Likewise, MDMA is not produced in the synthesis of PMA (Kraner et al., 2001). PMA shares the stimulant and hallucinogenic effects of MDMA as well as its risk of hyperthermia, and fatalities related to the use of PMA have been reported (Byard et al., 1999; Winstock, Wolff, and Ramsey, 2002; Caldicott et al., 2003). Another new synthetic sulphur derivative of amphetamine, 4-MTA (p-methylthioamphetamine), has been associated with deaths since it was first identified in Europe in 1997. Sold as "ecstasy" or "Flatliners," the drug is a potent serotonin releaser. Winstock, Griffiths, and Stewart (2001) queried 1151 subjects through a dance magazine survey and found 10% thought they had used 4-MTA. Those who had used 4-MTA tended to come from a subpopulation of heavy ecstasy users. Survey responses about the effects of the drug were mixed, although a quarter of those who thought they had tried 4-MTA said they would use it again.

Epidemiological Information

MDA was reported as early as the June, 1980 meeting of the Community Epidemiology Work Group (CEWG) (Newmeyer, 1980), and MDMA was first reported at the December, 1985 meeting (Hall, 1986). At the June and December, 2003 CEWG meetings, it was reported that in Atlanta, ecstasy use was no longer seen as a club drug, but was being used by low-income polydrug users and use had also spread to the Black community. Methamphetamine and ecstasy were being used in combination because the effects of ecstasy alone were "not enough," and ecstasy was being bought in larger quantities, with some users reported to be developing tolerance to the drug. "Trolling," which is using ecstasy and LSD together, was also reported. In Baltimore, ecstasy was more prevalent in the central city, and the increase was said to be due to the Hip-Hop culture and rap songs about ecstasy. In Chicago, ecstasy use was reported as down and the price was stable; however, it was spreading to new groups of White suburban youth. In Detroit, ecstasy use was stable, particularly outside Detroit, where it is known as a "Prom" drug. In Miami, ecstasy use was reported as "passé" but that when it was used, it was used in combination with other drugs, including Viagra, primarily in the gay "Party and Play" club scene. This same party and play phenomenon was reported in San Francisco, where ecstasy use was reported down.

In Minneapolis-St. Paul, ecstasy use was reported as level, and it was used in combination with ketamine and methamphetamine. Ecstasy and ketamine were often sold together in Philadelphia. In St. Louis, ecstasy was available in clubs and around colleges, and there were reports of gay males using Viagra and ecstasy ("Party Packs"). In New York City, ecstasy use was reported up, especially among Hispanics and Blacks. Use was reported as stable in Boston. In San Diego, use of ecstasy was reported as declining, and Mexican methamphetamine was being pressed into pills that look like ecstasy. In Seattle, use was higher among young males having sex with males, and there were reports of depression among users. In Los Angeles, ecstasy use was reported as down (Maxwell, 2003b). In Texas, the number of unduplicated, public treatment admissions with a problem with ecstasy had increased from nine in 1989 to 409 in 2003. The proportion of White clients was decreasing, while Black and Hispanic admissions was increasing—a further indication that ecstasy has spread beyond the White club culture (Maxwell and Spence, 2005).

The National Forensic Laboratory Information System (NFLIS), sponsored by the U.S. Drug Enforcement Administration (DEA), is a program that systematically collects results from toxicological analyses conducted by state and local forensic laboratories on substances seized in law enforcement operations. In 2003, there were 1,100,897 identified by NFLIS, and 6376 of these were MDMA, 866 were MDA, and two were PMA. The number of exhibits is down from the peak year of 2001, when there were 9529 MDMA, 735 MDA, and 21 PMA items identified (NFLIS, 2004).

School and Household Surveys

The U.S. Monitoring the Future Survey (MTF) is a survey conducted by the University of Michigan's Institute for Social Research for NIDA (Johnston et al., 2004a, 2004b). It reported that past year use of ecstasy peaked in 2001 and has declined since that time (Table 1). The decline in prevalence of use by secondary school students appears related to perceptions of risk and availability. In 2000, only 38% of twelfth graders said there was a great risk of harm associated with trying ecstasy; that percentage increased to 58% in 2004. And the perceived availability of ecstasy as reported by the students decreased from a high of 62% in 2001 to 48% in 2004, while the disapproval of people who tried ecstasy once or twice increased from 81% in 2001 to 88% in 2004.

The National Survey on Drug Use and Health (NSDUH), formerly called the National Household Survey on Drug Abuse (NHSDA), is conducted by the Office of Applied Studies of the Substance Abuse and Mental Health Services Administration (SAMHSA) and collects information on the prevalence, patterns, and consequences of alcohol, tobacco, and illegal drug use and abuse in the general U.S. civilian noninstitutionalized population age 12 and older. In 2003, NSDUH reported that 4.6% of the U.S. population aged 12 and over had ever used ecstasy, 0.9% had used in the past year, and 0.2% had used in the past month. Some 2.4% of those ages 12–17 had ever used ecstasy, as compared to 14.8% of those 18–25 and 3.1% of those 26 and older. Initiation of ecstasy use began rising in 1993 when there were 168,000 new users. By 2000, there were 1.9 million new users, but that number decreased to 1.8 million new users in 2001 (Figure 1) (SAMHSA, 2004). In comparison, the Centre for Addiction and Mental Health surveyed 7800 university students in Canada in 1998 and found 4% had ever used MDMA (Gilman et al., 1998).

In Australia, the National Household Survey of persons age 14 and older, which is sponsored by the Australian Institute of Health and Welfare, reported lifetime use of ecstasy rose from 2.4% in 1995 to 4.8% in 1998 to 6.1% in 2001, with past year use in the same time periods rising from 0.9% to 2.4% to 2.9%. The survey reported 10.4% of teenage ecstasy users (8500 persons) and 6.9% of users in their twenties (20,400 persons) used the drug on a daily or weekly basis. Respondents reported multiple sites where they used ecstasy: 70.1% at raves or dance parties, 53.8% at private parties, 50.2% at public establishments, and 46.1% in a home (Australian Institute of Health and Welfare, 2002).

In comparison, annual prevalence of ecstasy use was 2.4% in Ireland in 1998, 2.2% in the UK in 2001, 1.8% in Spain in 2001, 1.7% in Belgium in 2000, 1.5% in Canada in 1999–2000, 1.2% in the Netherlands in 2001, 0.7% in Latvia in 1999, 0.6% in Germany in 2000, and 0.5% or less in Thailand, Estonia, Poland, the Czech Republic, Denmark, Colombia, Israel, France, Croatia, Mexico, Bulgaria, Italy, and the Russian Federation (Office on Drugs and Crime, 2003).

A household probability sample of 627 Chicago adults ages 18–40 years found the prevalence rate for those who used a variety of club drugs was nearly twice that of those

Table 1
Past-year prevalence of club drugs from the Monitoring the Future Surveys: 1991–2004

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Past year use of MDMA (ecstasy)														
8th grade						2.3	2.3	1.8	1.7	3.1	3.5	2.9	2.1	1.7
10th grade						4.6	3.9	3.3	4.4	5.4	6.2	4.9	3.0	2.4
12th grade						4.6	4.0	3.6	5.6	8.2	9.2	7.4	4.5	4.0
College students	0.9	2.0	0.8	0.5	2.4	2.8	2.4	3.9	5.5	9.1	9.2	6.8	4.4	...
Young adults	0.8	1.0	0.8	0.7	1.6	1.7	2.1	2.9	3.6	7.2	7.5	6.2	4.5	...
Past year use of GHB														
8th grade										1.2	1.1	0.8	0.9	0.7
10th grade										1.1	1.0	1.4	1.4	0.8*
12th grade										1.9	1.6	1.5	1.4	2.0
College students												0.6	0.3	...
Young adults												0.8	0.6	...
Past year use of ketamine														
8th grade										1.6	1.3	1.3	1.1	0.9
10th grade										2.1	2.1	2.2	1.9	1.3*
12th grade										2.5	2.5	2.6	2.1	1.9
College students												1.3	1.0	...
Young adults												1.2	0.9	...
Past year use of Rohypnol														
8th grade						1.0	0.8	0.8	0.5	0.5	0.7	0.3	0.5	0.6
10th grade						1.1	1.3	1.2	1.0	0.8	1.0	0.7	0.6	0.7
12th grade						1.1	1.2	1.4	1.0	0.8	0.9	1.6	1.3	1.6
College students												0.7	0.4	...
Young adults												0.3	0.5	...

Note: Levels of significance of difference between the two most recent classes: *p = 0.05.
... indicates data are not available.

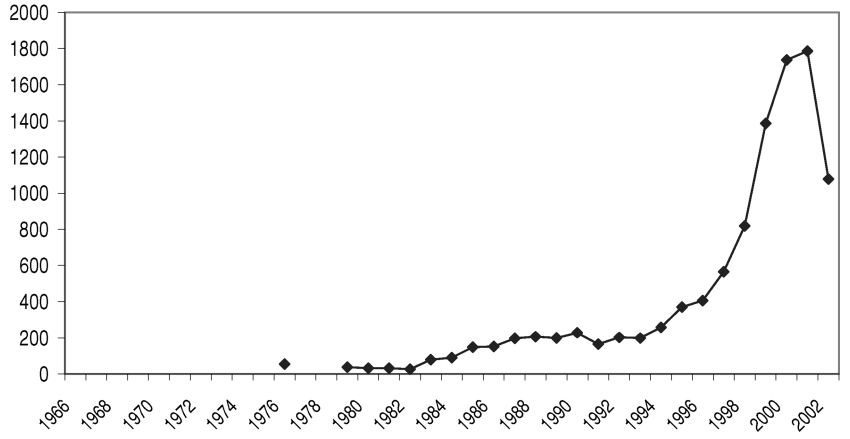

Figure 1. Numbers (in thousands) of persons who first used ecstasy during the years 1966–2002: 2003 NSDUH.

who only used MDMA and they were more likely to report having been in treatment for substance use. A majority of lifetime club drug users never attended a rave, although rave attendees were more likely to report frequent use of MDMA. Use was associated with gender, race, and sexual orientation. The authors suggested that research should not only focus exclusively on rave attendees, as they are only a subset of club drug users, but also should focus on high-risk consumption (Fendrich et al., 2003).

Lifetime use of ecstasy among tenth grade students in Turkey rose from 2.7% in 1998 to 3.3% in 2001. Male gender, older age, use of alcohol, cannabis, heroin, and cocaine, nonmedical use of psychotherapeutic drugs, and participation in an education meeting about the adverse effects of ecstasy were found to be significant variables in predicting lifetime use of ecstasy (Corapcioglu, 2004).

A survey of 3606 undergraduates at a large Midwestern U.S. university found the number of sexual partners increased the likelihood of ecstasy use as did self-reported sexual identity. Gay, lesbian, and bisexual students were more than two times as likely to have used ecstasy in the past year. Significant relationships existed between ecstasy use and other substance use, such as binge drinking, marijuana use, and cigarette smoking (Boyd, McCabe, and d'Arcy, 2003).

Surveys of Users and Attendees at Dance Parties

Ecstasy use is often reported at "raves" or all-night dance parties. Twenty percent of 96 individuals at raves in the Baltimore-Washington corridor in 2000 who provided a saliva sample tested positive for ecstasy. These individuals were more likely than nonusers or past users of ecstasy to have used marijuana and powder cocaine in the past year (Arria et al., 2002). In contrast, 70 rave attendees surveyed in the same area in 2002, whose saliva was not tested, self-reported 86% lifetime use of ecstasy and 30% reported use in the 2 days prior to the interviews (Yacoubian et al., 2003).

A survey of 210 Canadian youth attending raves in Montreal in 2000 found lifetime use of cannabis at 91%; alcohol, 90%; MDMA, 75%; amphetamine, 73%; GHB, 19%; and ketamine, 14%. Of those who had used drugs in the past month, 53% had used MDMA (Gross et al., 2002). Urine samples collected from 149 persons at a disco-dancing club in Taipei City in 2001 confirmed that 76% tested positive for MDMA and 3% tested positive

for MDA; 43% tested positive for MDMA and ketamine in combination. Urine samples were also collected at the same time from 100 police detainees in Taipei, and only 6% tested positive for MDMA (Lua et al., 2003).

A survey of 122 people at three dance events in Edinburgh in 1998–1999 who had reported past year substance use found that 82% had used ecstasy, 81% had used amphetamines, and 48% had used cannabis. Sixty-six percent of them mixed drugs, and 90% of the mixes contained amphetamines and ecstasy. The participants were also vulnerable to other risks: 85% always or sometimes drank alcohol while using drugs, one-third had unprotected sex and "took too many drugs," and one-quarter drove while high on drugs (Riley et al., 2001).

The survey of 1151 subjects queried through a dance music magazine found that polysubstance use was the norm. Many of those reporting use of "ecstasy" were regularly using multiple tablets that were often consumed in combination with other substances. Seventy percent were drinking alcohol at hazardous levels based on their score on the Alcohol Use Disorders Identification Test (AUDIT) and 86% had used ecstasy in the past month. The mean number of ecstasy pills consumed in a session was 2.8, with a quarter of the subjects reporting regular use of four or more tablets. Some 58% reported developing tolerance to ecstasy; 55% reported continuing to use ecstasy despite experiencing problems with their health, work, or relationships; 36% reported loss of interest in activities or friends not connected with ecstasy; and 25% reported difficulty in controlling the amount of ecstasy they took (Winstock, Griffiths, and Stewart, 2001).

A survey of 329 ecstasy users in three Australian cities found extensive polydrug use was the norm. High rates of intravenous drug use were recorded, which may relate to an overrepresentation in the sample of chaotic intravenous polydrug users. Subjects had experienced an average of eight physical and four psychological side-effects, which they attributed to their ecstasy use in the preceding 6 months. Some 40% reported financial, relationship, and occupational problems. Young female polydrug users and those who binged on ecstasy for 48 hours or more appeared most at risk of experiencing problems related to their ecstasy use. One-fifth of the sample had received treatment for an ecstasy-related problem, and 7% were currently in treatment. One-quarter wanted to reduce their use because of financial, relationship, and psychological problems; 15% wanted formal treatment for an ecstasy-related problem; and 85% requested more information. The authors concluded their findings stood in contrast to the conventional wisdom that ecstasy was a relatively benign drug with few associated risks (Topp et al., 1999).

A study of 760 club-goers at eight different events in six nightclubs in southeast England in 2000 found that ecstasy was the most commonly used drug, followed by cannabis and cocaine. Despite high levels of use, only a quarter felt that taking drugs was an integral part of their social life. A third had used both drugs and alcohol on the night of the interview and two-thirds were classified as "hazardous drinkers" based on the AUDIT. Most users were aware of the risks of drug taking, had sought information about the physical and mental health consequences, and had taken measures to minimize those risks, although the study found some of those strategies were based on urban myths. Few interviewees expressed concerns about the potential long-term impact of their drug use on physical or mental health (Deehan and Saville, 2003).

Studies of rave attendees may have a sampling bias in that they may have attracted a sample of high-risk-taking drug-using club attendees that is not a representative sample of all attendees (McKeganey, 2001). However, comparison of the 2001 Australian National Household Survey and the 2001 Australian Illicit Drug Strategy Party Drugs Module, which was a purposive sample, found the similarities between the demographic and drug use

characteristics of the two samples "striking," which suggests that purposive sampling that seeks to draw from a wide cross-section of users and to sample a relatively large number of individuals can give rise to samples of ecstasy users that may be considered sufficiently representative to reasonably warrant the drawing of inferences relating to the entire population (Topp, Barker, and Degenhardt, 2004).

Surveys of Use by Gay and Bi-Sexual Men

Circuit parties, which are multi-event weekends that cater to gay and bisexual men, are another venue for use of ecstasy (Tong and Boyer, 2002; Klitzman et al., 2002). Some 72% of 1169 patrons at three major circuit parties in 1999 had used ecstasy at such parties, and unsafe sexual behavior at the parties was associated with frequent ecstasy use (Mattison et al., 2001). There were two major reasons to attend these parties: a social and celebratory one to be with friends and dance, and a sensation-seeking one to have sex and drugs. Using a greater number of drugs, sexual activity while on drugs, and unsafe sex were more closely associated with the sensation-seeking dimension of attendance (Ross, Mattison, and Franklin, 2003). A survey of 237 men attending a winter party in Miami in 2003 found 90% had used one or more illicit drugs in the past 6 months: 79% had used ecstasy, 62% had used crystal methamphetamine, 64% had used ketamine, 57% had used marijuana, 54% had used Viagra, 49% had used GHB, and 46% had used amyl nitrite. Crystal methamphetamine users were much more likely to ingest a wide variety of other drugs, to have had a sexually transmitted infection, and to have more anal sex partners (Kurtz and Inciardi, 2003).

Although known as the "Love Drug," MDMA has been reported to reduce libido and cause loss of erection (Drug Developments and STD News, 2001; Zemishlany, Aizenberg, and Weizman, 2001), so "Party Packs" containing Viagra and MDMA are used. A study of 4295 men in six U.S. cities who have sex with men found that drug and alcohol use was significantly associated with unprotected anal sex. Marijuana was the drug most likely to be used (46%) followed by poppers or amyl nitrates (37%); hallucinogens, including ecstasy (24%); cocaine (19%); and amphetamines (13%) (Koblin et al., 2004). A 1999 survey of 295 gay and bisexual San Francisco men who had attended a circuit party in the previous year found that one-fourth reported a drug "overuse" incident in the past year, and 75% had taken ecstasy during a circuit party weekend (Mansergh et al., 2001).

Of concern is the potential interaction between recreational drugs and drugs commonly used in the management of HIV-positive patients. Many classes of recreational drugs are metabolized by the liver and can potentially interact with antiretroviral drugs. Overdoses secondary to interactions between MDMA or GHB and protease inhibitors have been reported, and these interactions may be associated with serious clinical consequences (Antoniou and Tseng, 2002; Schifano, 2003). MDMA tablets often contain contaminants as well. In most cases the contents are analogues of MDMA, combinations of stimulant drugs such as ephedrine or amphetamines, or hallucinogens such as LSD or ketamine that mimic the sought-after effects of MDMA (Winstock, Wolff, and Ramsey, 2001). The clinical effects of these contaminants and their potential for interacting with antiretrovirals should be considered. Fluid status changes can intensify the effects of antiretroviral-induced diarrhea, and dehydration may precipitate indinavir-associated nephrolithiasis. Patients with underlying wasting syndrome may be more prone to the appetite-suppressant effects of MDMA, and "power drinks" consumed with MDMA may contain amino acids and other vitamin supplements that may lead to compound toxicity. In addition, many HIV-seropositive patients with depression may be managed with selective serotonin reuptake inhibitors (SSRIs).

These patients should be aware that concomitant use of SSRIs with MDMA might result in the serotonin syndrome (Romanelli, Smith, and Pomeroy, 2003).

Contents of Ecstasy Tablets

Most tablets containing MDMA are produced in clandestine laboratories in Belgium, Luxemburg, or in Asia. The simplest method of manufacturing MDMA and MDA is through 3,4-methylenedioxyphenyl-2-propanone (PMK), a commercially available ketone. Other common precursors include saffrol, isosaffrol, piperonal, and safrole (often from sassafras oil). Different starting materials and reaction schemes will result in different by-products which may contaminate or alter the final product if it is not adequately purified (Winstock, Wolff, and Ramsey, 2001).

A review of surveys on the contents of ecstasy tablets found in the 1980s and early 1990s showed there were few problems with purity, and tablets nearly always contained MDMA. During the mid-1990s, the majority of ecstasy tablets continued to contain MDMA, but others contained MDA, MDEA, or amphetamine drug mixtures. However, between 4% and 20% of tablets contained other drugs. During the late 1990s, the proportion of tablets containing MDMA increased to between 80% and 90% purity, and in the early 2000s, purity levels have reached 90% to 100% (Parrott, 2004).

Many dance parties offer on-sight testing of pills. The tests are based on a color reaction that occurs when a reagent is applied to the drug substance. The color tests are nonspecific and even if MDMA is present, the tests will not show if other harmful substances are also present. In addition, even if the pill contains MDMA, the user cannot gauge the strength of a pill. Commercially available test kits are slightly better in identifying MDMA, but they cannot detect the presence of substitute compounds such as 4-MTA or PMA. Only gas chromatography-mass spectrometry (GC-MS) can provide a thorough chemical analysis of a pill (Winstock, Wolff, and Ramsey, 2001).

Analysis of contents of items deposited into an amnesty bin at a London dance venue in 1998–1999 found that 46 of 105 tablets that could be identified contained MDMA, three contained MDEA, and two contained 4-MTA (Ramsey et al., 2001).

Pills can be mailed in to a U.S. laboratory that uses GC-MS to analyze their contents. The results are then posted to the DanceSafe website. A review of the last 100 drugs tested in the mail-in category as of October 4, 2003, found 44% contained only MDMA and 4% contained only MDA. Ten percent contained no drug and 8% contained an unidentified substance. Ingredients in the other pills (which might also contain MDMA or MDA) included acetaminophen, benzyl-piperazine (BZP), caffeine, codeine, ketamine, methamphetamine, MDE, pseudoephedrine, and n-(3-trifluormethylpheno) piperazine (TFMPP) (DanceSafe, 2003).

An analysis of street drugs seized in Denmark between 1995 and 2000 found that of 39 samples purported to be ecstasy, 23 contained MDMA, two contained MDE, one contained MDMA and MDE, two contained MDMA and MDA, two contained MBDB, and one contained PMA/PMMA. Ten did not contain any designer drug (Simonsen et al., 2003).

Adverse Effects

Common adverse effects of MDMA include agitation, anxiety, tachycardia, and hypertension; more serious adverse reactions include hyperthermia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, cardiac complications, intracranial hemorrhage, and hepatotoxicity (Teter and Gutherie, 2001; Smith, Larive, and Romanelli, 2002; Goss, 2001). Another term used to describe these adverse effects is "serotonin syndrome," which

is characterized by enhanced physical activity, sweating, lack of coordination, mental confusion, trismus, jaw clenching, agitation, hyperreflexia, hyperthermia, shivering, rhabdomyolysis, metabolic acidosis, myoclonus, tremor, and nystagmus (Schifano, 2003). There is no antidote for MDMA, only supportive care similar to treatment of amphetamine or methamphetamine overdose (Smith, Larive, and Romanelli, 2002). No withdrawal syndrome from MDMA has been reported (Bialer, 2002).

The Drug Abuse Warning Network (DAWN) of SAMHSA collects data on drug-related visits to a sample of the nation's emergency departments (EDs). Visits can include drug abuse and misuse, adverse reactions, accidental ingestion, overmedication, malicious poisoning, suicide attempts, underage drinking, and patients seeking detoxification or drug abuse treatment. The number of mentions of ecstasy in emergency rooms monitored by DAWN increased from 253 in 1994 to 5542 in 2001 and then dropped back to 4026 in 2002, a nonsignificant change (SAMHSA, 2003). Fifty percent of the patients mentioning ecstasy were male, 64% were White, 12% Black, and 9% Hispanic, and they were the youngest of the club drug patients discussed in this paper: 75% were under age 26 (Figure 2). Seventy-two percent mentioned MDMA in combination with other drugs, which included alcohol (40%), marijuana (39%), cocaine (20%), heroin (5%), GHB (5%), methamphetamine (4%), LSD (3%), amphetamine (2%), and ketamine (1%). The motive for using ecstasy was psychic effects (56%), dependence (21%), other/unknown (15%), and suicide (8%), and the reason for contacting the emergency department was unexpected reaction (39%), overdose (30%), or seeking detoxification (13%).

In a study of 173 adolescents and young adults interviewed with the Composite International Diagnostic Interview, Substance Abuse Module, 43% met the DSM-IV criteria for dependence on ecstasy and 34% met the criteria for abuse of ecstasy (Cottler et al., 2001). However, articles on evidence-based treatment protocols for persons seeking help for MDMA dependence do not appear to exist.

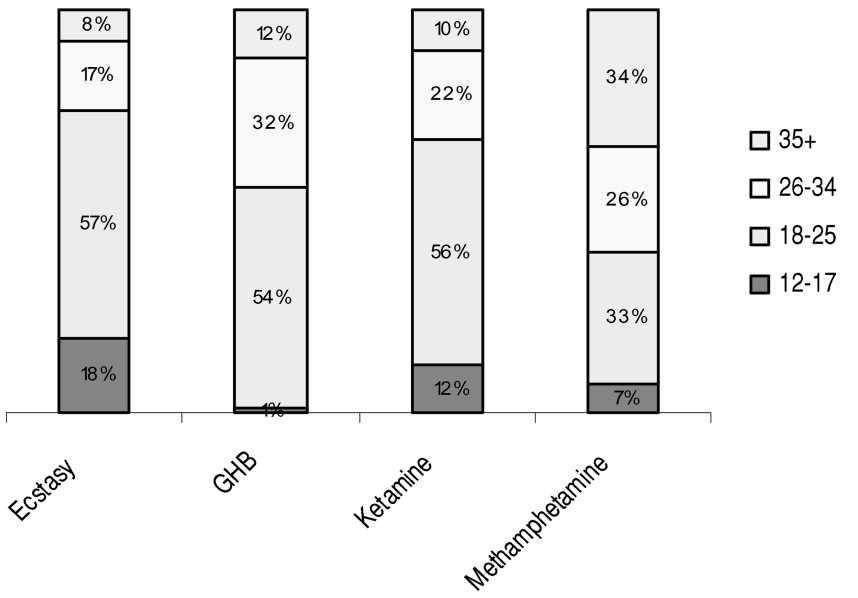

Figure 2. Age groups of patients mentioning club drugs in DAWN emergency departments in coterminous U.S.: 2002.

The incidence with which MDMA has been implicated in driving under the influence is increasing, but there is no clear correlation between the blood concentration of MDMA and the specific demeanor of the subject (Logan and Couper, 2001). A group of young participants who completed test rides in an advanced driving simulator shortly after using MDMA were not affected in the sense of lateral and longitudinal vehicle control, although this deteriorated to a "dangerous" level after use of other drugs with MDMA (Brookhuis, de Waard, and Samyn, 2004).

Five deaths due to use of MDMA and MDEA were reported in 1987 (Dowling, McDonough, and Bost, 1987). Henry and Jeffreys in 1992 reported seven fatalities and concluded MDMA is capable of causing severe toxicity. A study of all deaths related to taking ecstasy in England and Wales between August 1996 and April 2002 found that of the 202 fatalities, 17% involved only ecstasy while the remaining deaths involved ecstasy and other drugs, including alcohol, cocaine, amphetamines, and opiates. Chemically, 86% of all the ecstasy cases were MDMA, 13% were MDA, one case was MDEA, and another PMA. The number of deaths increased each year. The ratio was 4:1, male to female, and 75% were younger than age 29 (Schifano et al., 2003). A review of 22 MDMA fatalities in New York City found seven of 13 that were due to acute MDMA intoxication also involved cocaine and/or opiates; seven more were due to blunt trauma or gunshot wounds, and two were due to combination of natural disease and drug intoxication. Other deaths due to "ecstasy" use actually were caused by hyperthermia following ingestion of PMA (Gill et al., 2002). PMA appears to be more unsafe than MDMA, and its clinical effects may also contribute to a tendency to overdose since the initial "rush" is not as great and users may think they are taking weak doses of MDMA and take more (Caldicott et al., 2003).

Cognitive/Psychiatric Associations

A study of 3634 conscripts entering military service in northern Spain found MDMA users had more extensive drug use histories and those who had used MDMA in the year prior to the study had significantly higher scores on the Neuroticism and Psychoticism Subscales of the Eysenck Personality Questionnaire Adult Form and reported higher levels of sensation-seeking behaviors (Bobes et al., 2002). Another study found that high novelty-seeking scores were characteristic of ecstasy takers, which might predispose those individuals to use ecstasy initially (Dughiero, Schifano, and Forza, 2001).

MDMA has been shown to damage serotonin neurons. Animals exposed to MDMA show decrements that persist in several axon terminal markers including serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAAA), tryptophan hydroxylase (TPH), and the serotonin transporter (SERT) (Koprich et al., 2003). MDMA-associated reductions of serotonergic neurotransmission in those at risk for depression, bulimia nervosa, alcoholism, etc., may push the individual over the threshold for psychopathology (Taffe et al., 2003). An information booklet by the National Drug and Alcohol Research Centre in Australia warns that people in these categories are at higher risk of problems from ecstasy: those with or with a family history of any heart disorder or cardiovascular disease; psychiatric condition, including depression, manicdepression, schizophrenia, and anxiety disorders; kidney disease; neurological or nervous system impairment (e.g., Parkinson's disease, Tourette's syndrome); taking any antidepressant; taking weight-loss medication; or taking medication for blood pressure (Topp, Dillon, and Hando, 1998).

Long-term neurotoxic effects of MDMA, particularly in the serotonergic system, are not fully known. Studies in rodents and nonhuman primates typically treated with higher-dose

MDMA have demonstrated short- and long-term central nervous system (CNS) neuronal damage with attendant reductions in serotonin (O'Leary, Nargiso, and Weiss, 2001).

Fox et al. (2002) found initial cognitive deficits in ecstasy polydrug users may be more apparent in tasks known to be sensitive to temporal functioning. They were significantly more impaired on a recognition task for complex visual patterns and spatial working memory as a function of task difficulty rather than systematic search strategy. They also showed a trend towards impairment on several learning paradigms. They remained relatively unimpaired on most measures associated with prefrontal functioning, with the exception of verbal fluency "letter" generation.

A study of four groups (nonusers, novice users, regular users, and currently abstinent users of MDMA) found evidence of impairments of verbal but not visual memory in MDMA users. The deficits were not attributable either to differences in general reasoning ability or to impairment of working memory. The observed impairment may be attributable to a combination of reversible acute effects of MDMA resolving over a period of 2–3 weeks and more long-term changes associated with extent of lifetime consumption (Bhattachary and Powell, 2001). Evidence has also been found that MDMA use may be associated with deficits in executive functioning (planning, initiation, and self-regulation of goal-directed behavior) (Zakzanis and Young, 2001).

Studies have suggested use of MDMA affects depression, other mood disorders, impulsiveness or hostility, psychotic symptoms, anxiety and panic disorders, and other psychopathologic disturbances. The selective impairments of neuropsychological performance associated with regular ecstasy use have been found not to be reversed by prolonged abstinence, which is consistent with evidence that ecstasy has potent and selective neurotoxic effects on brain serotonergic systems in humans (Morgan et al., 2002). A prospective longitudinal study of mental disorders in ecstasy users found users were at significantly increased risk of DSM-IV substance-related disorders and at higher risk of alcohol use disorders than users of other illicit substances. They also had significantly higher rates for almost all DSM-IV mental disorders than did nonusers or users of other illicit drugs. However, the ecstasy use might be associated with use of multiple substances, and onset of mental disorder is more likely to precede rather than follow use of ecstasy and related substances (Lieb et al., 2002). Individuals who have taken a larger number of MDMA tablets have a higher risk of developing psychiatric disorders, and polydrug use itself may lead to different problems. It may be beneficial to assess the consequences of ecstasy use within the wider context of recreational drug use as a whole (Soar, Turner, and Parrott, 2001).

A review of studies of chronic recreational use of MDMA showed repeated use of ecstasy to be associated with sleep, mood, and anxiety disturbances, elevated impulsiveness, memory deficits, and attention problems that may persist for up to 2 years after cessation. In a subset of humans, particularly adolescents, depletion of serotonin by MDMA use may hasten or enhance vulnerability to a wide array of neuropsychiatric problems such as persistent depression of mood, manifestations of anxiety, psychosis, increases in impulsiveness, hostility, aggression, and sleep disturbances (Montoya et al., 2002).

The levels of past use of ecstasy affect psychological problems. In a web-based survey of 282 ecstasy users, depression, memory problems, anxiety, mood fluctuation, poor concentration, infections, tremors/twitches, and weight loss were all significantly associated with the extent of ecstasy use. Memory problems attributed to ecstasy were reported by 19% of novice users, 52% of moderate users, and 73% of heavy users (Parrott et al., 2002). Further analysis of this dataset found typical ecstasy users (not just heavy or chronic users) reported significantly more difficulties in long-term prospective memory and they made

more completion errors than users of other substances and drug-naïve controls (Rodgers et al., 2003).

Former chronic ecstasy users who had not consumed ecstasy in the last 14 days had higher levels of depression than their matched controls and might be at risk with regard to the development of a more severe depressive syndrome (MacInnes, Handley, and Harding, 2001). Another study found that ex-users of ecstasy could be divided into two groups: those who had quit for mental health reasons and those who had quit for circumstantial reasons. Half of those who quit for mental heath reasons scored in the range for clinical depression and current levels of depression, and anxiety correlated significantly with the cumulative amount of MDMA they had taken several years previously. This study suggests that some users may either be more vulnerable to the adverse effects of MDMA or have preexisting mental health problems for which they self-medicate by using ecstasy. Some of these users experienced mental health impairment that persisted for years after they stopped using the drug (Verheyden, Maidment, and Curran, 2003).

Analysis of a survey of 466 regular MDMA users found that 83% of respondents reported experiencing low mood and 80% reported impaired concentration between ecstasy-taking sessions. Factors affecting mood and cognition included age, gender, extent of MDMA use, and concomitant use of cocaine or amphetamine. The long-term effects most frequently reported included the development of tolerance to MDMA (59%), impaired ability to concentrate (38%), depression (37%), and "feeling more open towards people" (31%). The most prominent concern of the users was the drug's long-term effects on mental health (Verheyden, Henry, and Curran, 2003).

Heavy ecstasy polydrug users reported significantly higher scores than nondrug users on several Symptom Checklist-90 (SCL-90) factors, including phobic anxiety, obsessive-compulsive behavior, anxiety, psychosis, somatization, and significantly higher rates of "loss of sex or pleasure" (Parrott et al., 2001). There were no significant differences between nonusers and moderate MDMA users in scores on a battery of neuropsychological tests. However, heavy users displayed significant deficits on many measures, particularly those associated with mental processing speed and impulsivity, which augments the evidence that MDMA itself, rather than some associated factor, is responsible for the deficits observed (Halpern et al., 2004). Another study found these psychobiological deficits were greatest in heavy ecstasy users and may reflect serotonergic axonal loss in the higher brain regions, especially the frontal lobes, temporal lobes, and hippocampus. These problems seem to remain long after the recreational use of ecstasy has ceased, suggesting that the neuropharmacologic damage may be permanent (Parrott, 2001). However, irreversible ecstasy effects on psychological well-being, cognitive performance, and SERT availability were not confirmed in another study, which found no significant mean differences between the current and past users of ecstasy and the polydrug controls in any of the measures of psychopathology or cognitive performance (Thomasius et al., 2003).

Structural magnetic resonance imaging (MRI) scans of 31 MDMA polydrug users as compared to 29 non-MDMA users found several brain regions had decreased gray matter concentration in MDMA polydrug users, which could account for previously reported neuropsychiatric impairments in MDMA users. Additional studies are needed, but potential explanations could include preexisting brain differences predisposing to MDMA polydrug use, direct MDMA and polydrug toxicity, indirect changes due to MDMA and polydrug toxicity, or combinations of all these factors (Cowan et al., 2003).

MDMA users are reported to be taking selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or sertraline or antioxidants such as vitamin C or vitamin E to minimize their risks. Animal experiments suggest these substances may reduce serotonin depletion

by MDMA but they have not shown they protect against brain damage, and SSRIs may block the metabolism of MDMA by the liver (Harvard Mental Health Letter, 2001) as well as facilitate the occurrence of serotonin syndrome (Schifano, 2003). Underground websites give specific information as to "preloading" and "postloading" and the use of over-the-counter supplements such as 5-hydroxytryptophan (5-HTP), although this information does not appear to have been medically evaluated.

Gender Differences

Research has also shown evidence of gender differences in the effects of MDMA. Equal doses of MDMA per kilogram body weight produced stronger responses in women than men consistent with an increased susceptibility of women to 5-HT-releasing effects of MDMA. Increasing doses of MDMA produced more hallucinogen-like perceptual alterations, particularly in women (Liechti, Gamma, and Vollenweider, 2001). Women have also been found to be more susceptible than men to mid-week low moods following weekend use of MDMA; however, both men and women showed increased self-rated aggression. These results are interpreted in terms of an attenuation of 5-HT function for the period following acute use of MDMA (Verheyden et al., 2002). Rodgers et al. (2003), however, found women were not more vulnerable to the long-term impact of use.

Reneman et al. (2001, 2002) reported that heavy use of MDMA was associated with neurotoxic effects on serotonin neurons, that women might be more susceptible than men, and that MDMA-induced neurotoxic changes in several brain regions of female ex-MDMA users were reversible. However, these findings have raised questions among other researchers (Ricaurte and McCann, 2001; Kish, 2002; Haddad et al., 2002; Ratzenbock, 2002).

There is also a substantial risk for fetal exposure from women who are, or become pregnant, while using MDMA. Pregnant women who use MDMA tend to be young, single, and report psychological morbidity and have a clustering of risk factors that may compromise the pregnancy and fetus. Smoking, heavy alcohol intake, and polydrug use, combined with a higher than expected rate of unplanned pregnancies, increases the risk of fetal exposure to potentially harmful substances (Ho, Karimi-Tabesh, and Koren, 2001). And MDMA may pose a previously unrecognized risk during stages of fetal brain development. Pregnant rats exposed to MDMA during a period that was developmentally equivalent to the human first trimester days had pups with significant neurochemical and behavioral alterations, which is the first report of its kind following a prenatal MDMA exposure (Koprich et al., 2003). Neonatal rats administered MDMA on days analogous to early and late human third trimester brain development evidenced dose-related impairments of sequential learning and spatial learning and memory. This raises concerns about the safety of MDMA when exposure occurs during stages of brain development in the human late fetal period (Broening et al., 2001).

Methodological Criticisms

Research on the effects of ecstasy are continuing to emerge, but the methodological problems inherent in studies of humans give users a reason to discount the evidence amassed thus far. Some of these human studies have relied on patients to report both the extent and timing of MDMA use, some have lacked control groups, and some were based on the assumption that subjects of the studies would match controls before MDMA exposure.

Findings are complicated by the frequent use of other drugs (cannabis and amphetamines) that are known to be associated with cognitive impairment (Freese, Miotto, and Reback, 2002), and this may confound studies of ecstasy users (Croft et al., 2001;

Gouzoulis-Mayfrank et al., 2002). Rodgers et al. (2001) found everyday memory problems were related to cannabis use, with long-term prospective memory deficits related to past ecstasy use. Daumann et al. (2004) have suggested that self-reported psychopathological symptoms in recreational ecstasy users are associated with regular cannabis use. At 18-month follow-up, higher levels of obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, phobic anxiety, and paranoid ideation were significantly correlated with the duration of regular cannabis use. However, Thomasius et al. (2003) found no difference between ecstasy user groups and polydrug controls in any of the measures of psychopathology or cognitive performance. Furthermore, Dafters, Hoshi, and Talbot (2003) found that cannabis users, whether or not they also used MDMA, showed significantly impaired memory function as compared to noncannabis users and concluded that the findings showed the importance of controlling for other drug use (particularly cannabis) when investigating the persistent effects of MDMA on humans.

Other questions have arisen regarding dosing in animal vs. human studies and the inability to test the effects of MDMA on nondrug-using humans. Controlled clinical trials would clarify these issues but legal, ethical, and clinical complications prevent or limit human studies of MDMA (O'Leary, Nargiso, and Weiss, 2001). Cole, Sumnall, and Grob (2002a, 2002b) provided an extensive critique of ecstasy studies and their methodological difficulties, to which others have replied (Morgan, 2002; Croft, 2002; Parrott, 2002).

A major study, "Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ('Ecstasy')" (Ricaurte et al., 2002) was retracted by its authors on September 12, 2003 (Ricaurte et al., 2003). This article suggested that humans who use repeated doses of MDMA over several hours were at high risk for incurring severe brain dopaminergic neural injury (along with significant serotonergic neurotoxicity) and were at increased risk for developing Parkinsonism and other neuropsychiatric diseases involving brain dopamine/serotonin deficiency. This article was previously questioned (Mithoefer, Jerome, and Doblin, 2003) because of the high death rate in the studied primates who were originally reported to have been given a "common recreational dose regimen." Ricaurte retracted his findings after he was unable to replicate the results. The original study utilized a batch of (+)-methamphetamine that had been mislabeled and the brains of the animals who died shortly after treatment with this batch were found to contain only methamphetamine and its metabolite, amphetamine; no MDMA was found. This event lead to an editorial requesting that individual case studies presented in the literature be subjected to rigorous peer review to ensure that all statements are justified on scientific grounds and presented in a balanced manner so that neurologists and the general public are not misled (Kish, 2003).

Further studies are needed. Since data from their studies did not support nor rule out memory decline following use of MDMA, Gouzoulis-Mayfrank et al. (2005) recommended that research strategies move to prospective designs that shed light on the course of possible adverse cognitive effects of ecstasy use. Lastly, Volkow (2004) wrote that over 15 years of research conducted on animals had proven that MDMA damages specific neurons in the brain, and that while there is still much that is not known about the effects of MDMA in humans, the studies in animals show that MDMA is not a benign drug and "has the potential for serious, adverse effects."

Toxicology

Laboratory identification of MDMA is difficult. As many as one-third of immunoassay urine screens have failed to detect it in standardized specimens (Tong and Boyer, 2002),

although some cross-reactivity with amphetamines may occur if the concentration is high. Toxicologists have now developed procedures for detection or quantification of MDMA and its metabolites (Moeller and Kraemer, 2002).

GHB

Gamma hydroxybutyrate (sodium hydroxybutyrate, sodium oxybutyrate, GHB), a naturally occurring fatty acid found in mammals, is a CNS depressant that has intoxicating effects and, at sufficiently high doses, anesthetic properties (Nicholson and Balster, 2001). It was first isolated and investigated in 1960, and early testing showed GHB could produce a dose-dependent sedation and anesthesia in laboratory animals and humans. It was originally available in the U.S. as a consumer product sold as a dietary supplement and for sedative and body-building effects. Because of its intoxicating effects, it became known as a club drug. In 1990, after reports of adverse events, the U.S. Food and Drug Administration (FDA) ordered the removal of GHB from the market. GHB produces anterograde amnesia and may cause victims to lose consciousness and be unable to resist or recall sexual assault. Because of its use to commit assault and its use as a club drug, it is now a Schedule I drug in the U.S. and Schedule IV of the 1971 UN Convention. However, GHB is a Schedule III drug when used under an FDA-approved protocol to treat cataplexy in patients with narcolepsy. To minimize diversion, Orphan Medical, Inc. is distributing Xyrem to users on a registry through a central pharmacy system rather than through local pharmacies.

GHB is known on the street by terms such as Fantasy, liquid ecstasy, liquid X, Grievous Bodily Harm, scoop, cherry meth, soap, salty water, organic quaalude, G, Growth Hormone Booster, Somatomax PM, Gamma OH, and Georgia Home Boy. It is available as a powder or a solution.

One of its precursors, gamma butyrolactone (GBL), is converted to GHB by endogenous lactonases. GBL is used as an industrial solvent and has been marketed as a dietary supplement and cleaner for computer parts. Various brand names include Fire Water, Revivarant, Revivarant G, RenewTrient, GH Revitalizer, Verve, GH Release, Gamma-G, InvigorateX-Depress, Furomax, Insom-X, and Blue Nitro. GBL is a List I chemical in the U.S. and requires documentation and justification of all purchases and sales. If intended for human consumption, GBL and related substances are regarded as controlled-substance analogues (Smith, Larive, and Romanelli, 2002).

Another precursor is 1,4-butanediol (1,4-BD), which is a Class I health hazard and is an industrial solvent sold to misusers under names such as (Revital)ize Plus, Serenity, Enliven, GHRE, SomatoPro, NRG3, Weight Belt Cleaner, Thunder Nectar, Pine Needle Extract, and Pine Needle Oil. It is metabolized in the body by alcohol dehydrogenase to GBL, which is then metabolized to GHB (Smith, Larive, and Romanelli, 2002), and this conversion from 1,4-BD to GBL to GHB raises important issues about sample types for forensic scientists and law enforcement personnel (Ciolino, 2001). It possesses a higher potency than GHB (Carai et al., 2002).

Illegal GHB and its precursors, GBL and 1,4-BD, can be obtained over the Internet and sometimes are marketed as solvents such as ink jet printer fluid or as GHB alternatives in health food stores, gyms, raves, and nightclubs. Chemistry kits, reagents, and recipes are available on the web to convert the precursors into GHB (Nicholson and Balster, 2001; Mason and Kerns, 2002), and GHB itself can be ordered from websites in some other countries.

Epidemiological Information

GHB was first reported at a CEWG meeting in December, 1990 (Hall, 1986). At the June and December, 2003 CEWG meetings, reports of GHB use varied across the nation. In Atlanta, it was prevalent in the gay scene. In Chicago, levels of use of GHB were low and it tended to be used by young heroin inhalers. In Miami, Minneapolis-St. Paul, Detroit, and San Francisco, use was reported as down. In Los Angeles, typical users were older White males. Use in Texas was centered in the Dallas-Fort Worth metroplex area (Maxwell, 2003b), and the number of unduplicated, public treatment admissions has gone from two in 1997 to 21 in 2003 (Maxwell and Spence, 2005).

The NFLIS system reported that in 2003, 572 items were identified as GHB or GBL, down from a high of 767 in 2000 (NFLIS, 2004).

Surveys

The MTF survey showed that between 2000 and 2004, use for eighth and tenth graders decreased while use by twelfth graders varied (Table 1) (Johnston et al., 2004a). Past year use in 2003 by college students and by young adults was as low or lower than for secondary school students (Johnston et al., 2004b). The NSDUH did not survey for use of GHB.

In Australia, a study of 76 GHB users found they were stable, highly educated, and well functioning. They had extensive experience with a range of other drugs and typically used GHB with other drugs. But even though the users did not have a long or extensive experience with GHB, 99% reported at least one negative side effect. Over half (52%) reported becoming unconscious. The high rate of problems reported by a group with limited use of this drug suggests that in a context of polydrug use, GHB is associated with significant risks to users (Degenhardt, Darke, and Dillon, 2002, 2003).

A survey of 1151 readers of a dance music magazine found that 13% had ever used GHB and that 3% had used it in the past month, but it was not a substance that was used with ecstasy (Winstock, Griffiths, and Stewart, 2001). The Montreal survey of rave attendees found that 19% had ever used GHB and of those who had used drugs in the past month, 28% had used GHB (Gross et al., 2002).

A survey of gay and bisexual men in San Francisco who attended circuit parties found that among those who reported a drug overuse incident, 53% reported GHB or GBL was involved. Of those who used three or more drugs in the most recent circuit party weekend, 25% used GHB or GBL (Mansergh et al., 2001).

Adverse Effects

Illicit use of GHB has been associated with little consistency and precision in the doses consumed. An oral dose of 10 mg/kg has been reported to cause euphoria, amnesia, and hypotonia; doses of 20–30 mg/kg have resulted in somnolence within 15 minutes. Doses greater than 50 mg/kg result in unconsciousness and coma (Bialer, 2002; Okun et al., 2001).

GHB and alcohol together have been reported to have a synergistic (McCabe et al., 1971) or additive effect. The steep dose-response curves of both ethanol and GHB for many of their behavioral effects may account for the serious effects seen clinically when seemingly "moderate" doses of the two drugs are combined, rather than any synergistic actions of the drug combination (Lamb et al., 2003).

DAWN emergency room mentions of GHB increased from 56 in 1994 to a high of 4969 in 2000, and then declined to 3330 in 2002 (SAMHSA, 2003). Of the patients in 2002, 66% were male and 89% were White. They were the oldest of the "club drug" patients; 44% were ages 26 and older (Figure 2). Eighty percent mentioned using other drugs with GHB: alcohol (64%), cocaine (15%), marijuana (14%), methamphetamines (7%), MDMA (7%), and amphetamines (6%).The motive for using GHB was psychic effects (80%) or other/unknown (19%), and the reason for the visit to the emergency department was overdose (61%) or unexpected reaction (36%).

GHB should be used with caution by HIV-seropositive patients with predisposing seizure disorders or with opportunistic infections that may lower seizure thresholds. GHB may also cause severe nausea, vomiting, and gastrointestinal tract irritation that may complicate antiretroviral therapy and affect adherence to the regimen for HIV drugs (Romanelli, Smith, and Pomeroy, 2003).

The survey of 76 GHB users in Sydney found that 29% typically drank more than five alcoholic drinks when using GHB and that 53% had overdosed on GHB. Those who had overdosed had used it more frequently than those who had not overdosed. Of those who had used GHB more than 15 times, 75% had overdosed at least once and a third had overdosed more than three times (Degenhardt, Darke, and Dillon, 2003). Likewise, use of GHB and a depressant drug can result in greater CNS depressant effects than seen with either drug alone (Nicholson and Balster, 2001).

The most serious effects of a GHB overdose are sudden onset of coma and respiratory depression. Withdrawal from GHB can be complicated, especially if other drugs or alcohol are involved. The one distinguishing feature of GHB toxicity is the sudden awakening of the patient from a comatose state to a normal or hyperactivated state of arousal. Severe withdrawal reactions have been reported, with some dependent persons escalating their use to every 2 to 4 hours in a pattern of around-the-clock dosing (Bialer, 2002; Freese, Miotto, and Reback, 2002; McDaniel and Miotto, 2001; Mahr, Bishop, and Orringer, 2001; Schneir, Ly, and Clark, 2001). For a detoxification protocol, see http://www.tcada.state.tx.us/research/GHB_Withdrawal.pdf. and McDonough et al. (2004).

While these case studies show the abuse potential, there is little information on chemical dependency treatment. For some who use GHB or its precursors regularly, tolerance and dependence seem to build rapidly. Intervention and treatment efforts for GHB users are often delayed due to the fact many providers lack knowledge of symptoms of GHB intoxication and dependence. Information about GHB on the Internet and other lay sources may be misleading and imply that GHB is nonaddictive and has health benefits (Freese, Miotto, and Reback, 2002).

GHB is also a factor in cases of driving under the influence of drugs. It should be considered and tested for when drivers exhibit symptoms of CNS depression not accounted for by alcohol or other drugs or where the drivers exhibit a tendency to fall asleep or lose consciousness (Couper and Logan, 2001).

An analysis of forensic cases in the Netherlands involving use of GHB from the second half of 1999 through the second half of 2001 found that six cases involved "chemical submission" in which GHB might have been given to influence the consciousness of a person and to make the person defenseless. Another 13 cases involved driving under the influence of alcohol and/or drugs, and in seven of these cases, other drugs and/or alcohol were found. Another 16 cases of unknown causes of death were studied, and in 12 of these, other drugs and/or alcohol were used with GHB. Three were bodybuilders (Bosman and Lusthof, 2003).

Cognitive/Psychiatric Associations

GHB is a drug with a complex pharmacology and it has potentially important therapeutic uses to promote normalization of sleep patterns, treatment of narcolepsy, and alcohol withdrawal. Since it is also an abused drug, the extent to which the potential therapeutic actions of GHB-like drugs can be separated from the abuse of GHB-like drugs will require the development of compounds that act specifically at the GHB receptor while not undergoing conversion to a GABA-active compound (Lamb et al., 2003).

GHB has been shown to alleviate withdrawal syndrome for alcoholics in European studies. In a double-blind comparative study of the effects of GHB and clomethiazole (CLO) in ameliorating the symptoms of alcohol withdrawal, no difference was found in ratings of alcohol withdrawal symptoms or requests for additional medication. After tapering off the active medication, there was no increase in withdrawal symptoms, indicating that physical tolerance did not develop to either GHB or CLO (Nimmerrichter et al., 2002). Thirty-five alcohol-dependent patients who met the criteria for treatment resistance were given doses of GHB in an open 1-year study. Sixty percent completed the protocol, with 11.4% showing complete abstinence, 14.3% showing strongly reduced alcohol intake, and 34.3% still under treatment after a year (Maremmani, Lamanna, and Tagliamonte, 2001).

Caputo et al. (2003) evaluated the efficacy of GHB as compared to naltrexone in maintaining abstinence from alcohol after 3 months of treatment and found that in patients who failed to be abstinent, no relapses in heavy drinking were observed in the naltrexone group, while in the GHB group, all patients relapsed. The study found GHB was more effective than naltrexone in maintaining abstinence from alcohol in a short-term treatment period, but naltrexone confirmed its ability to reduce alcohol relapses.

Toxicology

Knowledge about the extent of abuse of GHB and its precursors has also been hampered because they are not detected by routine urine screens, and other immunoassays for GHB and GBL are not available (Moeller and Kraemer, 2002). They are reliably detected by specific requests for GC-MS, but timing is important, as GHB is rapidly excreted as carbon dioxide through exhalation (Bialer, 2002). GHB has a half-life of 27 minutes (Schneir, Ly, and Clark, 2001) and it is virtually undetected in the urine 12 hours after ingestion (Smith, Larive, and Romanelli, 2002). Since GHB continues to be produced after death, it should not be stored in tubes containing citrate, but should be collected in tubes containing NaF (Bosman and Lusthof, 2003). In cases of chemical submission, both urine and blood should be analyzed, since GHB is present longer in urine than in blood, and a detailed case history should be obtained. It is the policy of the U.S. Federal Bureau of Investigation (FBI) laboratory to report only "positive" GHB results when substantial amounts of GHB are found in both urine and blood (Karch, Stephens, and Nazareno, 2001).

A sensitive and specific GC-MS method using selective ion monitoring has recently been developed for the quantification of GHB in blood. This method uses liquid-liquid extraction and disilyl-derivatization, without conversion to GBL, followed by GC-MS analysis using GHB-d_6 as the internal standard. It is sensitive in that it requires only 50 mL of sample blood (Elian, 2001). GHB has also been found to distribute into the hair root bulb (Kalasinsky et al., 2001).

Ketamine

Ketamine, a derivative of phencyclidine hydrochloride, is an anesthetic that has been approved for human and animal use, both in trauma and emergency surgery as well as

veterinary medicine. The drug's potential for abuse was recognized early (Reier, 1971; Collier, 1972). Ketamine on the street is also known as Special K, Vitamin K, K, kit-kat, keets, super acid, super k, and jet.

Ketamine users try to achieve or "fall into" a "k-hole," which is described as physical immobilization and social detachment lasting up to an hour. It is characterized by a distorted sense of space, such as a small room appearing the size of a football field, and an indistinct awareness of time, such as a few minutes seeming like an hour. As the body slows and disengages from time and space, the mind turns to experiential realms such as spiritual journeys, interactions with famous or fictitious persons, and hallucinatory visions. The k-hole ends rather abruptly but can be quickly reentered following another injection of ketamine (Lankenau and Clatts, 2002).

Ketamine is a Schedule III controlled substance and is available in powder and tablet forms as well as an injectable formulation. It is difficult to manufacture and most users acquire it through diversion of the prescription product or theft from veterinary supplies. Recreational users usually administer ketamine intranasally, although it is also injected. Ketamine users will often take several sequential doses of the drug in order to maintain psychotropic effects over time. Elimination half-life is approximately 2 hours. Anesthesia doses are 2 to 10 mg/kg while recreational doses can range between 50–100 mg (Koesters, Rogers, and Rajasingham, 2002).

Epidemiological Information

Abuse of ketamine was first reported at a CEWG meeting in December 1991 (Frank, Galea, and Simeone, 1992). At the June and December, 2003 CEWG meetings, ketamine use was reported as higher and demand was greater than availability in Detroit; use was down in Boston, Los Angeles, Newark, and San Francisco. In Texas, there were eight calls in 1998 to poison control centers about misuse or abuse of ketamine and there were 12 calls in the first half of 2003 (Maxwell, 2003b). The number of unduplicated, public admissions to Texas treatment programs with a primary, secondary, or tertiary problem with ketamine went from one in 2001 to 18 in 2003 (Maxwell and Spence, 2005).

The NFLIS system reported that there were 691 ketamine exhibits identified in 2003, down from a high of 1457 in 2002 (NFLIS, 2004).

Surveys

The MTF survey reported past year use of ketamine declined for secondary students (Table 1). The decrease between 2003 and 2004 for tenth graders was statistically significant (Johnston et al., 2004a). Use of ketamine by college students and young adults was as low or lower than for secondary students (Johnston et al., 2004b). The NSDUH did not survey for ketamine.

A survey of 1151 readers of a dance music magazine found that 22% had ever used ketamine and that 4% had used it in the past month; 14% had used it in combination with ecstasy (Winstock, Griffiths, and Stewart, 2001a).

Twelve percent of the respondents in the Edinburgh dance party survey had used ketamine in the past year (Riley et al., 2001). Fourteen percent of the attendees at raves in Montreal reported lifetime use of ketamine, and of those individuals who had used drugs in the past month, 35% had used ketamine (Gross et al., 2002).

A survey of 100 individuals in Sydney who had ever used ketamine found they were a well-educated older group of party drug users who used ketamine while dancing. Many

users had experienced significant negative effects such that some had either reduced their dose or stopped use altogether. Users reported regularly experiencing an inability to speak, blurred vision, lack of coordination, and increased body temperatures. However, these symptoms were seen by the users as positive effects of the drug that encouraged, rather than discouraged, experimentation among regular party drug users (Dillon, Copeland, and Jansen, 2003).

While ketamine is typically inhaled, a study of 25 young ketamine injectors in New York City found intramuscular injecting more common than intravenous injection. Injection groups were often large, multiple injections within a single episode were common, and bottles of ketamine were shared. Most use was not in club or rave settings but in a street or park, as injecting ketamine often created an experience that did not require a specialized setting such as a rave. Ketamine injectors represent an emerging, though often hidden, population of injection drug users who are at high risk both because of their injecting practices and their homelessness, drug dealing, and sex work (Lankenau and Clatts, 2002).

The survey of gay and bisexual men in San Francisco who attended circuit parties found that among those who reported a drug overuse incident in the past year, 45% said ketamine was the drug most often involved. In the most recent circuit party weekend, among those who had used three or more drugs, 58% had used ketamine (Mansergh et al., 2001). In addition, a study of gay and bisexual males attending circuit parties in three cities found over 60% had used ketamine at parties in the past year and the relationship with unsafe sexual behavior was significantly associated with frequent use of ketamine (Mattison et al., 2001).

Adverse Effects

The number of mentions of ketamine in the DAWN emergency room system increased from 19 in 1994 to 679 in 2001, but dropped to 260 in 2002. In 2002, 77% of the patients were male; 64% were White, 8% Hispanic, and race/ethnicity was unknown for 21% (SAMHSA, 2003). Ketamine users were older than ecstasy users but younger than users of GHB; 68% were under age 26 (Figure 2). Eighty percent of patients mentioning ketamine in 2002 also mentioned concurrent use of other drugs: alcohol (29%), heroin (24%), marijuana (19%), cocaine (13%), MDMA (12%), methamphetamine (7%), amphetamines (4%), LSD (3%), and GHB (3%). The motives for use were psychic effects (68%), suicide (16%), or other/unknown (16%). The reason for going to the emergency department was overdose (47%), unexpected reaction (28%), chronic effects (11%), or seeking detoxification (9%).

Cognitive/Psychiatric Associations

Frequent users often take ketamine in a pattern of cyclical binges similar to cocaine or amphetamine dependence. Tolerance builds rapidly and can be very high. Users can become psychologically dependent, with craving and a high tolerance, but there is little documented evidence of a physiological withdrawal syndrome (Jansen, 2000), although the literature does contain case reports (Jansen and Darracot-Cankovic, 2001). At high doses, ketamine can cause delirium, amnesia, impaired motor function, high blood pressure, depression, and potentially fatal respiratory problems. Low dose effects are described as "mild, dreamy, floaty, and slightly outside their bodies." Higher doses produce hallucinogenic "trippy" effects that make one seem far away from one's body, and reaching the "k-hole" is described as being a near-death experience that can be frightening or "spiritually significant," according to websites. Flashbacks can recur days or weeks after use (Freese, Miotto, and Reback, 2002).

In recreational users, ketamine appears to induce acute and severe impairments of working, episodic, and semantic memory as well as psychotogenic and dissociative effects (Curran and Morgan, 2000). These effects could reflect chronic or residual effects of taking the drug or pre-existing differences in ketamine users (Curran and Monaghan, 2001), but they also suggest that repeated use of ketamine produces chronic impairments to episodic memory, findings that have worrying implications for the burgeoning population of ketamine abusers (Morgan et al., 2004b).

Taffe et al. (2002) concluded that recreational exposure to subanaesthetic doses of ketamine was likely to induce wide-ranging compromise of cognitive function ranging from mnemonic to attentional to motor domains. Even if such acute compromise of function was short lasting, it might produce significant secondary and tertiary health risks ranging from disruption of the ability to operate a motor vehicle to poor decisions regarding risky sexual behavior, which may be of particular importance for ketamine-using subpopulations.

Long-term cognitive or neuropsychiatric effects have not been sufficiently studied in ketamine users (Freese, Miotto, and Reback, 2002). Earlier studies found that chronic abuse of ketamine may be associated with persisting impairment of memory and other cognitive function in humans, although it may not affect attentional processes or spatial memory but may interfere only selectively with cognition. A study of rhesus monkeys found that ketamine interferes with multiple aspects of cognition at subanesthetic doses (Taffe et al., 2002). As with other "club drugs," drug-challenge investigations of the effects of ketamine in humans are limited by ethical concerns.

Morgan et al. (2004a) sought to understand the mechanisms of compulsive ketamine use and found ketamine acutely impaired response inhibition and had related biphasic effects on the subjective reinforcing effects of the drug. It altered glutamatergic transmission, which may underlie the continued compulsive abuse of ketamine. They found no residual cognitive effects following a single dose of ketamine, but found it increased schizophrenic-like and dissociative symptoms.

An HIV-specific issue is that adherence to antiretroviral regimens is a primary concern and the hallucinogenic effects of ketamine may affect drug-taking behavior, and cardiovascular effects of the drug may be deleterious among patients with underlying heart disease or lipid abnormalities (Romanelli, Smith, and Pomeroy, 2003).

No antidote exists for ketamine overdose; management is supportive care with special attention to cardiac and respiratory functions (Smith, Larive, and Romanelli, 2002). Two ketamine-dependent patients who presented to psychiatric services in Singapore had psychedelic and psychotic effects that were dose-related and included multimodal hallucinatory experiences; a sense of slowing; paranoid ideation; and enhancement of sexual, musical, and sensory enjoyment. The psychotic symptoms resolved quickly with symptom-targeted treatment, but breaking the ongoing compulsion to use seemed more difficult (Lim, 2003).

After detoxification, one treatment protocol recommended following the model used for cocaine and amphetamine dependence, with abstinence from all drugs from day one. As with stimulant dependence, the therapist should avoid confrontation, as the likelihood of the person dropping out of treatment was very high. Relapse prevention involved discovering what situations and triggers occur before taking the steps that lead to relapse so alternative responses could be developed (Jansen and Darracot-Cankovic, 2001). Additional studies are needed to better understand the extent of ketamine abuse and dependence and to identify symptoms of withdrawal and effective treatments (Freese, Miotto, and Reback, 2002).

Toxicology

Ketamine is not detected in routine drug screens, and clinicians should be aware that immunoassays for PCP may cross react with ketamine assays (Smith, Larive, and Romanelli, 2002). High-performance liquid chromatography is required to reliably detect ketamine (Koesters, Rogers, and Rajasingham, 2002).

Rohypnol

Rohypnol (flunitrazepam) is a benzodiazepine originally formulated for preoperative anesthesia or sedation and treatment of insomnia. At low doses, flunitrazepam acts as a muscle relaxant and a sedative-hypnotic. At higher doses, it can cause lack of muscle control and loss of consciousness. Flunitrazepam has had a long history of abuse by heroin and cocaine addicts, and because it was specifically formulated to produce anterograde amnesia, it has been used to commit sexual assault. In addition, it has gained popularity among youths as a "cheap drunk."

Street names include roofies, la rocha, roche, R2, rope, FM2, forget-me pill, rowie, run-trip-and-fall, los dos, and Mexican valium.

Epidemiological Information

Rohypnol (flunitrazepam) was first reported at a CEWG meeting in June 1993 (Hall, 1994). It was introduced by Hoffman-LaRoche in Europe in the 1970s; it was never legally marketed in the U.S. or Canada. There were occasional mentions of the drug in calls to the Florida Drug Hotline in the 1980s, and these often involved airline employees who had bought the drug in Latin America. The problem grew after Hurricane Andrew struck south Florida in August 1992, which resulted in an influx of out-of-state construction workers ("roofers from hell") who found cocaine in Miami, introduced speed, and began trading drugs for drugs (hence the name "roofies") (Maxwell and Hall, 1995).

By November, 1994, it was identified as a problem along the Texas-Mexico border, where an estimated 1.4 million pills were being declared and brought through Laredo in 1995 (Shepherd and McKeithan, 1995). It subsequently spread northward and was identified in at least 32 states (Hall, 1995). In 1996, the U.S. government prohibited the importation of the drug into the country, but it remains available in other countries and continues to be illegally brought into the U.S. New Zealand and Sweden have prohibited or limited its use. Roche has withdrawn Rohypnol from the Australian market, although 1-mg Hypnodorm, which is flunitrazepam produced by another company, remains available.

Since 2001, only the 1-mg Roche tablet has been available, although generic products continue to be available in the 2-mg strength (McGarry-Ross, 2002), which has been the strength preferred for misuse, since street lore holds that the 2-mg pill produces a quicker "high" than two 1-mg pills. Although the generic pills may be white and round, Roche has reformulated the 1-mg pill to be a grayish-green oval tablet. In an attempt to deter sexual assault, it now contains a dye that will turn the liquid blue. However, some sexual predators have been reported to serve blue punches and blue fruit drinks (Maxwell, 2004).

At the June and December 2003 CEWG meetings, Rohypnol use was reported down in Miami, "quiet" in St. Louis, and a continuing problem along the Texas-Mexico border. While Texas poison control centers and Texas NFLIS data show Rohypnol use was dropping (Maxwell, 2003b), the number of admissions to public treatment for a primary, secondary, or tertiary problem with Rohypnol increased from 104 in 1994 to 303 in 1999 and then dropped to 230 in 2003 (Maxwell and Spence, 2005).

In 2000, Taiwan moved all benzodiazepines from over-the-counter status to scheduled drugs, and three, including flunitrazepam, were placed on Schedule III. A duplicate prescription sheet was required and it could only be filled in the Department of Pharmacy at Taipei Medical University-Wan Fang Hospital. The number of flunitrazepam pills prescribed dropped from 33,610 in the quarter June 2000 through September 2000 to 12,108 in the quarter February 2001 through May 2001 (Shen et al., 2002).

School and Household Surveys

The MTF survey reported that past year use of Rohypnol by eighth graders peaked in 1996 and peaked for tenth graders in 1997 (Table 1). It peaked for twelfth graders in 2002 and again in 2004 (Johnston et al., 2004a). In 2004, the Texas Secondary School Survey found that students in grades 7–12 who lived on the Texas border reported 5.4% past year use of Rohypnol, as compared to 1.4% past year use by Texas students not living on the border (Liu, 2005). The NSDUH survey reported in 2002 that 0.2% of the population had ever used Rohypnol. Some 0.2% of those ages 12–17 reported lifetime use, as compared to 0.6% of those 18–25 and 0.1% of those 26 and older (SAMHSA, 2004).

Adverse Effects

Adverse effects of flunitrazepam include hypotension, dizziness, confusion, visual disturbances, urinary retention, and in some users, aggressive behavior. Acute patient management of overdose is supportive care and attention to the possible ingestion of other CNS depressants (Smith, Larive, and Romanelli, 2002).

DAWN emergency department mentions peaked in 1996 and have decreased since. Seventy-nine percent of the patients in 2002 were male and 68% were Hispanic. Sixty-eight percent were under age 26 (Figure 2). Their motives for using Rohypnol were psychic effects (74%), suicide (17%), or dependence (9%), and their reason for emergency department contact was unexpected reaction (57%) or overdose (28%) (SAMHSA, 2003).

The effect of flunitrazepam is confounded by the concurrent use of alcohol or other drugs. The drug is used nonmedically because it reinforces the depressant effects of heroin and blunts the "crash" after use of cocaine (Druid, Holmgren, and Ahlner, 2001). Where available, it has been called the "most preferred" benzodiazepine among heroin users, but there are individuals who use the drug for its own effect to get high, rather than using it to enhance the effect of other drugs (Samyn et al., 2002).

Studies of juvenile delinquent populations have found flunitrazepam use can lead to serious violent behavior in these groups ("unpredictable," "very aggressive," and "frightening") and in subjects characterized by vulnerable personality traits (Daderman et al., 2002). Of 60 nonpsychotic young male forensic psychiatric patients in Sweden, 18 were flunitrazepam users. The frequency of previous admissions and actual sentences of these users deviated significantly from forensic patients who did not use flunitrazepam. Flunitrazepam abuse per se might be more responsible for their tendency to commit crimes characterized by danger and thrill-seeking than their personality traits. The most important conclusion from this study was that an accurate assessment of flunitrazepam use is needed in forensic psychiatry (Daderman and Edman, 2001).

Rohypnol has been found in cases of driving under the influence. In Norway, of 818 blood samples taken from suspected impaired drivers between 1987 and 1998, those who were actually impaired had significantly higher blood levels of diazepam, oxazepam, and flunitrazepam than those not impaired (Bramness, Skurtveit, and Morland, 2002).

Interactions between flunitrazepam and the opioids are neither simple nor predictable. High-dose flunitrazepam augments lethality two-fold in methadone-treated rats and six-fold in buprenorphrine-treated rats. Flunitrazepam administration appeared to have no significant effect on morphine lethality. However, time to death was altered in the buprenorphrine plus flunitrazepam group, suggesting differing mechanisms of death. The mechanisms for flunitrazepam-induced alteration of opioid toxicity remain to be seen (Borron et al., 2002). The interaction between flunitrazepam and buprenorphrine could pose a significant problem in the U.S., given the continuing illegal importation of Rohypnol into border states and the recent implementation of buprenorphrine for treatment of opiate addiction in the U.S.

Toxicology

While a standard component of most urine drug screens is testing for benzodiazepines, flunitrazepam is administered in such small amounts and distributed so rapidly that detection methods commonly fail. Flunitrazepam has an elimination half-life of about 3.5 hours. Samyn et al. (2002) reported a method for onsite screening for flunitrazepam in oral fluids that could detect the drug within 6 hours of use, but the screen should be confirmed. Typical toxicological tests can only detect flunitrazepam in blood and urine for up to 72 hours after ingestion due to quick metabolism and elimination. ElSohly Laboratories had a contract from Roche to receive and test samples submitted by law enforcement agencies, and flunitrazepam was found in less than 1% of the 3308 samples, as compared to 38% alcohol, 4% GHB, 8% benzodiazepines other than flunitrazepam, and 18% tetrahydrocannabinol. Negrusz and Gaensslen (2003) found the electron ionization gas chromatography-mass spectrometry method used by ElSohly did not provide enough sensitivity to detect flunitrazepam in urine after a single dose.

Drug-facilitated sexual assault cases require toxicological analysis in addition to the usual forensic biological examinations and DNA typing routine in most sexual assault cases. Because persons who have been sexually assaulted may not report the crime for days or weeks, forensic hair testing can be used in the case of flunitrazepam-facilitated sexual assault (Negrusz and Gaensslen, 2003).

Conclusion

Party drug use has been conceptualized as a very simple phenomenon that involved dancing at raves and taking drugs. A closer examination of the published literature has shown that each drug has different properties and often different users in different settings. Each has different adverse effects and requires different acute care protocols. Even though the "club drug" phenomenon was identified early, scientific information about these drugs, their identification, and short- and long-term effects are still evolving. The lack of research-based information on the adverse effects of these drugs has led to the emergence of a range of web sites that may or may not provide accurate information, and the limitations on research on human subjects has meant that some findings may be discounted by users. Treatment protocols based on the latest research on the psychological and physiological effects of these drugs need to be developed and evaluated.

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RÉSUMÉ

Ce compte rendu résume la littérature la plus récente (datant des années 2002–2004) concernant les pilules de fêtes (“ club drugs ”), c’est-à-dire la MDMA, le GHB, la kétamine et le Rohypnol, drogues utilisées aux rave-parties et soirées dansantes. La littérature indique que les caractéristiques, les usagers, et le cadre de consommation varient d’une drogue à l’autre. Aussi, chaque drogue a ses propres effets nocifs et donc exige un protocole de soins urgents individuel. Quoique ces drogues aient été identifiées de bonne heure, les informations scientifiques les concernant, y compris les tests toxicologiques pour les identifier, sont toujours en cours d’évolution. Des études publiées sur les effets de ces drogues sur les humains à court et long terme deviennent de plus en plus disponibles, mais à cause de la protection des sujets humains dans le cadre de la recherche, elles ne sont pas toujours aussi rigoureuses que l’on souhaiterait, et elles peuvent même être citées par les usagers de drogues pour discréditer les conclusions que ces drogues sont dangereuses. Le manque d’informations sur ces drogues qui soient basées sur la recherche a encouragé la parution de sites internet dont les informations fournies peuvent ne pas être toujours de bonne qualité. Ce qu’il faudrait maintenant est d’utiliser les données les plus récentes et de la meilleure qualité pour évaluer des protocoles de traitement pour chacune de ces drogues différentes.

RESUMEN

Esta revisión resume lo último en la literatura de las drogas de “fiesta” o “club,” como MDMA, GHB, ketamine, y Rohypnol, publicadas en 2002, 2003, y los principios del 2004. Las drogas de “club” se catergorizan por su uso en fiestas y raves. La literature demuestra que cada una tiene diferentes propiedades, usuarios, alrededores, diferentes efectos adversos, y requeren diferentes cuidados. Aunque estas drogas han sido identificadas, la información científica al respeto a ellas-incluso los examenes de toxicología para identificarlas, siguen evolucionando. A pesar de que los estudios sobre los efectos de corto y largo plazo usando estas drogas se han aumentado, los estudios estan limitados por tener sujetos humanos, no estan rigurosos como deseados, y los usarios podrían descréditar la información. Por esa razón, se encuentran más páginas en la internet que podrían tener información equivocada. Por eso se requere tener tratamientos de una dependencia química evaluada con lo último de las investigaciónes sobre estas drogas.

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Glossary

Amyl nitrite. An inhalant that is often used for its intoxicating effects; also known as "poppers."

Anterograde amnesia. Loss of memory following an event.

Antiretrovirals. Substances used to kill or inhibit the multiplication of retroviruses such as HIV; antiretroviral drugs attack HIV, which is a retrovirus.

Anxiety disorder. These psychological disorders are characterized by fear and discomfort. Some anxiety disorders include panic disorder, phobias, obsessive-compulsive disorder, and acute stress disorder.

Benzodiazapines. A class of sedative/hypnotics drugs that act as tranquilizers and are commonly used in the treatment of anxiety.

Biphasic. Having two phases.

Bipolar disorder. Previously called manic-depression, bipolar disorder is a mood disorder characterized by varying combinations of high (mania) and low (depression) mood swings.

Bulimia nervosa. An eating disorder characterized by recurrent episodes of binge eating and inappropriate behavior to prevent weight gain, such as excessive exercise, misuse of laxatives, self-induced vomiting, etc.

Buprenorphrine. An opiate drug used to relieve moderate to severe pain and also used as an opioid substitute in managing drug dependency.

Cataplexy. A medical condition where a person suddenly feels weak and collapses at moments of strong emotion, including laughter, anger, fear, or surprise.

Circuit parties. Multi-event weekends that cater to gay and bisexual men, and can be a venue for use of drugs and alcohol.

Clomethiazole (CLO). A sedative and anticonvulsant often used in the treatment of alcohol withdrawal.

Dependence. A pattern of substance misuse characterized by a combination of factors, such as withdrawal, tolerance, cravings, out-control use, and use despite negative effects.

Depression. A mood disorder characterized by poor appetite or overeating, sleeplessness or hypersomnia, low energy or fatigue, low self-esteem, feelings of hopelessness, and difficulty concentrating or making decisions.

Disseminated intravascular coagulation. A complex and controversial systemic thrombohemorrhagic disorder involving the generation of intravascular fibrin and the consumption of procoagulants and platelets. It is seen with a number of well-defined clinical situations, including sepsis and major trauma.

Dissociative. Of, relating to, or tending to produce dissociation, such as the dissociative phenomena associated with schizophrenia.

DSM-IV. Diagnostic and Statistical Manual, 4th edition, which is the diagnostic criteria of psychiatric disorders published by the American Psychiatric Association.

Empathogen. A term that describes a drug's ability to increase feelings of empathy and pleasure.

Enactogen. A term that describes a drug's ability to facilitate retrieval of "inner" material and to enhance introspective states; to produce a "touching within."

Executive functioning. Associated with mental operations such as planning, working memory, and initiation and self-regulation of goal-directed behavior.

5-HT. Serotonin.

Frontal lobes. The anterior division of each cerebral hemisphere having its lower part in the anterior fossa of the skull and bordered behind by the central sulcus.

Glutamatergic transmission. Transmission of glutamate, the main excitatory neurotransmitter in mammals.

Gray matter. Neural tissue, especially of the brain and spinal cord, that contains cell bodies as well as nerve fibers, has a brownish gray color, and forms most of the cortex and nuclei of the brain, the columns of the spinal cord, and the bodies of ganglia.

Half-life. The time required for half the amount of a substance (such as a drug or radioactive tracer) in a living system or ecosystem to be eliminated or disintegrated by natural processes.

Hepatotoxicity. A state of toxic damage to the liver, a common cause of acute liver disease, morbidity, and mortality.

Hippocampus. An area of the brain buried deep in the forebrain that helps regulate emotion and memory. The hippocampus is part of the olfactory cortex, the part of the brain essential to processing smell.

Hyperreflexia. An abnormal triggering of the autonomic nervous system. The body is unable to turn off the nerves that cause blood pressure to rise.

Hypertension. High blood pressure.

Hyperthermia. Exceptionally high fever.

Hypotension. Low blood pressure.

Hypotonia. Decreased skeletal muscle tone resulting in a state of "floppiness."

Indinavir. A protease inhibitor that interferes with the protease enzyme that HIV uses to produce infectious viral particles.

K-hole. Described as a "desired" state of physical immobilization and social detachment lasting up to an hour caused by abuse of ketamine.

Metabolic acidosis. A disturbance of the body acid-base balance in which there is excessive acidity of the blood. Metabolic acidosis can occur as a result of many different diseases, such as kidney failure, poisoning, diabetic ketoacidosis, and shock.

Mnemonic. Assisting or intended to assist memory.

Mood disorder. This class of psychological disorders include depressive and bipolar disorders that can include symptoms of depression or mania.

Myoclonus. Irregular involuntary contraction of a muscle, usually resulting from functional disorder of controlling motorneurons.

Naltrexone. A narcotic antagonist that is effective orally, longer lasting, and more potent than naloxone, and has been proposed for the treatment of heroin addiction. The FDA has approved naltrexone for the treatment of alcohol dependence.

Narcolepsy. A condition characterized by brief attacks of deep sleep.

Nystagmus. A rapid involuntary oscillation of the eyeballs.

Nephrolithiasis. A condition marked by the presence of renal calculi.

Neurotransmission. The transmission of nerve impulses across a synapse.

Opiates. A class of sedatives that depress the CNS, reduce pain, and induce sleep.

Parkinson's disease. A chronic progressive nervous disease chiefly of later life that is linked to decreased dopamine production in the substantia nigra and is marked by tremor and weakness of resting muscles and by a shuffling gait.

Party packs. Refers to the use of Viagra in combination with drugs such as ecstasy, methamphetamine, or other club drugs to prolong the male sexual experience.

Power drinks. Drinks containing carbohydrates and fluids for energy, protein for muscle growth and repair, antioxidants to reduce inflammation and post-exercise soreness, and vitamins and other health food supplements.

Protease inhibitors. One of a class of anti-HIV drugs designed to inhibit the enzyme protease and interfere with virus replication.

Psychosis. A thought disorder in which reality is grossly distorted. Symptoms can include seeing, hearing, smelling, or tasting things that are not there; paranoia; delusions. Psychosis can occur as a result of brain injury or disease, and is seen particularly in schizophrenia and bipolar disorders.

Psychotogen. A chemical agent (as a drug) that induces a psychotic state.

Rave. An all-night dance party.

Rhabdomyolysis. The breakdown of muscle fibers with leakage of potentially toxic cellular contents into the systemic circulation.

Schizophrenia. A severe mental illness whose symptoms may include loss of personality (flat effect), agitation, catatonia, confusion, psychosis, unusual behavior, and withdrawal. The illness begins in early adulthood in many cases.

Serotonin. A phenolic amine neurotransmitter $C_{10}H_{12}N_2O$ that is a powerful vasoconstrictor and is found especially in the brain, blood serum, and gastric mucous membrane of mammals; also called 5-HT 5-hydroxytryptamine.

Serotonin syndrome. Characterized by enhanced physical activity, sweating, lack of coordination, mental confusion, trismus, jaw clenching, agitation, hyperreflexia, hyperthermia, shivering, rhabdomyolysis, metabolic acidosis, myoclonus, tremor, and nystagmus.

SERT. Seratonin transporter.

Somatization. The unconscious process by which psychologic distress is manifested as physical symptoms.

Somnolence. Drowsiness.

SSRI. Selective serotonin reuptake inhibitors.

Tachycardia. Relatively rapid heart action whether physiological (as after exercise) or pathological.

Temporal lobes. A large lobe of each cerebral hemisphere that is situated in front of the occipital lobe and contains a sensory area associated with the organ of hearing.

Tourette's syndrome. A familial neuropsychiatric disorder of variable expression that is characterized by multiple recurrent involuntary tics involving body movements (as eye blinks, grimaces, or knee bends) and vocalizations (as grunts, snorts, or uncontrolled utterance of inappropriate or offensive words).

Trolling. Using ecstasy and LSD together.

Verbal fluency letter generation. A classic neuropsychological test of language production that involves subjects generating and articulating a word in response to a cue. As an example, in the letter category, participants are asked to produce as many words as possible beginning with a specified letter in 1 minute.

Wasting syndrome. Characterized by a gradual loss of weight; deterioration in condition; emaciation.

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