Acute Toxic Effects of Club Drugs

Robert S. Gable, J.D., Ph.D.*

Abstract—This paper summarizes the short-term physiological toxicity and the adverse behavioral effects of four substances (GHB, ketamine, MDMA, Rohypnol[®)]) that have been used at late-night dance clubs. The two primary data sources were case studies of human fatalities and experimental studies with laboratory animals.   A "safety ratio" was calculated for each substance based on its estimated lethal dose and its customary recreational dose. GHB (gamma-hydroxybutyrate) appears to be the most physiologically toxic; Rohypnol[®] (flunitrazepam) appears to be the least physiologically toxic. The single most risk-producing behavior of club drug users is combining psychoactive substances, usually involving alcohol. Hazardous drug-use sequelae such as accidents, aggressive behavior, and addiction were not factored into the safety ratio estimates.

*Professor of Psychology, School of Behavioral and Organizational Sciences, Claremont Graduate University, Claremont, CA. Please address correspondence to Robert Gable, 2738 Fulton Street, Berkeley, CA 94705, or to robert.gable@cgu.edu.

In 1999, the National Institute on Drug Abuse launched its *Club Drug Initiative* in order to respond to dramatic increases in the use of GHB, ketamine, MDMA, and Rohypnol® (flunitrazepam). The initiative involved a media campaign and a 40% increase (to $54 million) for club drug research (Zickler, 2000). In February 2000, the Drug Enforcement Administration, in response to a Congressional mandate (Public Law 106-172), established a special Dangerous Drugs Unit to assess the abuse of and trafficking in designer and club drugs associated with sexual assault (DEA 2000). These substances, which had been previously used in the 1980s at secretive after-hours dance parties, had clearly become a matter of wide public concern. This paper compares four club drugs—gamma-hydroxybutyrate, ketamine, methylenedioxymethamphetamine, and flunitrazepam—on the variables of acute physiological toxicity and short-term adverse behavioral effects.

ACUTE PHYSIOLOGICAL AND BEHAVIORAL TOXICITY

"Toxicity" generally refers to the extent to which a chemical substance causes functional or anatomical damage to a living organism. One possible measure of acute toxicity is the number of calls for medical assistance received by poison control centers. Of more than 2,000,000 phone calls received during 2001 at 63 regional centers in the United States, fewer than 2% were the result of "the intentional improper or incorrect use of a substance where the victim was likely attempting to achieve a euphoric or psychotropic effect" (Litovitz, et al. 2002, p. 395). The number of poisoning incidents (for both suicide and psychotropic purposes) for club drugs was: GHB 1,205 calls with 6 deaths, ketamine 278 calls with 4 deaths, and MDMA 2,088 calls with 16 deaths. Rohypnol was not disaggregated in the poison control center survey from a much larger group of benzodiazepines. All of the benzodiazepines, both legal and illegal, resulted in 54,354 calls and 146 deaths. (Because the data collection system of the Drug Abuse Warning Network is undergoing restructuring, nationwide mortality statistics for club drugs is not available from that source.)

Tabulating morbidity and mortality incidents across national data collection systems is a complex and inconsistent process. Much of the time, the medical staff must rely on the report of the patient or acquaintances as to what substance was presumably used. Misidentification of an illicit substance such as MDMA is common and sometimes intentional (Baggott, et al. 2000). Even when an illicit substance is positively identified during emergency treatment or a forensic autopsy, medical personnel may choose not to report the finding accurately in order to avoid subsequent police investigation or embarrassment to the family. Furthermore, postmortem drug redistribution in tissue and blood may cause significant differences in drug concentration at different sites of the body at different time intervals (De Letter, et al. 2002; Stephens, Coleman & Baselt 1999); thus, making estimates of the antemortem drug dose more problematic.

Even if all incidents of drug-induced illness or fatality were accurately identified and reported, we still would not have a valid measure of toxicity because the number of reported incidents is related to the prevalence of use. There are more alcohol-related deaths (348 in 2001) than ketamine-related deaths because, in part, more people use alcohol than ketamine (National Center, 2002). Obviously, variables such as age and general health status, as well as prevalence-of-use, have an impact on mortality rates. In brief, the frequency of illness or death within a population is not, in itself, a useful statistic for comparing the relative toxicity of psychoactive substances.

 An alternative metric for assessing potential harm is the "therapeutic index" or "therapeutic ratio." One component of the therapeutic index assumes the basic principle of toxicology that all toxic effects are dose-dependent. Any substance can become lethal if a sufficient quantity is administered. This point is often made by popular writers who cite reports of fatalities that have occurred from drinking excessive amounts of water (Iwanami, 2001; Riggs et al. 1991). In contrast, all toxicants presumably have a no-observed-effect-level below which no alteration in structure or function can be detected.

Neubert (1999, p. 1156) emphasized the general relationship between toxic effects and dosage by asserting that "toxicity *per se* is not a property of a substance but of the dose."

Dose-response curves of lethality can be generated by plotting, at various dosage levels and time intervals, the number of laboratory animals that exhibit a specified reaction against the number of animals that die (cf., Gad & Chengelis 1998). The traditional therapeutic index is the ratio of the median lethal dose (LD_{50}) to the median effective dose (ED_{50}) as observed within an exposed population during a specified interval of time. For example, the ED_{50} of alcohol (ethanol) that will induce a strong effect in a healthy 70k human who has not developed tolerance to the substance is approximately 27g consumed within 20 to 30 minutes. This is roughly equivalent to two beers. The estimated LD_{50} of alcohol is 280g, equivalent to approximately 20 beers (or fewer alcohol drinks with a higher proof) in the same amount of time. Thus, the therapeutic ratio for alcohol is approximately 10 ($LD_{50}/ED_{50} = 280g/27g$). As a general rule, the larger the therapeutic index, the less toxic the substance. It is important to note that traumatic reactions cannot be predicted for any particular individual due to the existence of idiosyncratic biological factors such as a person's health status or metabolic anomalies.

Although the traditional LD_{50} is being slowly replaced by more humane laboratory methods that require fewer live animals (Interagency 2002), many federal safety standards still cite the LD_{50} as a toxicological benchmark (see, e.g., 16 Code of Federal Regulations § 1500.3; 29 Code of Federal Regulations, § 910.1200). LD_{50}s are commonly reported in material safety data sheets that the Occupational Safety and Health Administration requires of all chemical manufacturers and importers. Because humans may be more sensitive than rodents to some chemicals, government regulations (e.g., U.S. Food Quality Protection Act, PL 104-170) and forensic practice (cf., Eaton & Klaassen 2001; Neubert 1999) customarily specify that the estimated LD_{50} for humans be reduced from the rodent LD_{50} by a factor of 10. The present paper follows this protocol.

Any LD_{50} must be interpreted with caution because it is a deceptively simple standard packed with ambiguities and limitations. For example, the LD_{50} is just one data-point along an entire range of responses that a group of organisms might exhibit in reaction to various amounts of a substance. A median dose does not provide any information about the *shape* of a dose-response curve. Consider the situation where two chemicals have an identical LD_{50}. The chemicals might appear to be equally toxic because they have the same LD_{50}, but one chemical could, in the normal course of its use, cause substantially more deaths. The more lethal chemical would have a lower absolute threshold of lethality and continually add more casualties up to the 50% level. In contrast, the less lethal chemical might cause no deaths within the normal range of therapeutic or recreational doses, but suddenly become extremely toxic in small increments above the normal-use range until the 50% group fatality level is reached.

The route of administration, in addition to the amount of the substance administered, is critical in determining the intensity, latency, and duration of drug effects. A very general ordering of vulnerability to adverse reactions, in terms of increasing rates of absorption, is: dermal, oral, intramuscular, subcutaneous, intranasal, inhalation, and intravenous (Klaassen 2001). References to lethal dosages that do not state the route of administration have little, if any, practical value. Once a substance is absorbed, other factors of pharmacokinetics such as tissue distribution, metabolism, and elimination determine physiological reactions. The fact that a substance has psychoactive properties does not necessarily imply that a large amount of the substance reaches the brain. Rather, the wide distribution of the substance in other parts of the body often accounts for acute toxicity. In the case of ketamine, for example, higher concentrations of ketamine, at autopsy, have been found in the liver, spleen, and kidney than in the brain (Moore, et al. 1997; Licata, Pierine & Popoli 1994).

The median nonmedical or recreational dose of a psychoactive substance may differ from its medical application with respect to both the route of administration and the dosage. Again, ketamine, for example, is typically used intranasally in powdered form for recreational purposes with a dose ("bump") of 75 – 125 mg, compared to an intramuscular injection of 450 – 750 mg for medical anesthesia. Because the drug doses referenced in this paper are based on nonmedical ED_{50}s, the term

"safety ratio," rather than "therapeutic index" or "therapeutic ratio," is preferred. The safety ratios cited in Table 1 below have been calculated using estimates of the ED_{50} of a single nonmedical dose administered via the indicated route to a healthy 70k adult.

Table 1.
Safety Ratio of "Club Drugs" and Alcohol

Common/popular name	Alternate generic/trade name	Route of administration	Safety ratio*
GHB	gamma-hydroxybutyrate	oral	10
Ketamine	Ketalar®	insufflation (snorted)	25
MDMA	methylenedioxy-methamphetamine	oral	15
Rohypnol®	flunitrazepam (benzodiazepine)	oral	40
Alcohol	ethanol	oral	10

——————————

* Safety ratios should not be used as a dosage guide because individuals differ greatly with respect to metabolism and psychophysical vulnerability. Safety ratios do not reflect hazards such as accidents or dangerous behavior facilitated by the substance.

It should be apparent that estimates of a safety ratio may fluctuate substantially depending upon the criteria that are chosen and the measurement procedure. The primary justification for attempting a task as daunting as specifying safety ratios is that the more common indices —surveys of emergency calls, death statistics unadjusted for prevalence of use, randomly published case studies, anecdotal accounts, and personal opinion—have even *less* apparent validity.

Assessing the adverse behavioral effects ("behavioral toxicity") of drug use is certainly as challenging as assessing physiological toxicity. The range of possible dependent variables, as well as their method of measurement, is exceptionally broad and complex. The variables most often mentioned as having social relevance are drug-induced psychotic reactions, aggressive/violent behavior, and impairment of psychomotor or cognitive functions. Behavioral toxicity tends to show an inverted U-shaped curve such that very low doses produce low rates of the observed response, moderate doses increase the strength of the observed response, and very high doses reduce the strength of the response. This familiar dose-response sequence has been convincingly demonstrated in many drug self-administration studies (e.g., Fantegrossi et al. 2002; Munzar et al. 2001).

Although the ecological validity of laboratory studies is always to some degree suspect (Spilich, June & Renner 1992), many well-designed and ingenious experimental studies with both humans and laboratory animals have documented patterns of behavioral responses most likely to occur with specific

psychoactive substances (cf., Spencer 1990; Fischman & Mello 1989). Only a few characteristic behavioral responses to the club drugs will be noted in this review.

GHB (GAMMA-HYDROXYBUTYRATE)

GHB generally acts as a central nervous system depressant that alters dopamine activity (Tunnicliff 1997). It was previously marketed as a food supplement in powdered form for body building until April 2000 when it was simultaneously placed in DEA Schedules I and III (depending upon its medical or nonmedical use). Two readily hydrolyzed GHB precursors, gamma-butyrolactone (GBL) and 1,4-butanediol (BD), have been often substituted for GHB in the illicit drug market, as well as in toxicological studies (NTP 2002).   Some neurochemical and behavioral differences between GHB and its precursors have, however, been noted (cf., Nicholson & Balster 2001).

With the typical recreational 20% solution of GHB, a low oral dose of 0.5 –1.5 g characteristically results in disinhibition, sociability, and light inebriation similar to two 15 g alcoholic drinks. Onset of altered consciousness occurs in 5 – 15 minutes, and peaks in about 30 minutes (Palatini, et al. 1993). At a medium dose of 1.5 – 2.5 g, simultaneous relaxing and stimulating effects tend to increase physical disequalibrium, grogginess, tactile sensitivity, euphoria, and slight nausea, but without the mental "fogginess" of alcohol. In a series of pharmacokinetic studies with 24 healthy volunteers, a 2.25 g dose of GHB resulted in a peak plasma concentration of 26.6 mg/L (Borgen, Lane & Lai 2000).

Because the elimination half-life increases with higher dosages (Palatini et al. 1993), GHB has a steep dose-response curve. Hence, a dose above 5 g may induce severe respiratory depression. The most common hazards to the user are respiratory depression and aspiration of vomited material. The usual clinical course for overdose—if other sedative-hypnotics (most commonly alcohol) have not been used—is spontaneous awakening and uneventful recovery in 5 – 8 hours (Miro, et al. 2002; Ingels, et al. 2000; Chin, R.L., et al.1998; Louagie et al.1997).

Deaths attributed solely to GHB or its precursors are rare, and the fatal dosage is seldom documented. Two fatalities have been reported from the use of BD by Zvosec et al. (2001). The reported dose of the first fatality was 20 g; the dose of the second fatality was estimated to be 5.4 – 10.8 g. The oral LD_{50} of BD and GBL among laboratory rodents and rabbits is approximately 2 g/kg (Irwin 1996; NTP 1991; Laborit 1964). Extrapolated to a 70 kg human, the LD_{50} would be 14 g when reduced by a factor of 10 to account for interspecies differences. Published reports of *non-fatal* GBH/GBL human doses have ranged from 17.5 – 29 g (Dupont & Thornton 2001; CDC 1999; Iten et al. 1999; Ross 1995).

Blood and urine samples from human fatalities have been utilized to estimate antemortem toxic doses of GHB (cf., Hornfeldt, Lothridge & Upshaw-Downs 2002). Unfortunately, toxicological investigations are not easily accomplished because the low-dose potency of GHB requires a targeted and relatively expensive analysis that measures only one drug at a time (LeBeau et al 1999). Moreover, the rapid metabolism of GHB, as well as the fact that GHB is endogenously present, makes determination of toxicity more difficult.

In a review by Baselt (2002) which cited six cases where death was attributed to GHB, the average postmortem blood concentration was 228 mg/L. In twelve cases cited by Hornfeldt, Lothridge & Upshaw-Downs (2002) BD or GHB postmortem blood concentrations averaged 223 mg/L. Kalasinsky et al (2001) reported a fatality with femoral blood concentration of 330 mg/L, and Kraner et al. (2000) reported a fatality with 280 mg/L of GHB. The majority of these fatalities involved ethanol which prevents GHB breakdown and raises blood concentrations (Karch, Stephens & Nazareno 2001). Mozayani, Small & De Cuir (1998) documented one death having postmortem blood concentration of 309 mg/L where both ethanol and cocaine were also detected.

The blood concentration data suggest that a median lethal concentration of GHB is about 10 times the amount that would result from a typical 2 g recreational dose. In a similar manner, dose-response studies suggest an LD_{50} of about 20 g; thus resulting in a safety ratio for GHB of approximately 10.

The hazard profile of GHB is less favorable than many psychoactive substances because its safety ratio is relatively low and the dosage range is quite narrow. Namely, 1.5 –2.0 g of oral GHB is an effective recreational dose, but 5.0 – 6.0 g may result in a coma, depending upon the weight of the individual. This narrow range probably explains the results of a survey in which 66% of 42 of GHB users reported some degree of loss of consciousness (Miotto et al. 2001).

Similar to other central nervous system depressants, the behavioral sequelae of GHB (of approximately 4 g) is poor coordination, incoherent speech, confusion, amnesia, fecal incontinence, and sometimes combativeness and hallucinations (Hernandez, McDaniel & Hernandez 1998; McDaniel & Miotto 2001; Li, Stokes & Woeckener 1998). Doses at the 4 g level also produce general anesthesia. It is not surprising to be informed that GHB can impair driving ability (Couper & Logan 2001).

One potential hazard of GHB that requires further substantiation is its use as a "date rape" drug (cf., Hilary J. Farias and Samantha Reid Date-rape Drug Prohibition Act of 2000; Public Law 106-172). The capacity of GHB to induce a comatose state, particularly when ingested with ethanol, has led to this reputation. However, very few cases (e.g., Stillwell 2002) have been published that document the existence or concentration of GHB where sexual assault has been alleged (cf., Deveaux et al 2002). This situation may be due, in part, to the complexity of toxicological investigations, as previously mentioned (LeBeau et al 1999).

KETAMINE

Ketamine hydrochloride is a relatively unique psychoactive substance inasmuch as it produces, at normal medical or recreational doses, increased blood pressure and a dissociative anesthesia while maintaining awareness. Ketamine has a well-established and acceptable safety profile in emergency surgical procedures (Marshall & Longnecker 1990). There are occasional reports of ketamine causing emesis, tachycardia, and sudden involuntary movement (Weiner et al. 2000), but the major limitation in medical practice has been the occurrence of vivid dreams, delirium, or proprioceptive disturbances (Marshall & Longnecker 1990). Recreational doses are typically 10 –25 percent less than the medical anesthetic dose, and the novel perception induced by ketamine (e.g., disembodied consciousness) is the desired effect (cf., Jansen 2000). The common nonmedical intranasal dose, in powdered form, is about 50 mg.

In a series of 20 cases presenting to emergency departments after abuse of ketamine, the most common complaints were chest pains, palpitations, and tachycardia (Weiner et al. 2000). The symptoms were short-lived, and 18 of the 20 patients were discharged within 5 hours.

The rodent oral ketamine LD_{50} averages about 600 mg/kg (Derelanko & Hollinger 1995) or approximately 4.2 g for a 70 kg human. (As before, the rodent data are reduced by a factor of 10 to take into account interspecies differences.) Assuming a human oral LD_{50} of 4.2 g, with an oral recreational dose of 175 mg (Hansen et al. 1988), the safety ratio would be about 25.

Generally, "ketamine is considered to have a wide margin of safety, with no adverse outcomes reported even in the setting of profound overdose" (Long, Nelson & Hoffman, 2002, p. 614). Exceptions have occurred where there is an underlying illness or when substances are combined. Long, Nelson & Hofman (2002) reported a medication error resulting in a fatal IV overdose of 500 mg; the patient was 69-year-old with a history hypertension and asthma. Two cases of intravenous or intramuscular ketamine deaths at doses of 1,000 and 900 mg, possibly combined with other drugs, have been reported by Licata, Pierini & Popli (1994) and by Peyton, Couch & Bost (1988). The danger of sudden paralysis is illustrated in these two cases inasmuch as the syringe remained in the body at the injection site. Assuming a 35 – 40 mg IV/IM dose for nonmedical purposes, the safety ratio would again be approximately 25 a for healthy individual. Green et al. (1999) reported no adverse outcomes in a series of 9 cases in which children in emergency departments were inadvertently injected with 5 to 100 times the intended dose of ketamine. It should be noted, however, that intubation and other medical support procedures were immediately available. A reasonably conservative estimate of the

safety margin of ketamine would seem to be about 25 for intranasal administration (insufflation) and somewhat higher margin for oral administration.

Although relatively small intranasal doses of ketamine can provide unique perceptions, the potential for adverse reactions are always present. As with GHB, accurate measurement of dosages is difficult, particularly in a club setting where the drug must be furtively administered. Many recreational settings also encourage the use of alcohol that is known to significantly lower drug safety margins (e.g., Moore, et al., 1997; Poldrugo et al., 1985).

The most noticeable consequence of high ketamine doses is numbness accompanied by loss of balance and coordination. Also at higher dosages (over 100 mg), vomiting and convulsions may occur. Anecdotal reports suggest a substantial risk of psychological dependence (Jansen & Darracot-Cankovic 2001; Dalgarno & Shewan 1996; Turner 1994).

Because ketamine is an anesthetic, the user may not be aware of injury or other physical assault, and may therefore fail to take necessary remedial action. Two individuals known for praising the spiritual aspects of the ketamine experience (cf., Turner 1994; Moore & Alltounian 1978) succumbed while using ketamine—not from overdose but from injuries secondary to loss of voluntary motor control or accurate assessment of danger (Jansen 2000). In what might be considered a classic understatement, a study of psychological side-effects of ketamine anesthesia among military personnel concluded that "ketamine sequelae are considered incompatible with the battlefield environment" (Jago, Restall & Thompson 1984, p.1).

MDMA (3,4-METHYLENEDIOXYMETHAMPHETAMINE, "ECSTASY")

Not since LSD of the 1960s has an illicit psychoactive substance drawn as much attention as MDMA. The desired psychological effects of MDMA such as gregariousness, empathy, and reduced fear are well-known (Greer & Tobert 1998; Peroutka, Newman & Harris 1988). By 2001, more than 900 peer-reviewed experimental studies or case reports had been collected by Baggott, Jerome, & Stuart (2001). Several well-documented reviews have been published in recent years summarizing much of what is known about this drug (e.g., Vollenweider et al. 2002; Kalant 2001; Parrott 2001; Teter & Guthrie 2001). Nonetheless, because of its legal prohibition, few, if any, prospective controlled studies have been conducted with MDMA under the typical conditions of nonmedical use. Therefore, the usual epistemological limitations of uncontrolled research protocols (e.g., lack of information regarding the health status of participants or the use of concomitant substances) must be taken into account when assessing the validity of information regarding health risks.

The average LD_{50} of MDMA via intraperitoneal administration has been reported as 97, 49, and 98 mg/kg for the mouse, rat, and guinea pig respectively; via intravenous administration, the LD_{50} has been reported as 26 mg/kg for the monkey (Hardman, Haavik & Seevers 1973). Because MDMA is almost always administered orally for human recreational or psychotherapeutic use, the experimental oral LD_{50} is noteworthy, and has been reported with a range from 160 mg/kg (deSouza 1997) to 325 mg/kg (Goad, 1985) among rats. Non-drug factors such as housing conditions may partly account for this substantial variation (Malberg & Seiden 1998). Frith et al. (1987) reported no deaths among rats dosed orally up to 100 mg/kg every day for 28 days. Four methoxyamphetamines (PMA, DMA, DOM, DOB) orally administered to mice averaged an LD_{50} of 300 mg/kg (Davis, et al. 1978).

Anecdotal accounts and clinical reports of human fatalities show considerable variation in MDMA dosages and postmortem blood concentrations. Deaths or near-fatal complications have ranged from ingestion of "1 tablet of MDMA" (Barrett & Taylor 1993, p. 233) to "50 tablets of Ecstasy (in combination with oxazepam and alcohol)" (Ramcharan at al. 1998, p. 727). Garbino et al. (2001) listed 49 published cases of hepatic toxicity that included 13 deaths and several liver transplants. Baggott, Jerome & Stuart (2001) catalogued 26 fatal cases having blood MDMA concentrations ranging from 0.04 to 7.15 mg/L. The lowest MDMA concentrations involved hyponatreamia as a result of drinking excessive fluid. Henry, Jeffreys & Dowling (1992) cited one case of an attempted suicide in which ingestion of 42 pills of ecstasy produced 7.72 mg/L of plasma MDMA with the primary side effects

being hypertension and tachycardia. Kalant (2001, p. 924) noted that most of the cases of fatality or serious toxicity have involved blood levels "up to 40 times higher than the usual recreational range." He also noted (p. 924) that reported toxic blood levels have overlapped the normal recreational range—thus demonstrating "the degree to which the seriousness of effects can be dependent on environmental factors other than the drug concentration." A reasonable estimate of the acute LD_{50} of MDMA for a healthy 70 k person would appear to be approximately 2 grams, or about 15 –16 times a single recreational oral dose of 125 mg/kg.

Transient adverse physical effects, often typical of amphetamines, include tachycardia, hyperthermia, trismus (jaw clenching), anorexia, and insomnia (Gowing et al. 2002; Peroutka, Newman & Harris 1988). Less frequent but serious psychological complications may involve mild hallucinations, memory deficits, decreased motor coordination, and psychosis (Cole, Sumnall & Grob 2002; Hartung et al. 2002; Ricaurte et al. 2002; Morland 2000). The extent of documented neurotoxicity of MDMA, and its behavioral significance, is the subject of continuing investigation and debate (cf., Kish 2002; Mechan et al. 2002; Parrott 2002; Hegadoren, Baker & Bourin 1999). Allegedly, "the available evidence on MDMA does not show any major harmful social consequences for users arising directly from its use, in terms of family or other social relations, problems concerning education, employment, or marginalization" (European Monitoring Centre 2001, p. 7). This general assessment does not, of course, preclude individual incidents of adverse psychological effects (e.g., Vaiva et al 2001; Van Kampen & Katz 2001).

ROHYPNOL[®] (FLUNITRAZEPAM)

An estimated 2,000 benzodiazepines have been synthesized world-wide by the pharmaceutical industry (United nations 1998), and they differ substantially in terms of their potency, speed of onset, and duration of effects.   Flunitrazepam is one of the most widely prescribed benzodiazepines in more than 70 countries although it was never legally marketed in the United States. In response to international concern about flunitrazepam being used as a "date rape" drug, the manufacturer, Hoffman-LaRoche, added a blue coloring agent to the tablet in October 1998. This modification has proven efficacious in assisting drug identification at autopsy (Tsokos 1999).

A "medium" single recreational dose of 1.25 mg used in a study by Roset et al. (2001) was found to balance pleasant and unpleasant sensations. A 2 mg dose was described by participants as unpleasant. The sedative-hypnotic effects of flunitrazepam appear in about 20 minutes after ingestion, and peak plasma concentrations occur between 1 and 2 hours (Snyder et al. 2001; Jochemsen et al. 1983). Flunitrazepam is extensively converted to its metabolite, 7-aminoflunitrazepam after ingestion. Wickstrom et al. (1980) reported an average peak plasma concentration of 2 _g/L of 7-aminoflunitrazepam at 9 hours following a single 2 mg oral dose of flunitrazepam.

As a group, benzodiazepines have the reputation of being quite safe. The LD_{50} of orally administered flunitrazepan in the rat has been reported as 415 mg/kg (MSDS 1988)—equivalent to almost 3 grams for a 70k human when the rodent dose is reduced by a factor of 10. This is an unusually large dose for a drug with the potency of flunitrazepam. A very much lower dose of only 28 mg of flunitrazepam was fatal in a case reported by Heyndrickx (1987), but the patient was over 80 years of age.

A series of 1,989 poison control center cases involving flunitrazepam, loflazepate, prazepam, and triazolam reported doses reaching 70 to 120 times the usual therapeutic dose (Pulce et al. 1992). All patients recovered. On the basis of 112 cases involving children who had ingested flunitrazepan, Pulce et al. calculated that a "dangerous" dose for children would be about 0.28 mg/kg. This dangerous pediatric dose, equivalent to about 20 mg for a 70k adult, is presumably well below the lethal level for a mature individual. Brammer et al. (2000) reported a successful medical intervention with a woman who had ingested 100 mg of flunitrazepam.

Robertson & Drummer (1998) cited 43 cases having an average postmortem blood or plasma concentrations of approximaely 0.06 mg/L of 7-aminoflunitrazepam. Earlier reports by Drummer & Ranson (1996) and by Dummer, Syrjanen & Cordner (1993) reported much higher 7-aminonitrazepam postmortem concentrations of 0.2mg/L and 0.45mg/L. If it is conservatively assumed that 0.06 mg/L (60 _g/L) of 7-aminoflunitrazepam represents a median lethal concentration, and that a 1 mg dose of flunitrazepam yields a peak concentration of about 1.5 _g/L of 7-aminoflunitrazepam, flunitrazepam would then have a safety ratio of about 40 (60 _g / 1.5 _g). This tends to affirm the observation of Woods, Katz, & Winger (2000, n.p.) that "the relative safety of the benzodiazepines is most clearly evident in cases of overdose. Even massive overdoses, if taken without other CNS depressants, are almost never fatal."

Undoubtedly, high-risk side effects are more likely to occur when flunitrazepam is combined with other substances, but the interaction is apparently complex and unpredictable. Pretreatment of rats with 40 mg/kg (equivalent to 2.8 g human) of flunitrazepam significantly increased methadone and buprenorphine lethality but not morphine lethality (Borron et al. 2002). Druid, Holmgren, & Ahlner (2001) reported that in only 9% of 1,505 fatalities was flunitrazepam considered to be the sole cause of death. A survey of 900 women by Rickert,   Wiemann & Berenson (1999) found that about 75% of the time, flunitrazepam was taken with alcohol, and 50% of the time with another drug. Minnasch et al. (1999) report an unusual incident in which 3 men died at a party where a toxicological investigation confirmed the concurrent use of flunitrazepan, alcohol, THC, and pentobarbital.

In contrast to diazepam, but similar to abused inhalants, flunitrazepam has vasodilatory properties (Dowd et al. 2002; Brenneisen & Raymond, 2001). It also produces some memory impairment at or above a 2 mg oral dose (Dowd et al. 2002; Verwey, et al. 2002). Dose-related decrements in psychomotor and cognitive performance have also been documented (Mintzer & Griffiths 1998). These attributes make flunitrazepam, at minimum, a candidate for facilitating sexual assault (e.g., Marc et al. 2000). Most studies, however, indicate that flunitrazepam has been a minor factor in sexual assault incidents: Mullins (1999) and Hindmarch & Brinkmann (1999) reported that of more than 1,000 urine samples from "date rape" cases, only 6 assays were positive for flunitrazepam. Slaughter (2000) analyzed 2,003 urine sample obtained from sexual assault victims; 63% tested positive for alcohol, 30% for marijuana, and fewer than 3% for flunitrazepam. From 3,303 urine samples, collected in the course of 4 years, ElSohly (2001) and ElSohly & Salamone (1999) reported fewer than 1% positive for flunitrazepam.

DISCUSSION

Statistically, direct and serious physiological harm from club drugs is insignificant. Drug-related emergency department visits in the United States (totaling 638,484 in 2001) accounted for fewer than 1% of all emergency department visits, and of this 1%, "club drugs are truly rare events, occurring in only 4% of the drug-related visits" (Kissin & Ball, 2002, p. 2). An accurate assessment of the risk of recreational drug use is further complicated by overdoses that occur as a result of attempted suicide, estimated to be approximately one-third of emergency department drug-related visits (DAWN, 2002). Indeed, the fact that so few deaths have occurred might be considered a perverse testimonial to the safety of the club drugs—considering the millions of haphazardly measured doses of questionably pure substances self-administered by uninformed users under minimally restrained circumstances. This observation must be qualified, however, because most all ravers are young and healthy enough to withstand occasional and severe chemical assaults. Furthermore, many aversive effects are not treated in emergency departments or officially recorded. Mortality and morbidity statistics are very gross and questionably valid indicators of trauma.

The Food and Drug Administration (*Code of Federal Regulation*s, Sec. 320.33c) has officially defined a drug product as having a "narrow therapeutic ratio" if there is "less than a 2-fold difference in median lethal dose and median effective dose" and if safe and effective use requires careful titration and patient monitoring. None of the club drugs have a therapeutic (or safety) ratio under 2, although careful titration is certainly recommended for drugs with a steep dose-response curve such as GHB and

ketamine. The safety ratio of club drugs ranges from 10 to 40. In this respect, they are generally equivalent to tricyclic antidepressants such as imipramine or desipramine having ratios of 10 to 30. The club drugs do present a greater physiological hazard than several other well-known psychoactive substances that have higher safety ratios such as caffeine, dimethyltryptamine, kava kava, marijuana, nitrous oxide, and psilocybin (Gable, 1993).

The club drug that appears to be the most physiologically hazardous is GHB, having a safety ratio of 10. Alcohol has the same safety ratio as GHB, but because alcohol has low potency and is legally distributed, doses of alcohol can be more easily standardized and measured. Alcohol users titrate ethanol in units of 150 ml (equivalent to 5 fluid ounces or one medium wineglass) while GHB users must titrate their drug in units of 5 ml (equivalent to 1 fluid dram or 1 teaspoon or soda bottle cap). For this reason, dosage control, especially in recreational situations, is more problematic for users of GHB than for users of alcohol.

The single most common risk-producing practice of drug users is the intentional combining of various psychoactive substances (e.g., Borron, Lane, & Lai 2002; Tanaka 2002; Funahashi et al. 1988). As many as 80% of the GHB-related deaths have involved other substances, most often alcohol (Miro et al. 2002; Dyer & Haller 2001). One particularly egregious example is the alleged distribution of "trail mix," a manufactured combination of MDMA, ketamine, cocaine and sometimes Viagra[®] (Narvaez 2001). Alternatively, the mixing of substances may be unintentional on the part of the user as a result purposeful misidentification by the dealer of the illicit substance (Department of Justice, 2001; Hayner, 2002). Of 87 ketamine-positive autopsies conducted over a 2-year period in New York City, no fatality was caused exclusively by ketamine (Gill & Stajic 2000).

In terms of behavioral effects at doses usually desired in large social settings, club drugs do not appear to be more dangerous than alcohol. According to a study by the National Research Council (Reiss & Roth, 1994; Roth 1994, p. 4) alcohol is "the only drug that in many individuals tends to increase aggressive behavior temporarily while it is taking effect." 1MDMA is demonstrably more socially benign than alcohol (cf., Holland 2001; Liester et al. 1992).

The primary short-term hazard of club drugs does not reside in their chemical composition but in the manner of their use. The four most common causes of drug-related deaths—suicide, use of multiple substances, pre-existing medical conditions, and automobile or gun incidents—are not the direct result of physiological toxicity of any single administered substance. When these four factors are removed, the remaining fatalities are most often the result of a woeful disregard of safety (e.g., Winek, Wahba & Rozin 1999; Pereira & Nishioka 1994; Rouse & Fysh 1992; Leadbeatter 1988). A focus on chemical toxicity does not, therefore, appear to be the most effective way of reducing drug-related deaths.

REFERENCES

Baggott, M.J.; Heifets, B.; Jones, R.T.; Mendelson, J.; Sferios, E. & Zehnder, J. 2000. Chemical analysis of ecstasy pills. *Journal of the American Medical Association* 284: 2190.

Baggott, M.; Jerome, L. & Stuart, R. 2001. 3,4-methylenedioxyethyamphetamine (MDMA): A review of the English-language scientific and medical literature. Retrieved December 5, 2002, from http://www.maps.org/research/mdma/protocol/litreview.html

Barrett, R.J. & Taylor, G.T. 1993. "Ecstasy" ingestion: A case report of severe complications. *Journal of the Royal Society of Medicine* 86 (4): 233-34.

Baselt, R.C. 2002. *Disposition of Toxic Drugs and Chemicals in Man* (6th edit.) (p. 473). Foster City, CA: Biomedical Publications.

Borgen, L.; Lane, E. & Lai, A. 2000. Xyrem[®] (sodium oxybate): A study of dose proportionality in healthy human subjects. *Journal of Clinical Pharmacology* 40 (4): 1053.

Borron, S.W.; Monier, C.; Risede, P. & Baud F.J. 2002. Flunitrazepam variability alters morphine, buprenorphine, and methadone lethality in the rat. *Human and Experimental Toxicology* 21 (11): 599-605.

Brammer, G.; Bey, T.; Torres, R. & Kohler, S. 2000. Continuous intravenous flumazenil infusion for benzodiazepine poisoning. *Veterinary and Human Toxicology* 42 (5): 280-81.

Brenneisen, R. & Raymond, L. 2001. Pharmacology of flunitrazepam and other benzodiazepines. In S. J. Salamone (ed.) *Benzodiazepines and GHB: Detection and Pharmacology* (pp. 1-20). Totowa, NJ: Humana Press.

CDC (Centers for Disease Control and Prevention). 1999. Adverse events associated ingestion of gamma-butyrolactone—Minnesota, New Mexico, and Texas, 1998-1999. *Morbidity and Mortality Weekly Report* 48: 137-40.

Chin, R.L.; Sporer, K.A.; Cullison, B.; Dyer, J.E & Wu, T.D. 1998. Clinical course of gamma-hydroxybutyrate overdose. *Annuals of Emergency Medicine* 31 (6): 716-22.

Cole, J.; Sumnall, H. & Grob, C. 2002. Where are the casualties? *The Psychologist*, 15 (9): 474.

Couper, F.J. & Logan, B.K. 2001. GHB and driving impairment. *Journal of Forensic Toxicology* 46 (4): 919-23.

Dalgarno P.J. & Shewan, D. 1996. *Journal of Psychoactive Drugs* 28 (2):191-2.

Davis, W.M.; Bedford, J.A.; Buelke, J.L.; Guinn, M.M.; Hatoum, H.T.; Waters, I.W.; Wilson, M.C. & Braude, M.C. 1978. Acute toxicity and gross behavioral effects of amphetamine, four methoxyamphetamines, and mescaline in rodents, dogs, and monkeys. *Toxicology and Applied Pharmacology* 45 (1): 49-62.

DAWN (Drug Abuse Warning Network). 2002 February. *Emergency Department Trends*. Office of Applied Studies, SAMHSA, table 2.10. Retrieved July 12, 2002, from http://www.samhsa.gov.oas/dawn/ TrndED/2001/Text/TrndEDtxt

DEA (Drug Enforcement Administration) 2000. Club drugs: An Update. *Drug Intelligence Brief* (September 2001). Retrieved December 22, 2002, from http://dea.gov/pubs/intel/ 01026/index.html

De Letter, E.A.; Clauwaert, K.M.; Lambert, W.E.; Van Bocxlaer, F.J.; De Leenheer, A.P. & Piette, M.H.A. 2002. Distribution study of 3,4-methylenedioxymethamphetamine and 3,4-methylenedioxyamphetamine in a fatal overdose. *Journal of Analytical Toxicology* 26 (1):113-8.

Department of Justice. 2001 April. PCP tables sold as MDMA. *Information Bulletin*. Product number 2001-LO424-003. Washington, DC: U.S. Dept. of Justice.

Derelanko, M.J. & Hollinger, M.A. 1995. *CRC Handbook of Toxicology*. Boca Raton, FL: CRC Press.

De Souza, I.; Kelly, J.P.; Harkin, A.J. & Leonard, B.E. 1997. An appraisal of the pharmacological and toxicological effects of a single oral administration of 3,4-methylenedioxymethamphetamine (MDMA) in the rat. *Pharmacology and Toxicology* 80 (5):207-10.

Deveaux, M.; Renet, S.; Renet, V.; Gaulier, J.M.; Kintz, P. & Verstraete, A. et al. 2002. [Use of gamma-hydroxybutyric acid (GHB) at rave parties and in date rape in France: Myth or reality?] *Acta Clinica Belgica,* Supplement 1: 37-40 [Medline abstract].

Dowd, S.M.; Strong, M.J.; Janicak, P.G. & Negrusz, A. 2002. The behavioral and cognitive effects of two benzodiazepines associated with drug-facilitated sexual assault. *Journal of Forensic Sciences* 47 (5): 1101-07.

Druid H.; Holgrem, P. & Ahlner, J. 2001. Flunitrazepam: An evaluation of use, abuse and toxicity. *Forensic Science International* 122 (2-3): 136-41.

Drummer, O.H. & Ranson, D.L. 1996. Sudden death and benzodiazepines. *American Journal of Forensic Medicine and Pathology* 17 (4): 336-42.

Drummer, O.H.; Syrjanen M.L. & Cordner, S.M. 1993. Deaths involving the benzodiazepine flunitrazepam. *American Journal of Forensic Medicine and Pathology* 14 (3): 238-43.

Dupont. P. & Thornton. J. 2001. Near-fatal gamma-butyrolactone intoxication—first report in the UK. *Human and Experimental Toxicology* 20 (1):19-22.

Dyer, J.E. & Haller, C.A. 2001. GHB-related fatalities (Abstract of conference paper). *Journal of Toxicology—Clinical Toxicology* 39 (6): 518.

Eaton, D.L. & Klaassen, C.D. 2001. Principles of toxicology. In C.D. Klaassen (Ed.), *Casarett and Doull's Toxicoloy: The Basic Science of Poisons,* 6th edit. (chpt. 2, pp. 11-39). New York, NY: McGraw- Hill.

ElSohly, M.A. 2001. Drug-facilitated sexual assault. *Southern Medical Journal*, 94 (6): 655-6.

ElSohly, M.A. & Salamone, J.S. 1999. Prevalence of drugs used in alleged sexual assault. *Journal of Analytical Toxicology* 23 (3): 141-6.

European Monitoring Centre for Drugs and Drug Addiction. 2001 (October 29). *Report on the Risk Assessment of PMMA in the Framework of the Joint Action on New Synthetic Drugs*. Lisbon, Spain: Author.

Fantegrossi, W.E.; Ullrich, T.; Rice, K.C.; Woods, J.H. & Winger, G. 2002. 3,4-methylenedioxy-methamphetamine (MDMA "ecstasy") and its stereoisomers as reinforcers in rhesus monkeys: Serotonergic involvement. *Psychopharmacology (Berl)*.161 (4): 356-64.

Fischman, M.W. & Mello, M.K. (Eds.) 1989. *Testing for Abuse Liability of Drugs in Humans*. (NIDA research monograph #92). Rockville, MD: National Institute on Drug Abuse.

Frith C.H.; Chang, L.W.; Lattin, D.L.; Walls, R.C.; Hamm, J. & Doblin, R. 1987. Toxicity of methylenedioxy-

methamphetamine (MDMA) in the dog and the rat. *Fundamental and Applied Toxicology* 9 (1): 110-9.

Funahashi, M.; Kohda, H.; Shikata, I. & Kimura, H. 1998. Potentiation of lethality and increase in body temperature by combined use of d-methamphetamine and morphine in mice. *Forensic Science International* 37 (1): 19-26.

Gable, R. S. (1993). Toward a comparative overview of dependence potential and acute toxicity of psychoactive substances used nonmedically. *American Journal of Drug and Alcohol Abuse* 19 (3): 263-281.

Gad, S.C. & Chengelis, C.P. 1998. *Acute Toxicology Testing* (2nd edit.). San Diego, CA: Academic Press.

Garbino, J.; Henry, J.A.; Mentha, G. & Romand, J-A. 2001. Ecstasy ingestion and fulminant hepatic failure: Liver transplantation to be considered as a last therapeutic option. *Veterinary and Human Toxicology* 43 (2): 99-102.

Gill, J.R. & Stajic, M. 2000. Ketamine in non-hospital and hospital deaths in New York City. *Journal of Forensic Sciences* 45 (3): 655-8.

Goad, P.T. 1985. *Acute and Subacute Oral Toxicity of Methylenedioxymethamphetamine in Rats*. Project EMD-AT-001 report. Redfield, AK: Intox Laboatories.

Gowing, R.L.; Henry-Edwards, S.M.; Irvine, R.J. & Ali, R.L. 2002. The health effects of ecstasy: A literature review. *Drug and Alcohol Review* 21 (2): 53-63.

Green S.M.; Clark, R.; Hosteller, M.A.; Cohen, M.; Carlson, D., & Rothrock, S.G. 1999. Inadvertent ketamine overdose in children: Clinical manifestation and outcome. *Annuals of Emergency Medicine* 34 (4): 492-7.

Greer, G.R. & Tolbert, R.T. 1998. A method of conducting therapeutic sessions with MDMA. *Journal of Psychoactive Drugs* 30 (4): 371-9.

Hansen, G.; Jensen, S.B.; Chandresh, L. & Hilden, T. 1988. The psychotropic effect of ketamine. *Journal of Psychoactive Drugs* 20 (4): 419-25.

Hardman, H.F.; Haavik, C.O. & Seevers, M.H. 1973. Relationship of the structure of mescaline and seven analogs to toxicity and behavior in five species of laboratory animals. *Toxicology and Applied Pharmacology* 25 (2): 299-309.

Hartung, T.K.; Schofield, E.; Short, A.J.; Parr, M.J. & Henry J.A. 2002. Hypoatreamic states following 3,4-methylenedioxymethamphetamine. *QJM: An International Journal of Medicine* 95 (7): 431-7.

Hayner, G. N. (2002). MDMA misrepresentation: an unresolved problem for ecstasy users. *Journal of Psychoactive Drugs* 34 (2): 195-8.

Hegadoren, K.M; Baker & G.B., Bourin, M. 1999. 3,4-methylenedioxy analogues of amphetamine: Defining the risks to humans. *Neuroscience and Biobehavior Review* 23(4):539-53.

Henry, J.A.; Jeffreys, K.J. & Dawling, S. 1992. Toxicity and deaths from 3,4 methylenedioxymethamphetamine (ecstasy). *The Lancet 340*, 384-387.

Hernandez, M.; McDaniel, C.H. & Hernandez, O.J. 1998. GHB-induced delirium: A case report and review of the literature on gamma hydroxybutyric acid. *American Journal of Drug and Alcohol Abuse* 24 (1): 179-83.

Heyndrickx, B. 1987. Fatal intoxication due to flunitrazepam. *Journal of Analytical Toxicology* 11 (6): 278.

Hindmarch, I. & Brinkmann, R. 1999. Trends in the use of alcohol and other drugs in cases of sexual assault. *Human Psychopharmacology* 14 (4): 225-31.

Holland, J. 2001. *Ecstasy: The Complete Guide, A Comprehensive Look at the Risks and Benefits of MDMA*. Rochester, VT: Park Street Press.

Hornfeldt, C.S.; Lothridge, K. & Upshaw-Downs, J.C. 2002. Forensic science update: Gamma-hydroxybutyrate (GHB). *Forensic Science Communications*, 4 (1) n.p. Retrieved December 30, 2002, from http://www.fbi.gov/hq/lab/fsc/backissue/jan2002/hornfelt.htm

Ingels, M.; Rangan, C.; Bellezzo, J. & Clark, R.F. 2000. Coma and respiratory depression following the ingestion of GHB and its precursors: Three cases. *Journal of Emergency Medicine* 19 (1): 47-50.

Interagency Coordinating Committee on the Validation of Alternative Methods. 2002. *The Revised Up-and-Down Procedure: A Test Method for Determining the Acute Ora Toxicity of Chemicals and Products* (NIH publication 02-4501). Bethesda, MD: National Toxicology Program. Retrieved August 1, 2002 fromhttp://iccvan.niehs.nih.gov/methods/udpdocs/ udpfin/vol_1.pdf

Irwin, R.D. 1996. NTP Summary Report on the Metabolism, Disposition, and Toxicity of 1,4-butanediol. NIH publication 96-3932 (National Toxicology Program report series #54).

Iten, P.X.; Oestreich, A.; Lips, R. & Brabetz, M. 1999. Coma after intake of gamma-hydroxybutyric acid (GHB): Two case reports. Paper presented at the 37th Triennial Conference, September 5-9, TIAFT (The International Association of Forensic Toxicologists). Cracow, Poland, September 5-9.

Iwanami. A. 2001. Psychotropic-induced water intoxication and its countermeasures. *Journal of the Japanese Medical Association* (English version) 44 (9): 417-22.

Jago, R.H.; Restall, J. & Thompson, M.C. 1984. Ketamine and military anaesthesia: The effect of heavy

papaveretum premedication and Althesin induction on the incidence of emergence phenomena. *Anaesthesia* 39 (9): 925-7.

Jansen, K.L.R. 2000. A review of the non-medical use of ketamine: Part 1: Use, users and consequences. *Journal of Psychoactive Drugs* 32 (4): 419-33.

Jansen, K.L.R. & Daracot-Cankovic, R. 2001. The nonmedical use of ketamine: Part II: A review of problem use and dependence. *Journal of Psychoactive Drugs* 33 (2): 151-8.

Jochemsen, R.; van Boxtel, C.J.; Hermans, J. & Breimer, D.D. 1983. Kinetics of five benzodiazepine hypnotics in healthy subjects. *Clinical Pharmacology and Therapeutics* 34 (July): P42-7.

Kalant, H. 2001. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. *Canadian Medical Association Journal* 165 (7): 917-28.

Kalasinsky, K.S.; Dixon, M.M.; Schmunk, G.A. & Kish, S. J. 2001. Blood, brain and hair GHB concentrations following fatal ingestion. *Journal of Forensic Sciences* 46 (3): 728-30.

Karch, S.B.; Stephens, B.C. & Nazareno, G.V. 2001. Club drug or confusing artifact? *American Journal of Forensic Medicine and Pathology* 22 (3): 266-9.

Kish, S.J. 2002. How strong is the evidence that brain serotonin neurons are damaged in human users of ecstasy? *Pharmacology, Biochemistry and Behavior* 71 (4): 845-51.

Kissin, W. & Ball, J. 2002. Club drugs, 2001 update. *The DAWN Report.* Rockville, MD: Office of Applied Studies, SAMHSA.

Klaassen, C.D. (Ed.) 2001. *Casaret and Doull's Toxicology: The Basic Science of Poisons (6th edition).* New York: McGraw-Hill.

Kraner, J.; Plassard, J.; McCoy, D.; Rorabeck, J.; Witeck, M. & Evans, M. 2000. Fatal overdose from ingestion of 1,4-butanediol, a GHB precursor. (Abstract of conference paper). *Journal of Toxicology—Clinical Toxicology* 38 (5): 534.

Laborit, H. 1964. Sodium 4-hydroxybutyrate. *International Journal of Neuropharmacology*, 3, 433-52.

Leadbeatter, S. 1988. Dental anesthetic death: An unusual autoerotic episode. *American Journal of Forensic Medicine and Pathology* 9 (1): 60-3.

LeBeau, M.; Andollo, W.; Hearn, W.L.; Baselt, R.; Cone, E. & Finkle, B. et al. 1999. Recommendations for toxicological investigations of drug-facilitated sexual assaults. *Journal of Forensic Sciences* 44 (1): 227-30.

Li, J.; Stokes, S.A. & Woeckener, A. 1998. A tale of novel intoxication: Seven cases of gammahydroxybuyric acid overdose. *Annals of Emergency Medicine* 31 (6): 723-8.

Licata, M.; Pierini, G. & Popoli G. 1994. A fatal ketamine poisoning. *Journal of Forensic Sciences* 39 (5): 1314-20.

Liester, M.B.; Grob, C.S.; Bravo, G.L. & Walsh, R.N. 1992. Phenomenology and sequelae of 3,4-methylenedioxy methamphetamine use. *Journal of Nervous and Mental Disease*, 180 (6): 345-52.

Litovitz, T. L.; Klein-Schwartz, W.; White, S.; Cobaugh, D.J.; Youniss, J. & Omslaer, J. C. et al. 2002. 2001 annual report of the American Association of Poison Control Centers toxic exposure surveillance system. *American Journal of Emergency Medicine* 20 (5):391-445.

Long, H.; Nelson, L.S. & Hofmann, R.S. 2002. Ketamine medication error resulting in death. (conference abstract). *Journal of Toxicology – Clinical Toxicology* 40 (6): 614.

Louagie, H.K.; Verstraete, A.G.; DeSoete, C.J.; Baetens, D.G. & Calle, P.A. 1997. A sudden awakening from a near coma after combined intake of gamma-hydroxybutyric acid (GHB) and ethanol. *Journal of Toxicology—Clinical Toxicology* 35 (6): 591-4.

Malberg, J.E. & Seiden, L.S. 1998. Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat. *Journal of Neuroscience* 18 (13): 5086-94.

Marc, B.; Baudry, F.; Vaquero, P.; Zerrouki, L; Hassnaoui, S. & Douceron, H. 2000. Sexual assault under benzodiazapine submission in a Paris suburb. *Archives of Gynecology and Obstetrics* 263 (4): 193-7.

Marshall, B.E. & Longnecker, D.E. 1990. General anesthetics. In L.S. Goodman, A. Gilman, T.W. Rall, A.S. Nies & P. Taylor (eds.). *The Pharmaceutical Basis of Therapeutics* (pp. 285-310). New York: Pergamon Press.

McDaniel, C.H. & Miotto, K.A. 2001. Gamma hydroxybutyrate (GHB) and gamma-butyrolactone (GBL) withdrawal: Five case studies. *Journal of Psychoactive Drugs* 33 (2): 143-9.

Mechan, A.O.; Moran, P.M.; Elliott, J.M.; Young, A.M.J.; Joseph, M.H. & Green, A.R 2002. A study of the effect of a single neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) on the subsequent long-term behaviour of rats in the plus-maze and open-field. *Psychopharmacology* 159 (2): 167-75.

Minnasch, P.; Reiter, A.; Meissner, C. & Oehmichen, M. 1999. [Accidental death caused by simultaneous mixed intoxication in three men.] *Archiv fuer Kriminologie* 203 (5-6): D-23562 (article in German, from Biosis

abstract).

Mintzer, M.Z. & Griffiths, R.R. 1988. Flunitrazepam and triazolam: A comparison of behavioral effects and abuse liability. *Drug and Alcohol Dependence* 53 (1): 49-66.

Miotto, K.; Darakjian, J.; Basch, J.; Murray, S.; Zogg, J. & Rawson, R. 2001. Gamma-hyrodoxybutyric acid: Patterns of use, effects and withdrawal. *American Journal of Addictions* 10 (3): 232-41.

Miro, O.; Nogue, S.; Espinosa, G.; To-Figueras, J. & Sanchez, M. 2002. Trends in illicit drug emergencies: The emerging role of gamma-hydroxybutyrate. *Journal of Toxicology: Clinical Toxicology* 40 (2):129-35.

Moore, K.A.; Kilbane, E.M.; Jones, R.; Kunsman, G.W.; Levine, T. & Smith, M. 1997. Tissue distribution of ketamine in a mixed drug fatality. *Journal of Forensic Sciences* 42 (4):1183-5.

Moore, M. & Alltounian, H. 1978. *Journeys into the Bright World*. Rockport, MA: ParaResearch.

Morland, J. 2000. Toxicity of drug abuse – amphetamine designer drugs (ecstasy): Mental effects and consequences of a single dose. *Toxicology Letters* 112 (3): 147-52.

Mozayani, A.; Small, P. & De Cuir, L. 1998. A fatality involving GHB. Presented at October 1998 conference of The International Association of Forensic Toxicologists, Albuquerque, NM.

MSDS (Material Safety Data Sheet) 1998. F9261 Flunitrazepam. St. Louis, MO: Sigma Chemical Company [referencing a clinical report in *Kiso to Rinsho* (Tokyo), 1985, 19:1277].

Mullins, M.E. 1999. Laboratory confirmation of flunitrazepam in alleged cases of date rape. *Emergency Medicine* 6 (9): 966-8.

Munzar, P.; Yasar, S.; Redhi, G.H.; Justinova, Z. & Goldberg, S.R. 2001. High rates of midazolam self-administration in squirrel monkeys. *Behavioral Pharmacology* 12 (4):257-65.

Narvaez, R. 2001. MDMA in combination: "Trail Mix" and other powdered drug combinations. Abstract of paper presented at *MDMA/Ecstasy Research: Advances, Challenges, Future Directions* conference July 19-20. Bethesda, MD: NIDA.

National Center for Health Statistics. 2002. *Total deaths for each cause by 5-year age groups, United States, 1999-2000 (GMWKI)* November 13. Retrieved December 20, 2002, from http:www.cdc.gov/nchs/datawh/ statab/unpubd/mortabs/gmki10.htm

Neubert, D. 1999. Risk assessment and preventative hazard minimization. In H. Marquardt; S.G. Schafer; R. McClellan & F. Welsch (eds.). *Toxicology* (pp. 1153-86). San Diego, CA: Academic Press.

Nicholson, K. L. & Balster, R. L. 2001. GHB: A new and novel drug of abuse. *Drug and Alcohol Dependence* 63 (1): 1-22.

NTP (National Toxicology Program) 1991. Gamma-butyrolactone (material safety data sheet), *NTP Technical Report*, Vol. 406.

NTP (National Toxicology Program). 2002. Short-term study abstracts (#54): NTP summary report on the metabolism, disposition and toxicity of 1, 4-butanediol. Retrieved January 28, 2003, from http://ntp-server.niehs.nih.gov/htdocs/ST-studies/TOX054.html

Palatini, P.; Tedeschi, L.; Frison, G.; Padrini, R.; Zordan, R.; Orlando, R.; Gallimberti, L.; Gessa, G.L. & Ferrara, S.D. 1993. Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *European Journal of Clinical Pharmacology* 45 (4): 353-6.

Parrott, A.C. 2002. Human psychopharmacology of Ecstasy (MDMA): A review of 15 years of empirical research. *Human Psychopharmacology*, 16 (8): 557-77.

Parrott, A.C. 2002. Recreational ecstasy/MDMA: The serotonin syndrome, and serotonergic neurotoxicity. *Pharmacology, Biochemistry and Behavior* 71 (4): 837-44.

Pereira,C. A. & Nishioka, S. de A. 1994. Poisoning by the use of *datura* leaves in a homemade toothpaste. *Clinical Toxicology* 32 (3): 329-31.

Peroutka, S.J.; Newman, H. & Harris, H. 1988. Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology* 1 (4): 273-7.

Peyton, S. H.; Couch, A. T. & Bost, R.O. 1988. Tissue distribution of ketamine: Two case reports. *Journal of Analytical Toxicology* 12 (5): 268-9.

Poldrugo, F., Barker, S., Basa, M., Mallardi, F. & Snead, O. C. (1985). Ethanol potentiates the toxic effects of 1,4-butanediol. *Alcoholism: Clinical and Experimental Research* 9 (6):493-7.

Pulce, C.; Mollon, P.; Pham, E.; Frantz, P. & Descotes, J. 1992. Acute poisonings with ethyl loflazepate, flunitrazepam, prazepan, and triazolam in children. *Veterinary and Human Toxicology*, 1992, 34 (2): 141-3.

Ramcharan, S.; Meenhorst, P.L.; Otten, J.M.; Koks, C.W.; DeBoer, D. & Maes, R. A. et al. 1998. Survival after massive Ecstasy overdose. *Journal of Toxicology: Clinical Toxicology* 36 (7): 727-31.

Reiss, A. J. Jr. & Roth, J.A. (Eds.) 1994. *Understanding and Preventing Violence. Vol 3: Social Influences.* Washington, D.C.: National Academy Press.

Ricaurte, G.A.; Yuan, J.; Hatzidimitriou, G.; Cord, B.J. & McCann, U.D. 2002. Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("Ecstasy"). *Science* 297 (5590): 2260-3.

Rickert, V.I.; Wiemann, C.M. & Berenson, A.B. 1999. Prevalence, patterns, and correlates of voluntary flunitrazepam use. *Pediatrics*, 103 (1): E61-3.

Riggs, A.T.; Dysken, M.; Kim, S.W. & Opsahl, J.M. 1991. A review of disorders of water homeostasis in psychiatric patients. *Psychosomatics* 32 (2): 133-46.

Robertson, M.D. & Drummer, O.H. 1998. Postmortem distribution and redistribution of nitrobenzodiazepines in man. *Journal of Forensic Sciences* 43 (1): 9-13.

Roset, P. N.; Farre, M.; de la Torre, R.; Mas, M.. & Menoyo, E., et al. 2001. Modulation of rate of onset and intensity of drug effects reduces abuse potential in healthy males. *Drug and Alcohol Dependence* 64 (3): 285-98.

Ross, T.M. 1995. _-hydroxybutyrate overdose: Two cases illustrate the unique aspects of this dangerous drug. *Journal of Emergency Nursing* 21 (5): 374-6.

Roth, J.A. 1994. Psychoactive Substances and Violence. *Research in Brief* report series. Washington, D.C.: Office of Justice Programs, National Institute of Justice.

Rouse, D. A. & Fysh, R. 1992. Body packing presenting as sudden collapse. *Medicine, Science, and Law* 32 (3): 270-2.

Slaughter, L. 2000. Involvement of drugs in sexual assault. *Journal of Reproductive Medicine* 45(5): 425-30.

Snyder, H.; Schwenzer, K.S.; Pearlman, R.; McNally, A.J.; Tsilimidos, M. & Salamone, S.J. 2001. Serum and urine concentrations of flunitrazepam and metabolites, after a single oral dose, by immunoassay and GC-MS. *Journal of Analytical Toxicology* 25 (8): 699-704.

Spencer, J. (Ed.) 1990. *Residual Effects of Abused Drugs on Behavior.* (NIDA research monograph #101). Rockville, MD: National Institute on Drug Abuse.

Spilich, G.J.; June, L. & Renner, J. 1992. Cigarette smoking and cognitive performance. *British Journal of Addiction* 87 (9):113-26.

Stephens, B. G.; Coleman, D. E. & Baselt, R. C. 1999. In vitro stability of endogenous gamma-hydroxybutyrate in postmortem blood. *Journal of Forensic Sciences* 44 (1): 231.

Stillwell, M. E. 2002. Drug-facilitated sexual assault involving gamma-hydroxybutyric acid. *Journal of Forensic Sciences* 47 (5): 1133-4.

Tanaka, E. 2002. Toxicological interactions between alcohol and benzodiazepines. *Clinical Toxicology* 40 (1): 69-75.

Teter, C.J. & Guthrie, S.K. 2001. A comprehensive review of MDMA and GHB: Two common club drugs. *Pharmacotherapy* 21 (12): 1486-1513.

Tsokos, M. 1999. Colouration of the gastric mucosa following ingestion of Rohypnol I film tablets: morphological findings following peroral intake and experimental post-mortem investigations. *Rechtsmedizin* 9 (4): 138-140.

Tunnicliff. G. 1997. Sites of action of gamma-hydroxybutyrate (GHB)—A neuroactive drug with abuse potential. *Clinical Toxicology* 35 (6): 581-90.

Turner, D.M. 1994. *The Essential Psychedelic Guide*. San Francisco: Panther Press.

United Nations 1998. *Terminology and Information on Drugs*. Vienna: Office on Drugs and Crime.

Vaiva, G.; Boss, V.; Bailly, D.; Thomas, P.; Lestavel, P. & Goudemand, M. 2001. A "accidental" acute psychosis with ecstasy use. *Journal of Psychoactive Drugs* 33 (1):95-97.

Van Kampen, J. & Katz, M. 2001. Persistent psychosis after a single ingestion of 'ecstasy.' *Psychosomatics* 42 (6): 525-7.

Verwey, B.; Eling, P.; Wientjes, H. & Zitman, F.G. 2000. Memory impairment in those who attempted suicide by benzodiazepine overdose. *Journal of Clinical Psychology* 61 (6):456-9.

Vollenweider, F.X.; Liechti, M.E.; Gamma, A.; Greer, G. & Geyer, M. 2002. Acute psychological and neurophysiological effects of MDMA in humans. *Journal of Psychoactive Drugs* 34 (2): 171-84.

Weiner, A.L.; Vieira, L.; McKay; C.A. & Bayer, M.J. 2000. Ketamine abusers presenting to the emergency department: A case series. *Journal of Emergency Medicine* 18 (4): 447-51.

Wickstrom, W.; Amrein, R.; Haefelfinger, P. & Hartmann, D. 1980. Pharmacokinetic and clinical observations on prolonged administration of flunitrazepam. E*uropean Journal of Clinical Pharmacology* 17 (3): 196-8.

Winek, C.L.; Wahba, W.W. & Rozin, L. 1999. Heroin fatality due to penile injection. *American Journal of Forensic Medicine and Pathology* 20 (1): 90-2.

Woods, J.H.; Katz, J.L. & Winger, G. 2000. Abuse and therapeutic use of benzodiazepines and benzodiazepine-like drugs. In F.E. Bloom & D.J. Kupfer (Eds.) *Psychopharmacology — The Fourth Generation of Progress* (n.p.) [on-line edition]. New York: Raven Press.

Zickler, P. 2000. NIDA launches initiative to combat club drugs. *NIDA Notes*, 14 (6): March [electronic version].
  Retrieved December 24, 2002, from http://165.122.78.61/NIDA_Notes/NVol14N6/Launched.html
Zvosec, D.L.; Smith, S.W.; McCutcheon, J.R.; Spillane, J.; Hall, B.J. & Peacock, E.A. 2001. Adverse events,
  including death, associated with the use of 1,4-butanediol. *New England Journal of Medicine* 344 (2): 87-93.