Review

Use of Club Drugs by HIV-Seropositive and HIV-Seronegative Gay and Bisexual Men

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Abstract. *Club drugs such as methylenedioxymethamphetamine (MDMA, ecstasy), gamma hydroxybutyrate (GHB), and ketamine are among the fastest-growing drugs of abuse in the United States. Reports have shown that some gay and bisexual men are likely to engage in club-drug use in a myriad of venues. This is concerning given that the use of club drugs has been linked to high-risk sexual behaviors. Further, the use of club drugs by HIV-seropositive individuals may have detrimental outcomes on disease progression by either influencing adherence, resulting in drug-drug interactions with antiretrovirals, or potentially compounding immune suppression. Clinicians caring for HIV-seropositive and -seronegative individuals should be aware of the clinical effects and management guidelines associated with these chemicals. This article reviews the available literature with regard to the use of club drugs by HIV-seropositive and -seronegative gay and bisexual men. Although club-drug use may be associated with many risk behaviors for HIV infection, this review focuses on risk behavior among gay and bisexual men since this is the group for which the most data have been reported. The clinical effects and management guidelines associated with these agents are described, and the potential detrimental effects of these substances on HIV disease are discussed.*

Introduction

Recent reports of increasing incidences of both HIV and AIDS within the United States emphasize the need to improve preventive efforts and better identify concomitant behaviors that contribute to the spread of HIV and AIDS among persons at risk.[1] Many public health researchers are examining the social factors that contribute to the spread of HIV, including behaviors that increase the chances that individuals will choose to engage in high-risk practices such as unprotected sex.[2] One underrecognized concern is the use of club drugs among gay and bisexual men and the contribution that drug use may make in encouraging high-risk sexual practices. Although abuse of club drugs and the potential adverse consequences of such abuse are associated with many risk behaviors, this review focuses on risk behaviors of gay and bisexual men, since this is the population for which the most data have been published.

Club drugs are substances used in a recreational fashion to enhance social experience. Because these drugs produce social disinhibition, they have been used to heighten sexual experiences. In addition, club drugs have been used to facilitate date rape because they produce retrograde amnesia.[3] The use of club drugs first gained popularity in Europe and later in the Americas with the advent of raves, all-night parties with a prolonged style of dance to fast-paced, repetitive music often accompanied by laser light displays. Methylenedioxymethamphetamine (MDMA, ecstasy), gamma hydroxybutyrate (GHB), and ketamine are the chemical substances most commonly referred to as "club drugs."[4] Each of these chemicals may be consumed to heighten the user's rave or party experience by increasing the energy to dance for prolonged periods of time or by decreasing social inhibitions.

The incidence of club-drug use among the general population continues to increase at an exponential rate.[5,6] The National Drug Intelligence Center equates the expanding production, availability, and use of MDMA to that of cocaine and heroin.[5] Use of MDMA is now estimated to be the fastest-growing drug-abuse problem in the United States. In 2000, 1.3 million high-school seniors had consumed MDMA, and approximately 450,000 admitted to being current users.[6] MDMA has become the most common stimulant used in bars and clubs in many areas of the country, a figure that has increased as traffickers target such venues. Although not as well quantified, anecdotal reports indicate distressing increases in the use of GHB and ketamine as well.[5,6] Some highly publicized deaths have been associated with the use of club drugs, and it should be emphasized that these drugs may contribute to HIV infection and many more deaths by encouraging high-risk behaviors. To further define this problem, we reviewed the available literature regarding use of club drugs by gay and bisexual men.

Epidemiology

No controlled trials have compared the prevalence of club-drug use among gay and bisexual men to that of the general population or among other individuals at higher risk of HIV transmission. Several studies have, however, examined prevalence particularly among gay and bisexual men alone. Mansergh and colleagues conducted a cross-sectional survey study of 295 gay and bisexual men in the San Francisco Bay Area who had attended a circuit party in the previous year.[7] Circuit parties most often encompass 2- or 3-day-long weekend events attended primarily

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by gay and bisexual men from across the country. The typical circuit party weekend involves a series of social gatherings that culminate with one main dance event. Anecdotally, circuit parties are associated with a high incidence of drug use and sexual behavior, leading many to hypothesize an increased incidence of high-risk sex. In this study, all respondents reported use of club drugs during circuit party weekends. Specifically, 75% of respondents reported having used MDMA; 58%, ketamine; and 25%, GHB. Two-thirds of the men reported having some form of oral or anal sex, 49% reported having anal sex, and 28% reported having unprotected anal sex during the 3-day period. An association was found between the use of club drugs and the incidence of high-risk sexual behavior. These researchers concluded that use of club drugs might encourage high-risk behaviors and that targeted preventive efforts are needed for gay and bisexual men who attend circuit parties.

Klitzman and colleagues conducted a pilot study to examine the correlation between MDMA abuse and high-risk sexual behaviors among 169 gay and bisexual men through the use of an anonymous questionnaire distributed at 3 New York City dance clubs.[8] One-third of all respondents reported MDMA use at least monthly, and there was a strong and statistically significant correlation between MDMA use and history of recent repeated unprotected anal intercourse. This association remained equally strong following control for age, ethnicity, and all other forms of drug abuse, including ethanol.

Waldo and colleagues examined correlates of drug use and risky sexual behavior in a group of young gay and bisexual men (aged 15-17 years) and their older counterparts (aged 18-22 years).[9] An interviewer-administered cross-sectional survey was administered to 719 gay and bisexual men. Blood specimens were collected and tested for HIV and evidence of other known sexually transmitted diseases. HIV seroprevalence was lower among those aged 15 to 17 (2%) than among those aged 18 to 22 (6.8%). Men aged 15 to 17 used MDMA less frequently than those aged 18 to 22. In both age groups use of MDMA was associated with unprotected anal intercourse.

Suspecting that club-drug use among gay and bisexual men would mirror or exceed national trends and recognizing that club-drug use might predispose to high-risk sexual practices, Colfax and colleagues conducted a cross-sectional survey study in San Francisco to examine the prevalence of club-drug use and high-risk sex practices during circuit party weekends.[10] They found that 80% of circuit party attendees had used MDMA; 66%, ketamine; and 29%, GHB. Drug use was statistically more common during circuit party weekends than during non-circuit party weekends ($P<.001$). Also concerning was that the incidence of unprotected anal sex with partners of unknown HIV serostatus or opposite serostatus was reported by 21% of HIV-seropositive and 9% of HIV-seronegative respondents. The authors concluded that, at least during circuit party weekends, the use of club drugs is strongly associated with the incidence of behaviors that place individuals at risk for HIV transmission.

Mattison and colleagues also examined the use of club drugs within circuit party settings.[11] A brief questionnaire involving demographics, drugs used, sexual activity, and reasons for attendance at circuit parties was provided to a nonrandom sample of party attendees at 3 separate venues in 1998 and 1999. A total of 1169 usable questionnaires were obtained. Club-drug use during the previous 12 months was high, with greater than 50% of all respondents reporting having used MDMA or ketamine. Frequent use of MDMA and ketamine was associated with high-risk sexual practices such as unprotected anal sex. Interestingly, the most common reasons for attending a circuit party were "to be uninhibited and wild" and "to have sex." These responses are consistent with the high incidence of unprotected sex observed in the cohort. Although several limitations, such as lack of randomization, characterize this trial, researchers concluded that intensive preventive and interventional efforts are needed among gay and bisexual men who use club drugs and attend circuit parties.

Authors from each of these trials expressed concern about the degree to which club drugs influence a user's decision to have unprotected anal sex. This is not surprising given the disinhibiting effect of most club drugs. Although most of these studies had several limitations, they do reveal important and unrecognized factors that may contribute to high-risk sexual behaviors among gay and bisexual men in the United States. These trials demonstrate the need for HIV clinicians to be familiar with the clinical effects and issues surrounding the use of club drugs.

Club Drugs in HIV-Seropositive Individuals

Concerns have been raised regarding the dangers of club-drug use among HIV-seropositive individuals on antiretroviral medications. The abuse of any drug or chemical substance inherently results in obstacles to adherence. Serious drug interactions may also result from concurrent use of club drugs and antiretroviral medications. Clinicians should also be cognizant of the fact that most club drugs are rarely sold in their pure form and are often adulterated with other chemicals such as dextromethorphan, aspirin, lysergic acid, or pseudoephedrine.[12]

Harrington and colleagues reported the case of a 29-year-old man with AIDS on a regimen consisting of twice-daily doses of saquinavir 400 mg and ritonavir 400 mg who ingested approximately a half teaspoonful (2.5 mL) of GHB. Within 20 minutes he became unresponsive with clonic contractions of the left side of his body.[13] Emergency medical personnel found the patient responsive only to painful stimuli and with a heart rate of 40 beats per minute. The patient eventually required intubation and over a 3-hour period was stabilized and extubated. Upon questioning, the patient admitted to ingesting 2 MDMA tablets 29 hours prior to admission, a half teaspoonful of GHB 6 hours prior to admission, and an additional half teaspoonful of GHB just prior to his loss of consciousness. The patient reported ingesting GHB in order to counteract the stimulant effects of MDMA. Interestingly, the patient reported that prior to taking protease inhibitors (PIs), he often used similar quantities of GHB as a sleep aid without any adverse effects. The patient maintained that his last dose of MDMA was 29 hours prior, yet its effects persisted and prompted him to ingest GHB.

Many amphetamines, including MDMA, are metabolized via the cytochrome P450 (CYP450) system. More specifically, MDMA is metabolized by the CYP2D6 isoform. The majority of commercially available PIs, including ritonavir, will inhibit this isoenzyme and others (eg, CYP2C9, CYP2C19). It is likely that in this case ritonavir inhibited the metabolism of the MDMA,

resulting in prolonged and persistent effects of the substance. Clearance of GHB is mediated partially by systemic oxidation and partially by first-pass metabolism via the CYP450 system. Inhibition of the CYP450 system by ritonavir might explain this patient's exaggerated response to the agent. This case report illustrates the potential adverse effects that may be seen when club drugs such as MDMA and GHB are coadministered with antiretrovirals, particularly PIs with CYP450 inhibitive properties.

Henry and colleagues described a fatal interaction involving MDMA and ritonavir in a 32-year-old white man with AIDS.[14] The patient had been taking zidovudine and lamivudine for a number of years, and ritonavir was added to his regimen 1 month prior to admission. The patient reported commonly using MDMA without any untoward adverse effects. On the night of admission, the patient visited a club and reported ingesting 2.5 MDMA tablets (estimated MDMA dose of 180 mg, calculated from the MDMA content of a remaining tablet found in the patient's supply). While at the club, the patient became tachycardic with a pulse rate of up to 200 beats per minute. He experienced tonic-clonic convulsions, vomited, and later experienced cardiorespiratory arrest. Attempts at resuscitation were unsuccessful. In autopsy, the only illicit drug detected was MDMA at a serum level of 4.56 mg/L. Previously reported toxic ingestions of 42 and 18 MDMA tablets led to serum levels of 7.72 mg/L and 4.05 mg/L, respectively. Similar to the case reported by Harrington and colleagues, it was hypothesized that ritonavir acted as an inhibitor of the CYP450 system and in this case may have resulted in lethal MDMA serum levels. In evaluating potential interactions between club drugs and antiretrovirals, clinicians should be careful to review metabolic pathways and properties of the agents in question.

Some reports are now finding correlations between club drugs and transient immune suppression. This is particularly concerning given the number of HIV-seropositive patients who may be using these agents. Pacifici and colleagues conducted a placebo-controlled crossover study in which 17 healthy adult men were administered 2 repeated doses of 100 mg of MDMA at 4- and 24-hour intervals.[15] The researchers found that MDMA produced a time-dependent decrease in the CD4+/CD8+ cell ratio due to a decrease in CD4+ cells. They also noted a reduction in functional responsiveness of lymphocytes to mitogenic stimulation and a simultaneous increase in natural killer cell activity. Significant residual effects were noted up to 48 hours following exposure to MDMA. The researchers hypothesized that the immunosuppressive effects of MDMA are related to inductions in cortisol secretion. While US research in this area is hampered by MDMA's status as a controlled substance, this trial suggests significant implications for future research.

Pacifici and colleagues also examined the immune effects of administration of MDMA with and without ethanol in 6 healthy adult men.[16] Single oral doses of MDMA (100 mg), ethanol (0.8 g/kg), a combination of MDMA and ethanol, and placebo were administered, with a washout interval of 1 week between each. Acute MDMA administration produced time-dependent immune dysfunction in association with serum concentrations of the drug, as well as increased serum cortisol levels. Similar to the previously mentioned trial, a reduction in CD4+ cell counts and simultaneous increases in natural killer cell activity were noted. The largest reductions in CD4+ cells were seen in individuals who received MDMA combined with ethanol, indicating some synergism between the 2 agents. Immune function appeared to trend toward baseline 24 hours after MDMA administration.

Both of these pilot studies of the effects of club drugs on immune status have limitations. The reported CD4+ cell count variations appear short-lived and transient and may simply reflect normal diurnal fluctuations. Sample sizes are also small and have yet to show any clinical significance. Recognizing the limitations of the research, larger well-controlled trials must be designed to truly elucidate drug effects from confounding factors. As previously mentioned, research in this area is limited by MDMA's controlled-substance status within the United States.

Clinical Effects and Management of Club-Drug Ingestions

As common as club-drug use is among gay and bisexual men, regardless of HIV serostatus, little information is available in the literature regarding antiretroviral medications and club-drug interactions. Also, many health care professionals, including pharmacists, are unfamiliar with the clinical effects and management strategies for toxic ingestions of these substances. Clinicians caring for HIV-seropositive patients should be particularly familiar with the clinical effects of these agents. Patients should be questioned regarding their consumption of these substances, and clinicians should be prepared to counsel and advise patients regarding their use. In many instances it may be advisable to involve psychiatric and substance abuse counselors, as the issues surrounding drug abuse of any kind are often complex and multifactorial. The 3 major club drugs—MDMA, GHB, and ketamine—are reviewed below.

Methylenedioxymethamphetamine

MDMA was initially developed in 1914 as an appetite suppressant.[17] The drug was never marketed, but some efficacy was demonstrated in the 1970s as a means to enhance communication in behavioral therapy sessions.[18] In the 1980s, MDMA became popular among young adults attending raves and all-night clubs, and its increasing abuse and evidence of adverse health effects contributed to the drug being classified as a schedule I controlled substance in 1985.[19] In 2001, however, the US Food and Drug Administration (FDA) approved a clinical trial examining MDMA's effects on posttraumatic stress disorder. This was the first FDA-approved clinical trial involving MDMA since the drug became a controlled substance.[20]

MDMA is commonly manufactured in clandestine laboratories throughout Europe and the United States. A great deal of the product is imported from Amsterdam. In addition to ecstasy, various street names for MDMA exist, including X, ADAM, XTC, and hug drug.[19] Tablets, which typically contain from 50 mg to 150 mg of active drug, are usually imprinted with a popular icon such as the Nike swoosh or Motorola symbol. Users sometimes refer to MDMA by these imprints (eg, "a smurf pill"). MDMA is typically purchased in the setting where it will be used, most commonly at raves. Prices range from $20 to $40 per tablet, and it is not uncommon for tablets to be adulterated

with other chemicals, including aspirin, dextromethorphan, and pseudoephedrine.[21]

MDMA is structurally similar to the stimulant methamphetamine and to the hallucinogen mescaline, lending to its effects as both a stimulant and hallucinogen.[21] MDMA affects neurotransmitters, including serotonin, dopamine, and norepinephrine.[22] Release of these neurotransmitters by presynaptic neurons is often increased and their metabolism by monoamine oxidases inhibited, resulting in excessive synaptic concentrations.[22]

The clinical effects of MDMA typically begin within 30 to 60 minutes of ingestion, with a duration of action lasting approximately 6 to 8 hours.[23] The term "ecstasy" comes from many of the effects produced by the drug, which include euphoria, feelings of closeness, altered visual and sensory perception, increased libido, and increased energy.[24] Diminished hunger and thirst are also common effects. MDMA use is usually accompanied by characteristic paraphernalia, including pacifiers or candy suckers, which are used to avoid bruxism, a common effect associated with the drug. Glowsticks and brightly colored necklaces and bracelets may be displayed to heighten visual hallucinations. Vicks VapoRub is also commonly used to enhance the effects of MDMA.[25] VapoRub may be directly inhaled, rubbed above the upper lip, or applied to the inside of a surgical or painter's mask. The distinctive odor and sensations produced by the product are often amplified and exaggerated by MDMA use. Because MDMA alone or in combination with physical activity can quickly result in elevated body temperature, consumption of large quantities of water or other fluids is a common practice. Users must be cautious as excessive consumption of water may result in hyponatremia. MDMA may also promote excessive dancing, a phenomenon commonly known as marathon dancing. Marathon dancing may contribute to dehydration and hyperthermia.[26] In an effort to combat dehydration, many raves supply beverages known as "power drinks" or "smart drinks" that are fortified with amino acids and vitamins.

Serious adverse effects have been reported following the ingestion of as little as 1 MDMA tablet.[27] Tachycardia and hypertension are the result of sympathomimetic stimulation, and the psychedelic effects of the drug are a result of serotonergic stimulation.[27] More severe complications of ingestion, including seizures, cerebral edema, and serotonin syndrome, have been reported.[28] Confusion, depression, insomnia, anxiety, and paranoia have been reported to occur for weeks following ingestion.

Chronic use of MDMA has been correlated with cognitive impairment in both humans and animals. Cognitive impairment is believed to be related to changes in the structural components of serotonergic neurons.[29] Positron emission tomography brain scans of MDMA users have revealed significant reductions in the number of serotonin transporters; the magnitude of transporter loss was associated with extent of use of MDMA.[29]

Diagnosis of MDMA intoxication is based primarily upon history and examination. The most common findings on presentation include agitation, anxiety, tachycardia, and hypertension.[27] Clinicians should be particularly suspicious of patients presenting with MDMA-associated paraphernalia (eg, brightly colored bracelets and other jewelry, pacifiers, and bottled water).

No antidote exists for MDMA ingestion, but management should involve monitoring for serious adverse effects including arrhythmias, hyperthermia, and rhabdomyolysis. Gastric decontamination with activated charcoal may be helpful within 60 minutes of MDMA ingestion; unfortunately, few patients will present within this time frame. Supportive care should be provided. Agitation and anxiety may be controlled with benzodiazepines, and hypertension with labetalol, phentolamine, or nitroprusside. Pure beta-adrenergic blocking agents may worsen hypertension by causing unopposed alpha-stimulation and should be avoided.[21] Hyperthermia can be managed with rapid external cooling using tepid water. Neuromuscular blockade to induce paralysis is the most effective method for core body temperature reduction, but requires intubation. Treatment of serotonin syndrome with dantrolene or cyproheptadine may be effective, but aggressive supportive care with rapid cooling remains the mainstay of therapy.[28] Rhabdomyolysis is managed by alkalinizing the urine with the administration of intravenous sodium bicarbonate. In severe cases of renal failure, hemodialysis may be indicated.

Detection of MDMA remains a conundrum for clinicians. MDMA may be detected in samples by immunologic assay for related chemicals such as amphetamine and methamphetamine.[30] In order to detect the presence of MDMA alone, larger concentrations of the drug must be present in the serum, and testing procedures for MDMA alone are only 50% as sensitive as those for amphetamine and methamphetamine.[23] Traditional toxicology screens that employ thin-layer chromatography can detect MDMA metabolites in the urine. Gas chromatography/mass spectrometry may be used to confirm positive immunoassay tests.

Numerous HIV-specific issues surrounding acute and chronic ingestion of MDMA exist. As noted, clinicians should be cognizant that MDMA tablets often contain contaminants. The clinical effects of these contaminants as well as their potential for interacting with antiretrovirals should be considered. Fluid status changes associated with excessive hydration from copious water ingestion or dehydration from excessive dancing can complicate the adverse effects associated with specific antiretrovirals. Fluid status changes can intensify the effects of antiretroviral-induced diarrhea, and dehydration may precipitate indinavir-associated nephrolithiasis.[31] Patients with underlying wasting syndrome might be more prone to the appetite-suppressing effects of MDMA and should be carefully monitored for reductions in weight. "Power drinks," which are often consumed with MDMA, may contain amino acids and other vitamin supplements that may lead to compound toxicity. Patients on amprenavir should particularly avoid supplements containing vitamin E.[32] Lastly, 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.

Gamma Hydroxybutyrate

GHB is a naturally occurring fatty-acid derivative of the central nervous system (CNS) neurotransmitter gamma aminobutyric acid (GABA).[33] In the United States, GHB was originally intro-

duced as an anesthetic agent, but a lack of analgesic effects coupled with reports of seizure-like activity destined the drug for failure.[34] Since that time, placebo-controlled trials have examined the role of the GHB analogue oxybate sodium for the management of narcolepsy-associated cataplexy. Recently, the FDA approved oxybate sodium, a GHB analogue, for the treatment of cataplexy. The drug is a schedule III controlled substance that will be available only through a stringent FDA closed-distribution system.[35] Street and slang names for GHB include liquid ecstasy, G, Georgia home boy, gib, liquid X, salty water, and soap.[3]

Originally introduced as a dietary supplement in 1990, GHB was touted by many trainers and body builders as a means to increase muscle mass, metabolize fat, and stimulate libido.[36] As the agent's popularity increased, users became familiar with its ability to produce a euphoric state. In late 1990, the FDA banned all over-the-counter sales of GHB.[37] By this time GHB had already entered the club-drug scene and many had become aware of its potential use as a "date-rape" drug. In early 2000, GHB was designated a schedule I controlled substance in the United States, but it is often imported from European sources or manufactured in clandestine laboratories. Many Internet sites advertise "recipes" for the home production of GHB and GHB manufacturing kits. GHB is most commonly available as an oral solution (ie, "Liquid X," "Liquid E"). In settings of abuse, the chemical is commonly available in small vials or mixed with bottled water. A common dose of GHB is 1 capful of the liquid, which typically sells for $5 to $10.

Since the reclassification of GHB to schedule I, chemical precursors of GHB have become popular sources of the drug. Gamma butyrolactone (GBL) and 1,4-butanediol (1,4-BD) are both chemical precursors of GHB that produce similar effects. GBL is widely used in the chemical industry and is available from chemical supply companies and health stores.[38] Following ingestion, GBL is rapidly converted to GHB by endogenous lactonase enzymes.[23] GBL is more rapidly absorbed and produces a longer duration of action than GHB.[39] In 1999, the FDA issued a warning alerting the public of the dangers of GBL and asked manufacturers for a voluntary recall of the product.[40] 1,4-BD is also available in health stores and the FDA has warned of its abuse potential. Following ingestion, 1,4-BD is metabolized by alcohol dehydrogenase to gamma hydroxybutyraldehyde, which is in turn metabolized to GHB by aldehyde dehydrogenase.[23] Because ethanol preferentially binds alcohol dehydrogenase, prolonged toxicity may occur when 1,4-BD is ingested concurrently with ethanol.[41]

GHB is thought to mediate various processes including sleep cycles, temperature, cerebral glucose metabolism, and memory.[42] GHB, a metabolite of GABA, is normally found within the CNS in concentrations that are 1/1000 that of GABA.[43] GHB is also believed to influence endogenous dopamine levels, possibly increasing concentrations through interactions with GABA receptors.[42] GHB is commonly abused by bodybuilders who believe in the agent's purported ability to increase muscle mass. The agent is thought to prolong slow-wave sleep, which is the period when the greatest concentration of growth hormone is released.[45] Although use of GHB has been associated with some short-term increases in growth hormone, these findings have not been demonstrated in large, well-controlled clinical trials. GHB's lipophilic properties facilitate its ability to rapidly cross the blood-brain barrier.[46] The drug is primarily metabolized by the lungs and expired as carbon dioxide.[47] Additionally, 2% to 5% of the drug is eliminated renally. Peak plasma concentrations occur within 20 to 60 minutes of ingestion, and the half-life of the agent is 20 minutes.

Clinical effects following GHB ingestion usually develop within 15 to 30 minutes.[3] These effects are amplified with coingestions of alcohol or other CNS depressants.[21,41] Dose-related CNS depression is the most common manifestation of ingestion.[43,46] With increasing doses, CNS depression progresses from amnesia and hypotonia to drowsiness, dizziness, and euphoria. GHB is often ingested to counteract the stimulant properties associated with other club drugs such as MDMA. Tonic-clonic seizures have been reported in a number of cases and electroencephalogram changes have been seen in animal models. Garrison and colleagues reported a case series of 78 patients who had ingested GHB; 9% of the users developed some form of seizure-like activity.[48] However, in another case series involving 88 patients with GHB ingestion, no patients had reported any seizure activity.[49] These reports are difficult to interpret because random muscular contractions caused by GHB are often misinterpreted as seizures.

Respiratory depression is also a common manifestation of GHB ingestion. Most patients will maintain airway patency, although some may require intubation with mechanical ventilation.[49] Cardiovascular effects include bradycardia and hypotension. Bradycardia has been reported in as many as 36% of users and is correlated with level of consciousness. Gastrointestinal effects include vomiting and hypersalivation.[50] Vomiting is more common when GHB is coingested with ethanol. Hypothermia (ie, a core body temperature of less than 35ºC) has been reported commonly in as many as 31% of patients.[49]

GHB has been associated with cases of sexual assault or "date rape."[3] The drug is easily administered because of its liquid dosage form. GHB's powerful intoxicating properties will cause victims to lose consciousness as well as the ability to resist or recall a sexual assault.[51] These effects make assault cases involving GHB difficult to prosecute because attackers may claim that the incident was consensual.

No antidote exists for GHB ingestion.[51] Generally, most ingestions are self-limiting and patients can be managed with supportive care. Most patients recover within 7 hours of ingestion without the need for intubation,[49,51] although severe ingestions may require intubation. Since GHB is a sedative amnestic, rapid-sequence intubation may be accomplished with paralytics alone.[43] Aggressive suction will be needed as patients may have large amounts of oral secretions. Clinicians should be cognizant of cases involving 1,4-BD and ethanol coingestion, since these patients may present with prolonged or recalcitrant toxicity requiring more aggressive management.

GHB is not detected by routine urine or serum toxicology screening.[52] Diagnosis is most often made based upon history and presentation.[3,43] Gas chromatography and mass spectroscopy are the most precise methods for the detection of GHB; however, these testing methods will not differentiate GHB from its precursors, GBL and 1,4-BD. Serum levels greater than 50 mg/mL are associated with a loss of consciousness, and levels greater than 260 mg/mL with unresponsive coma.[53] GHB is

rapidly metabolized and therefore any delay in testing will lower the likelihood of detection. Generally, delays beyond 12 hours after ingestion will lead to undetectable results.[3]

There are several issues around GHB use specific to HIV-infected patients. Because of GHB's powerful sedative effects, it may be used by HIV-seropositive patients with insomnia in attempts to promote or enhance sleep. GHB should be used with caution by HIV-seropositive patients with predisposing seizure disorders or with opportunistic infections that may lower seizure threshold (ie, toxoplasmosis, cryptococcal meningitis). Use of GHB in these situations may precipitate seizure-like activity. Lastly, GHB use may cause severe nausea, vomiting, and gastrointestinal-tract irritation that may complicate antiretroviral therapy and affect adherence. GHB detoxification may precipitate a withdrawal phenomenon, which may necessitate hospitalization for symptomatic management and to ensure antiretroviral adherence.

Ketamine

Ketamine, a derivative of phencyclidine hydrochloride (PCP), was introduced in the 1960s as a dissociative anesthetic.[54] The advent of safer, more effective anesthetic products has greatly diminished the clinical use of ketamine. Ketamine may still be used in some pediatric critical-care settings and is commonly used in veterinary medicine for animal sedation. Street and slang names for ketamine include special K, K, kit-kat, super acid, super K, and jet.[12]

Prescription ketamine is available as an injection formulation and is classified as a controlled substance in most states. Federally, the substance is classified as a schedule III drug product. Ketamine is difficult to manufacture and therefore the most common mode of acquisition is through diversion of the prescription product. Theft of ketamine from veterinary clinics and animal hospitals is common. Ketamine is believed to have entered the club-drug scene in the 1980s. Originally, the drug is thought to have been a common adulterant in MDMA tablets.[55] As users became familiar with ketamine's effects, its use as a sole agent emerged. Street cost of ketamine is estimated to be approximately $80 per gram. Users may inject, ingest, or snort the product. However, ingestion is less common because the product undergoes extensive first-pass metabolism.

Ketamine's structural resemblance to PCP lends to its ability to interact with the N-methyl-D-aspartate channel, inhibiting it noncompetitively and also preventing glutamate activation.[56] Ketamine also indirectly interacts with a number of cellular receptors including the muscarinic, nicotinic, cholinergic, and opioid receptors. Inhibition of neuronal reuptake of norepinephrine, dopamine, and serotonin has also been demonstrated.[54]

In social settings, ketamine is most commonly snorted, and its effects are abrupt in onset and last only 30 to 45 minutes.[55] Lower doses of the drug result in analgesic effects, and higher doses will produce amnestic effects.[3] Patients often describe a dissociative feeling of "floating over one's body."[57] These out-of-body experiences are often referred to by users as "trips to K-land" or "K-holes."[57] Visual hallucinations and a lack of coordination are also common and not surprising given the drug's similarities to PCP.[3,57] Cardiovascular toxicity has been reported in the form of reflex sympathetic activation, hypertension, tachycardia, and arrhythmias.[54] Because ketamine is an amnestic agent, respiratory depression and apnea are also commonly encountered manifestations of ingestion. Interestingly, many ketamine users report that the drug's effects are dependent upon the setting in which it is used. Noisy or rowdy settings may be correlated with negative effects and therefore certain users prefer not to use the drug in rave or club settings.[58]

The tasteless, odorless, and colorless characteristics of ketamine have made it an increasingly common date-rape drug.[3] The chemical can be easily and surreptitiously added to most beverages, and increasing numbers of facilitated sexual assault cases involving ketamine have been reported.[56] Loss of consciousness accompanied by anterograde amnesia and vivid hallucinations are common. Thus, the victim is rendered uncombative and potentially unreliable as a witness.

Similar to PCP ingestion, supportive care remains the cornerstone of management for ketamine ingestion.[3] Attention should be paid to respiratory and cardiac function. The vivid hallucinations associated with ketamine may be minimized by placing the patient in a tranquil environment with minimal external stimuli. Clinicians should be aware that coingestion of ethanol or other club drugs will only compound toxic effects. Death from ketamine ingestion is rare.[59] Serum levels of both ketamine and its active metabolite norketamine can be obtained, but testing is not generally available to most clinicians.[60] Of note, many immunoassays to detect PCP will cross-react with ketamine.[61]

Few HIV-specific issues relating to ketamine exist. Adherence to antiretroviral regimens is the primary concern, and the hallucinogenic effects of the drug may affect drug-taking behavior. Cardiovascular effects of the drug may be deleterious among patients with underlying heart disease or lipid abnormalities. As a substrate of the CYP450 system (specifically 3A4), ketamine may interact with certain antiretrovirals, particularly the PIs.

Conclusion

Club drugs are popular substances of abuse among gay and bisexual men, particularly at circuit parties and other social gatherings. Commonly used to decrease social inhibitions, these agents also appear to promote high-risk sexual behaviors and have been associated with increased HIV transmission rates. Additionally, club drugs may produce significant and potentially lethal drug interactions with antiretroviral medications. Therefore, clinicians caring for HIV-seropositive individuals as well as officials designing preventive public health programs should be familiar with the clinical effects and management guidelines for these substances of abuse. Additionally, clinicians should be aware that use of club drugs or any other mind-altering substance by any individual might lead to high-risk sexual behavior contributing to HIV transmission.

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Correction

An error was made in "Antiretroviral Treatment for Adult HIV Infection in 2002: Updated Recommendations of the International AIDS Society–USA Panel," which was reprinted in the September/October 2002 issue from *JAMA* (2002;288:222-235). In the second paragraph on page 266, the third sentence should have read, "Ritonavir inhibits enzymes of the cytochrome P450 system; it may act early on absorption and first-pass metabolism, increasing peak plasma concentrations with a coadministered PI (eg, with *lopinavir or saquinavir*); or it may inhibit subsequent metabolism and extend the half-life of the second PI with an increase in trough level of drug (eg, with *indinavir or amprenavir*)." In the original version the examples in parentheses, indicated above with italic type, were incorrectly reversed.