Club Drugs and HIV Infection: A Review

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Club drug use is common among populations with human immunodeficiency virus (HIV) and populations at high risk for HIV infection. Club drugs have a myriad of acute and chronic medical consequences. Club drug–related visits to the emergency department and admissions for treatment of substance use have increased dramatically over the past 15 years. Most epidemiological data support the role of club drugs in increasing sexual risk behavior, with some studies demonstrating an independent association between use of certain club drugs and HIV infection. The direct influence of club drugs on progression of HIV disease remains to be determined; however, club drugs may interact with certain retroviral medications and have been associated with decreased adherence to medication. Clinicians should ask all patients about patterns of club drug use, counsel patients about the risks associated with club drug use, and refer patients to appropriate behavioral treatment programs for substance use when clinically indicated.

Drugs that are frequently used in dance clubs or at circuit parties or rave parties are known collectively as “club drugs” [1]. Because of the frequent use of club drugs among persons who are at risk for HIV infection or are infected with HIV, this review will include 3,4-methylenedioxymethamphetamine (MDMA; also known as “Ecstasy”), methamphetamine, ketamine, γ-hydroxybutyrate (GHB), and inhaled nitrites (known as “poppers”). The present article provides a general overview of the epidemiological profile and medical consequences of club drugs and also provides recommendations for clinicians treating patients who use club drugs, emphasizing the implications of club drug use among persons with HIV infection and persons at high risk for HIV infection.

OVERVIEW OF CLUB DRUGS

Use of club drugs is a public health concern. In 2004, according to the population-based National Survey on Drug Abuse and Health, it was estimated that, in the United States, 1.9 million persons aged ≥12 years used MDMA and 1.4 million used methamphetamine; in comparison, 1.3 million used crack cocaine and 398,000 used heroin [2]. The burden of club drug use on the health care system is great: the Drug Abuse Warning Network showed that, between 1994 and 2001, emergency department visits associated with MDMA, ketamine, and GHB use increased ∼22-, 35-, and 60-fold, respectively [3].

As is the case with substance use in general, club drug use is more prevalent among men who have sex with men (MSM), compared with the general population [4]. A population-based study of urban gay men found that, in the 6 months before being interviewed, 20% of the men reported using poppers, 12% reported using MDMA, and 10% reported using methamphetamines; HIV-infected men were more likely to report use of multiple drugs and frequent drug use [5]. A probability-based sample of young men (age range, 15–22 years) from 7 cities in the United States found that, in the 6 months before interviews were conducted, 14% of the men reported using poppers, 19% reported using MDMA, and 20% reported using amphetamines [6]. Use of ketamine and GHB is also high among MSM; one study found that 53% of young MSM reported lifetime use of ketamine, and studies of MSM who were circuit-party attendees reported that up to 25% of participants used GHB and 43% used ketamine [7, 8]. There are considerably fewer studies of club drug use among heterosexuals either infected with HIV or at high risk for HIV infection, but some studies have shown high rates of club drug use in these populations [9, 10].

SUMMARY DESCRIPTIONS OF CLUB DRUGS

Methamphetamine. Methamphetamine is a synthetic stimulant derived from ephedrine or pseudoephedrine, ingredients
that are commonly found in cold preparations and asthma medications [11]. Methamphetamine may be ingested, snorted, smoked, injected, or administered as a rectal suppository. The effects of methamphetamine, which last up to 10–12 h, include increased energy and alertness, decreased appetite, and endowment of users with feelings of power and invulnerability. These effects can escalate until users develop severe insomnia and anxiety, which sometimes develop into symptoms similar to those associated with paranoia and schizophrenia. Additional acute effects include tachycardia, hypertension, myocardial ischemia, cerebrovascular accidents, and hyperthermia. Acute methamphetamine intoxication is treated with supportive care and antipsychotics [12].

Methamphetamine causes increases in the release of epinephrine, serotonin, and dopamine [11]. Most research has focused on the effects of methamphetamine on dopamine levels. Methamphetamine increases synaptic levels of dopamine through inhibiting dopamine reuptake transporters and increasing release of vesicular dopamine stores [13]. The resulting high levels of dopamine are thought to be responsible for the acute physiological and psychological effects of methamphetamine. Prolonged exposure to methamphetamine is associated with decreased dopamine levels, which are thought to be caused by reductions in dopamine transporter activity and degeneration of dopamine nerve terminals [13]. Long-term consequences of methamphetamine use include weight loss, depression, and impaired cognitive performance. Chronic methamphetamine use is associated with severe dental disease, likely because of a convergence of methamphetamine-related effects, including bruxism (excessive teeth grinding), xerostomia (persistent dry mouth due to the sympathomimetic properties of methamphetamine), poor dental hygiene, and diet [14]. The behavioral effects of methamphetamine include excessive picking and scratching of skin, which put users at increased risk for skin infections, including infection with methicillin-resistant Staphylococcus aureus [15].

Methamphetamine withdrawal is associated with depression, anergia, agitation, and insomnia. Symptoms can last from weeks to months, with relapses to methamphetamine use common [16].

**MDMA.** MDMA is chemically similar to amphetamine and the hallucinogenic drug mescaline [17]. Usually ingested as a pill, MDMA has empathogenic, euphoric, and stimulant effects that last for 3–6 h [17]. Although the most serious medical consequences of MDMA use are infrequent, the effects of MDMA include tachycardia, hypertension, hyperthermia, hyponatremia, rhabdomyolysis, hepatic failure, and death [18–21]. Although these sequelae may be a direct effect of the drug itself, it should be noted that the long dance marathons often associated with MDMA use, as well as the subsequent volume depletion that occurs, may contribute to MDMA-associated morbidity and mortality [22]. In addition, MDMA pills frequently contain other substances, including methamphetamine and pseudoephedrine, that could either have additional medical effects or compound the effects due to MDMA alone [23]. Treatment of acute MDMA intoxication includes restoration of fluid and electrolyte balance and careful evaluation and management of hepatic function [18].

MDMA is thought to exert its acute psychological effects primarily through increasing serotonin levels, by both increasing serotonin release and inhibiting its reuptake [24, 25]. Although MDMA typically is used only intermittently, MDMA dependence has been reported [26]. Animal studies have demonstrated that exposure to MDMA results in reduced serotonergic activity, possibly as a result of the down-regulation of the serotonergic neurons caused by MDMA-associated toxicity [27, 28]. Although studies of the long-term consequences of MDMA use in humans suffer from a number of design flaws, evidence suggests that there are clinically significant neurological consequences of MDMA use [29]. Some, but not all, studies report high rates of depression, anxiety, insomnia, and impaired cognitive performance among MDMA users [17, 26, 30, 31].

**Ketamine.** Ketamine is a dissociative anesthetic frequently used in veterinary medicine; ketamine for recreational use is therefore usually illicitly obtained from medical sources [18]. A derivative of phencyclidine hydrochloride, ketamine exerts strong hallucinogenic and euphoric effects, and it is often combined with other club drugs [18, 32]. It may be snorted, injected, or ingested [33]. The effects associated with ketamine have a rapid onset (1–30 min, depending on the route of administration used) and last 30–180 min [18]. Overuse can cause catatonia, inducing a dissociative state; users refer to this state as falling into a “k-hole.” Additional adverse effects include delirium, amnesia, hypertension, depression, tachycardia, rhabdomyolysis, vomiting, agitation, and respiratory depression [17, 18]. Treatment for acute complications involves supportive care, including volume repletion. For cases of severe agitation, treatment with benzodiazepines may be indicated [18].

Ketamine is thought to exert its effects primarily through its effects on the N-methyl-d-aspartate receptor, where it functions as an antagonist [34]. N-methyl-d-aspartate dysfunction has been associated with psychoses and schizophrenia; similar symptoms are seen in association with ketamine use [18]. Ketamine dependence has been reported, with symptoms of craving and tolerance but with no physiological withdrawal symptoms reported [35, 36]. Although data are inconclusive, they suggest that memory deficits and perception distortions associated with acute ketamine use may persist [37].

**GHB.** GHB is a naturally occurring metabolite in the human brain. Synthetic GHB and its precursors (γ-butyrolactone and 1,4-butanediol) are used for their euphoria-inducing effects [38]. GHB typically is taken orally as a liquid, begins to affect...
users within 10–20 min, and has effects that can last for up to 4 h [17]. GHB has been used to treat narcolepsy and alcohol withdrawal [39]. A controlled substance, GHB is manufactured using readily available chemicals and instructions available on the Internet. Small doses of GHB can induce nausea and vomiting and can cause a comalike state in users, particularly when GHB is combined with alcohol. Because of these effects, GHB has been implicated as a date-rape drug [17]. Other documented adverse effects of GHB include depression, confusion, alternating states of agitation and coma, amnesia, syncope, hypotonia, ataxia, nystagmus, random clonic movements of the face and extremities, and seizures [40–43]. GHB-related deaths have been attributed to respiratory depression, aspiration, and pulmonary edema. Treatment for acute GHB intoxication involves mainly supportive care, often involving intubation for airway support [18].

GHB binds to both GHB and γ-aminobutyric acid receptors, which modulate sleep and memory; the drug-induced effects of exogenous GHB are thought to occur primarily as a result of its interaction with γ-aminobutyric acid type B receptors [44]. GHB has been associated with changes in dopaminergic activity in the CNS, and there exists evidence of GHB causing increases in dopamine levels in brain tissue [45]. GHB has a narrow safety index, with small increases in dosages resulting in a switch from a euphoric, relaxed state to a drug-induced coma and respiratory depression in users [18]. This is especially of concern because the purity of GHB preparations varies by as much as 10-fold, so persons may inadvertently overdose by taking highly concentrated preparations of the drug. These variations in drug concentrations, as well as the fact that the safety index narrows considerably when alcohol is used in conjunction with GHB, probably account for the numerous cases of GHB-related comas seen in emergency departments.

GHB dependence is well-documented, with acute withdrawal symptoms (tremors, vomiting, and insomnia) lasting up to 2 weeks and prolonged withdrawal (characterized by dysphoria, memory problems, and anxiety) lasting several months [38, 44]. Acute withdrawal is treated with benzodiazepines and supportive care [44].

**Poppers.** Although they are not always included in the definition of club drugs, we include poppers in our definition in the present review because they are frequently used in party settings and by populations at risk for HIV infection or infected with HIV [7]. This inhaled drug may consist of various forms of amyl, alkyl, or butyl nitrites. Poppers are readily available for purchase via the Internet, where they are legally sold as cleaning products, although their use as a drug is acknowledged and even encouraged on some Internet sites. Nitrites are usually nasally inhaled and cause rapid onset of vasodilation, resulting in light-headedness and euphoria that may progress to severe headaches; these symptoms are accompanied by decreased blood pressure and tachycardia [46]. Poppers are rapidly metabolized, with their effects generally lasting only a few minutes.

The popularity of poppers in sexual settings is attributable to their orgasm-enhancing effects and to the belief that they relax the anal sphincter, making receptive anal sex more comfortable [46]. Coadministration of poppers with sildenafil citrate (Viagra; Pfizer) or other phosphodiesterase inhibitors is contraindicated, given the potential for the combination of these vasodilators to cause cardiovascular collapse [47]. Negative consequences of popper use include allergic reactions, methemoglobinemia, and hemolytic anemia [48]. Popper use has also been associated with an increased risk of human herpesvirus 8 infection [49]. Although the reasons for this association remain to be determined, it is likely that this association results from the sexual practices associated with popper use [46].

### Club Drugs, Sexual Risk Behavior, and Sexually Transmitted Infections (STIs)

Studies of club drug use, sexual risk behavior, and STIs are complicated by a myriad of factors. Because many of these studies have a cross-sectional design, it is difficult to ascertain whether club drug use in general preceded high-risk sexual behavior. Even in longitudinal studies, the timing of club drug use in relation to sexual behavior is not always ascertained; in such cases, the potential causal pathway between club drug use and sexual risk behavior cannot be determined. Among most club drug users, polydrug use is common, making it difficult to measure the effect of any single drug on outcomes. Furthermore, many studies do not control for other contextual factors, such as partner type, the location(s) where club drug use and sexual behavior occurred, and the presence of other comorbid conditions that may be expected to contribute to sexual risk, such as depression.

Despite the aforementioned limitations, most, but not all, studies show significant associations between increased sexual risk behavior and methamphetamine and poppers use; these drugs have also been independently associated with HIV infection and other STIs [50–54]. Popper use has been associated with a doubling of the risk for HIV infection in several studies; similarly, an increased risk for HIV infection has been noted in association with methamphetamine use [55–57]. A recent study of MSM tested for HIV found that the seroincidence of HIV was 6.3% among methamphetamine users, compared with 2.1% among nonusers [58].

MDMA, ketamine, and GHB have also been associated with increased sexual risk, although less consistently than have methamphetamine or poppers. Use of MDMA has been associated with unprotected anal sex and an increased number of sexual partners in some, but not all, studies [59–64]. Frequent ketamine use and any ketamine use have also been associated with sexual risk behaviors, but not all studies demonstrate such an...
association [61, 65]. GHB has also been associated with unprotected anal sex [64, 65].

Although not all studies have controlled for the multiple factors that may confound the association between club drug use and heightened sexual risk, the disinhibitory effects of the drugs are believed to result in greater numbers of sex partners, an increased frequency of sex, and decreased condom use. However, other factors, including prolongation of sexual encounters while taking club drugs, increased mucosal trauma, and the possible immunosuppressive effects of club drugs have been postulated as additional factors that may increase the risks for STI found to be associated with club drug use, even after controlling for sexual behavior [66]. Some club drugs have also been associated with increased rates of condom failure, which suggests that, even in settings where safer sex practices are attempted, club drugs may lead to increases in risk [67].

**CLUB DRUGS AND HIV DISEASE**

No studies have demonstrated conclusively that club drugs directly influence the progression of HIV disease; the challenges of examining the effects of drug use on HIV disease have been reported elsewhere [68]. Methamphetamine, MDMA, and poppers have been shown to influence cellular immune responses, but the clinical implications of these findings are unknown [69–72]. Recent studies have demonstrated that methamphetamine increases cytokine levels; this finding suggests that these drugs may play a role in enhancing the immune activation seen in subjects with chronic HIV disease [73–75]. Methamphetamine also increases rates of viral replication and mutation in cells infected with feline immunodeficiency virus, a retrovirus closely related to HIV [76, 77]. Nevertheless, most natural history studies do not report significant associations between club drug use and HIV-disease progression. However, these analyses were limited with regard to their examination of the effects of particular club drugs on HIV-disease progression, because composite club drug variables were often examined, or because club drugs were combined with other drug-use variables [78, 79]. One study found that methamphetamine use was associated with higher viral loads and decreased effectiveness of antiretroviral therapy (ART), after controlling for self-reported medication adherence [80].

**Club drugs and medication adherence.** Although substance users report suboptimal adherence to ART, relatively little research has focused specifically on ART adherence among club drug users [81–83]. Methamphetamine users have reported decreased adherence to ART during episodic methamphetamine “binges” that last for many days; similar binging patterns have also been noted among users of other club drugs [7, 81]. Such sporadic treatment interruptions could lead to the development of drug-resistant HIV and, potentially, to treatment failure. However, patterns of drug resistance among club drug users remain to be determined.

**Club drugs and interactions with ARTs.** The combination of club drugs with ART may produce serious and even fatal interactions. Patients starting retroviral therapy should be advised that their “normal” doses of club drugs may produce untoward effects when coadministered with ART. MDMA, GHB, ketamine, and methamphetamine are all at least partially cleared through the cytochrome P-450 system, as are a variety of retroviral medications [1]. Thus, concomitant use of club drugs and antiretrovirals can delay clearance of club drugs, dramatically increasing blood levels and leading to adverse events. In case reports, ritonavir has been implicated in increasing both MDMA and GHB levels, with at least 1 death attributed to the effect of ritonavir on delaying MDMA clearance [84, 85]. The interactive effects of nucleoside reverse-transcriptase inhibitors and nonnucleoside reverse-transcriptase inhibitors on club drug levels remain less understood, although ketamine levels may increase when individuals are taking nonnucleoside reverse-transcriptase inhibitors [86].

**TREATMENT OF CHRONIC CLUB DRUG USE**

Few studies have evaluated the efficacy of approaches to treating abuse of and dependence on club drugs or club-drug–related sexual risk behavior. One study found that, compared with users of alcohol and other drugs, users of club drugs were more likely to complete treatment, but they had higher addiction indices, even at discharge [87]. Most research has focused on the treatment of methamphetamine use, for which interventions have been adapted mainly from alcohol and cocaine treatment programs. Greater duration of and patient retention in treatment are correlated with better outcomes, although relapse rates are high [16]. One recently completed randomized trial involving a large sample of methamphetamine-dependent persons compared intensive behavioral counseling with treatment-as-usual outpatient treatment; reductions in methamphetamine use were noted in both groups, with no differences noted at 6 months of follow-up [88]. Current harm-reduction approaches to methamphetamine use exist, but they have not been rigorously evaluated [89]. Contingency management, a behavioral intervention that involves providing vouchers if individuals have drug-negative urine samples, has been used successfully among methamphetamine-using MSM, and it compares favorably with intensive behavioral counseling [90].

To our knowledge, there have not been rigorous evaluations of the effects of behavioral interventions for use of other club drugs or for club drug–related sexual risk behavior. The Centers for Disease Control and Prevention–funded Project MIX intervention is a randomized, controlled group intervention for MSM who are substance users, including those who use club drugs. Project MIX will determine whether a risk-reduction
Providers should ask all their patients about club drug use, keeping in mind that patients frequently use multiple club drugs and that club drug use may vary in intensity throughout a week or month, with weekends and party events noted as periods during which particularly high use occurs. Patients should be informed of the acute and long-term consequences of club drug use; those who continue to use club drugs should be provided with information on how to reduce the risks of use, such as ensuring adequate, but not excessive, hydration during party events; avoidance of mixing club drugs with alcohol; and knowing the risks of combining poppers with sildenafil citrate or other phosphodiesterase inhibitors. Patients who inject club drugs should be referred to needle-exchange programs. All club drug users should be informed of the sexual risk behaviors and STIs associated with club drug use, and they should be provided with safer-sex counseling and condoms. For patients receiving ART, a frank discussion about plans for adherence and possible interactions of ART with club drugs is warranted. Comorbidities, including skin infections, dental disease, and depression, should be evaluated and treated.

Patients who are dependent on club drugs should be referred for behavioral treatment. Clinicians should become familiar with substance-use treatment programs within their communities, and they should pay particular attention to determining whether staff are familiar with club drugs and are comfortable accepting a club drug user for treatment. Programs that serve specific populations (e.g., MSM and HIV-infected persons) may be particularly familiar with the management of individuals who use club drugs.

Acknowledgments


References


