Crystal Methamphetamine, Its Analogues, and HIV Infection: Medical and Psychiatric Aspects of a New Epidemic

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The use of the recreational drug crystal methamphetamine among younger homosexual men is expanding, and with it, unsafe sex behaviors that increase the transmission of human immunodeficiency virus (HIV). This article reviews available literature on the medical and psychiatric morbidities associated with methamphetamine abuse in HIV-infected patients. Medical complications include hypertension, hyperthermia, rhabdoymyolysis, and stroke. One fatal case of ingestion of methamphetamine with HIV medication has been documented. Two fatal cases of ingestion of HIV medication with the amphetamine analogue n-methyl-3,4 methylenedioxymethamphetamine (MDMA, or "ecstasy") have also been reported. Some molecular researchers suggest that dopaminergic systems are vulnerable to the combined neurotoxicity of HIV infection and methamphetamine. Population surveys indicate high rates of HIV infection among methamphetamine abusers and high rates of unprotected anal intercourse during drug intoxication. Intoxication can sometimes produce paranoia, auditory hallucinations, and, occasionally, violent behavior. Amphetamine withdrawal commonly results in symptoms of depression. Methamphetamine is a new challenge related to treatment and prevention of HIV infection.

The use of the recreational drug crystal methamphetamine (MA) among younger members of the community of men who have sex with men (MSM) is expanding, and with it, unsafe sex behaviors that may worsen the HIV epidemic. This article describes medical and psychiatric morbidities associated with amphetamine abuse in HIV-infected patients.

EPIDEMIOLOGY

According to the World Health Organization, amphetamine and MA are the most widely abused illicit drugs after cannabis. More than 35 million individuals reg-

ularly use/abuse amphetamine and/or MA, whereas 15 million persons regularly abuse cocaine [1].

Studies conducted in New York suggest that MA use presents a serious problem for the MSM community because of its relationship with high-risk sexual behaviors associated with HIV transmission [2]. The drug is used to initiate, enhance, and prolong sexual encounters. Intoxication can lead to lapses in judgment with regard to safe sex, leading to unprotected receptive anal intercourse [3].

A study of 68 gay and bisexual men seeking treatment for MA dependence in California found that 61% of participants had HIV infection. Persons with HIV infection were found to be more likely to have injected MA, to have contracted another sexually transmitted disease, and to have engaged in unprotected anal intercourse with significantly more sexual partners. Seventy-seven percent of the subjects in the sample were white men, and 17% were Latino men. All were aged in their mid-30s and had some college education. Subjects reported a mean of 14 different sexual partners in the 30 days before study enrollment and of 66 different

sexual partners in the 6 months before study enrollment [4]. Similarly, a survey of 169 gay and bisexual men using the amphetamine analogue N-methyl-3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy") found a strong association between MDMA use and high-risk sexual behavior. Seventy-nine percent of the sample self-reported being HIV negative, 17% left the question blank, and 4% reported being HIV positive. A total of 57% of the sample reported having had unprotected anal insertive and/or receptive intercourse in the last year. MDMA use was associated with high-risk sexual behavior (OR, 2.77; 95% CI, 1.35–5.65). The study did not find an association between high-risk sexual behavior and methamphetamine use for the 20% of respondents who reported using MA. These data were collected by questionnaire in 3 New York City dance clubs. Fifty-six percent of the sample subjects were white, 20% were Latino, and 4% were African American, and the mean age was 24.2 years. No data were gathered about whether the sexual partner's HIV infection status was known or whether sexual encounters were anonymous [5]. A recent report in *Morbidity and Mortality Weekly Report* [6] about an outbreak of 130 cases of syphilis in California found that 51% of the sample subjects were MSM and noted that the most commonly abused drug was MA (use of MA was reported by 18% of the subjects). Of the 57 patients who knew their HIV serostatus, 60% reported that they were HIV positive.

MEDICAL COMPLICATIONS

The short-term effects of MA use are protean and are mediated primarily through the release of large amounts of dopamine and smaller amounts of norepinephrine. These include tachycardia, hypertension, tachypnea, hyperthermia, and CNS excitation effects similar to those induced by immediate ingestion of cocaine [7]. MA toxicity can also lead to rhabdomyolysis and cardiovascular events [8]. A retrospective review of emergency department admissions with a final diagnosis of rhabdomyolysis over a 5-year period in California reported that 43% of subjects had detectable urine levels of MA [9]. Cardiovascular responses elicited by binge administration of MA include vasoconstriction, vasculitis, and focal myocyte necrosis [10].

Cardiopulmonary events associated with long-term MA use are well documented and include myocardial infarction and stroke. These potentially devastating events usually occur in relatively young patients. Four cases of stroke associated with MA use in patients aged 29–45 years have been documented [11]. Smoking of MA has been associated with acute pulmonary hypertension and dilated cardiomyopathy [12].

MA may also have immunomodulatory activity, particularly by impairing CD8 cell–mediated cytotoxic T lymphocyte func-

tion [13]. This may be of clinical importance in primary HIV infection, because CD8 cell activity is responsible for early suppression of lentiviral replication and viral set point [14].

Long-term MA abuse also results in bruxism and periodontal disease [15, 16], which were found to increase dental costs by 200% in a prison study [17]. Illicit MA may also be contaminated with multiple harmful byproducts. Acute lead poisoning has been reported and presents with anemia, encephalopathy, myalgias, and hepatitis [18].

METABOLISM

MA and MA-related compounds, including dextroamphetamine and MDMA, are metabolized by the CYP2D6 isoform of the cytochrome P450 enzyme system. The genetic polymorphism associated with the P450 system results in significant individual differences in responses to these compounds [19]. For instance, 3%–10% of the white population is deficient in CYP2D6 and may be at increased risk for MA-related toxicity [20].

DRUG INTERACTIONS BETWEEN MA AND ANTIRETROVIRALS

Fatal interactions between amphetamine analogues and protease inhibitors (PIs) used to treat HIV infection have been recently reported. PIs are metabolized primarily by the CYP3A4 isoform and also inhibit—and, in some cases, induce—this enzyme in varying degrees. The PI ritonavir can also affect 3 other P450 enzymes, including CYP2D6. Because ritonavir has greater affinity for this enzyme than does either MA or its analogues, concomitant administration may result in 3- to 10-fold increases in levels of MA or MDMA [21]. Delavirdine is partially metabolized by CYP2D6 and may have similar pharmacokinetic interactions with amphetamines.

A case report from Australia describes an HIV-infected patient who had been receiving a combination of stavudine, saquinavir, and ritonavir and who died after injecting MA. Toxicology reports showed MA levels of 0.5 mg/L, consistent with MA overdose [22]. Two case reports document fatalities that occurred after ingestion of ritonavir-containing regimens and MDMA [23, 24].

NEUROTOXICITY

MA's neurotoxic effects are the most devastating and potentially permanent medical sequelae of its chronic abuse. Studies involving rats indicate that MA accumulates in the brain, with a ratio of brain concentration to plasma concentration of 10:1

[25]. This, coupled with the long plasma half-life of ~12 h, probably accounts for the majority of CNS toxicity.

NEUROTRANSMITTER TOXICITY

MA causes neurodegeneration in the dopaminergic and the serotonergic nerve terminals in animals [26]. Human studies provide evidence that MA use leads to a reduction of dopamine transporter (DAT) levels, which are markers of dopamine cell terminals. One study of 15 HIV-negative MA abusers who were examined using positron emission tomography (PET) scans found significant reductions in DAT levels. Subjects had used MA for up to 11 years and abstained from MA use for ≥2 weeks before PET was performed. This finding was associated with neuropsychiatric testing evidence of impaired motor function and impaired verbal learning. In 3 of the subjects, DAT levels had decreased to within the range seen for low-severity Parkinson disease. Although the subjects were found to be impaired by tests of both gross and fine motor speed, extrapyramidal symptoms were not seen. Investigators hypothesized that this was due to the young age of the subjects (mean age, 32 years) [27]. It is not known whether these reductions in DAT levels reflect irreversible dopamine terminal damage or neuroadaptive changes that may recover with protracted abstinence. Another study of 5 former MA users showed that, although DAT levels recovered significantly with 12–17 months of abstinence, neuropsychological function did not. Neither the gross nor fine motor speed test results improved significantly, nor was there improvement on the Rey auditory verbal learning test (in which subject has to learn and recall lists of unrelated words) [28].

SYNERGY BETWEEN MA AND HIV

The clinical features of HIV-related dementia are those of a subcortical type, including psychomotor slowing, apathy, and memory deficits. In advanced HIV-related dementia, symptoms such as bradykinesia, altered posture, gait, and incontinence can occur [29].

The etiology of HIV-related dementia is poorly understood, but it is a metabolic encephalopathy that involves both brain cell loss and neuronal dysfunction. Supporting neuronal cells (such as microglial cells, macrophages, and astrocytes) induce damage by secreting inflammatory substances that damage or kill brain cells. Neurons themselves are not infected with HIV [30, 31].

Experimental evidence suggests that the HIV-1 proteins gp 120 and Tat are toxic to dopamine neurons [32, 33]. There is overlap in that both MA and HIV target dopamine neurons. HIV affects the dopamine neurons in subcortical structures, particularly the basal ganglia [34]. MA targets dopamine in many regions of the brain, including the orbitofrontal cortex (which is thought to be implicated in impulsive behavior), as well as the dorsolateral prefrontal cortices and the amygdala [35]. Some researchers on the underlying mechanisms for the neurotoxicity of combined HIV infection and use of MA have suggested that dopaminergic systems are most vulnerable to such combined neurotoxicity [36–38].

Researchers found that exposing feline astrocytes infected with feline immunodeficiency virus (FIV) to MA increased FIV's ability to replicate and mutate by 15-fold [39]. These findings imply that MA use in patients with HIV infection could increase the prevalence of HIV-related dementia in patients who are not receiving antiretrovirals. This awaits verification in human studies.

INTOXICATION, WITHDRAWAL, AND TOLERANCE

Colloquially known as "crystal," "tina," "meth," or "speed," MA is injected, smoked, snorted, or ingested. Effects occur ~5 min after snorting, 20 min after ingestion, and almost instantaneously when smoked or injected. Some users report mixing MA with water and inserting the solution rectally with a syringe. The half-life of MA is estimated to be 12 h, and the drug may be detectable in the urine for 3–5 days, depending on route of administration [40, 41]. Estimates by addicts of the amount of the drug consumed in 1 day are 0.7–1 g [42].

Subjective symptoms of intoxication reported by users include alertness, euphoria, and an increased sense of well-being. Psychiatric effects include personality changes, restlessness, tension, irritability, insomnia, appetite suppression, and weight loss. Verbally threatening behavior and physical aggression have also been observed [43].

Continual use of the drug, with little or no sleep over a period of 2–5 days, can lead to an extremely irritable and paranoid state [44]. In ~10% of persons, heavy, long-term abuse can lead to psychosis, which is characterized by paranoia, impaired reality testing, and vivid visual, auditory and tactile hallucinations [45]. Amphetamine-produced psychoses mimic schizophrenia [46].

Prolonged use can result in tolerance for the drug and increased levels of use, creating dependence. Withdrawal symptoms, which occur 24 h after last use of MA, resemble Major Depressive Disorder, including depressed mood, anhedonia, fatigue, and suicidal ideation [46].

Psychopharmacologically, animal-based evidence associates repeated administration of large doses of d-amphetamine or MA with decreased tissue concentrations of dopamine and serotonin [47]. This suggests a biological explanation for the

depressive symptoms observed in chronic abusers who present for treatment.

PSYCHIATRIC STUDIES OF MA ABUSERS

Data on the psychiatric symptomatology of MA users is sparse. Overall findings suggest that, although acute psychosis tends to resolve, depressive symptoms tend to persist [48]. A California study of 170 MA abusers 2–5 years after completion of outpatient treatment indicated that, of the 23% of the sample subjects who reported paranoia at baseline, only 7.2% reported paranoia at follow-up, whereas 62% of subjects reported having depressive symptoms at both baseline and follow-up. Importantly, 27.6% of respondents reported violent behavior in the past year [49]. Cocaine-induced psychosis has a brief duration, whereas MA-induced psychosis may last as long as several days or weeks [50]. A study from California of 25 HIV-positive gay men using MA reported that, in addition to use of the drug for sexual enhancement, respondents reported that use of the drug "provided temporary escape from being HIV positive," "helps manage negative self-perception and social rejection associated with being HIV positive," and was "a method of coping with the specter of death." Finally, one-half of the subjects reported that using MA commonly made it easier to approach sexual partners and to have anonymous sex with multiple partners [51].

TREATMENT

Acute psychotic symptoms are treated with neuroleptic medication and perhaps hospitalization. Drug rehabilitation for MA addiction aims at inpatient detoxification and treatment for depression with antidepressant medication and harm-reduction counseling. Psychiatrically, there is no research evidence to guide medication use. Thus, treatment for MA abuse is modeled after that for cocaine abuse. However, randomized controlled trials of the dopamine agonists bromocriptine and pergolide have shown that they have no efficacy when given to cocaine abusers [52–54].

Although dopaminergic reward pathways have been implicated in stimulant addiction, the roles of D1 receptors, which may reduce drug cravings, and D2 receptors, which may increase drug cravings, are not well understood. The authors of the pergolide study suggested that, because pergolide is a mixed D1/D2 agonist, this may have been the reason for the trial's findings of failure. A study of methylphenidate, a stimulant and indirect dopamine agonist, did not decrease cocaine use but was associated with a lower dropout rate from drug abuse treatment than was placebo [55]. Although research data are lacking, psychiatrists treating HIV-infected patients use bupropion, an antidepressant with noradrenergic and dopaminergic activity, to treat depressive symptoms, although it is not useful for management of acute stimulant withdrawal [56].

CONCLUSIONS

MA abuse in the MSM population poses a serious new health risk by predisposing a young section of this population to high-risk sexual behavior, thus increasing HIV transmission. MA has serious acute cardiovascular effects and may interact with HIV medications to cause increased toxicity or death. Neurological complications resulting from dopamine depletion can result in irreversible neuropsychiatric symptoms, including memory loss, and may be synergistic with HIV-related dementia symptoms. Psychiatric morbidity in MA abusers with HIV infection includes acute psychotic reactions and long-term depression. MA abuse represents a new challenge in HIV treatment and prevention.

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