The Methamphetamine Epidemic: Implications for HIV Prevention and Treatment

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Methamphetamine and related amphetamine compounds are among the most commonly used illicit drugs, with over 35 million users worldwide. In the United States, admissions for methamphetamine treatment have increased dramatically over the past 10 years. Methamphetamine use is prevalent among persons with HIV infection and persons at risk for HIV, particularly among men who have sex with men. In addition to being associated with increased sexual risk behavior, methamphetamine causes significant medical morbidity, including neurologic deficits, cardiovascular compromise, dental decay, and skin infections, all of which may be worsened in the presence of HIV/AIDS. Methamphetamine use may also result in decreased medication adherence, particularly during "binging" episodes. Behavioral counseling remains the standard of treatment for methamphetamine dependence, although the effectiveness of most counseling interventions has not been rigorously tested. Pharmacologic and structural interventions may prove valuable additional interventions to reduce methamphetamine use.

Introduction

Methamphetamine use contributes to substantial morbidity and mortality among persons with HIV infection and those at risk for HIV infection. This review covers the epidemiology of methamphetamine use and its multifactorial influence on HIV transmission and on HIV disease. Current and future research on methamphetamine and recommendations for treatment of methamphetamine users are described.

Prevalence of Methamphetamine Use

Methamphetamine is a synthetically derived psychostimulant manufactured from ephedrine, a common ingredient in many decongestants. Methamphetamine—also known as "speed," "ice," "tina," "crystal," and "crank"—is injected, smoked, snorted, or ingested orally or anally and results in feelings of euphoria, increased energy, decreased appetite, feelings of invulnerability, and heightened sexual desire [1]. Worldwide, methamphetamine is second only to cannabis as the most commonly abused illicit drug, with an estimated 35 million persons regularly using methamphetamine [2].

Amphetamines were first synthetically derived in 1887 and were subsequently used as appetite suppressants; currently, the Food and Drug Administration has approved dextroamphetamine and methyphenidate for treatment of narcolepsy and attention deficit disorder [3]. Reports of amphetamine abuse date from the 1930s [3]; the current methamphetamine epidemic emerged in the 1980s, with widespread use of methamphetamine first documented in Hawaii and the West Coast and corresponding proliferations of illegal "meth labs" run by drug cartels manufacturing large quantities of methamphetamine [4••]. However, the methamphetamine epidemic is now nationwide; in 2003, over 1.2 million people over the age of 12 reported use of amphetamine-type stimulants in the past month [5]. Methamphetamine is the primary drug of abuse at admission to treatment in 14 states in the United States [6]. Admissions for stimulant treatment, believed to be primarily methamphetamine, increased fivefold between 1992 and 2002 and exceeded 344,000 in 2003 [7]. Because methamphetamine is currently the most popular amphetamine, for the remainder of this article "methamphetamine" will be used to refer to both methamphetamine and its metabolite, amphetamine [8].

Methamphetamine use is disproportionately represented among populations at risk for HIV and infected with HIV. Among men who have sex with men (MSM), prevalence of use of methamphetamine and other amphetamine-type stimulants is approximately 10 times higher than in the general population, although heavy use (>weekly) is reported by a minority of MSM who use methamphetamines [9,10]. In a probability-based sample of young, American MSM (aged 15–22 years), 20% reported use of methamphetamine in the prior 6 months, [11]. Studies of targeted populations of MSM show even higher rates of methamphetamine use [12]. Among persons with HIV infection in clinical care, methamphetamine use is also high; a recent clinic-based

survey of persons with HIV found that 40% of MSM, 30% of heterosexual men, and 19% of women reported methamphetamine use in the prior year [13].

Mechanisms of Methamphetamine Effects

Methamphetamine's effects last 10 to 12 hours, considerably longer than that of cocaine [14••]. Methamphetamine increases extracellular dopamine levels through the release of dopamine from vesicular stores [15••]. Although acute use of methamphetamine is associated with high dopamine levels, chronic use is associated with deceased dopamine levels, which correlate with degeneration of dopamine nerve terminals and reductions in dopamine transporter activity [15••]. Even though the mechanisms causing these deficiencies remain to be fully understood, methamphetamines and methamphetamine-analogues have been shown to have neurotoxic effects on dopamine neurons. The severity of neurotoxicity appears to be related to the dose of methamphetamine, as well as dependent on the chronicity of methamphetamine exposure [16]. Although most research has focused on methamphetamine's effects on the dopaminergic system, methamphetamine also influences the noradrenergic, serotonergic, and glutamatergic systems [17,18].

Medical Consequences of Methamphetamine Use

Psychologic effects of methamphetamine begin with euphoria, behavioral disinhibition, and goal-directed behavior, and escalate to anxiety, insomnia, hypervigilance, paranoia, and often persecutory delusions that are indistinguishable acutely from paranoid schizophrenia [19]. The clinical sequalae of long-term methamphetamine use remain to be fully described, but a number of neurologic deficits have been noted among chronic methamphetamine users compared with controls, including differences in brain metabolism that correlates with mood disorders [20,21]. Other work demonstrates that long-term methamphetamine use is correlated with impaired cognitive performance and depression [22,23], although there is some evidence that these abnormalities improve after prolonged abstinence from the drug [24,25].

Appetite suppression induced by methamphetamine can result in severe weight loss [15••]. Methamphetamine effects on the cardiovascular system include increased heart rate and blood pressure, tachycardia, and dysrhythmias [26]. Methamphetamine use has been identified as a risk factor for acquisition of methicillin-resistant *Staphylococcus aureus* [27], and the behavioral effects of methamphetamine include excessive scratching and picking behaviors that can cause severe dermatologic lesions [24]. Methamphetamine is also associated with severe dental disease, due to xerostomia (persistent dry mouth attributable to methamphetamine's sympathomimetic properties), bruxism (excessive teeth grinding), the high intake of soft drinks frequently observed among methamphetamine users, and decreased oral hygiene during periods of methamphetamine use [28]. Less frequent consequences of acute methamphetamine intoxication or overdose are severe hyperthermia and convulsions [29], rhabdomyolysis [30], ischemic episodes including stroke [31], and myocardial infarction [32].

Withdrawal from methamphetamine use produces a syndrome that includes severe anxiety, anhedonia, anergia, and mild to moderate depression [14••,22]. These symptoms are thought to be largely due to rapidly decreasing levels of dopamine in the nucleus accumbens following drug cessation [3].

Methamphetamine and HIV Transmission

Methamphetamine use is a driving force in the transmission of HIV. Methamphetamine's effects on sexual behaviors include increasing sexual drive and decreasing inhibitions, factors that lead persons to engage in high-risk sex [33]. Research demonstrates that the vast majority of MSM methamphetamine users report that sex and methamphetamine "always" or "often" go together [34], and qualitative studies report that MSM use methamphetamine specifically to enhance performance of sexual acts [35]. Most studies estimate that methamphetamine use doubles or triples the probability of engaging in high-risk sexual behavior and acquisition of sexually transmitted infections, including HIV [36–41]. In our study of MSM who attend circuit parties, for instance, use of methamphetamine was independently associated with engaging in unprotected anal sex with an unknown or opposite serostatus partners (odds ratio [OR], 2.4; 95% CI, 1.1–4.9) [12]. Wong *et al.* [42] found that methamphetamine was independently associated with syphilis among gay and bisexual men (OR, 3.2; 95% CI, 3–7.6). Among MSM testing anonymously for HIV in San Francisco, HIV incidence was 6.3% among methamphetamine users compared with nonusers [43]. Methamphetamine use also corresponds with high numbers of sexual partners [44,45], and decreased condom use [46]. Stone *et al.* [47] reported that methamphetamine use was independently associated with condom breakage (OR, 1.6; 95% CI, 1.0–2.3). Most research on methamphetamine use and HIV risk behavior has focused on MSM populations, but the relationship between methamphetamine use and sexual risk has been documented among heterosexual populations of men and women [48,49], including among persons who inject methamphetamine [50].

Methamphetamine and HIV Pathogenesis

The potential direct effects of methamphetamine on HIV and HIV disease progression remain to be determined. One study found that methamphetamine use was associated with

higher viral loads and decreased effectiveness of antiretroviral therapy, including after controlling for self-reported adherence to antiretroviral therapy [51]. Even though the cross-sectional design of this study makes it impossible to determine whether methamphetamine use was causal in increasing viral loads, these intriguing findings reinforce the need for further research in this area. Methamphetamine has been shown to increase viral replication and mutation rates in feline cells infected with feline immunodeficiency virus, prompting speculation that methamphetamine may have some direct proviral effects on HIV [52]. Within the central nervous system, HIV and methamphetamine may have additive neurotoxic effects leading to neuropsychologic impairment [53]; autopsy studies suggest that the combination of methamphetamine use and HIV infection may increase neuronal injury [54].

Methamphetamine and Antiretroviral Medications

Metabolism

Methamphetamine is metabolized through the CYPD6 of the P450 system, which also interacts with a variety of antiretroviral therapy (ART) medications. Co-administration of methamphetamine with antiretrovirals, especially protease inhibitors, may result in elevated methamphetamine levels [55]. There have been several case reports of possible fatal interactions between protease inhibitors and methamphetamine or the methamphetamine analogue n-methyl-3,4 methylendioxymethaphetamine (MDMA, "ecstasy") [56,57].

Medication adherence

Methamphetamine users report suboptimal adherence to ART regimens and are therefore at risk for the development of resistant virus [58]. Although the prevalence of drug-resistant HIV among methamphetamine users with either acute or established HIV infection is unknown, patterns of methamphetamine use may result in especially favorable conditions for the selection of drug-resistance. Among many methamphetamine users, drug use is episodic, consisting of "speed runs" that last for 24 to 72 hours, followed by days or even weeks of drug abstinence [59]. Qualitative research shows that speed runs are frequently associated with "medication holidays," during which medication schedules are often altered or ignored due to altered sleep and food schedules and a singular focus on sexual behavior [58]. Such sporadic treatment interruptions could result in favorable selective pressure of drug-resistant virus.

Treatment of Methamphetamine Abuse

Behavioral interventions

Behavioral counseling, in the form of either outpatient or inpatient programs, is the current standard of treatment for methamphetamine abuse. Most programs have been adapted from cocaine and alcohol treatment programs and vary in intensity [14••]. Among persons who do access behavioral treatment services, methamphetamine use is reduced during treatment in nearly all instances [60,61]. Drop-out rates in these programs are as high as 75%, and relapse is common. The minimum number of counseling sessions required to reduce methamphetamine use and the elements of the behavioral counseling that produce optimal drug reduction remain to be determined. Even though research has demonstrated that persons enrolled in substance use treatment programs report reduced sexual risk, the effects of methamphetamine treatment programs on reducing drug-related sexual risk behaviors are for the most part unmeasured [62].

Most behavioral approaches involve components of motivational interviewing and cognitive-based therapy. A multisite evaluation of the Matrix Model, a behavioral therapy intervention delivered using 48 outpatient group and individual sessions over 16 weeks, was based on an approach previously used to treat cocaine-dependent individuals. Outcomes in a large sample of mostly heterosexual methamphetamine-dependent participants showed that at the 6-month follow-up visit there were no differences in methamphetamine use among persons assigned to Matrix intervention compared with those assigned to a treatment-as-usual comparison condition of outpatient substance treatment; however, methamphetamine use declined in both groups from baseline, and the Matrix intervention was associated with more consecutive methamphetamine-negative urines during the intervention phase compared with treatment as usual [63••].

Harm-reduction models are also being used to treat methamphetamine users; the Stonewall Project in San Francisco is designed specifically for methamphetamine users and is well-received by participants but has not been evaluated in a randomized, controlled trial [64]. The Project MIX study funded by the Centers for Disease Control and Prevention, which includes large numbers of methamphetamine-using MSM, is a current, randomized, controlled, multisite trial evaluating whether a risk-reduction approach reduces methamphetamine use and sexual risk; final results will not be available for several years.

Contingency management

Contingency management involves the provision of vouchers of escalating value for successive urine samples documenting drug abstinence, with reset of the voucher to lower values in the case of positive drug urine. Strategies using contingency management have been shown to reduce use of heroin and cocaine [65,66].

Shoptaw *et al.* [67] recently reported on the comparative efficacy of contingency management, cognitive-behavioral therapy (based on the Matrix Model), their combination, and a culturally tailored version of cognitive-behavioral therapy for MSM who were methamphetamine-dependent. During the 16-week treatment period, conditions containing contingency management produced more methamphet-

amine-negative urine samples and greater participant retention compared with standard cognitive-behavioral therapy arm, whereas the culturally tailored therapy version produced greater reductions in sexual risk behaviors compared with standard cognitive-behavioral therapy. By 1-year follow-up evaluations, all conditions sustained over threefold reduction in methamphetamine use and concomitant sexual risk behaviors from baseline [67]. Although the acceptability and feasibility of contingency management implemented outside formal treatment settings remain to be determined, this approach may be more acceptable to persons unwilling to participate in counseling programs but who would seek to reduce their methamphetamine use.

Pharmacologic interventions

Compared with extensive research on pharmacologic interventions for treating cocaine and heroin dependence, research on pharmacologic interventions for methamphetamine dependence has only recently expanded [60]. Several observational studies have prescribed stimulants as "replacement therapy" to treat methamphetamine use; however, the only randomized, controlled trial of dextroamphetamine demonstrated no significant differences between the treatment arm and the placebo arm, although both groups reduced their methamphetamine use [68]. Concerns have been raised about providing methamphetamine users with controlled substances given their abuse potential [69]. A phase II, multisite trial to treat methamphetamine dependence with bupropion (Wellbutrin®, GlaxoSmithKline, Philadelphia, PA), an antidepressant drug with dopaminergic properties, is ongoing with results expected in the near future. Phase I studies of vigabatrin, an anticonvulsant, have demonstrated that trial completers reduced their methamphetamine use from baseline, but nearly half of the participants did not complete the study [70]. The depletion of the amino acid tyrosine significantly dampened subjective and objective effects of methamphetamine in a double-blind, placebo-controlled phase I crossover study [71]; however, this work has not been evaluated outside the pharmacology laboratory. Randomized, controlled phase II studies of medications evaluated for methamphetamine dependence that have shown no effects on methamphetamine use or any of a variety of subjective effects of include the calcium channel blocker, amlodapine [72], the serotonin reuptake inhibitor, fluoxetine [73], the tricyclic antidepressant, imipramine [74], and the serotonergic antagonist, ondansetron [75].

Structural interventions

The production of methamphetamine may be particularly susceptible to regulation of methamphetamine precursors. Unlike marijuana, cocaine, or heroin, which are derived directly from agricultural products that can be grown in a variety of geographic areas, the precursors to methamphetamine require substantial technology to produce and are manufactured by a limited number of companies. Federal regulations of the sales of bulk ephedrine, pseudoephedrine, and ephedrine-containing products have been associated with reductions in methamphetamine-related hospitalizations, arrests, and methamphetamine purity [4••,76,77]. A recently enacted Oklahoma law requires that pseudophedrine-containing products be sold behind pharmacy counters and requires personal identification for drug purchase [4••]. The proposed Federal Combat Meth Act of 2005 is modeled after the Oklahoma law and would also provide additional financial resources for methamphetamine-related law enforcement activities. Several national United States pharmacy chain stores have recently voluntarily placed all pseudoephedrine-containing products behind counters. Additional structural interventions could potentially include requiring that ephedrines be combined with additives that would impair the process of methamphetamine synthesis or an outright ban on all pseudophedrine-containing products, substituting medications that cannot be synthesized into methamphetamine.

Conclusions

Treatment providers should ask all patients who are HIV positive and those at risk for HIV infection whether they are currently using methamphetamine. If patients report use, the frequency of use and route of administration should be determined: patients who report injection use should be provided with needle exchange referrals and discouraged from sharing needles or works. All sexually active methamphetamine users should be provided with HIV risk reduction counseling with regard to sexual risk behavior [78], and condoms (both male and female, if possible) should be provided if patients report high-risk sexual behaviors. Patients on ART should be assessed for adherence patterns during methamphetamine use periods, especially if they engage in methamphetamine-binging behavior. Medical comorbidities, including skin infections, dental problems, and depression, should be assessed and treated.

Behavioral counseling remains the mainstay of treatment, and patients should be referred to treatment programs whenever possible. It is imperative that providers become familiar with programs in their communities that address methamphetamine use, including the treatment philosophies of such programs (eg, requiring total abstinence or based on achieving risk reduction), their approach (group, individual, or both), the cost and availability of programs, and the population served (gay men, heterosexuals, etc.). If patients are initially hesitant to seek treatment for methamphetamine use, providers should continue to inquire about their willingness to seek treatment at subsequent visits. Finally, health care providers should consider advocating for more stringent controls on methamphetamine precursors through lobbying both pharmaceutical companies and elected politicians to exert more controls over the manufacture and distribution of precursors of this drug.

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