Mirtazapine to Reduce Methamphetamine Use

A Randomized Controlled Trial

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Context: No approved pharmacologic treatments for methamphetamine dependence exist. Methamphetamine use is associated with high morbidity and is a major cofactor in the human immunodeficiency virus epidemic among men who have sex with men (MSM).

Objective: To determine whether mirtazapine would reduce methamphetamine use among MSM who are actively using methamphetamine.


Setting: San Francisco Department of Public Health.

Participants: Participants were actively using, methamphetamine-dependent, sexually active MSM seen weekly for urine sample collection and substance use counseling.

Interventions: Random assignment to daily oral mirtazapine (30 mg) or placebo; both arms included 30-minute weekly substance use counseling.

Main Outcome Measures: The primary study outcome was reduction in methamphetamine-positive urine test results. Secondary outcomes were study medication adherence (by self-report and medication event monitoring systems) and sexual risk behavior.

Results: Sixty MSM were randomized, 85% of follow-up visits were completed, and 56 participants (93%) completed the final visit. In the primary intent-to-treat analysis, participants assigned to the mirtazapine group had fewer methamphetamine-positive urine test results compared with participants assigned to the placebo group (relative risk, 0.57; 95% CI, 0.35-0.93, P=.02). Urine positivity decreased from 67% (20 of 30 participants) to 63% (17 of 27) in the placebo arm and from 73% (22 of 30) to 44% (12 of 27) in the mirtazapine arm. The number needed to treat to achieve a negative weekly urine test result was 3.1. Adherence was 48.5% by medication event monitoring systems and 74.7% by self-report; adherence measures were not significantly different between arms (medication event monitoring systems, P=.82; self-report, P=.92). Most sexual risk behaviors decreased significantly more among participants taking mirtazapine compared with those taking placebo (number of male partners with whom methamphetamine was used, P=.009; number of male partners, P=.04; episodes of anal sex with serodiscordant partners, P=.003; episodes of unprotected anal sex with serodiscordant partners, P=.003; episodes of insertive anal sex with serodiscordant partners, P=.001). There were no serious adverse events related to study drug or significant differences in adverse events by arm (P=.99).

Conclusion: The addition of mirtazapine to substance use counseling decreased methamphetamine use among active users and was associated with decreases in sexual risk despite low to moderate medication adherence.

Trial Registration: clinicalTrials.gov Identifier NCT00497081

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The lack of an effective medication, in contrast to the success of medications to treat opioid, nicotine, and alcohol dependencies, has been identified as a major barrier to treatment of stimulant dependence. Trials of multiple agents, including antidepressants, calcium channel blockers, and antipsychotics, have failed to show efficacy despite encouraging early data. Clinical trials of several serotonergic medications, including fluoxetine hydrochloride, sertraline hydrochloride, and ondansetron hydrochloride, did not significantly reduce methamphetamine use. Recently, trials of modafinil and bupropion hydrochloride, 2 dopaminergic agents, similarly have failed to show efficacy.

Mirtazapine is an FDA-approved antidepressant; it has no apparent abuse potential, has an onset of action within 2 weeks, and is relatively inexpensive. Adverse effects of mirtazapine include somnolence, weight gain, and dry mouth. Less than 1% of patients taking mirtazapine report decreased erectile dysfunction, suggesting greater acceptability of this drug among sexually active MSM when compared with other psychotropic medications for which erectile dysfunction is a relatively common adverse effect. Mirtazapine is a mixed monoamine agonist/antagonist that facilitates the release of norepinephrine, serotonin, and dopamine in the central nervous system, including areas of the mesocorticolimbic system involved in drug reward, drug craving, and drug-seeking behavior. Although methamphetamine administration increases monoamine activity, methamphetamine users have depressed neurotransmitter activity in the absence of the drug; drug-taking behavior is thought, at least partly, to be reinforced when administration boosts monoamine levels. We postulated that mirtazapine’s effect of increasing monoamine levels would alleviate methamphetamine craving and withdrawal symptoms. In a randomized, placebo-controlled study of 20 methamphetamine-dependent men in a probational detoxification center, mirtazapine significantly reduced methamphetamine withdrawal symptoms at 2-week follow-up. Prior studies of mirtazapine’s efficacy in reducing methamphetamine use were inconclusive because of open-label designs and poor retention. This randomized, double-blind, placebo-controlled trial tested the hypothesis that mirtazapine would reduce methamphetamine use among MSM actively using methamphetamine.

**METHODS**

**STUDY PARTICIPANTS**

Sixty methamphetamine-dependent, sexually active MSM received mirtazapine or placebo for 12 weeks. Eligibility criteria included methamphetamine dependence by the Structured Clinical Interview for DSM-IV-TR (SCID), an interest in reducing or ceasing methamphetamine use, age of 18 to 60 years, self-reported anal sex with men in the past 3 months while using methamphetamine, a methamphetamine metabolite-positive urine test result at screening, no acute medical or psychiatric illness, and baseline safety laboratory results without clinically significant abnormalities. Exclusion criteria included current major depression by SCID; history of antidepressant use within the past 4 weeks; and for HIV-infected individuals, a CD4 cell count below 200/µL.

**PRIMARY AND SECONDARY OUTCOMES**

The primary study outcome was reduction in methamphetamine metabolite-positive urine test results. Secondary outcomes were study medication adherence and sexual risk behavior. Study procedures and materials were approved by the Committee on Human Research of the University of California, San Francisco’s Institutional Review Board.

**STUDY DESIGN**

This was a randomized, double-blind, placebo-controlled, 2-arm study with 1:1 randomization to mirtazapine vs placebo (n=60). To calculate sample size, we assumed that, on average, 8 of the planned 12 postrandomization urine samples would be available for analysis, that within-subject correlation would be between 50% and 90%, and that 70% to 90% of samples would be positive in the placebo group. The sample size also was inflated by 10% to account for loss of precision due to adjustment for baseline covariates associated with loss to follow-up. The sample of 60 participants provided 80% power to detect net reductions in the urine positivity rate of 14 to 33 percentage points, depending on within-subject correlation of the outcome, the positivity rate in the placebo group, and missing visit rates. Sample size was determined by approximating the standard error of the regression coefficient, capturing the treatment effect in the model for the primary analysis.

**STUDY RECRUITMENT**

Participants were recruited at STD and HIV clinics, bars, and community-based organizations and through posted recruitment flyers and Web sites serving MSM. Participants were given materials to recruit peers. Potential participants completed brief telephone screens to assess initial eligibility and, if eligible, were scheduled for in-person screening visits. Participants gave full informed consent and signed institutional review board-approved consent forms.

**SCREENING**

Two screening visits involved taking complete histories and physical examinations, blood cell counts, metabolic panels, liver function tests, and rapid qualitative urine methamphetamine tests using immunochromatographic methamphetamine metabolite detection (Medtox Diagnostics, Inc, Burlington, North Carolina). Participants reporting HIV-negative or unknown HIV status underwent HIV rapid testing; HIV-positive participants underwent CD4 and HIV viral load tests. All participants received HIV risk reduction counseling based on Centers for Disease Control and Prevention guidelines. For each participant, staff collected extensive contact information using institutional review board-approved materials and procedures. Participants were asked to provide their personal contact information and to include 2 backup individual contacts. Information on contact forms was used to transmit visit reminders.

**RANDOMIZATION AND STUDY PROCEDURES**

The study statistician generated the 1:1 random allocation sequence using a fixed-block size of 4 to ensure balanced study arms. All procedures were conducted at the San Francisco Department of Public Health. Participants were seen weekly for urine specimen collection. Symptom-directed physical examinations,
safety laboratory results, and behavioral assessments were performed at baseline and at 4-, 8-, and 12-week visits. Human immunodeficiency virus risk reduction counseling and testing was repeated for HIV-negative participants at the 12-week visit. Participants were reimbursed $10 for weekly visits and $35 for screening, baseline, and 4-, 8-, and 12-week visits. All participants received reminder telephone calls and were e-mailed, if possible, 24 hours before each appointment. Staff contacted participants' backup contacts if 2 consecutive weekly visits were missed. Confidentiality was preserved at all times; contacts were not told about the study or of the participant's enrollment.

SUBSTANCE USE COUNSELING

All participants were offered weekly 30-minute substance use counseling based on a standardized, manual-driven psychosocial treatment program using cognitive behavioral therapy and motivational interviewing techniques. Trained staff supervised by a clinical psychologist delivered counseling.

MEDICATION DISPENSING

Mirtazapine, 15 mg, and matched placebo were prepared by an off-site pharmacist in identical-looking gel capsules to maintain the double-blind condition for study staff and participants. Health care professionals dispensed medication in masked medication event monitoring system (MEMS) capped bottles that were sequentially numbered to correspond with the treatment allocation sequence. The allocation assignment was only accessible to the statistician and the pharmacist—neither had participant contact or access to participant information. Participants were instructed to take 1 capsule (15 mg) nightly for 1 week and then 2 capsules (30 mg) nightly for the remainder of the study.

MEDICATION ADHERENCE COUNSELING AND EVALUATION

Health care professionals provided adherence counseling and discussed the importance of taking medication daily and how to handle missed doses. Adherence was measured by MEMS caps and by self-report using the AIDS Clinical Trial Group measure. Adherence by MEMS was defined as the number of distinct days that the MEMS cap bottle was opened divided by the number of doses expected. Participants were asked weekly about adverse events, which were classified by standardized criteria (available upon request from the authors).

AUDIO COMPUTER-ASSISTED SELF-INTERVIEW MEASURES

Audio computer-assisted self-interview was used to standardize data collection and to minimize reporting bias. Standardized measures were used to assess drug use, substance use treatment, and sexual risk behavior. The Center for Epidemiologic Studies–Depression Scale (CES-D) was used to assess depressive symptoms; scores higher than 16 suggest clinically significant depression.

DATA ANALYSIS

Primary Outcome: Urine Methamphetamine Metabolite Positivity

Data were analyzed by intent to treat without regard to adherence using a generalized estimating equations (GEE) model with robust standard errors to account for within-participant clustering of binary responses. To obtain direct estimates of risk ratios (RRs), log-link models were used. The form of the model was prespecified based on the a priori hypothesis that mirtazapine would have gradually increasing efficacy after a short initial delay to achieve steady-state levels of the study drug. The analysis compared trends in urine positivity from baseline through week 12, omitting the week-1 result, modeled as group-specific linear functions of time since randomization. The effect of treatment was captured by the divergence of the mirtazapine and placebo trends at 12 weeks and was assessed using a test for the time-by-treatment interaction. Use of robust standard errors allowed us to account for within-subject correlation of the responses without making parametric assumptions. Model fit was assessed informally by plotting the group-specific fitted trends along with the raw percentages. Four sensitivity analyses were conducted: including the week-1 results, imputing a positive result for all missing urine samples, sequentially adjusting for imbalanced baseline characteristics and baseline correlates of missing urine samples or those with positive test results, and omitting data from participants found to be ineligible after randomization. Although the primary analysis rests on the stringent assumption that urine test results are missing completely at random, given time and treatment, the second sensitivity analysis was conducted with the assumption that the data are not missing at random and the third is consistent with the weaker assumption that the data are covariate dependent missing completely at random, conditional on the baseline covariates included in the model. All available data were included in each analysis. Also, we performed an as-treated analysis using cumulative adherence, calculated as the number of MEMS cap openings between baseline and the day of each urine test divided by the length of that interval in days as a time-dependent covariate in a log-link model for urine positivity, controlling for the placebo effects of adherence. Quadratic terms were used for adherence in this model to account for nonlinearity. Finally, we assessed the correlation of monthly summary measures of urine positive test results with secondary outcomes, including sexual behaviors and depression.

Secondary Outcomes

We used GEE models to assess treatment effects on secondary outcomes. Included were CES-D scores and high-risk sexual behaviors.

Acceptability and Safety

The percentage of adherence by MEMS was compared by arm using the Wilcoxon rank sum test. To assess safety, we compared the incidence of at least 1 adverse event of various types by arm using the 2-tailed Fisher exact test.

RESULTS

SCREENING, RANDOMIZATION, AND RETENTION

The study period was from September 5, 2007, to March 4, 2010. The target sample size was achieved. Figure 1 shows the results for screening, study arm assignment, and retention. Of those eligible by telephone screening, 212 were assessed for eligibility, 110 of whom were ineligible. The most common reasons for ineligibility were not meeting methamphetamine dependence criteria by SCID (40%).
n = 44), having major depression (20%, n = 22), or having another exclusionary medical illness (15%, n = 17). Seventy-two individuals (34% of those assessed) were deemed eligible, and 60 (83% among those eligible) agreed to participate and were randomized in the trial. Those who were eligible but did not participate in the trial were similar in age, race/ethnicity, and HIV status to those who were randomized (data not shown).

**BASELINE CHARACTERISTICS**

As indicated in Table 1, participant characteristics were similar in both arms, with the exception of the number of unprotected receptive anal sex partners (Table 2) and those who reported that they were motivated to participate in the trial to receive counseling services (Table 1), which were significantly more prevalent in the mirtazapine arm. Among HIV-positive participants, the mean CD4 cell count at baseline was 598/µL for the mirtazapine arm and 540/µL for the placebo arm (P = .45). Thirty-six participants (60%) reported using methamphetamine between 3 and 7 days each week; 41 participants (68%) used methamphetamine during sex more than 50% of the time.

**PARTICIPATION AND RETENTION**

Sixty MSM were randomized; 85% of follow-up visits were completed. Fifty-six participants (93%) completed the trial; no significant differences were observed by arm (28 [93%] in the mirtazapine arm and 28 [93%] in the placebo arm; P = .99). After randomization, 1 participant dropped out after his enrollment visit, 2 participants dropped out after their week 2 visits, and 1 participant dropped out after his week 3 visit. Of monthly follow-up visits, 227 of 240 (94.6%) were completed (mirtazapine, 94.2% [113 visits]; placebo, 95% [114 visits]; P > .99); also, 673 of 780 (86%) weekly urine samples were collected (mirtazapine, 84.9% [342 samples]; placebo, 87.7% [331 samples]; P = .30). The median number of samples collected was 12 (interquartile range, 11-13); Figure 2 shows the numbers of participants in each group providing urine samples by week. For self-reported sexual risk behaviors, 227 of 240 audio computer-assisted self-interview surveys (94.6%) were completed (mirtazapine, 94.2% [113 surveys]; placebo, 95% [112 surveys]; P ≈ .99). For weekly substance use counseling, completion rates did not differ by arm (mirtazapine, 81.1% [292 sessions]; placebo, 78.9% [284]; P = .14); 33 of 720 sessions (4.6%) were declined by participants.

**PRIMARY OUTCOME: URINALYSIS RESULTS**

At baseline, 42 participants (70%) had methamphetamine metabolite–positive urine test results (20 [67%] in the placebo group and 22 [73%] in the mirtazapine group; P = .78). The proportion of positive urine test results at follow-up visits decreased in both groups. The mirtazapine arm had a 46% reduction in positive urine test results from 73% urine positivity (22 of 30 participants) at baseline to 44% (12 of 27) at the final visit; the placebo arm had a 6% reduction from 67% urine positivity (20 of 30) to 63% (17 of 27) (Figure 2). In the intent-to-treat GEE analysis, the risk of testing positive for methamphetamine use decreased faster in the mirtazapine arm compared with the placebo arm (RR, 0.57; 95% CI, 0.35-0.93; P = .02); the fitted trends also are shown in Figure 2. The number needed to treat to achieve a negative weekly urine test result was 3.1. This protective effect in favor of mirtazapine remained significant in sensitivity analyses after including week-1 urine test results (RR, 0.58; 95% CI, 0.38-0.90; P = .02), imputing of positive results for missing urine samples (0.62; 0.42-0.93; P = .02), adjusting for imbalanced baseline characteristics (0.53; 0.32-0.89; P = .02), and controlling for baseline correlates of missing urine samples or positive urine test results (P < .04). In checking the assumptions of the model for urine positivity, we found no persuasive evidence for departures from linear trend during the 12 weeks in the mirtazapine (P = .22) or placebo (P = .58) arm. In the as-treated analysis, the expected effect of treatment for a participant with mean adherence of 48.5% was a 54% (95% CI, 21%-74%) reduction in the urine positivity rate at 12 weeks (P = .02).

The within-subject correlation of urine test results (observed, 45%; expected, 50%-90%), the placebo urine positivity rate (observed, 63%-67%; expected, 70%-90%), and missing urine sample rates (observed, 14%; expected, 33%) were slightly lower than the values used in the sample size calculation. However, the observed treatment effect was larger (observed, 43%; minimum detectable rates, 14%-33%).

After randomization, 2 participants revealed they had been taking psychiatric medications that would have excluded them from the trial. At unmasking, both were found to be randomized to the mirtazapine arm. Omitting these 2 participants from the efficacy analysis did not change the protective effect of mirtazapine in reducing methamphetamine use compared with placebo (RR, 0.57; 95% CI, 0.34-0.93; P = .03).

**SECONDARY OUTCOMES**

**Medication Adherence**

Adherence by MEMS was 48.5% (48.3% in the mirtazapine group and 48.7% in the placebo group; P = .82); self-reported adherence was 74.7% (75.9% in the mirtazapine arm compared with placebo (RR, 0.57; 95% CI, 0.35-0.93; P = .02); the fitted trends also are shown in Figure 2. The number needed to treat to achieve a negative weekly urine test result was 3.1. This protective effect in favor of mirtazapine remained significant in sensitivity analyses after including week-1 urine test results (RR, 0.58; 95% CI, 0.38-0.90; P = .02), imputing of positive results for missing urine samples (0.62; 0.42-0.93; P = .02), adjusting for imbalanced baseline characteristics (0.53; 0.32-0.89; P = .02), and controlling for baseline correlates of missing urine samples or positive urine test results (P < .04). In checking the assumptions of the model for urine positivity, we found no persuasive evidence for departures from linear trend during the 12 weeks in the mirtazapine (P = .22) or placebo (P = .58) arm. In the as-treated analysis, the expected effect of treatment for a participant with mean adherence of 48.5% was a 54% (95% CI, 21%-74%) reduction in the urine positivity rate at 12 weeks (P = .02).

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pine group and 73.5% in the placebo group; \( P = .92 \). Common reasons for nonadherence at the final visit included “simply forgot” \(( n = 34 \ [61\%])\), “slept through dose” \(( n = 30 \ [54\%])\), “busy with other things” \(( n = 25 \ [43\%])\), and “change in daily routine” \(( n = 25 \ [43\%])\). Seven participants \((23\%)\) in the placebo arm and 10 \((33\%)\) in the mirtazapine arm had at least a weeklong discontinuation of medication use before study completion. Time to the first weeklong discontinuation of medication use did not differ by arm \(( P = .71)\).

### Change in Depression Scores

At baseline, the mean CES-D score was 16.7. At the 12-week visits, the mean scores were 13.8 in the mirtazapine arm and 11.8 in the placebo arm. Mean CES-D scores

<table>
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<tr>
<th>Table 1. Baseline Characteristics of Trial Participantsa</th>
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<tr>
<td><strong>Characteristic</strong></td>
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<td><strong>Age, mean (SD), y</strong></td>
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<td><strong>Race/ethnicity</strong></td>
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<td>Wanted to cease methamphetamine use</td>
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<td>Wanted to reduce methamphetamine use</td>
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<td><strong>Methamphetamine use</strong></td>
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<td>Methamphetamine severity of dependence scale score (range, 0-15), mean (SD)</td>
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<td>CES-D score (range, 0-60), mean (SD)</td>
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Abbreviations: CES-D, Center for Epidemiologic Studies–Depression Scale; HIV, human immunodeficiency virus.

aData are presented as number (percentage) of patients unless otherwise indicated. Percentages may not total 100 because of rounding. Binary and categorical characteristics compared using the Fisher exact test and group means compared using the Wilcoxon rank sum test.

bPercentages may exceed 100 because some participants stated more than 1 reason.

cP < .05 indicates characteristic imbalanced at baseline; sensitivity analyses were conducted to adjust for imbalanced characteristics.
decreased 3.6 points overall (95% CI, 0.9-6.2; \( P = .01 \)), but the difference between arms during follow-up was not significant (1.5 points; −3.7 to 6.7; \( P = .57 \)).

**Sexual Risk Behaviors**

After controlling for imbalanced baseline characteristics, sexual risk behaviors decreased faster in the mirtazapine arm compared with participants taking placebo (Table 2). Reductions were statistically significant for most sexual risk behaviors analyzed (\( P < .05 \)).

**Correlation of Primary and Secondary Outcomes**

Summary monthly measures of testing negative for methamphetamine were associated with reductions in the numbers of partners with whom methamphetamine was used (\( P < .001 \)), male partners (\( P = .10 \)), episodes of anal sex with serodiscordant partners (\( P = .04 \)), episodes of insertive anal sex with serodiscordant partners (\( P = .005 \)), and episodes of receptive anal sex with serodiscordant partners (\( P = .001 \)). However, urine positivity was not associated with depression (\( P = .54 \)).
Safety and Tolerability

No differences were found overall in frequency of adverse events between treatment arms (P ≥ .99). Two serious adverse events were observed: a methamphetamine-induced paranoia in a participant in the mirtazapine arm and a vertebral fracture in a participant in the placebo arm. Neither event was deemed related to the study drug. The most common adverse events reported in both arms were increased alanine aminotransferase levels (9 [23%] in the mirtazapine group and 7 [30%] in the placebo group; P = .77), increased aspartate aminotransferase levels (5 [17%] in the mirtazapine group and 8 [27%] in the placebo group; P = .53), gastroenteritis (4 [13%] in the mirtazapine group and 4 [13%] in the placebo group; P = .99), upper respiratory tract infection (3 [10%] in the mirtazapine group and 4 [13%] in the placebo group; P = .99), and hyperglycemia (4 [13%] in the mirtazapine group and 3 [10%] in the placebo group; P = .99). Expected adverse effects reported exclusively in the mirtazapine arm included drowsiness (13 participants [43%]), increased appetite (4 [13%]), and weight gain (3 [10%]). One participant gained 12.5 kg from baseline to the final visit; another gained 9.5 kg. The third gained 7.9 kg from baseline to the month-1 follow-up visit but declined to be weighed on subsequent follow-up visits. None of these participants discontinued use of the study medication.

Assessment of Unmasking

At study completion, participants were asked to guess their treatment assignment. No evidence of unmasking was observed: in the placebo arm, 14 participants (50%) guessed correctly; in the mirtazapine arm, 15 participants (56%) guessed correctly (P = .79). With regard to a possible placebo effect, we found no persuasive evidence that guessing assignment to receive mirtazapine (correctly or not) was associated with the primary or secondary outcomes. Specifically, urine positivity was only nominally reduced among men who guessed they were assigned to receive mirtazapine (RR, 0.76; 95% CI, 0.54-1.07; P = .12). Similarly, most sexual risk behaviors were nominally less common in this group (RRs, 0.42-0.77), but none of these differences was statistically significant (all P ≥ .18).

Mirtazapine significantly reduced methamphetamine use among current users who also were receiving substance use counseling. Our findings were robust; despite multiple adjustments for possible confounders, our efficacy estimates from the intent-to-treat analysis essentially were unchanged. Mirtazapine’s effects on methamphetamine use appeared to be independent of its effects on depression; no significant difference was observed in depression scores at follow-up between arms. The study had very high visit completion and retention rates, factors that often limit the interpretation of results in pharmacologic trials among substance-using populations.7 These results compare favorably to those of other recent trials of pharmacologic agents for methamphetamine dependence. In 1 placebo-controlled study15 that required amphetamine abstinence at baseline, naltrexone significantly reduced relapse among amphetamine-dependent individuals. Another placebo-controlled trial among actively using, methamphetamine-dependent individuals reported that dexamphetamine maintenance reduced amphetamine dependence scores; however, no significant differences were observed in self-reported methamphetamine use or median methamphetamine concentrations in hair samples between study arms. Also, only 46% of participants completed the trial.32

Mirtazapine was efficacious in the setting of low to moderate adherence. It is possible that with higher adherence rates, mirtazapine may be more effective in reducing methamphetamine use. As monitored by MEMS, fewer than half of medication doses were taken, although self-reported adherence was considerably higher. These adherence rates are comparable to rates among other samples of active drug users and are not unexpected because the trial population was comprised of active methamphetamine users who were required to provide a positive methamphetamine metabolite urine test result to enroll.33 Although it may have increased adherence, an intensive adherence intervention deliberately was not included in the trial to reflect the amount of adherence counseling that could be delivered realistically in a non-research, routine clinical setting. The finding that self-reported adherence was higher than MEMS-measured adherence is consistent with results seen in the adherence literature.33 Although often used as a “gold standard” of adherence, MEMS may underestimate adherence, as would be the case if participants took out multiple capsules at a single cap opening and then otherwise dosed according to instructions. To facilitate adherence, long-acting formulations, including patch delivery systems designed to sustain mirtazapine levels without daily dosing or intramuscular depot formulations, could be explored. Most adverse events were mild to moderate; no differences were observed overall by arm. No evidence of unmasking due to adverse events was observed. The weight gain documented for 3 participants in the treatment arm is consistent with the known adverse effects of mirtazapine use.10

Most sexual risk behaviors decreased significantly more in the mirtazapine arm compared with the placebo arm despite the fact that both study arms received HIV risk reduction counseling at baseline. Of importance, these reductions in sexual risks were associated with testing negative for methamphetamine use, suggesting a possible causal pathway between the 2 outcomes. These findings suggest that mirtazapine combined with HIV risk reduction and substance use counseling may be an effective HIV prevention intervention. Larger studies are needed to confirm these findings and to determine whether mirtazapine-driven reductions in sexual risk behavior correspond to reductions in STD and HIV incidence. The fact that we found no difference in changes in unprotected receptive anal sex with serodiscordant partners may be due to the relatively low prevalence of this high-risk activity; also, the point estimate for the relative reduction was consistent with the significant reductions in other risky behaviors.

Although it had high participation and retention rates, this study has limitations. Whereas this is the first study, to our knowledge, to show the efficacy of mirtazapine for methamphetamine dependence, the sample size was rela-
tively small; larger studies are needed to replicate our findings. Only MSM were included; mirtazapine should be tested in other populations of methamphetamine users. The trial was powered to determine the net difference in methamphetamine use between the study arms; it was not designed to assess the efficacy of mirtazapine in achieving or maintaining methamphetamine abstinence. The efficacy of mirtazapine beyond 12 weeks of treatment remains unknown, as is whether its treatment effect is sustained after treatment is stopped. Because of ethical concerns regarding the possibility of randomization to placebo, we did not enroll individuals with major depression. This may explain why we detected no significant change in CES-D scores between study arms. Also, we could not assess the effect of mirtazapine in methamphetamine users with major depression. Weight gain, a known adverse effect of mirtazapine, was assessed only through self-report; the net difference in weight gain could not be determined between the study arms. However, it is notable that all 3 participants reporting weight gain nevertheless continued use of their study medication.

Despite these limitations, this study demonstrated that mirtazapine for methamphetamine dependence improved outcomes when added to substance use counseling. Our findings are consistent with those of trials of other agents used to treat substance dependence in the setting of counseling, including those to treat opioid, nicotine, and alcohol dependence.5,33 Mirtazapine was safe and well tolerated among active methamphetamine users and, despite low to moderate adherence rates, significantly reduced methamphetamine use.

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