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Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men
A Placebo-Controlled Randomized Clinical Trial

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IMPORTANCE Methamphetamine use is increasingly prevalent and associated with HIV transmission. A previous phase 2a study of mirtazapine demonstrated reductions in methamphetamine use and sexual risk behaviors among men who have sex with men.

OBJECTIVE To determine the efficacy of mirtazapine for treatment of methamphetamine use disorder and reduction in HIV risk behaviors.

DESIGN, SETTING, AND PARTICIPANTS This double-blind randomized clinical trial of mirtazapine vs placebo took place from August 2013 to September 2017 in an outpatient research clinic in San Francisco, California. Participants were community-recruited adults who were sexually active; cisgender men, transgender men, and transgender women who (1) had sex with men, (2) had methamphetamine use disorder, and (3) were actively using methamphetamine were eligible. Participants were randomized to receive the study drug or placebo for 24 weeks, with 12 more weeks of follow-up. Data analysis took place from February to June 2018.

EXPOSURES Mirtazapine, 30 mg, or matched placebo orally once daily for 24 weeks, with background counseling.

MAIN OUTCOMES AND MEASURES Positive urine test results for methamphetamine over 12, 24, and 36 weeks (primary outcomes) and sexual risk behaviors (secondary outcomes). Sleep, methamphetamine craving, dependence severity, and adverse events were assessed.

RESULTS Of 241 persons assessed, 120 were enrolled (5 transgender women and 115 cisgender men). The mean (SD) age was 43.3 (9.8) years; 61 (50.8%) were white, 31 (25.8%) were African American, and 15 (12.5%) were Latinx. A mean (SD) of 66% (47%) of visits were completed overall. By week 12, the rate of methamphetamine-positive urine test results significantly declined among participants randomized to mirtazapine vs placebo (risk ratio [RR], 0.67 [95% CI, 0.51-0.87]). Mirtazapine resulted in reductions in positive urine test results at 24 weeks (RR, 0.75 [95% CI, 0.56-1.00]) and 36 weeks (RR, 0.73 [95% CI, 0.57-0.96]) vs placebo. Mean (SD) medication adherence by WisePill dispenser was 38.5% (27.0%) in the mirtazapine group vs 39.5% (26.2%) in the placebo group (P = .77) over 2 to 12 weeks and 28.1% (23.4%) vs 38.5% (27.0%) (P = .59) over 13 to 24 weeks. Changes in sexual risk behaviors were not significantly different by study arm at 12 weeks, but those assigned to receive mirtazapine had fewer sexual partners (RR, 0.52 [95% CI, 0.27-0.97]; P = .04), fewer episodes of condomless anal sex with partners who were serodiscordant (RR, 0.47 [95% CI, 0.23-0.97]; P = .04), and fewer episodes of condomless receptive anal sex with partners who were serodiscordant (RR, 0.37 [95% CI, 0.14-0.93]; P = .04) at week 24. Participants assigned to mirtazapine had net reductions in depressive symptoms (Center for Epidemiologic Studies Depression Scale score, 6.2 [95% CI, 1.3-11.1] points lower; P = .01) and insomnia severity (Athens score, 1.4 [95% CI, 0.1-2.7] points lower; P = .04) at week 24. There were no serious adverse events associated with the study drug.

CONCLUSIONS AND RELEVANCE In this expanded replication trial, adding mirtazapine to substance use counseling reduced methamphetamine use and some HIV risk behaviors among cisgender men and transgender women who have sex with men, with benefits extending after treatment despite suboptimal medication adherence.

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Supplemental content

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Methamphetamine continues to dominate the drug market globally[1]; 1.4 million individuals reported having used this drug in the past year, 667 000 reported currently using it in the United States in 2016,[2] and prevalence is increasing in several US regions.[3] Methamphetamine use among men who have sex with men is prevalent and associated with considerable medical and social risks,[4-14] including HIV transmission.[15-20]

There are no pharmacotherapies approved for methamphetamine use disorders, notwithstanding decades of research,[21-23] which constitutes a major gap in addiction medicine. Mirtazapine is a generic US Food and Drug Administration–approved antidepressant with no apparent abuse potential, onset of action within 2 weeks, and notable adverse effects of somnolence and weight gain.[24-26] Mirtazapine acts as a mixed monoamine agonist-antagonist, facilitating norepinephrine, serotonin, and dopamine release in mesocorticolimbic areas involved in drug reward, craving, and seeking.[27-29] Increased monoamine levels produced by mirtazapine may alleviate methamphetamine craving and withdrawal symptoms, which is in turn thought to help facilitate reductions in methamphetamine use and methamphetamine-associated risk behaviors. Indeed, our prior 12-week trial supported this hypothesis, because it demonstrated significant reductions in methamphetamine use and associated sexual risk behaviors among 60 men who have sex with men and were treated with mirtazapine.[30] We sought to replicate and expand on these results by determining if mirtazapine, compared with placebo, reduced methamphetamine use and sexual risk behaviors at 12 and 24 weeks of treatment and 12 weeks posttreatment.

Key Points

Question Does treatment with mirtazapine reduce the use of methamphetamine and sexual HIV risk behaviors among cisgender men and transgender women who have sex with men?

Findings In this analysis, mirtazapine reduced the use of methamphetamine over 24 weeks of treatment and 12 weeks of follow-up after treatment was concluded. Mirtazapine also reduced several sexual HIV risk behaviors; both findings were consistent with a previous study.

Meaning Mirtazapine is the first medication to demonstrate efficacy in treating methamphetamine use disorder in 2 independent randomized clinical trials.

Methods

We conducted a double-blind, placebo-controlled randomized clinical trial of daily mirtazapine, 30 mg, vs placebo in a 1:1 ratio in a study for which the eligible population was cisgender men, transgender men, and transgender women who (1) reported having sex with men and (2) had methamphetamine use disorder. Data collection occurred in San Francisco, California, from August 2013 to October 2017. Study procedures were approved by the University of California, San Francisco institutional review board. All participants provided written informed consent. This article was prepared based on Consolidated Standards of Reporting Trials guidelines.

Recruitment

Participants were recruited from clinics, community-based organizations, nightlife venues, and websites and screened by telephone to establish preliminary eligibility. At screening, participants gave informed consent and were evaluated for eligibility criteria, which included an age between 18 and 65 years, methamphetamine dependence per the Structured Clinical Interview for *DSM-IV-TR*,[31] interest in reducing or stopping methamphetamine use, having been assigned male at birth and identifying as any gender or having been assigned female at birth and identifying as male, and a self-report of engaging in anal sex with men while using methamphetamine within prior 6 months. Additionally, eligibility criteria included a positive test result for methamphetamine metabolites in urine and, for individuals with HIV, having more than 200 CD4 cells/mm^3 or 100 to 199 CD4 cells/mm^3 and an HIV viral load of less than 200 copies per mL of blood. Exclusion criteria included participation in a prior mirtazapine trial; use of mirtazapine, a monoamine oxidase inhibitor, or any antidepressant medications in the past 30 days, with the exception of fluoxetine, sertraline, paroxetine, citalopram, or escitalopram; current major depression or any psychiatric condition precluding safe participation; presence of alanine or aspartate aminotransferase or total bilirubin levels of greater than 5 times the upper reference limit; an estimated glomerular filtration rate less than 40 mL/minute; a known intolerance or hypersensitivity to mirtazapine; medical illnesses likely to progress clinically during participation; pending legal proceedings with a high risk of incarceration; and concurrent participation in another research study.

Procedures

Two screening visits included a physical examination, medical history, mental health and substance use history by the Structured Clinical Interview for *DSM-IV-TR*, qualitative urine testing for methamphetamine (MedTox EZ-Screen), a complete blood cell count, liver and renal function tests, and a pregnancy test for all participants assigned female at birth. All participants received HIV risk-reduction counseling, and those reporting being HIV negative or having an unknown status were tested by the OraQuick AdvanceRapid HIV-1/2 and a pooled viral load. Participants with HIV had CD4 and viral load testing. Two visits (termed *run-in visits*) to test retention were conducted before enrollment and included urine collection.

Enrolled participants were seen weekly for methamphetamine metabolite urine testing and manual-driven 30-minute substance use counseling sessions using cognitive behavioral therapy[32] and motivational interviewing.[33-35] Symptom-driven physical examinations were performed at the baseline visit and the 4-week visit. The study drug was dispensed at baseline, weekly for 2 weeks, then at every 4-week visit to mirror real-world practice. The drug was dispensed in WisePill dispensers to monitor adherence.[36] Safety laboratory tests were completed at the week-12 and week-24 visits. Counseling and

testing for HIV were conducted every 12 weeks for individuals who initially tested negative for HIV. Participants received up to $595 in study compensation for visits. The study drug was prepared by an off-site pharmacist with identical overencapsulation to maintain double blinding. Participants received mirtazapine, 15 mg, or matched placebo during week 1, then mirtazapine, 30 mg, or placebo through week 24. The 1:1 random-allocation sequence was generated by the study biostatistician. Only the off-site biostatistician and pharmacist knew the allocation assignment.

Measures

The primary outcome was a repeated weekly indicator of methamphetamine-positive urine. Secondary outcomes were sexual risk behaviors, including the number of male partners overall and male partners with whom methamphetamine was used; episodes of any anal sex, condomless anal sex, insertive condomless anal sex, and receptive condomless anal sex with partners who were serodiscordant; and adverse events associated with the study drug.[37] Audio computer-assisted self-interviews assessed substance use and cravings weekly.[38,39] At enrollment and monthly visits, these interviews assessed severity of methamphetamine dependence, sexual behaviors, sleep duration and difficulty via the Athens Insomnia Scale,[40-42] and depressive symptoms via the Center for Epidemiologic Studies Depression Scale.[43]

Data Analysis

The sample of 120 participants provided 80% power in a 2-sided test with a type I error rate of 5% to detect a 19% relative reduction in methamphetamine-positive urine test results among participants assigned to mirtazapine vs placebo during weeks 2 to 12 (risk ratio [RR], 0.81), 14% during weeks 13 to 24 (RR, 0.86), and 15% during weeks 25 to 36 (RR, 0.85).[44] These minimum detectable effects are based on 90% retention at week 12, 85% retention at week 24, and 80% retention at week 36; and a within-participant correlation of 0.45 for urine outcomes. Outcomes were analyzed by an intent-to-treat analysis using a generalized estimating equations model, with robust standard errors to account for within-participant clustering of the binary responses. To obtain direct estimates of risk ratios, log-link models were used. The prespecified model omits week-1 results (from the first postenrollment visit) based on the a priori hypothesis that mirtazapine would have a delayed, gradually increasing effect. The analysis compared trends in positive urine test results from baseline through week 36, modeled as group-specific piecewise linear functions of time, since randomization for the treatment effects in the 3 periods (weeks 2-12, weeks 13-24, and weeks 25-36). These treatment effects were captured by the divergence of mirtazapine and placebo trends at 12, 24, and 36 weeks after accounting for the fitted baseline difference and were assessed using a test for time-by-treatment interaction. Robust standard errors allowed accounting for within-participant correlation of responses without making parametric assumptions. Model fit was informally assessed by plotting the group-specific fitted trends along with raw percentages.

Five sensitivity analyses were conducted: (1) one including week 1 results, (2) one imputing positive results for missing urine samples, (3) one adjusting for imbalanced baseline characteristics and baseline correlates of missing or positive urine samples, (4) one including participants who completed final visits beyond the maximum allowable time window, and (5) one stratifying participants by their baseline intensity of methamphetamine use. All available data were included in each analysis. Although the primary analysis rests on the stringent assumption that urine test results are missing completely at random, given the 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 in a covariate-dependent missing-at-random pattern conditional on the baseline covariates included in the model.

We conducted as-treated analyses for cumulative adherence and past-week adherence, measured as the percentage of WisePill events recorded divided by the number of days since enrollment and the past 7 days, respectively, as time-dependent covariates. These analyses used the same models as the intent-to-treat analysis, restricted to participants with results in the upper 50th percentile of each measure for adherence (cumulative adherence and past-week adherence) to determine whether treatment effects are moderated among those with greater adherence to study medications. We compared consecutive weeks of continued abstinence from methamphetamine, with an outcome called the *number of beyond-threshold weeks of success* (eFigure in Supplement 1).[45] Consistent with McCann and Li,[45] this outcome was calculated as the number of consecutive weeks beyond the threshold of 1 week of abstinence (termed *end-of-study abstinence* [EOSA]), with a score of 1 corresponding to 2 consecutive weeks of EOSA, and so forth. Differences between arms at weeks 12, 24, and 36 were assessed using 0-inflated negative binomial models. In an exploratory analysis, we evaluated the association between achieving EOSA at weeks 12, 24, and 36 and the treatment arm using logistic regression models. We then calculated the risk difference from the Stata "margins, dydx" command, which was made inverse to estimate the number needed to treat for an EOSA at each point.

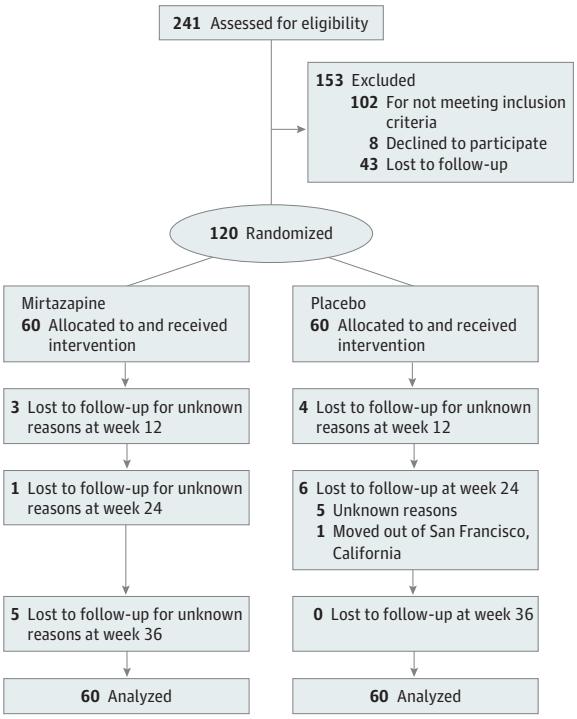
We used linear, logistic, and negative binomial generalized estimating equations models to assess treatment effects on secondary outcomes, including sexual risk behaviors, sleep scores, and depression scores. Adherence was evaluated as the percentage of the study medication taken, as measured by WisePill dispensers and participant self-reports and compared by study arm using the Wilcoxon tests. All analyses were conducted from February to June 2018 using Stata version 15.1 (StataCorp) with a 2-sided *P* value less than .05 considered significant. Further details of the protocol appear in Supplement 2.

Results

Participants

Figure 1 shows results for screening, study-arm assignment, and retention. In total, 241 persons were assessed, and 120 were

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Diagram for a Trial of Mirtazapine for Methamphetamine Use Disorder



enrolled (60 per study arm). The most common reasons for ineligibility were the presence of a psychotic disorder (n = 40), the absence of methamphetamine dependence (n = 18), a lack of methamphetamine-positive urine test results (n = 10), an inability to adhere to study procedures (n = 8), and a current regimen of an excluded antidepressant medication (n = 5).

Participant characteristics were similar by arm (**Table 1**). Briefly, 115 participants (95.8%) identified as cisgender men, and the remaining 5 participants identified as transgender women. Transgender male participants were eligible, but none enrolled. The mean (SD) age of participants was 43.3 (9.8) years. Of the 120 participants, 61 (50.8%) were white, 31 (25.8%) were African American, and 15 (12.5%) Latinx.

Retention and Adherence

A mean (SD) of 66% (47%) of weekly visits were completed (mirtazapine group, 69% [32%]; placebo group, 63% [31%]; *P* = .28). Both arms had similar trial completion rates, defined as completing the final study visit (mirtazapine group, 38 participants [48%]; placebo group, 42 participants [53%]; *P* = .56), and dropout rates (mirtazapine group, 20 participants [33%]; placebo group, 13 participants [22%]; *P* = .21). Participants in the mirtazapine and placebo arms completed 49 of 60 week-12 visits (82%) and 48 of 60 week-12 visits (80%), respectively (*P* > .99); 43 of 60 week-24 visits (72%) and 43 of 60 week-24 visits (72%), respectively (*P* = .28); and 38 of 60 week-36 visits (63%) and 42 of 60 week-36 visits (70%), respectively (*P* = .56). The mean (SD) number of urine samples collected was 23.0 (11.8) samples (mirtazapine group, 22.0 [11.8]; placebo group, 24.1 [11.7]; *P* = .32). Participants in both

Table 1. Baseline Characteristics of Trial Participants

Demographics	Participants, No. (%)			*P* Value[a]
	Receiving Mirtazapine (n = 60)	Receiving Placebo (n = 60)	Overall (N = 120)	
Age, mean (SD), y	42.65 (9.7)	43.85 (10.0)	43.3 (9.8)	.54
Race/ethnicity				
White	29 (48.3)	32 (53.3)	61 (50.8)	.90
African American	15 (25.0)	16 (26.7)	31 (25.8)	
Latinx	8 (13.3)	7 (11.7)	15 (12.5)	
Asian and Pacific Islander	4 (6.7)	2 (3.3)	6 (5.0)	
Other	4 (6.7)	3 (5.0)	7 (5.8)	
Sex and gender				
Cisgender male	59 (98.3)	56 (93.3)	115 (95.8)	.36
Transgender female	1 (1.7)	4 (6.7)	5 (4.2)	
Education				
High school or less	18 (30.0)	27 (45.0)	45 (37.5)	.24
Some college or 2-y college	21 (35.0)	17 (28.3)	38 (31.7)	
Bachelor degree or above	21 (35.0)	16 (26.7)	37 (30.8)	
Income, $				
<20 000	36 (60.0)	32 (53.3)	68 (56.7)	.75
20 000-39 999	14 (23.3)	16 (26.7)	30 (25.0)	
≥40 000	9 (15.0)	11 (18.3)	20 (16.7)	
Employment status				
Not employed	37 (61.7)	45 (75.0)	82 (68.3)	.20
Employed				
Full time	11 (18.3)	5 (8.3)	16 (13.3)	
Part time	12 (20.0)	10 (16.7)	22 (18.3)	
Methamphetamine use				
Frequency of methamphetamine use in past 4 wk				
≤1 d per wk	7 (11.7)	14 (23.3)	21 (17.5)	.16
2-4 d per wk	22 (36.7)	15 (25.0)	37 (30.8)	
5-7 d per wk	31 (51.7)	31 (51.7)	62 (51.7)	
Methamphetamine use during sex in past 4 wk				
≤50% of Time	23 (38.3)	27 (45.0)	50 (41.7)	.46
>50% of Time	37 (61.7)	33 (55.0)	70 (58.3)	
Route of methamphetamine administration				
Injection	23 (38.3)	26 (43.3)	49 (40.8)	.58
Inserted rectally	19 (31.7)	14 (23.3)	33 (27.5)	.31
Snorted	24 (40.0)	22 (36.7)	46 (38.3)	.71
Smoked	49 (81.7)	52 (86.7)	101 (84.2)	.45
Ingested orally	11 (18.3)	9 (15.0)	20 (16.7)	.62
Methamphetamine Severity of Dependence Scale score, mean (SD)	6.4 (3.3)	5.7 (3.1)	6.1 (3.2)	.32
Methamphetamine Brief Substance Craving score, mean (SD)	5.8 (3.2)	4.7 (3.0)	5.2 (3.1)	.08
History of methamphetamine self-help or treatment program	30 (50.0)	31 (51.7)	61 (50.8)	.86

(continued)

Table 1. Baseline Characteristics of Trial Participants (continued)

Demographics	Participants, No. (%)			P Value[a]
	Receiving Mirtazapine (n = 60)	Receiving Placebo (n = 60)	Overall (N = 120)	
Clinical				
HIV serostatus				
Negative	29 (48.3)	29 (48.3)	58 (48.3)	>.99
Positive	31 (51.7)	31 (51.7)	62 (51.7)	
Positive with detectable viral load	10 (16.7)	9 (15.0)	19 (15.8)	>.99
Has regular clinician	49 (81.7)	51 (85.0)	100 (83.3)	.62
Has health insurance	54 (90.0)	55 (91.7)	109 (90.8)	.75
Center for Epidemiologic Studies Depression Scale score, mean (SD)	20.7 (9.7)	19.8 (7.9)	20.2 (8.8)	.67

[a] Binary and categorical characteristics were compared using the χ^2 or Fisher exact test, and continuous characteristics were compared using the Wilcoxon rank sum test.

arms completed a similar number of audio computer-assisted self-interview surveys (mean [SD]: mirtazapine group, 7.5 [3.2] sessions; placebo group, 8.3 [3.1] sessions; *P* = .06) and counseling sessions (mean [SD]: mirtazapine group, 12.6 [7.6] sessions; placebo group, 14.8 [7.9] sessions; *P* = .16). There was no evidence of unblinding at week 24; 19 participants who received mirtazapine (46%) and 23 participants who received placebo (49%) correctly guessed their study arm (*P* = .83). Further details are in **Table 2**.

Methamphetamine Use

At baseline, 96 participants (80%) had methamphetamine-positive urine samples (mirtazapine group, 51 [85%]; placebo group, 45 [75%]; *P* = .16). Positive results on urine testing occurred in 25 of 38 samples (66%) in the mirtazapine arm and 32 of 41 samples (78%) in the placebo arm at week 12 (**Figure 2**); positive results were found in 20 of 32 samples (63%) and 29 of 39 samples (74%), respectively, at week 24, and 25 of 35 samples (71%) and 37 of 42 samples (88%), respectively, at week 36. In an intent-to-treat analyses, the rate of methamphetamine-positive urine samples significantly declined among participants assigned to mirtazapine vs placebo by week 12 (RR, 0.67 [95% CI, 0.51-0.87]), week 24 (RR, 0.75 [95% CI, 0.56-1.00]), and week 36 (RR, 0.73 [95% CI, 0.57-0.96]).

Methamphetamine-positive urine test results in the placebo arm (observed, 45 of 60 participants [75%]; expected, 70%-90%) and within-participant correlation of urine test results (observed, 43% [95% CI, 35%-51%]; expected, 45%) were within ranges assumed for sample-size calculation. However, missing urine sample rates were greater than expected (week 12: observed, 41 samples of 120 total samples [34%]; expected, 10%; week 24: observed, 49 of 120 samples [41%]; expected, 15%; week 36: observed, 43 of 120 samples [36%]; expected, 20%). Using the observed parameters, the updated minimum detectable effect net percentage reduction in positive urine test results was similar to a priori estimates. Minimum detectable effects estimates were not sensitive to loss to follow-up because of the weekly frequency of urine assessments and the substantial within-participant correlation of urine test result data in the sample, suggesting that the data after dropout events occurred resembled the data before dropout events occurred.

Sensitivity Analyses

Significant treatment effects favoring mirtazapine were observed in sensitivity analyses after week-1 urine test results were included, positive results for missing urine samples were imputed, and baseline correlates of missing or positive urine samples were controlled for (eTable in Supplement 1). No significant effect was observed stratifying by methamphetamine use intensity. Four participants (3%) were taking selective serotonin reuptake inhibitors, and this had no association with positive methamphetamine urine test results.

As-Treated Analyses

Results of as-treated analyses were consistent with intent-to-treat analyses with respect to direction and magnitude. In the as-treated analyses for cumulative adherence, the effect of mirtazapine was nonsignificant (RR, 0.70 [95% CI, 0.38-1.28]; *P* = .25) at week 12 and significant (RR, 0.69 [95% CI, 0.50-0.95]; *P* = .02) at week 24. In the as-treated analyses for adherence in the past 7 days, the effect of mirtazapine treatment was nonsignificant at week 12 (RR, 0.64 [95% CI, 0.36-1.13]; *P* = .13) and week 24 (RR, 0.73 [95% CI, 0.50-1.08]; *P* = .12), after accounting for any differences from weeks 2 to 12.

Number of Beyond-Threshold Weeks of Success

The median (IQR) number of beyond-threshold weeks of success was 0 (0-0) weeks among participants in the mirtazapine and placebo arms at weeks 12 (*P* = .97), 24 (*P* = .81), and 36 (*P* = .71; eFigure in Supplement 1). At both the week-12 and week-24 visits, 11 participants who were receiving mirtazapine (18%) and 5 who were receiving placebo (8%) had achieved EOSA from methamphetamine for at least the past 2 consecutive weeks (*P* = .11). At week 36, 7 individuals who had received mirtazapine (12%) and 3 who had received placebo (5%) had achieved abstinence for at least the past 2 consecutive weeks (*P* = .19). The odds of achieving EOSA were similar between the mirtazapine and placebo arms at weeks 12 and 24 (odds ratio, 2.50 [95% CI, 0.80-7.61] for both assessments) and at week 36 (odds ratio, 2.50 [95% CI, 0.62-10.20]). The numbers needed to treat to achieve EOSA at weeks 12, 24, and 36 were 10, 10, and 15 individuals, respectively.

Sexual Risk Behaviors

Sexual risk behaviors were similar by arm at baseline (**Table 3**), and there were no significant differences in changes by arm at week 12. Compared with placebo, mirtazapine at 24 weeks was associated with a net reduction in the number of male sexual partners (RR, 0.52 [95% CI, 0.27-0.97]; *P* = .04), partners who were serodiscordant with whom participants had condomless anal sex (RR, 0.47 [95% CI, 0.23-0.97]; *P* = .04), and partners who were serodiscordant with whom

Table 2. Primary and Secondary Outcomes and Sensitivity Analyses

Outcome	Risk Ratio or Coefficient (95% CI)	*P* Value
Primary Outcomes		
Intent-to-treat analyses[a]		
Treatment effect at 12 wk	0.67 (0.51-0.87)	.003
Net treatment effect at 24 wk[b]	0.75 (0.56-1.00)	.05
Net treatment effect at 36 wk[c]	0.73 (0.57-0.96)	.02
As-treated analyses[a,d]		
Treatment effect of cumulative adherence		
At 12 wk	0.70 (0.38-1.28)	.25
At 24 wk, net of any difference from weeks 2-12	0.69 (0.50-0.95)	.02
Treatment effect of adherence in past 7 d		
At 12 wk	0.64 (0.36-1.13)	.13
At 24 wk, net of any difference from weeks 2-12	0.73 (0.50-1.08)	.12
Secondary Outcomes[e]		
Athens Insomnia Scale Score		
Treatment effect at 12 wk	−1.15 (−2.33 to 0.02)	.06
Net treatment effect		
At 24 wk	−1.40 (−2.74 to −0.07)	.04
At 36 wk	−0.22 (−1.51 to 1.07)	.74
Center for Epidemiologic Studies Depression Scale score		
Treatment effect at 12 wk	−0.28 (−4.62 to 4.06)	.90
Net treatment effect		
At 24 wk	−6.18 (−11.07 to −1.30)	.01
At 36 wk	−1.38 (−6.56 to 3.80)	.60
Between-Group Comparisons of Other Secondary Outcomes		
Adherence percentage by WisePill dispenser, mean (SD)		
At week 12		
Mirtazapine	38.5 (27.0)	.77
Placebo	39.5 (26.2)	
At week 24		
Mirtazapine	28.1 (23.4)	.59
Placebo	38.5 (27.0)	
Self-reported adherence percentage, mean (SD)		
At week 12		
Mirtazapine	44.3 (23.0)	.52
Placebo	46.1 (24.8)	
At week 24		
Mirtazapine	38.8 (18.7)	.86
Placebo	37.5 (19.9)	
Number of beyond-threshold wks of success, median (IQR)		
Up to week 12		
Mirtazapine	0 (0-0)	.97
Placebo	0 (0-0)	
Up to week 24		
Mirtazapine	0 (0-0)	.81
Placebo	0 (0-0)	
Up to week 36		
Mirtazapine	0 (0-0)	.72
Placebo	0 (0-0)	
Achieved end-of-study abstinence, No. (%)[f]		
At week 12		
Mirtazapine	11 (18)	.11
Placebo	5 (8)	
At week 24		
Mirtazapine	11 (18)	.11
Placebo	5 (8)	
At week 36		
Mirtazapine	7 (12)	.19
Placebo	3 (5)	

Abbreviation: IQR, interquartile range.

[a] Risk ratio.

[b] Net treatment effects account for differences from the beginning of a stated period; this category shows the sustained treatment effect at 13 to 24 weeks of receiving treatment.

[c] Sustained treatment effect at 25 to 36 weeks of receiving treatment.

[d] Restricted to individuals with findings greater than the 50th percentile of adherence.

[e] Coefficient.

[f] End of study abstinence was defined as abstinence from methamphetamine during the last 2 weeks of the prespecified treatment evaluation points (at 12, 24, and 36 weeks).

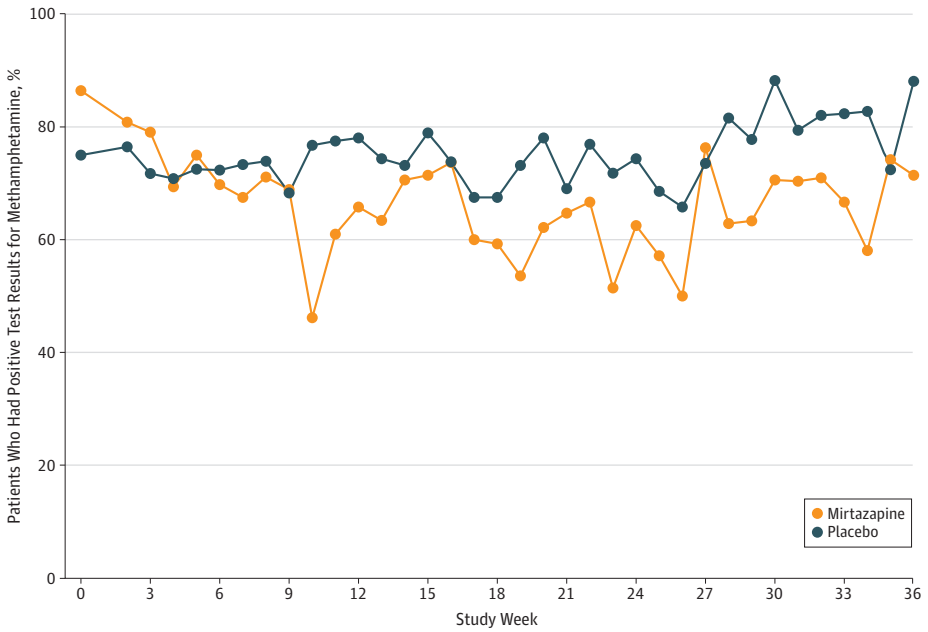
participants had condomless receptive anal sex (RR, 0.37 [95% CI, 0.14-0.93]; *P* = .04), as well as nonsignificant reductions in the number of sexual partners with whom methamphetamine was used and the total number of partners who were serodiscordant with whom participants had anal sex. No significant differences in risk behaviors were observed between arms at week 36.

Craving, Severity of Dependence, Depressive Symptoms, and Sleep

Baseline craving and severity of dependence scores were similar by arm (mean [SD] craving scores: mirtazapine group, 5.8 [3.2]; placebo group, 4.7 [3.0]; *P* = .08; mean [SD] severity of dependence scores: mirtazapine group, 6.4 [3.3]; placebo group, 5.7 [3.1]; *P* = .32), with no differences throughout follow-up. Baseline Center for Epidemiologic Studies Depression Scale scores were similar by arm (mean [SD] score: mirtazapine group, 20.7 [9.7]; placebo group, 19.8 [7.9]; *P* = .67), with no difference by arm at 12 or 36 weeks. At week 24, treatment with mirtazapine was associated with a net Center for Epidemiologic Studies Depression Scale score 6.2 points lower (95% CI, 1.3-11.1 points lower; *P* = .01).

The baseline mean (SD) number of sleep hours was similar by arm (mirtazapine group, 6.9 [4.7] hours; placebo group, 6.0 [3.5] hours; *P* = .42), with no significant change overall or by arm during follow-up. Baseline mean (SD) Athens Insomnia Scale score was similar by arm (mirtazapine group, 5.1 [3.9]; placebo group, 4.5 [3.1]; *P* = .61). The overall Athens score did not change significantly over time. There was a nonsignificant difference between arms in favor of mirtazapine at 12 weeks (1.2 [95% CI, 0.02-2.3] points lower; *P* = .06), a significant net effect of mirtazapine at 24 weeks (1.4 [95% CI,

Figure 2. Proportion of Participants With Positive Urine Test Results for Methamphetamine During Follow-up, by Arm



0.1-2.7] points lower; P = .04), and no difference by arm at week 36.

Medication Adherence

There were no significant differences in medication adherence by WisePill Dispenser data at week 12 (mean [SD] adherence: mirtazapine, 38.5% [27.0%]; placebo, 39.5% [26.2%]; P = .77) and week 24 (mean [SD] adherence: mirtazapine, 28.1% [23.4%]; placebo, 38.5% [27.0%]; P = .59). The number of participants who took at least 50% of their study medications was similar by arm (week 12: 22 participants receiving mirtazapine [37%]; 21 participants receiving placebo [35%]; P > .99; week 24: 13 participants receiving mirtazapine [22%]; 12 participants receiving placebo [20%]; P > .99). There were also no significant differences in mean (SD) medication adherence measured by self-report at week 12 (mirtazapine group, 44.3% [23.0%]; placebo group, 46.1% [24.8%]; P = .52) and week 24 (mirtazapine group, 38.8% [18.7%]; placebo group, 37.5% [19.9%]; P = .86).

Safety

Nine serious adverse events occurred, none of which were deemed associated with the study drug. In the mirtazapine arm, these included death by unintentional opioid overdose and hospitalizations for deep venous thrombosis, congestive heart failure, and soft-tissue infection; the infection occurred while the participant in question was not receiving the study drug. In the placebo arm, adverse events included hospitalizations for a shoulder injury, chronic obstructive pulmonary disease, an assault, and a lower respiratory tract infection. Of these, the last 2 events occurred while the involved participants were not receiving the study drug. The most common adverse events were hyperglycemia (mirtazapine, 14 participants [23%]; placebo, 11 participants [18%]), increased alanine transaminase level (mirtazapine, 6 participants [10%]; placebo, 9 participants [15%]), diarrhea (mirtazapine, 7 participants [12%]; placebo, 5 participants [8%]), soft-tissue infection (mirtazapine, 8 participants [13%]; placebo, 4 participants [7%]), upper respiratory infection (mirtazapine, 3 participants [5%]; placebo, 9 participants [15%]). Known mirtazapine adverse events observed included fatigue or drowsiness (mirtazapine, 18 participants [30%]; placebo, 6 participants [10%]), unintentional weight gain (mirtazapine, 4 participants [7%]; placebo, 1 participant [2%]), and increased appetite (each group, 1 participant [2%]).

Discussion

Consistent with a short-term and smaller trial conducted by our group, mirtazapine significantly reduced positive results of methamphetamine urine testing, with benefits extending to longer treatment and after treatment. In contrast with the original study, we observed significant reductions in some but not all sexual HIV risk behaviors and not until 24 weeks of treatment. This difference may be attributable to lower baseline prevalence of sexual risk behaviors compared with the first trial or the evolving landscape for HIV prevention while this trial was being conducted, marked by scaling up of preexposure prophylaxis and messaging that "an undetectable [HIV viral load] is untransmissible."[46]

Consistent with the known effects of mirtazapine on depression and sleep, mirtazapine was associated with significant reductions in Center for Epidemiologic Studies Depres-

sion Scale and Athens Insomnia Scale scores at 24 weeks. Reduced methamphetamine use has been associated with reduced depressive symptoms,[47,48] and thus the observed effect on depressive symptoms may be attributable to reduced methamphetamine use or a direct effect of mirtazapine. Methamphetamine withdrawal has been associated with sleep-onset delay, increased nighttime awakenings, and reductions in sleep quality,[49] and thus sleep improvements observed in the mirtazapine arm suggest a potential benefit to this medication.[50]

Mirtazapine was efficacious in the setting of suboptimal adherence. The adherence rates in this trial[51] were comparable with other trials of individuals who use methamphetamine and thus are not unexpected. An intensive adherence intervention was deliberately not implemented to reflect the amount of adherence counseling delivered in routine clinical care, yet long-acting formulations or paired technological or behavioral interventions could be explored to facilitate adherence. Furthermore, the reduction in use was modest overall and not significant with regard to analyses based on abstinence; it is conceivable that a combination approach could result in further reduction in use.

Limitations

This study has some limitations. First, our sample included cisgender men who have sex with men and transgender women who have sex with men, and results may not generalize to other populations. Also, we did not enroll persons with major depression to avoid ethical concerns, limiting assessment of the effect for people with comorbid major depression. Additionally, we evaluated a large number of secondary outcomes across multiple points without adjusting for multiple comparisons; some point estimates with marginal significance should be interpreted with caution. Moreover, although statistically significant, the clinical significance of the secondary outcomes on sexual risk behaviors are unclear.

Conclusions

In summary, the addition of mirtazapine treatment to substance use counseling reduced methamphetamine use among men and transwomen who have sex with men. The treatment had lasting effects after treatment despite suboptimal medication adherence.

Table 3. Sexual Risk Behavior Outcomes[a]

Factor	Relative Risk (95% CI)	*P* Value
No. of male partners		
Treatment effect at week 12	1.00 (0.62-1.62)	.98
Net treatment effect[b]		
At week 24	0.52 (0.27-0.97)	.04
At week 36	0.86 (0.44-1.66)	.65
No. of male partners with whom methamphetamine was used		
Treatment effect at week 12	1.03 (0.58-1.84)	.91
Net treatment effect[b]		
At week 24	0.54 (0.26-1.14)	.11
At week 36	1.03 (0.53-1.99)	.93
Episodes of anal sex with partners who are serodiscordant[c]		
Treatment effect at week 12	1.15 (0.57-2.32)	.70
Net treatment effect[b]		
At week 24	0.53 (0.28-1.01)	.05
At week 36	0.93 (0.42-2.06)	.87
Episodes of condomless anal sex with partners who are serodiscordant[c]		
Treatment effect at week 12	1.00 (0.47-2.13)	>.99
Net treatment effect[b]		
At week 24	0.47 (0.23-0.97)	.04
At week 36	1.01 (0.44-2.36)	.98
Episodes of condomless insertive anal sex with partners who are serodiscordant[c]		
Treatment effect at week 12	1.64 (0.66-4.06)	.29
Net treatment effect[b]		
At week 24	0.56 (0.24-1.31)	.18
At week 36	1.50 (0.57-3.93)	.41
Episodes of condomless receptive anal sex with partners who are serodiscordant[c]		
Treatment effect at week 12	0.70 (0.28-1.80)	.46
Net treatment effect[b]		
At week 24	0.37 (0.14-0.93)	.04
At week 36	0.93 (0.35-2.44)	.88

[a] Sexual behaviors are defined as self-reported sexual activity within the past 4 weeks.

[b] Net treatment effects account for differences from beginning of that period. Sexual behaviors were defined as self-reported sexual activity within the past 4 weeks.

[c] A partner who is serodiscordant is defined as an individual with HIV who has sex with a partner who does not have HIV or whose HIV status is unknown, or an individual without HIV who has sex with a partner who is HIV positive or had an unknown HIV status.

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