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Aripiprazole for the treatment of methamphetamine dependence: A randomized, double-blind, placebo-controlled trial

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Abstract

Aims—To test aripiprazole for efficacy in decreasing use in methamphetamine-dependent adults, compared to placebo.

Design—Participants were randomized to receive 12 weeks of aripiprazole or placebo, with a 3 month follow-up and a platform of weekly 30-minute substance abuse counseling.

Setting—The trial was conducted from January 2009 to March 2012 at the San Francisco Department of Public Health.

Participants—Ninety actively-using, methamphetamine-dependent, sexually active, adults were recruited from community venues.

Measurements—The primary outcome was regression estimated reductions in weekly methamphetamine-positive urines. Secondary outcomes were study medication adherence (by self-report and medication event monitoring systems [MEMS]), sexual risk behavior, and abstinence from methamphetamine.

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COMPETING INTERESTS
All authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS
PC directed study activities, participated in the interpretation of data, and drafted the manuscript. GS participated in study design, performed the statistical analysis and interpretation of data, and participated in drafting of the manuscript. MD participated in study design and coordination, and interpretation of data. DS coordinated the study, participated in study design, acquisition and interpretation of data, and participated in study activities. SH participated in the acquisition and interpretation of data. TM participated in study design and in study activities. JG participated in the design of the study. EV participated in the design of the study and the statistical analysis and interpretation of data. GC conceived and designed the study and participated in the conduct of the study and interpretation of data. All authors participated in the revision of the manuscript for important intellectual content and provided approval of the final version of the manuscript.

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Findings—Participant mean age was 38.7 years, 87.8% were male, 50.0% white, 18.9% African-American, and 16.7% Latino. Eighty-three percent of follow-up visits and final visits were completed. By intent-to-treat, participants assigned to aripiprazole had similar reductions in methamphetamine-positive urines as participants assigned to placebo (RR 0.88, 95% CI 0.66–1.19, P=0.41). Urine positivity declined from 73%(33/45 participants) to 45%(18/40) in the placebo arm, and from 77% (34/44) to 44% (20/35) in the aripiprazole arm. Adherence by MEMS and self-report was 42% and 74%, respectively, with no significant difference between arms (MEMS P=0.31; self-report P=0.17). Most sexual risk behaviors declined similarly among participants in both arms (all P>0.05). There were no serious adverse events related to study drug, although participants randomized to aripiprazole reported more akathisia, fatigue, and drowsiness (P<0.05).

Conclusion—Compared with placebo, aripiprazole did not significantly reduce methamphetamine use among actively-using, dependent adults.

Keywords

Methamphetamine; aripiprazole; sexual risk behaviors

BACKGROUND

Prevalence of methamphetamine and other amphetamine-group substance use is second only to cannabis in much of the world(1)and over a million people used methamphetamine in the U.S. in 2009.(2)Methamphetamine is associated with substantial morbidity and mortality,(3)decreased inhibitions, increased perceptions of invulnerability, high-risk sexual behaviors for HIV transmission, and incidence of HIV and other sexually-transmitted infections.(3, 4)In contrast to therapies for opioid, nicotine, and alcohol dependence, there are no FDA-approved medications to treat stimulant dependence.(3, 5, 6)

Aripiprazole is an atypical antipsychotic that acts as a dopamine (D2) receptor partial agonist. Partial agonists, such as buprenorphine and varenicline, have proven effective for other addictive disorders(7–10)and the positive mood effects of psychostimulants have been correlated with D2 receptor activation,(11)thus a D2 receptor partial agonist might reduce there warding properties of methamphetamine. This concept was supported by animal studies in which D2 receptor partial agonists reduced the rewarding effects of stimulants, stimulant-seeking behavior,(12–15)and discriminative effects.(16–18)A more recent mouse model demonstrated attenuated effects of methamphetamine.(19)Human laboratory studies of aripiprazole found reduced discriminative-stimulus and cardiovascular effects of methamphetamine, as well as reduced positive subjective effects and craving.(20–24)Finally, pilot clinical studies demonstrated reduced use or craving for other psychostimulants.(25, 26)

We conducted a randomized, double-blind, placebo-controlled trial to test the hypothesis that aripiprazole would reduce methamphetamine use among actively-using adults.

METHODS

This was a double-blind, placebo-controlled, randomized trial of daily oral aripiprazole in methamphetamine-dependent adults conducted at the San Francisco Department of Public Health. Study procedures and materials were approved by the University of California San Francisco Committee on Human Research.

Study design

Outcomes—The primary study outcome was reduction in methamphetamine metabolite-positive urines. Secondary outcomes were study medication adherence and sexual risk behavior. Our sample of 90 participants provided 80% power to detect net reductions in urine positivity rate of 15–25%, depending on within-subject correlation of the outcome, the positivity rate in the placebo group, and missing visit rates.(28)Estimates were calculated by approximating the standard error of the regression coefficient capturing the treatment effect in the model for the primary analysis.

Participants—Ninety methamphetamine-dependent adults were recruited from clinics, select neighbourhood streets, community-based organizations, websites, and posted recruitment flyers. 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 IRB-approved consent forms. Eligibility criteria included methamphetamine dependence by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV-TR(SCID); an interest in reducing or stopping methamphetamine use; age 18 to 60 years; methamphetamine metabolite positive urine at screening; no acute medical or psychiatric illness; and baseline safety labs without clinically significant abnormalities.(29)Seventeen months into enrolment the age upper limit was increased from 50 to 60 years and the sexual risk criterion was removed (sex while under the influence of meth in the past 3 months); these changes were made to optimize recruitment. Exclusion criteria included current major depression or bipolar disorder by SCID(to exclude those who might have unexpected reactions to study drug, benefit through pathways other than methamphetamine use, or for whom it would be unethical to dispense placebo); history of psychiatric medication within the past four weeks(to minimize risk of drug interactions); and, for HIV-infected individuals, a CD4 cell count below 200cells/μl.

Procedures—Two screening visits – designed to maximize retention post-enrollment – included complete histories and physicals, blood counts, metabolic panels, liver function tests, and rapid qualitative urine methamphetamine tests using immunochromatographic methamphetamine metabolite detection (Medtox Diagnostics, Burlington, NC). Participants reporting HIV-negative or unknown HIV status received HIV rapid testing; HIV-positive participants received CD4 and HIV viral load tests. All participants received HIV risk-reduction counseling based on CDC guidelines.(30)Staff collected extensive contact information using IRB-approved materials and procedures, including participant contact information and two back-up contacts. The 1:1 random allocation sequence used a fixed-block size of four to ensure balanced study arms and was generated from a SAS macro program.

Participants were seen weekly for urine collection and 30-minute substance use counseling delivered by trained staff supervised by a clinical psychologist and based on a standardized, manual-driven psychosocial treatment program using cognitive behavioral therapy and motivational interviewing techniques.(31)Symptom-directed physical exams, screening for movement disorders, safety labs, and behavioral assessments were performed at baseline and at 4, 8, and 12-week visits. HIV risk-reduction counseling and testing was repeated for HIV-negative participants at the12-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 phone calls and emails, if possible,24 hours prior to each appointment.

Pharmacotherapy—Aripiprazole and matched placebo were prepared by an off-site pharmacist in identical-looking gel caps to maintain the double-blind for study staff and participants. Clinicians dispensed medication in blinded MEMS cap bottles that were

sequentially numbered to correspond with the treatment allocation sequence. The allocation assignment was only accessible to the statistician and pharmacist. Participants were instructed to take 5 mg daily for one week, 10 mg daily for the next week, then 20 mg daily for the remainder of study. Patients reporting intolerance to known side effects of aripiprazole (e.g. akathisia) were provided with 5 mg or 10 mg pills, without unblinding, and advised by the clinician to decrease the dose. Clinicians provided adherence counseling and discussed the importance of taking medication daily and how to handle missed doses. Adherence was measured by MEMS caps (i.e. the number of distinct days that the MEMS cap bottle was opened, divided by the number of doses expected) and by self-report using the AIDS Clinical Trial Group measure.(32)

Measures—Audio-computer assisted self-interview (ACASI), programmed to maximize internal consistency, was used to standardize data collection and minimize reporting bias.(33)Standardized measures were used to assess drug use, substance use treatment, and sexual risk behavior.(34)Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms; scores above 16 suggest clinically significant depression.(35)Participants were asked weekly about adverse events, classified by standardized criteria.(36)

Data analysis

Primary outcome data were analyzed by intention-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, which omits the week 1 result, was pre-specified, based on the *a priori* hypothesis that aripiprazole would have gradually increasing efficacy after a short initial delay to achieve steady state levels. The analysis compared trends in urine-positivity from baseline through week 12 modeled as group-specific linear functions of time since randomization. The effect of treatment was captured by the divergence of aripiprazole and placebo trends at 12 weeks, net of the fitted baseline difference, 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. Fit of the model was informally assessed by plotting the group-specific fitted trends along with raw percentages.

Five sensitivity analyses were conducted: 1) including the week 1 results; 2) imputing a positive result for all missing urine samples; 3) sequentially adjusting for imbalanced baseline characteristics and baseline correlates of missing or positive urine samples; 4) omitting participants found to be ineligible post-randomization; 5) including participants who completed their final visit beyond the study's maximum allowable visit window. All available data were included in each analysis. In addition, we carried out an as-treated analysis, focusing on the effect of cumulative dose, calculated as the sum over weeks between randomization and the current week of the number of MEMS cap openings, multiplied by the dose-levels prescribed in each week, as a time-dependent covariate. In both these analyses, we controlled for the placebo effects of adherence, estimating the as-treated effect by the interaction between arm and cumulative or prior week dose. Finally, to evaluate for consecutive weeks of continued abstinence, we compared the "number of beyond-threshold weeks of success" (NOBWOS), as defined in McCann and Li (37), using the Wilcoxon test.

We also used linear, logistic and negative binomial GEE models to assess treatment effects on secondary outcomes, including CES-D scores and high-risk sexual behaviors. Acceptability was evaluated as percent MEMS adherence by arm using the Wilcoxon test.

To assess safety, we compared incidence of at least one adverse event of various types by arm using two-tailed Fisher's exact test.

RESULTS

Subjects

The target sample was achieved and study period was from 12 January2009 to 27 March 2012. Figure 1 shows results for screening, study arm assignment and retention. The most common reasons for ineligibility were: major depression (15%, n=35), bipolar disorder (4%, n=10), or another exclusionary mental health disorder (20%, n=47); not meeting methamphetamine dependence criteria by SCID (32%, n=73);or having an exclusionary medical condition (27%, n=61). Those who were eligible but did not participate in the trial (5 out of 95) were similar in age, race and ethnicity, and HIV-status to those who were randomized(data not shown).

Participant characteristics were similar in both arms(Table 1), although there were more HIV-positive participants randomized to aripiprazole compared to placebo (19 vs. 26; P = 0.04). Among HIV-positive participants, mean CD4 count at baseline was 599cells/μl for the aripiprazole arm and 394 cells/μl for the placebo arm ($P \leq 0.01$). Among all participants, 69% (n=71) reported using methamphetamine three to seven days weekly; 30% (n=27) used methamphetamine during sex more than 50% of the time.

Study retention and adherence

Seventy-five participants (83%) completed the trial; there were no significant differences by arm (aripiprazole 78%[n=35], placebo 89%[n=40]; $P \geq 0.99$). Seven participants dropped out after randomization(one participant was last seen at the enrollment visit, three at week one visit, and one each at weeks 3, 4, and 9). Eight additional participants came for their final visit 21–128 days past their expected final visit, outside of the maximum allowable window, and were not included in the primary analysis. Of monthly follow-up visits, 91% (329 out of 360) were completed (aripiprazole 87%[156 visits], placebo 95%[171 visits]; $P=0.59$). The mean number of urine samples collected was 9.8 (SD=3.3) overall (aripiprazole 9.1 [SD = 3.9], placebo 10.4 [SD = 2.5]; $P=0.22$); Figure 2 shows the numbers of participants in each group providing urine samples by week. Ninety-one percent of ACASI surveys(329 out of 360)were completed (aripiprazole 87%[156 surveys], placebo 95%[171 surveys]; $P=0.59$). Seventy-eight percent of weekly substance use counseling sessions (839 out of 1080) were completed (aripiprazole76%[408 sessions], placebo 80%[431]; $P=0.11$).

At study completion, participants were asked to guess their treatment assignment. There was no evidence of unblinding: 17 (53%) in the aripiprazole arm and 15 (47%) in the placebo arm guessed correctly ($P=0.36$).

Outcomes

Methamphetamine use—During screening, the median number of methamphetamine metabolite-positive urines among enrollees was 3 (IQR: 2–3). At baseline, 74% of participants(n=67)had methamphetamine metabolite positive urines (34 [77%] aripiprazole, 33 [73%] placebo; $P=0.81$). The proportion of positive urines at follow-up visits decreased in both groups; the aripiprazole arm had a 43% reduction in positive urines from baseline to final visit; the placebo arm had a 38% reduction (Figure 2). In the intention-to-treat GEE analysis, the risk of testing positive for methamphetamine was similar in the aripiprazole arm compared to the placebo arm (RR 0.88, 95% CI 0.66–1.19, $P=0.41$); see Table 2 for numerical results and Figure 2 for fitted trends.

There was no significant effect observed in favor of aripiprazole in sensitivity analyses after including week 1 urine results (RR 0.87,95% CI 0.66–1.16; *P*=0.34); imputing of positive results for missing urines (RR 1.00,95% CI 0.77–1.3; *P*=0.99); adjusting for imbalanced baseline HIV-status (RR 0.85, 95% CI 0.63–1.15; *P*=0.29);controlling for baseline correlates of missing or positive urines (*P*>0.05); or including final visit data from participants who completed their visit beyond the pre-specified cut-off date allowable (RR 0.88, 95% CI 0.66–1.18; *P*=0.40). There was no significant effect stratifying by intensity of methamphetamine use at baseline; effect of treatment over time had a p-value of 0.7 and 0.3 for light users and heavy users, respectively. In checking the assumptions of the model for urine positivity, we found no persuasive evidence for departures from linear trend over the 12 weeks (p=0.23). In the as-treated analysis, the expected effect of treatment on methamphetamine-urine positivity for every 100mg increase in cumulative dose was not significantly different in the aripiprazole versus the placebo group (RR 0.97, 95% CI 0.93–1.01, *P*=0.19). The effect of every 20 mg increase in past week dose on weekly methamphetamine-urine positivity was not significantly different in the aripiprazole versus the placebo group (RR 1.04, 95% CI 0.99–1.08, *P*=0.12). Post randomization, six participants revealed they had been taking psychiatric medications or had a psychotic disorder that would have excluded them from the trial. At unblinding, two were found to be randomized to the aripiprazole arm and four were randomized to placebo (P=0.677). Omitting these six participants from the efficacy analysis did not change the effect estimates of aripiprazole (RR 0.91, 95% CI 0.67–1.23 *P*=0.55). The placebo urine positivity rate (observed 73%; expected 70–90%)and missing urine sample rates(observed 17%; expected 17%)were within the parameters assumed in the sample size calculation, although the within-subject correlation of urines (observed 45%;expected 50–90%) was lower than assumed. Using observed parameters, the updated minimum detectable net percent reduction in urine positivity is at the upper range of *a priori* estimates.

The mean number of consecutive weeks of continued abstinence from methamphetamine (NOBWOS) was 1.2 (SD=2.84), with no significant difference in median NOBWOS by arm (aripiprazole 0 [IQR=0–0]; placebo 0 [IQR=0–1]; *P=0.16*). The maximum number of consecutive weeks of continued abstinence was 8 weeks in the aripiprazole arm (observed in 1 participant) and 11 weeks in the placebo arm (observed in 4 participants). At the end of the trial, twenty participants (25%) achieved abstinence (8 in aripiprazole [18%]; 15 in placebo [33%]; *P*=0.15; see Figure 3).

Changes in methamphetamine craving and severity of dependence—At baseline, mean meth-craving score by visual analog scale (VAS) was 46(SD = 29) overall (aripiprazole 45.4 [SD = 28.4] placebo 46.7 [SD = 30]. At the 12-week visit, mean score in the aripiprazole arm was 31.6; in the placebo arm, 28.5. Mean meth-craving scores decreased 14.8 points overall (95% CI 7.3–22.3; *P*≤0.01), but the difference between arms over follow-up was not significant (6.8 points, 95% CI −8.2 to 21.8; *P*=0.38). Baseline mean severity of dependence score (SDS) was 6.2 (SD = 3.2) overall (aripiprazole 6.4 [SD = 3.1], placebo 6.0 [SD = 3.3]). Mean SDS decreased 1.9 points overall (95% CI 1.04–2.7; *P*≤0.01), but the difference between arms over follow-up was not significant (0.04 points; 95% CI −1.7 −1.63; *P*=0.96).

Sexual risk behavior—After controlling for imbalanced baseline characteristics, sexual risk behaviors declined similarly in the aripiprazole and placebo arms (Table 3). We did find a larger reduction in unprotected receptive vaginal or anal sex in the aripiprazole arm, but in the presence of substantial baseline imbalance.

Adherence—MEMS-monitored adherence was 42% (46% aripiprazole, 39% placebo; *P*=0.31); self-reported adherence was 74% (69% aripiprazole, 79% placebo; *P*=0.17).

Common reasons for non-adherence at final visit included 'simply forgot' (n=31 [41 %]), 'away from home' (n=29 [39%]), 'busy with other things' (n=29 [39%]), 'high on meth' (n=25 [34%]), and 'wanted to avoid side effects' (n=21 [29%]). Seventeen participants(38%)in the placebo arm and twenty-five (56%) in aripiprazole arm had at least a week-long medication discontinuation prior to study completion(P=0.139). Time to the first week-long medication discontinuation did not differ by arm in the log-rank test (P=0.14).

Safety

There were no differences overall in frequency of adverse events between treatment arms (P≥0.99). Six participants experienced the following serious adverse events, none of which were deemed related to study drug: rhabdomyolysis, subdural hematoma, metastatic cancer, abscess (2 participants), pneumonia, and cellulitis. The most common adverse events reported in both arms were: akathisia (12 [27%] in aripiprazole, 2 [4%] in placebo; P=0.01);increased alanine aminotransferase(8 [18%] participants in aripiprazole, 7 [16%] in placebo; P≥0.99);increased aspartate aminotransferase(6[13%] in aripiprazole, 4[9%] in placebo, P=0.74); upper respiratory infection (6[13%] in aripiprazole, 4[9%] in placebo, P=0.74); skin and soft tissue infection (3[7%] in aripiprazole, 5[11%] in placebo; P=0.71); hyperglycemia (2 [4%] in aripiprazole, 6[13%] in placebo; P=0.27); and toothache(3 [7%] in aripiprazole, 4[9%] in placebo; P≥0.99). Side-effects reported exclusively in the aripiprazole arm included fatigue (8 participants [18%]; P=0.01) and drowsiness (6participants [13%]; P=0.03). Restlessness, another known side-effect of aripiprazole, was observed among 5 participants (4 [9%] in aripiprazole 1 [2%] in placebo). Overall, 17 (19%) participants reduced or stopped study drug due to side effects(14 [31%] in aripiprazole, 3 [7%] in placebo; P≤0.01). Eleven participants on aripiprazole (24%)reduced or stopped study drug due to akathisia, drowsiness or restlessness.

DISCUSSION

Aripiprazole did not reduce methamphetamine use more than placebo among actively using adults who also received weekly substance use counseling. Although adherence was low, MEMS cap and self-reported rates were similar between study arms, similar to our recent trial of mirtazapine that showed a robust effect on methamphetamine use,(38)and consistent with(39)or well above(40)the rates of other clinical trials with methamphetamine users. Moreover, the study had very high visit completion and retention rates, factors which often limit the interpretation of results in pharmacologic trials among substance-using populations. (5)Despite multiple adjustments for possible confounders, our efficacy estimates from the intention-to-treat analysis were essentially unchanged. We also conducted multiple analyses to determine if cumulative exposure to aripiprazole was associated with reduced methamphetamine use, but consistently found no effect. Notwithstanding promising pre-clinical results suggesting that aripiprazole might be effective at decreasing craving for methamphetamine and reducing its rewarding properties, we found no effect of this medication on methamphetamine use, severity of dependence, or craving. We also did not find evidence that aripiprazole was associated with increased methamphetamine use or reward, as suggested by some investigators.(41, 42)These findings are consistent with a recent randomized trial of aripiprazole for psychosis in methamphetamine-dependent patients that found no effect on methamphetamine use.(43)Aripiprazole targets a single neurobiologic pathway in the effects of methamphetamine, whereas the long term neurobiologic adaptations of drug dependence may recruit additional pathways(44); it may be necessary to address multiple pathways concurrently to reduce compulsive methamphetamine use.

As with methamphetamine use, sexual risk behaviors declined during the study similarly in both arms. Episodes of receptive, unprotected anal or vaginal intercourse with a sero-

discordant partner decreased more in the aripiprazole arm, although the high rate of this behavior initially and immediate decline among the aripiprazole recipients, as well as the isolated nature of this finding, reduce our confidence in this as a true effect of aripiprazole.

Notwithstanding high participation and retention rates, this study had limitations. The sample size was modest, so that we cannot rule out benefits on methamphetamine use as large as 34%, or adverse effects of 19%. Nonetheless, we interpret the consistently negative results as suggesting that aripiprazole is unlikely to have clinically significant effects on methamphetamine use. Adherence was limited, yet similar or superior to many trials in this population(27, 39, 40)and probably within range of real-world expectations. We also didn't evaluate the impact of aripiprazole on the quality of a methamphetamine high, an effect that might be important for individuals trying to avoid relapse to methamphetamine use. Because our study was limited to the San Francisco area, findings may not be generalizable to other methamphetamine-dependent populations. Finally, this study was of insufficient duration to determine any impact on long-term morbidity and mortality.

In summary, we found no evidence that aripiprazole is more effective than placebo at reducing methamphetamine use among actively-using, dependent adults. Future efforts to identify pharmacologic treatments for methamphetamine dependence may need to consider agents modifying multiple neurobiologic pathways concurrently.

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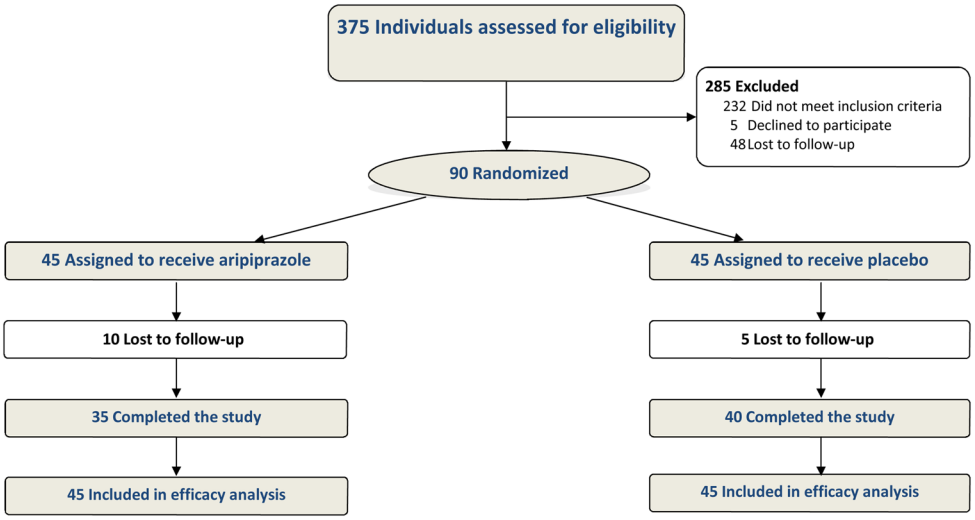

Figure 1.
Enrollment and Retention by treatment arm

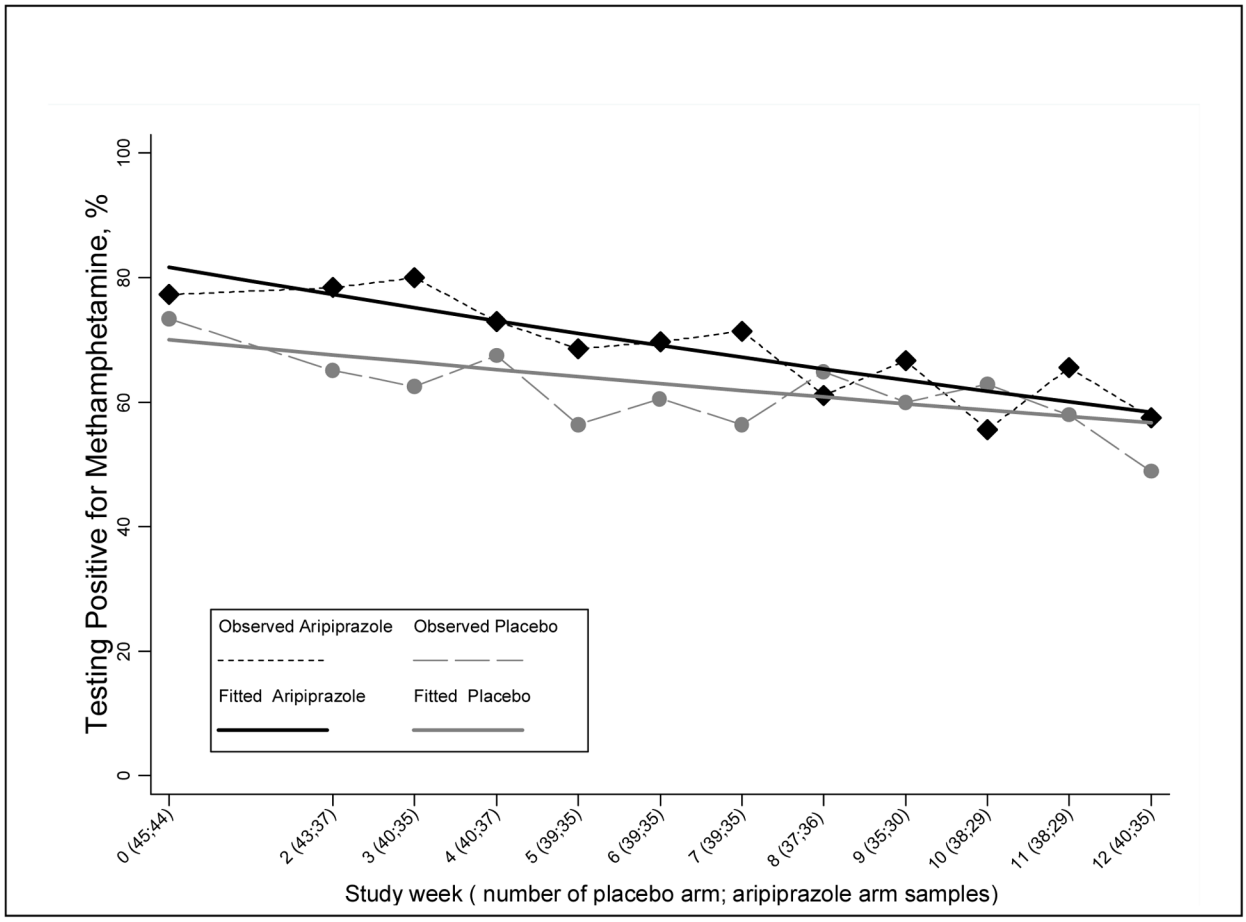

Figure 2.
Weekly Urine Positivity by treatment arm

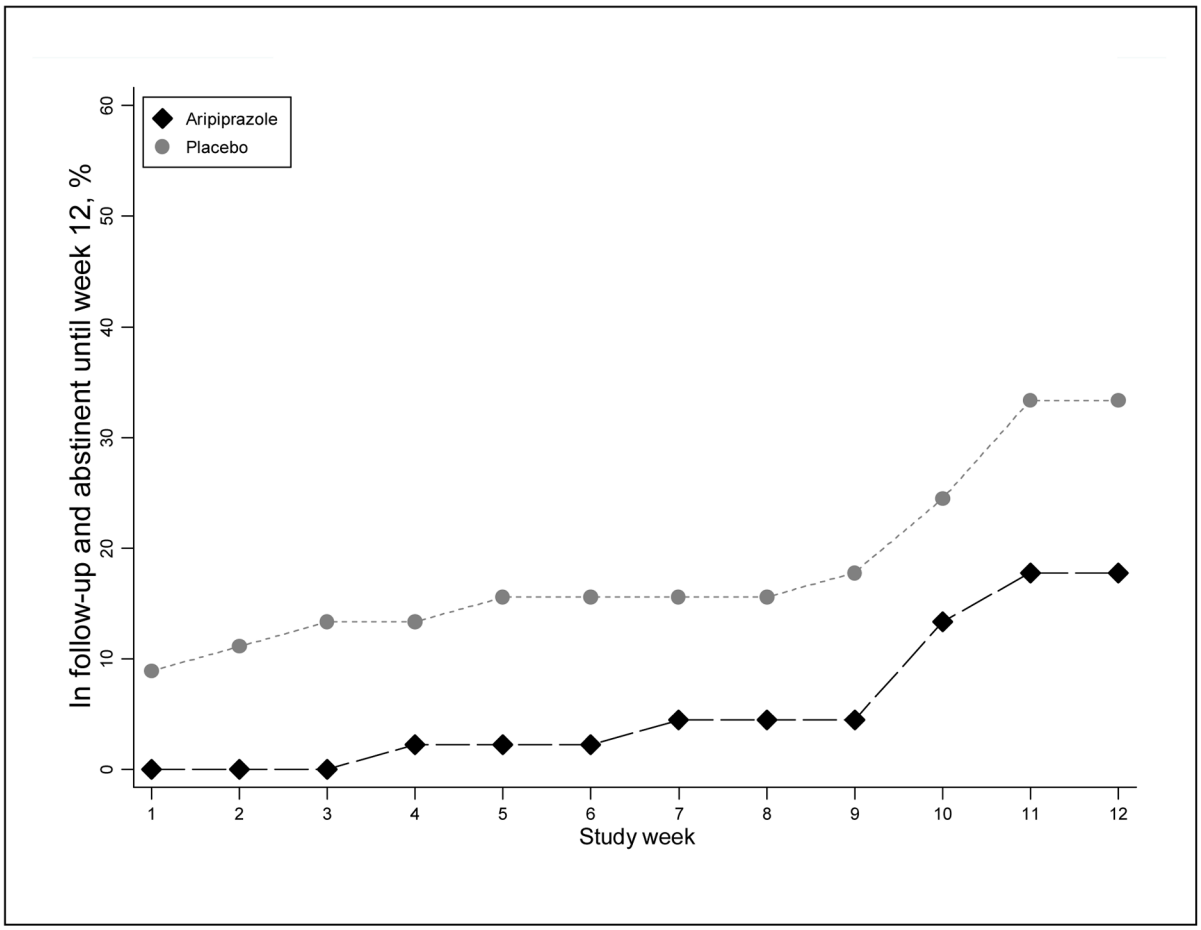

Figure 3.
Abstinence rates by week by treatment arm

Table 1

Baseline Characteristics of Trial Participants

Demographics	**Placebo No. (%)(n=45)**	**Aripiprazole No. (%)(n=45)**	**Overall No. (%)(n=90)**	***P* value‡**
Age, mean (SD), y Gender	40 (8.9)	37.4 (12.3)	38.7 (10.8)	0.39
Female	5 (11.1)	6 (13.3)	11 (12.2)	≥0.99
Male	40 (88.9)	39 (86.7)	79 (87.8)	
Race/Ethnicity				
White	22 (48.9)	23 (51.1)	45 (50.0)	0.70
African-American	9 (20.0)	8 (17.8)	17 (18.9)	
Latino	6 (13.3)	9 (20.0)	15 (16.7)	
Other	8 (17.8)	5 (11.1)	13 (14.4)	
Education				
High school or less	17 (37.8)	23 (51.1)	40 (44.4)	0.46
Some college	20 (44.4)	16 (35.6)	36 (40.0)	
College or above	8 (17.8)	6 (13.3)	14 (15.6)	
Income				
under $20,000	35 (77.8)	29 (64.4)	64 (71.1)	0.32
$20,000–39,999	6 (13.3)	12 (26.7)	18 (20.0)	
$40,000 and above	4 (8.9)	4 (8.9)	8 (8.9)	
Employment status				
Not employed	33 (73.3)	34 (75.6)	67 (74.4)	≥0.99
Part-time	4 (8.9)	3 (6.7)	7 (7.8)	
Full-time	7 (15.6)	6 (13.3)	13 (14.4)	
Employed student	1 (2.2)	2 (4.4)	3 (3.3)	
Reasons for participating in trial				
Wanted to try medication	13 (28.9)	13 (28.9)	26 (28.9)	≥0.99
Wanted counseling services	17 (37.8)	22 (48.9)	39 (43.3)	0.40
Wanted to stop methamphetamine use	32 (71.1)	35 (77.8)	67 (74.4)	0.63
Wanted to reduce methamphetamine use	17 (37.8)	16 (35.6)	33 (36.7)	≥0.99
Methamphetamine Use				
Frequency of methamphetamine use (past 4 weeks)				
2 days or less per week	16 (35.6)	12 (26.7)	28 (31.1)	0.54
3–6 days per week	19 (42.2)	24 (53.3)	43 (47.8)	
Daily	10 (22.2)	9 (20.0)	19 (21.1)	
Methamphetamine use during sex (past 4 weeks)				
50% or less of the time	34 (75.6)	29 (64.4)	63 (70.0)	0.36
Greater than 50% of time	11 (24.4)	16 (35.6)	27 (30.0)	
Route of methamphetamine administration				
Injection	21 (46.7)	19 (42.2)	40 (44.4)	0.83
Inserted rectally	5 (11.1)	6 (13.3)	11 (12.2)	≥0.99
Snorted	19 (42.2)	12 (26.7)	31 (34.4)	0.18

Demographics	**Placebo No. (%)(n=45)**	**Aripiprazole No. (%)(n=45)**	**Overall No. (%)(n=90)**	***P* value‡**
Smoked	33 (73.3)	35 (77.8)	68 (75.6)	0.81
Ingested orally	6 (13.3)	9 (20.0)	15 (16.7)	0.57
Methamphetamine severity of dependence scale (SDS) score, mean (SD)	6 (3.3)	6.4 (3.1)	6.2 (3.2)	0.88
Methamphetamine visual analog scale (VAS) craving score, mean (SD)	46.7 (30.0)	45.4 (28.4)	46 (29.0)	0.36
History of methamphetamine self-help or treatment program	19 (42.2)	21 (46.7)	40 (44.4)	0.83
Clinical				
HIV serostatus				
HIV positive	9 (20.0)	19 (42.2)	28 (31.1)	0.04
HIV negative	36 (80.0)	26 (57.8)	62 (68.9)	
Has regular health care provider	24 (53.3)	29 (64.4)	53 (58.9)	0.39
Has health insurance	19 (42.2)	21 (46.7)	40 (44.4)	0.83
Center for epidemiologic studies depression scale (CES-D) score, mean (SD)	16.7 (10.6)	17.5 (11.1)	17.1 (10.8)	0.89

‡ binary and categorical characteristics compared using the Fisher exact test, and group means compared using the Wilcoxon rank sum test

Table 2

Primary and Secondary outcomes and Sensitivity Analyses

Primary Outcome: Methamphetamine Urine Positivity			**N**	**Risk Ratio (RR)**	**95% CI**	**P-value**
	Primary analysis, omitting week 1 results		90	0.88	0.66–1.19	0.41
Intention-to- treat analyses	Sensitivity Analyses	Inclusion of week 1 results	90	0.87	0.66–1.16	0.34
		Imputing of positive results from missing urines	90	1.00	0.77–1.30	0.99
		Adjusting for imbalanced baseline HIV- status	90	0.85	0.63–1.15	0.29
		Including final visit data from participants who completed last visit beyond allowable window	90	0.88	0.66–1.18	0.40
		Omission of participants deemed ineligible post-randomization	84	0.91	0.67–1.23	0.55
As-treated analyses	Effect of 100mg increase in cumulative study drug dose		90	0.97	0.93–1.01	0.19
	Effect of 20mg increase in past week study drug dose		90	1.04	0.99–1.08	0.12
Secondary Outcomes			N	Coefficient	95% CI	P-value
Methamphetamine craving (Visual Analog Scale)			90	6.8	−8.2–21.8	0.38
Severity of Dependence Scale for Methamphetamine			90	−0.04	−1.7–1.63	0.96
Depression (CES-D)			90	1.47	−2.82–5.76	0.50
Between Group Comparisons of Other Secondary Outcomes						
				Placebo	Aripiprazole	P-value
MEMS Percent Adherence, mean (SD)				39 (27)	46 (32)	0.31
Self-reported Percent Adherence, mean (SD)				79 (19)	69(28)	0.17
Number of beyond-threshold weeks (NOBWOS), median (IQR)				0 (0–1)	0 (0–0)	0.16

Table 3

Changes in Sexual Risk Behavior by Treatment Arm

	mean						
	Baseline	**4-wk visit**	**8-wk visit**	**12-wk visit**	**Risk Ratio†**	**95% CI**	***P* value**
Number of partners with whom meth was used							
Placebo	2.8	1.4	1.4	2			
Aripiprazole	4.2	3.5	2.7	2	0.38	(0.07 – 2.01)	0.254
Number of sexual partners							
Placebo	5.6	2.7	2.8	3.4			
Aripiprazole	5.7	4.7	4.9	2.7	0.69	(0.28 – 1.7)	0.418
Episodes of anal and/or vaginal sex with sero- discordant partners							
Placebo	2.8	1.2	1.3	1.2			
Aripiprazole	3.9	3	1.8	1.7	0.42	(0.12 – 1.53)	0.190
Episodes of unprotected anal and/or vaginal sex with sero-discordant partners							
Placebo	2.1	0.9	1.1	1			
Aripiprazole	2.3	0.5	1.7	1.7	0.61	(0.09 – 4.2)	0.612
Episodes of insertive unprotected anal sex with sero-discordant partners							
Placebo	1.9	0.7	0.7	0.6			
Aripiprazole	3.6	2.8	0.9	1.5	0.54	(0.13 – 2.17)	0.385
Episodes of receptive unprotected anal and/or vaginal sex with sero-discordant partners							
Placebo	0.2	0.2	0.4	0.4			
Aripiprazole	2	0.2	0.3	0.2	0.02	(0.002 – 0.36)	0.007

Note: Sexual behaviors are self-reported activity within past 4 weeks. Sero-discordant partner is defined as HIV-positive person with HIV-negative or unknown HIV-status partner, or HIV-negative person with HIV-positive or unknown HIV-status partner. Point estimates were adjusted for HIV status and its interaction with time to control for imbalance at baseline.