Evaluation of subjective effects of aripiprazole and methamphetamine in methamphetamine-dependent volunteers

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Abstract
A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for methamphetamine (Meth) addiction. In this study, we investigated the safety and potential efficacy of aripiprazole, an antipsychotic agent acting on both dopamine and serotonin systems. We conducted a double-blind in-patient clinical pharmacology study to assess potential interactions between intravenous (i.v.) Meth (15 mg and 30 mg) and oral aripiprazole (15 mg). In addition, the effects of aripiprazole treatment on abstinence-related craving and cue-induced craving were evaluated. Participants included non-treatment-seeking, Meth-dependent patients (n = 16), aged 18–45 yr, currently using Meth. Following baseline Meth dosing (15 mg and 30 mg), participants received 2 wk treatment with aripiprazole (n = 8) or placebo (n = 8). Participants then completed cue exposure sessions using neutral and Meth-related cues. Meth dosing (15 mg and 30 mg) was then repeated. Aripiprazole treatment had no effect on cue-induced Meth craving, or on daily baseline craving assessed over the course of medication treatment, although aripiprazole treatment was associated with increased craving independent of Meth dosing. Aripiprazole treatment was associated with significantly higher ratings on Addiction Research Center Inventory (ARCI) subscales reflecting euphoria and amphetamine-like effects following Meth dosing. Aripiprazole treatment was also associated with significant reductions in ratings of ‘bad effects’ and reductions on the ARCI subscale for sedation effects following Meth dosing. Aripiprazole treatment reduced the increase in systolic blood pressure following Meth dosing, but had no other effects on cardiovascular responses to Meth. Aripiprazole treatment did not alter the pharmacokinetics of Meth. These findings indicate that aripiprazole treatment appears to be safe in volunteers with Meth dependence, although the finding that aripiprazole increased some of the rewarding and stimulatory effects produced by acute Meth suggests that 15 mg aripiprazole is unlikely to be efficacious for the treatment of Meth dependence. Further research with lower doses of aripiprazole, possibly using study designs aimed at evaluating efficacy for relapse prevention, are needed before ruling out aripiprazole as a treatment for Meth dependence.

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Introduction
In 2006 it was estimated that 4.5% of Americans used methamphetamine (Meth) at some point in their lives, that 1.3 million used Meth in the previous year, and that more than 512,000 used Meth in the previous month (SAMHSA, 2006). In some regions of the country, Meth is the most commonly abused illegal drug and Meth abuse poses a major criminal justice concern.

Currently available treatments for Meth dependence are marginally effective, at best. In a recent study evaluating optimal behavioural treatments (a combination of contingency management and cognitive
behavioural therapy), abstinence from Meth could be documented on 60% of study visits (Rawson et al., 2006). Other less-intensive commonly used treatments such as counselling are less effective (Rawson et al., 2004).

One way to improve the efficacy of available behavioural treatments is to employ adjunctive medication treatments. This approach has recently yielded some success for the development treatments for cocaine dependence (Carroll et al., 2004; Dackis et al., 2005). Although bupropion holds promise as an adjunctive medication for the treatment of Meth dependence (Elkashef et al., 2008), other more effective options are needed.

Meth dependence is associated with long-lasting neurobiological changes that may be relevant for selecting potential medication treatments. These include reductions in dopamine transporter (DAT) expression (Johanson et al., 2006; McCann et al., 1998; Sekine et al., 2001; Volkow et al., 2001b) and DA D<sub>2</sub> receptor binding availability (Volkow et al., 1993, 2001a). Preclinical and post-mortem human data are consistent with these findings and further suggest that chronic Meth exposure is associated with reduced DA levels in striatum (Wilson et al., 1996).

Medications that compensate for these neurobiological abnormalities are attractive candidates for evaluation as treatments for Meth dependence. We selected aripiprazole for evaluation as an adjunctive treatment based on its partial agonist activity at the DA D<sub>2</sub> receptor (Ozdemir et al., 2002). Partial agonists function as agonists under conditions of low neurotransmitter availability, but as antagonists under conditions of high neurotransmitter availability. In recently abstinent Meth users, DA availability is hypothesized to be low (Volkow et al., 1998), whereas Meth use greatly enhances synaptic DA concentrations. Thus aripiprazole is hypothesized to normalize the function of brain monoamine systems, yielding a range of possible beneficial impacts for Meth users.

Two previous studies of the effects of aripiprazole examined effects of aripiprazole on the discriminative stimulus and subjective effects produced by low doses of oral amphetamine in healthy volunteers (Lile et al., 2005; Stoops et al., 2006). Both found that aripiprazole significantly attenuated the discriminative stimulus and positive subjective effects produced by amphetamine, lending additional credence to the present study’s rationale.

We conducted this phase I randomized, double-blind, placebo-controlled in-patient study to assess the effects of Meth administration in acutely abstinent chronic Meth users during treatment with aripiprazole or placebo. We hypothesized that aripiprazole treatment would reduce the positive subjective effects of Meth. In addition, we hypothesized that aripiprazole treatment alone would be well tolerated and that aripiprazole treatment would not adversely exacerbate the cardiovascular effects of Meth.

Materials and methods

Subjects

Sixteen subjects completed the entire study (placebo, n = 8; aripiprazole, n = 8). The study was conducted at the University of California, Los Angeles (UCLA) and New York University (NYU). Participants were recruited through advertisements and were compensated for their time. All participants met DSM-IV-TR criteria for Meth dependence and were not seeking treatment at the time of screening or admission. Participants were aged between 18 yr and 45 yr, were in otherwise good health, and had normal physical examinations, EKGs, and clinical laboratory assessments. Exclusion criteria included history of asthma, pregnancy, and prior adverse reaction to Meth or aripiprazole, history of seizure disorder, head trauma, dependence on other drugs with the exception of nicotine, or other Axis I psychiatric disorder. Concomitant use of psychotropic medications or medications interacting with aripiprazole were not allowed. The institutional review boards at UCLA and NYU (medical school and main campus) approved the study. All participants gave informed consent after having the potential risks fully explained to them. The demographics of participants at the two sites were similar, although participants from the New York site tended to use Meth intermittently whereas those from the Los Angeles site were more frequent users.

Study design

The study employed a double-blind, placebo controlled, parallel group design. Following admission to the in-patient clinical research centre (CRC), participants received a series of three masked doses of i.v. Meth (placebo, 0 mg, 15 mg, and 30 mg, randomized with the constraint that the 15-mg dose preceded the 30-mg dose) for an initial safety and baseline response evaluation. The Meth doses were separated by 2 d. Participants were then randomized to receive oral aripiprazole (15 mg) or placebo once daily at 07:30 hours. Following 10 d treatment, participants received a second series of three doses of Meth and placebo on days 10, 12 and 15 of aripiprazole treatment following...
a similar constrained randomization schedule to evaluate the effects of Meth during treatment with aripiprazole/placebo. Subjects not completing all study activities were replaced.

Drugs

Aripiprazole tablets were encapsulated in gelatin capsules by research pharmacies at each site. Placebo was prepared similarly. The 15-mg dose was selected because this dose has been shown to be well tolerated and effective for other neuropsychiatric disorders (e.g. bipolar disorder and schizophrenia), and was the effective dose used by Rush and colleagues (Lile et al., 2005; Stoops et al., 2006). A NIDA contractor provided sterile Meth solution for human use and an equal volume of sterile saline solution was used as the placebo. The doses selected for study (15 mg and 30 mg) were chosen based on prior research in our laboratories showing they are safe to administer to Meth-dependent volunteers and because they produced significant elevations in positive subjective effects (Newton et al., 2005, 2006a, b). Meth and saline were provided from the pharmacy in indistinguishable syringes to maintain the blind. Both were dosed using a syringe pump over 2 min. This study was performed under an investigational new drug application (IND) from the Food and Drug Administration (FDA). Meth was administered intravenously over 2 min using a syringe pump with a physician in attendance. Heart rate (HR) and blood pressure (BP) were monitored frequently to ensure safety.

Acute Meth testing procedures

Subjective effects data were collected using computerized visual analogue rating scales (VAS) and the Addiction Research Center Inventory (ARCI; Haertzen, 1965, 1966). VAS data were collected 15 min before and 3, 6, 10, 15, 30, 45, 60, 90, 180, 210, 240, 300, 360, 420, and 480 min following each Meth injection. VAS ratings were obtained for ‘high’, ‘any drug effect’, ‘desire for methamphetamine’, ‘stimulated’, ‘depressed’, ‘anxious’, ‘good effects’, ‘bad effects’, ‘like methamphetamine’, and ‘likely to use’ on a continuous scale digitized between 0 and 100. The ARCI was administered prior to and 30 min following each injection of Meth or saline. The Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) was completed 60 min following each Meth or saline injection. Plasma samples for Meth pharmacokinetic (PK) analyses were collected at −5, 5, 15, 30, 60, 90, 120, 240, 360, 480 min and 12, 20, 24, 36 and 48 h after infusion and analysed using validated methods including liquid chromatography with either electrospray ionization and atmospheric pressure chemical ionization and tandem mass spectrometry (Meth quantitation limit = 2.0 ng/ml). Craving and mood symptoms were monitored throughout the screening and medication treatment periods using the Brief Substance Craving Scale (BSCS; Elkashef et al., 2005), the Beck Depression Inventory (BDI; Beck et al., 1996), the Brief Symptom Inventory (BSI; Derogatis, 1982), and the Profile of Mood States (POMS; McNair et al., 1992). Akathisia, a potential side-effect of aripiprazole, was assessed using the Barnes rating scale (Barnes, 1989).

On day 1, prior to receiving the first dose of treatment medication, and again on day 9 of treatment, cue-induced craving for Meth was assessed. Before and after cue presentation, subjective effects were measured using a VAS including items: ‘desire for methamphetamine’, ‘depressed’, ‘anxious’, ‘stimulated’, ‘likely to use methamphetamine’, and ‘methamphetamine-like effect’. In addition, all subjects completed the BSCS to further characterize craving. The cue procedures were performed between 11:00 and 13:00 hours. Each cue procedure started with baseline VAS and BSCS assessments (−10 min) followed by a 10 min relaxation period with baseline HR and BP recordings. Cue presentation included 5 min of Meth paraphernalia viewing and handling followed by 10 min of video viewing. The Meth paraphernalia included pipe stems, a lighter, and a small plastic bag containing white powder designed to simulate Meth crystals. Participants handled and inspected these items for 5 min after which they viewed a 10-min-long video segment of actors appearing to use Meth (by three distinct routes of administration: smoking, snorting and intravenous administration). The neutral cues consisted of pine cones, shells and rocks that were handled and inspected for 5 min followed by viewing a 10-min-long video segment of an aquarium and items found in nature. The VAS measures were assessed immediately after completion of the cue procedures and again 10 min later. BP and HR were assessed in 5-min intervals (−10 to 30 min) before, during, and after cue presentation. There was a 20-min rest period between the neutral and Meth cue sessions, which were conducted in random order.

Data analysis

For each subject and dose of Meth, a repeated-measures model was constructed to determine the effect of medication treatment on maximum change and the maximum change × Meth dose interaction.
Then, analyses were performed separately for each Meth dose level and the least square mean for the maximum change was calculated using ANOVA models. Statistics from models analysing each Meth dose level are reported, with the significance level set at $p < 0.05$. The ARCI, BDI, BSI, and Barnes Akathisia data were analysed using statistical models including terms for pre-dose rating and treatment. For plasma Meth PK analyses, $C_{\text{max}}$ and $T_{\text{max}}$ were calculated by computerized WinNonlin algorithm (Pharsight Corporation, Mt View, CA, USA), and area under the curve (AUC) was calculated using a linear trapezoidal rule up to the $C_{\text{max}}$ time-point and a logarithmic trapezoidal rule thereafter.

Results

Demographics

Completing participants included 16 Meth-dependent volunteers. Their gender, age, and preferred route of Meth administration are shown in Table 1. Participants in aripiprazole vs. placebo groups did not differ significantly along any of the demographic variable, although there was a trend for greater days of Meth use in the aripiprazole-treated group.

<table>
<thead>
<tr>
<th></th>
<th>Aripiprazole ($n=8$)</th>
<th>Placebo ($n=8$)</th>
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<tbody>
<tr>
<td>Gender (n)</td>
<td></td>
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<tr>
<td>Male</td>
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<td>Ethnicity* (n)</td>
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<tr>
<td>African American</td>
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<td>2</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>32.5 ± 6.4</td>
<td>28.3 ± 7.9</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>14.6 ± 1.8</td>
<td>14.6 ± 1.8</td>
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<tr>
<td>ASI drug</td>
<td>0.15 ± 0.07</td>
<td>0.076 ± 0.08</td>
</tr>
<tr>
<td>BDI</td>
<td>11.3 ± 10.9</td>
<td>8.8 ± 7.5</td>
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<tr>
<td>POMS</td>
<td>47.1 ± 44.7</td>
<td>23.0 ± 21.7</td>
</tr>
<tr>
<td>Days of Meth use in last 30 d</td>
<td>20.4 ± 9.4</td>
<td>10.3 ± 9.9$^b$</td>
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ASI, Addiction Severity Index; BDI, Beck Depression Inventory; POMS, Profile of Mood States.
Values (± s.d.).
* Some participants reported more than one race category and this accounts for the extra numbers shown.
$^b p < 0.06.$

Meth treatment

Physician-completed BPRS ratings indicated that Meth treatment was not associated with the development of psychotic symptoms. The BPRS scores prior to and following randomization are shown in Table 2. There were no differences between the placebo- and

<table>
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<th>Aripiprazole ($n=8$)</th>
<th>Placebo ($n=8$)</th>
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<tbody>
<tr>
<td>BPRS total score</td>
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<tr>
<td>Pre-randomization saline</td>
<td>27.5 (7.93)</td>
<td>28.6 (9.24)</td>
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<tr>
<td>Pre-randomization Meth (30 mg)</td>
<td>27.0 (2.51)</td>
<td>26.9 (4.41)</td>
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<tr>
<td>Post-randomization saline</td>
<td>24.9 (1.13)</td>
<td>25.8 (1.91)</td>
</tr>
<tr>
<td>Post-randomization Meth (30 mg)</td>
<td>27.5 (2.14)$^a$</td>
<td>27.9 (2.02)$^b$</td>
</tr>
</tbody>
</table>

BPRS, Brief Psychiatric Rating Scale.
Values (± s.d.).
$^a$ Differences between saline and Meth were greater in the aripiprazole-treated group ($p < 0.01$).
$^b$ Differences between saline and Meth tended to be greater in the placebo-treated group ($p = 0.051$).

Aripiprazole treatment

Mean ratings on the Barnes Akathisia scale on day 12 of treatment were (values in parentheses indicate standard deviation) 0.0 (± 0.0) for the placebo-treated group and 1.6 (± 2.61) for the aripiprazole treated group ($p=n.s.$). None of the placebo-treated participants had akathisia symptoms at any time during the study, whereas two of the aripiprazole-treated participants had symptoms of akathisia.

Depression, mood and psychiatric symptoms, indexed by the BDI, POMS and BSI, did not differ between the groups at baseline (Table 1) and there were no significant effects of aripiprazole treatment on subsequent measures. The mean BDI score after 10–14 d of treatment was 4.88 (± 3.83) in the placebo-treated group and 11.0 (± 8.40) in the aripiprazole-treated group ($t = 1.875, p = 0.08$). The mean BSI score after 10–14 d of treatment in the placebo-treated group was 17.4 (± 11.0) and 21.9 (± 29.3) in the aripiprazole-treated group ($p = n.s.$). POMS total score, as well as subscores for tension, anger, depression, fatigue, vigour, and confusion also did not differ between the groups (data not shown).
was slightly greater following randomization to study medication (aripiprazole/placebo) for both groups ($p = 0.051$ for the placebo-treated group and $p < 0.01$ for the aripiprazole-treated group).

Meth administration produced substantial increases in ratings of ‘high’, ‘any drug effect’, ‘desire for methamphetamine’, and ‘stimulated’ (Figure 1a–d). Overall, the group receiving aripiprazole appeared to exhibit enhanced Meth-induced positive subjective effects, although differences between the groups did not reach statistical significance for any of these positive affect measures. For ratings of ‘desire for methamphetamine’ there was a significant main effect of treatment ($p < 0.05$) but no treatment by Meth dose interaction, indicating that across all doses of Meth (including saline) aripiprazole treatment tended to increase ratings of ‘desire’. Aripiprazole treatment was also associated with a small but statistically significant reduction in ‘bad effects’ ratings (data not shown, $p < 0.05$).

Ratings on selected ARCI subscales at each dose of Meth are shown in Figure 2(a–c). Aripiprazole treatment was associated significant reductions in ratings on the pentobarbital, chlorpromazine, alcohol group (PCAG) subscale reflecting sedation effects ($p < 0.02$), increases in ratings on the morphine-benzedrine group (MBG) subscale reflecting euphoria ($p < 0.002$), and a trend towards increases in ratings on the amphetamine (A) subscale reflecting stimulation ($p < 0.10$).

**HR, BP and Meth pharmacokinetics**

Meth (30 mg) increased diastolic BP (mmHg) to a similar degree after treatment with placebo (24 ± 8) compared to aripiprazole (22 ± 5) ($p = n.s.$). Similarly,
Meth (30 mg) increased HR (bpm) to a similar extent during treatment with placebo (29 ± 12) vs. aripiprazole (27 ± 6) (p = n.s.). However, Meth (30 mg) increased systolic BP to a lesser degree after treatment with aripiprazole (29 ± 6) compared to placebo (43 ± 11) (p < 0.05). There were no statistically significant differences between treatment groups in the Meth PK parameters for Cmax, Tmax, and AUC.

Daily and cue-induced Meth craving

Craving assessments with the BSCS indicated a moderate level of craving (approximate range: 3–6 points out a maximum of 12) among study participants, which remained stable across the duration of their inpatient hospitalization (25 d). Analysis of the craving ratings during medication treatment revealed no significant effect of aripiprazole.

Exposure to Meth cues induced moderate increases in craving. Analyses of testing on day 9 following randomization to study medication (aripiprazole/placebo) revealed no significant effects of medication treatment on cue-induced Meth craving. Analysis revealed main effects of treatment on VAS measures ‘anxious’ (p < 0.01), ‘nervous’ (p < 0.1) and ‘irritable’ (p < 0.05), which were higher in the group receiving aripiprazole both pre- and post-cue exposure. There was no effect of aripiprazole treatment, or cue exposure, or on HR or BP.

Adverse events (AEs)

Most participants had at least one AE following randomization to study medication (aripiprazole/placebo). Six out of eight placebo-treated participants had at least one AE and 7/8 aripiprazole-treated participants had at least one such AE (p = n.s.). One participant in the placebo-treated group had an AE rated as ‘severe’ as did two participants in the aripiprazole-treated group (p = n.s.). The most common AEs following randomization to study medication occurring in at least three participants were fatigue (n = 3), psychiatric disorders (anxiety, n = 7; disturbance in attention, n = 3; restlessness, n = 3), central nervous system disorders (headache, n = 8; insomnia, n = 7; tremor, n = 6) predominating and gastrointestinal disorders (diarrhoea, n = 3). These tended to be equally distributed between the treatment groups, except for tremor, which was greater in the aripiprazole-treated group (n = 4) compared to the placebo-treated group (n = 2) ($\chi^2 = 0.667$, d.f. = 1, p = n.s.) and restlessness, which was greater in the aripiprazole-treated group (n = 3) compared to the placebo-treated group (n = 0) ($\chi^2 = 3.00$, d.f. = 1, p = 0.083).
Discussion

Overall, aripiprazole treatment had only moderate effects on the subjective responses produced by Meth administration. Aripiprazole treatment was associated with statistically significant reductions in ratings of ‘bad effects’ and significantly higher ratings for ‘desire for methamphetamine’. Further examination of these data revealed that the magnitude of change in ratings of ‘bad effects’ was extremely small and not clinically significant. Ratings of ‘desire for methamphetamine’ were higher across all Meth treatment doses as well as prior to the infusion, and thus reflect group differences rather than craving induced by Meth or interactions between aripiprazole treatment and Meth dosing. The pre-existing differences between the groups in recent Meth use may also have contributed to these findings. Robust findings were seen using the ARCI, as aripiprazole treatment was associated with significant reductions in the PCAG subscale score and increases in the MBG and (at a trend level) A subscale scores. Recently, Haney and Spealman (2008) presented data showing that aripiprazole treatment increased cocaine self-administration in a human laboratory study. This is consistent with our finding that aripiprazole increased ratings on several measures of stimulant effects.

These findings suggest that aripiprazole is unlikely to be beneficial for the treatment of Meth dependence, and could possibly worsen outcomes. Indeed, a clinical trial was halted recently when it was discovered that participants receiving 15 mg aripiprazole were at least twice as likely to provide a positive amphetamine urine test than participants receiving placebo, indicating more frequent amphetamine use in the aripiprazole-treated group (Tiihonen et al., 2007). However, the dose of aripiprazole used in all stimulant studies to date was limited to 15 mg, indicating the need to test a broader range of doses.

The results obtained in this study diverge substantially from those obtained previously (Lile et al., 2005; Stoops et al., 2006). Both found that aripiprazole significantly attenuated the effects produced by amphetamine, a finding not replicated here. Several differences in the studies’ designs (e.g. drug, dose, dosing duration, and route of administration) may account for this discrepancy.

A number of findings from this study, both research and clinically oriented, suggest that aripiprazole treatment may be associated with moderately aversive side-effects in Meth-dependent patients. AE ratings, although not statistically significant, indicated that aripiprazole treatment was associated with more symptoms of akathisia, tremor and restlessness. Moreover, a main effect of treatment on the VAS measures ‘anxious’, ‘nervous’, and ‘irritable’ during the Meth cue tests revealed that subjects in the aripiprazole group were experiencing unpleasant psychological side-effects. Finally, Meth-induced increases in BPRS measures were more pronounced post-randomization in the aripiprazole group. The reasons for these effects are not clear, but might be due to lower DA D₂ receptor levels (Volkow et al., 1993, 2001a) or lower endogenous DA levels (Wilson et al., 1996) seen in heavy Meth abusers. Further studies on medication tolerability, including a broader aripiprazole dose range, could address this clinically important question.

The primary limitations of this study include a small sample size, the use of a single dose level of aripiprazole, and the omission of behavioural measures of reinforcing effects of Meth. The sample size (n = 8 for aripiprazole and placebo) precludes detection of any but statistically large effects. The earlier studies (Lile et al., 2005; Stoops et al., 2006) included a smaller number (n = 6), but they used a within-subjects design, which is statistically more powerful. The use of several dose levels of aripiprazole would have allowed determination of the dose-dependency of any observed effects of aripiprazole. There were baseline differences between the aripiprazole- and placebo-treated groups, with the aripiprazole-treated group using Meth on almost twice as many days as did the placebo-treated group. It is unlikely that this baseline difference accounted for the finding that aripiprazole treatment was associated in increases in stimulant-like effects following Meth dosing, as more frequent use would, if anything, probably be associated with greater tolerance to the stimulant effects of Meth. Finally, treatment medications are intended to reduce drug-taking behaviour rather than to modify subjective effects, so it would be preferable to include behavioural measures of reinforcement (i.e. drug self-administration or the multiple-choice procedure; Fischman and Schuster, 1982; Griffiths et al., 1993). These limitations aside, further research with lower doses of aripiprazole, possibly using study designs aimed at evaluating efficacy for relapse prevention, are needed before ruling out aripiprazole as a treatment for Meth dependence.

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Statement of Interest
None.

References


