HHS Public Access

Author manuscript

Behav Pharmacol. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Behav Pharmacol. 2017 February ; 28(1): 63–73. doi:10.1097/FBP.0000000000000268.

Aripiprazole for cocaine abstinence: a randomized controlled trial with ecological momentary assessment

Landhing M. Moran, PhD[1], **Karran A. Phillips, MD**[1], **William J. Kowalczyk, PhD**[1], **Udi E. Ghitza, PhD**[2], **Daniel A. Agage, MD**[1], **David H. Epstein, PhD**[1], and **Kenzie L. Preston, PhD**[1]

[1] National Institute on Drug Abuse, Clinical Pharmacology and Therapeutics Research Branch, MD

[2] National Institute on Drug Abuse, Center for Clinical Trials Network, Bethesda, MD

Abstract

Objectives. Aripiprazole blocks psychostimulant seeking in a rat model of relapse. However, in humans, it may increase ongoing use. We tested aripiprazole specifically for relapse prevention.

Methadone-maintained outpatients who were abstinent from cocaine in weeks 11-12 were randomized to double-blind aripiprazole (15/mg daily) or placebo in weeks 13-27, after 12 weeks of contingency management. Participants reported craving via ecological momentary We stopped the trial because too few (18 of 41) participants met the abstinence criterion. The results were suggestive that aripiprazole delayed lapse (HR = 0.45, CI95 = 0.14 – 1.42, $p = 0.17$) and relapse (HR = 0.31. CI95 = 0.07 – 1.27, $p = 0.10$), but the effects did not reach statistical significance. Unexpectedly, the proportion of participants reporting cocaine craving was higher in the aripiprazole group (Fisher exact $p = .026$), though frequency of craving was similar in the aripiprazole and placebo groups (1.89% vs. 1.16%, $r_{effect} = .43$, CI95 = –.08 - .76). The results suggest that in recently abstinent cocaine users, aripiprazole might delay relapse, but might also slightly increase craving. Difficulty in trial implementation underscores the fact that initial abstinence from cocaine is not a trivial hurdle.

Keywords

cocaine; relapse prevention; D2 partial agonists; ecological momentary assessment; human

A major problem in treating substance-use disorders is the likelihood of relapse, which can occur after seemingly successful abstinence, with an array of precipitants that often include drug-associated environmental cues (Brandon et al., 2007). In the rat reinstatement model of relapse and craving, resumption of extinguished cocaine-seeking by either of two types of precipitants (cues and small priming doses of cocaine) was reduced by aripiprazole (Feltenstein et al., 2007, 2009; Shaham et al., 2003). Aripiprazole is a partial agonist at dopamine D_2 and serotonin 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors with

Corresponding Author: Dr. Kenzie L. Preston. NIH National Institute on Drug Abuse, Intramural Research Program, Treatment Section, 251 Bayview Blvd. Suite 200, Baltimore, Maryland 21224, Voice: (443) 740-2326, Fax: (443) 740-2318, kpreston@intra.nida.nih.gov.

Conflicts of Interest: All authors report no conflicts of interests.

affinity for several other dopaminergic, serotonergic, adrenergic and histaminergic receptors (Davies et al., 2004). It is used clinically for treatment of schizophrenia, manic or mixed episodes associated with Bipolar I Disorder, or adjunctive treatment for major depressive disorder in adults. The effect of aripiprazolein the rat model of relapse was specific, with no accompanying changes in cocaine self-administration, food self-administration, reinstatement of food-seeking behavior, or basal locomotor activity (Feltenstein et al., 2007). The effect persisted when aripiprazole was administered every day for one week (Feltenstein et al., 2009). The clinical implication of these findings is that aripiprazole might prevent cue-induced relapse in addicted cocaine users who have become abstinent.

Relapse prevention has not been an outcome measure in the extant human literature on aripiprazole for psychostimulant addiction. This might help explain some seemingly conflicting results. One group of investigators has consistently found beneficial effects of acutely administered aripiprazole in non-treatment-seeking misusers of d-amphetamine or methamphetamine: acute aripiprazole reduced amphetamine's discriminative-stimulus effects (Lile et al., 2005), positive subjective effects (Stoops et al., 2006), and rates of self-administration (Stoops et al., 2013). Yet when given chronically to non-treatment-seekers with psychostimulant dependence, aripiprazole increased amphetamine use (Tiihonen et al., 2007), increased positive subjective effects of cocaine (Lile et al., 2008), and increased self-administration of cocaine (though this may have been a compensatory response to blunted reward) (Haney et al., 2011). In the most recently published study, chronic aripiprazole had no effect on cocaine self-administration or subjective effects; again, the participants were non-treatment-seeking users (Lofwall et al., 2014). A meta-analysis concluded that antipsychotics, including aripiprazole, have no effects relative to placebo in terms of cocaine-use days, cocaine or amphetamine/methamphetamine abstinence or craving, or severity of addiction in patients with psychostimulant dependence (Kishi et al., 2013).

Yet none of these findings address the implications of the reinstatement results. Aripiprazole maintenance might be useful for relapse prevention in abstinent former users of cocaine—even though, as human studies and other rat models (Thomsen et al., 2008) suggest, it might actually exacerbate ongoing use in people who have not become abstinent. We designed a clinical trial with that difference in mind, randomizing only participants who achieved two weeks of initial abstinence. Because the reinstatement model is considered a model of both craving and relapse, we hypothesized that (1) aripiprazole would prevent or delay cocaine relapse more effectively than placebo, and (2) aripiprazole would reduce cocaine craving in daily life, as assessed by ecological momentary assessment (EMA). The design of this trial was almost identical to that of our successful, concurrently run trial of clonidine as an adjuvant to buprenorphine maintenance for opiate relapse prevention (Kowalczyk et al., 2015). The results, as we will discuss, were different.

Methods

Study Design

We conducted a randomized double-blind clinical trial with two treatment groups: aripiprazole (15 mg oral daily) and placebo. Figure 1 shows the timeline for the study. All patients received standard treatment (methadone daily and individual counseling weekly) for

41 weeks. To establish abstinence prior to aripiprazole induction, contingent vouchers were given for each cocaine-negative urine specimen during the first 12 weeks (weeks 1-12). Participants who were abstinent from cocaine during weeks 11 and 12 were randomized to receive aripiprazole or placebo in weeks 13 through 27 (induction with gradual dose escalation, as described below, weeks 13 and 14; intervention, weeks 15 through 26, and taper, week 27). All participants continued to receive standard individual counseling and were maintained on their stabilization dose of methadone. After the maintenance phase, participants' methadone dosages were tapered over another 8 weeks, or participants were assisted in transferring to another treatment program.

The primary outcome measures were time to lapse and relapse and longest duration of cocaine abstinence during intervention. The proportion of drug-negative urine specimens was also evaluated as a secondary measure. In addition, drug use, drug craving, and mood were assessed via EMA.

Participants

Participants were cocaine-using, opioid-dependent outpatient volunteers who were seeking treatment for both cocaine and opioid use, recruited from July 2009 to June 2012. Study candidates were evaluated with standardized interviews, physical examination, and laboratory screening. Inclusion criteria were physical dependence on opioids, current cocaine use on at least 3 of the last 30 days, lifetime cocaine-use duration of at least one year, seeking treatment for opiate and cocaine use, able to attend methadone clinic 7 days/week, and age between 18 and 60. The exclusion criteria were: any medical illness that would compromise participation; self-reported intolerance to either methadone or aripiprazole; severe immunocompromise; pregnancy or breastfeeding; orthostatic hypotension; marked, sustained high blood pressure; ECG abnormalities; contraindicated medications; cognitive impairment, schizophrenia or any other DSM-IV psychotic disorder, bipolar disorder, major depressive disorder, previous suicide attempts or ideation, dementia, current physical dependence on alcohol or sedative-hypnotics, or a body mass index (BMI) over 40.

Upon beginning the study, patients were maintained on methadone treatment at our outpatient treatment-research clinic in Baltimore, beginning at 30 mg on Day 1 and increasing over the next 14 days to a target dose of 100 mg. Further methadone dose adjustment was individualized on the basis of opioid withdrawal symptoms, craving, and use. Throughout the study, including baseline, we encouraged participants to become abstinent from opioids, but we did not discharge participants for testing positive for opioids. Throughout the study, participants attended the clinic 7 days a week for methadone; once a week, they received a session of individual counseling. Participants provided urine and breath samples under observation three times a week. Urine specimens were tested for opioids, cocaine, marijuana, amphetamines, barbiturates, and benzodiazepines; breath samples were tested for alcohol.

The Institutional Review Board of the National Institute on Drug Abuse Intramural Research Program approved the study, and all participants gave written informed consent.

Baseline/Cocaine abstinence initiation

Participants were told repeatedly—during intake, during consent, and weekly during the baseline—that they must become abstinent from cocaine by the end of their 10th week in the study and remain abstinent for the next two weeks (weeks 11 and 12) to qualify for continued participation. During the first fourteen weeks of the study, we tried to facilitate cocaine abstinence by using contingency management. All participants could earn vouchers (exchangeable for goods and services) for cocaine-negative urine specimens; the value of the vouchers began at $2.00 and increased in value by $2.00 for each consecutive negative specimen, to a maximum of $40. If a participant provided a cocaine-positive specimen or did not provide a scheduled specimen, the participant did not receive a voucher, and the value of the next earned voucher was reset to $2.00. On the second day of urine collection, in addition to earning a $2 voucher if they gave a cocaine-negative urine, the subject had the chance to receive another voucher of random value. The priming voucher ($8 to $40) was chosen out of a hat, and participants received a statement about how many consecutive cocaine-negative urines would be needed in order to obtain a voucher of that value.

Participants who were abstinent from cocaine during weeks 11 and 12 (verified by 6 consecutive cocaine-negative urines) were randomized to aripiprazole or placebo by an investigator (KLP) who had no contact with participants, using a computerized algorithm stratified by age, sex, race, and baseline cocaine and opioid use. All other staff and participants were blind to study group assignment. Participants who were randomized continued to undergo contingency management during a two-week aripiprazole/placebo induction phase. Participants who did not meet the abstinence criterion were offered twelve additional weeks of treatment, including an eight-week medication taper, or were helped to transfer to a community treatment program.

Aripiprazole/placebo

Aripiprazole (Bristol-Meyers Squibb) and placebo were administered in identical size 0 capsules filled with dextrose. Aripiprazole/placebo administration began at the start of week 13 for an induction period of 14 days, followed by a 12-week intervention period. One capsule containing aripiprazole or placebo was administered once daily at the time of methadone administration. Nurses conducted a mouth search and asked participants to speak after administration of the capsule.

During the 2-week induction, participants received increasing oral doses of aripiprazole (or placebo) once daily, starting at 5 mg and incrementing in 5 mg steps as tolerated to a maximum dose of 15 mg. Doses were lowered by the study physician (KAP) in a blinded fashion as necessary if side effects emerged. A participant could have remained in the study even if the aripiprazole dose had been lowered to zero, though this did not occur. The maximum tolerated dose was administered until the end of the 12-week intervention period. The dose of aripiprazole was tapered to zero in the first 7 days of the 7-week maintenance phase, in 5 mg decrements. Participants on placebo continued to receive placebo during the 7-day taper period.

Aripiprazole is not currently approved by the Food and Drug Administration for use as a treatment for cocaine relapse or craving.

Ecological Momentary Assessment of Craving and Mood

Participants' self-reported craving and mood were assessed by ecological momentary assessment (EMA). Each participant was issued a device (e.g., PalmPilot) and trained in its use as an electronic diary (ED). From the first week of intervention until the end of the maintenance phase (weeks 13-33), the ED randomly prompted participants 4 times a day to make EMA entries. Participants answered stress, craving, and mood questions with the response options "NO!!", "no??", "yes??", and "YES!!" and reported whether drug cues were encountered in the hour before the prompt. Participants were also asked to initiate EMA entries whenever they used cocaine or had an urge/craving for cocaine.

Adverse events

Our nursing staff monitored adverse events by participant self-report, vital signs, electrocardiogram (ECG), liver-function tests, and fasting glucose. Research assistants monitored participants for extrapyramidal symptoms (EPS), using a battery consisting of the Barnes Akathisia scale (Barnes, 1989), the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976), and the Simpson-Angus Scale (Simpson & Angus, 1970). Adverse events, including EPS, were further evaluated by the study physician as appropriate.

Data Analysis

Group differences in proportions of cocaine-negative urine samples, and lengths of longest periods of abstinence from cocaine, were analyzed with t-tests.

We defined lapse as the first cocaine-positive urine sample from week 13 to week 26. We defined relapse as two consecutive cocaine-positive urine samples or missed urines. Participants who dropped out (n = 4) were considered to have lapsed and relapsed. Those who remained abstinent until the end of the intervention phase were coded as right censored. Group differences in latency to lapse and relapse were analyzed using Cox proportional-hazards models (using SAS Proc PHreg); the assumption of proportional hazards across groups was met, except where indicated in the Results section.

There were four complications in the data analysis; we handled them as follows.

First, one participant randomized to the placebo group was providing urine specimens that were negative for methadone—a finding highly suggestive of falsification. This started on the day before randomization and continued for the first two weeks of placebo, at which point, clinic staff noticed it and asked him about it. He acknowledged that he had been using a commercial "urine cleansing" product. He was discharged from the study (he transferred directly to a community methadone clinic). Rather than try to determine which of his data were reliable or whether he had even been eligible for randomization, we omitted his data from all analyses.

Second, our full intent-to-treat (ITT) sample (n = 18) included one participant in each group whose outcomes cannot plausibly be interpreted as intervention-induced. One of them was

randomized (to the aripiprazole group) on a Friday after two weeks of abstinence from cocaine, but lapsed to cocaine use over the weekend before receiving his first dose of aripiprazole on Monday (and continuing to use cocaine thereafter). The other was randomized to placebo, took one placebo capsule, and then transferred out of the study to a community clinic due to a schedule conflict (but therefore had to be counted as having immediately "lapsed" and "relapsed"). We report ITT results for lapse and relapse in this paper, and we report ITT results for other outcomes in the appendix, but—for all results—we focus on an "as treated" analysis (n = 16) in which we do not include those two participants.

Third, the aripiprazole and placebo groups differed slightly on one relevant pre-enrollment measure, lifetime years of heroin use (more years in the participants randomized to aripiprazole; Table 1). We report our main results with and without years of heroin use as a covariate.

Finally, because our hypothesized group difference in lapse was not significant at a two-tailed alpha of .05, we used the hazard ratios to calculate Bayes factors, thereby testing whether our data were inconclusive or whether they actually supported the null hypothesis of no benefit (Dienes, 2014). Bayes factors greater than 3.0 suggest strong support for the alternative hypothesis over the null; Bayes factors less than 0.3 suggest strong support for the null; values in between indicate that the data are insensitive or inconclusive (Dienes, 2014). Bayes factors do not use investigator-specified estimates of prior probabilities; they simply test a null effect (e.g., no group difference) against an alternative hypothesized effect, which we took from the lapse results of our successful trial of clonidine maintenance for opiate users (Kowalczyk et al., 2015). We specified a half-normal theorized distribution (see Dienes, 2014, for description). For relapse, we did not calculate a Bayes factor because our clonidine study did not provide a basis for a theorized value.

EMA random-prompt data were analyzed with generalized linear mixed models (SAS Proc Glimmix). The independent variable was treatment group; the dichotomous dependent variable was craving for cocaine ("yes??" or "YES!!" coded 1; "no??" or "NO!!" coded 0). These models used a first-order autoregressive error structure and included a control term for the number of responses given by each participant. We used similar general linear mixed models (SAS Proc mix) to compare groups on EMA ratings of stress and mood at random prompts. We did not analyze the self-initiated event-contingent prompts because, in this data set, those data were too sparse.

For all analyses, we used a two-tailed alpha of 0.05. Where appropriate, we used F values to calculate effect-size r values (r_{effect} values) as specified by Rosnow et al. (2000).

Results

We had planned to enroll 55 participants in each of the two groups. After enrollment of 41 participants, we ended the study due to slow recruitment and an unexpectedly low rate of initial cocaine abstinence in people who did enroll. Figure 2 shows the flow of participants through the study. As described below in the section on adverse events: out of nine

participants randomized to receive aripiprazole, three received the maximum 15 mg dose as planned, five had the dose reduced to 5 mg for most of the intervention phase, and one discontinued aripiprazole after three weeks.

Demographics

Of the 41 participants enrolled, 18 (not counting the one who falsified his urine samples) met the cocaine-abstinence criterion for randomization to aripiprazole or placebo; they constituted the intent-to-treat (ITT) sample. Compared to the 22 who did not meet the cocaine-abstinence criterion, the 18 randomized participants were more likely to be male, and tended to be older, more educated, more likely to be employed, and more likely to be African American (demographics for ITT sample and nonrandomized enrollees shown in Table A1, Appendix).

Demographics for the "as treated" sample (n = 16) are shown in Table 1. Among these 16, participants in the aripiprazole group were older than those in the placebo group and, as noted above, had more lifetime years of heroin use. We controlled for years of heroin use rather than age because years of heroin use was more closely related to outcome.

The two groups did not differ in the percentage of urine samples positive for cocaine or heroin during the 10 weeks of baseline treatment (data not shown); randomization had been stratified on those variables.

Lapse to Cocaine Use (Assessed By Urine Screen)

Lapse in "as treated" sample—The aripiprazole group appeared to take longer to lapse, with a hazard ratio (HR) of 0.45 (Figure 3A), but this HR was not significantly different from 1.0, with a 95% confidence interval (CI) of 0.14 to 1.42, $p = 0.17$. To help determine whether the negative finding clearly indicated the absence of a treatment effect, we calculated a Bayes factor as prescribed in the appendix of Dienes (2014), using the natural log of the hazard ratio versus a theorized value. The observed hazard ratio had a natural log of −0.8 (SEM = 0.58); our theorized natural log was −.39 (SD = 2.19), taken from the significant protective effect of clonidine in our prior study. (The use of SEM for one value and SD for the other accords with the published procedure.) The resultant Bayes factor was 1.19, suggesting that the result was inconclusive rather than strongly supportive of the null.

Using the same methods (Dienes, 2014) to compare the two hazard ratios to each other directly, we found that they were not significantly different (z = .45, p = .65)—that is, we did not show that aripiprazole was less effective against cocaine lapse than clonidine had been against opiate lapse. This is consistent with the inconclusive Bayes factor.

Lapse in "as treated" sample, controlling for years of heroin use—Because aripiprazole participants tended to have longer histories of heroin use than placebo participants, we conducted a sensitivity analysis in which we included this as a covariate in our Cox models. (Years of heroin use did not meet the assumption of proportional hazards, so we also included its interaction with time.) Longer history of heroin use was associated with longer latency to lapse (HR = 0.89, 95% CI = 0.80 – 0.99, $p < 0.05$), but inclusion of the covariate did not appreciably change the aripiprazole/placebo comparison (HR = 0.32, 95%

CI = 0.06 – 1.76, $p = 0.19$). The Bayes factor for this comparison of lapses was 1.49, again suggesting that the result for lapses was inconclusive.

Lapse in ITT sample—For the full sample, lapse results were similarly suggestive (figure 3B), similarly nonsignificant (HR = 0.51, 95% CI = 0.18-1.48, $p = 0.21$), and similarly inconclusive (Bayes factor = 0.92). Covarying for years of heroin use did not change the findings appreciably (HR = 0.48, 95% CI = 0.11- 2.19, $p = 0.35$, Bayes factor = 0.84).

Relapse to Cocaine Use (Assessed By Urine Screen)

The group difference in time to relapse was, if anything, more pronounced than the group difference in time to lapse (Figures 4A and 4B), but again, this did not reach statistical significance ("as treated" sample, HR=0.31, 95% CI = 0.07 – 1.27, $p = 0.10$; ITT sample, HR=0.39, 95% CI = 0.11 – 1.37, $p = 0.14$). Years of heroin use as a sole predictor tended to predict longer latency to relapse ("as treated" sample, p = .09; ITT sample, p = .07); when we included years of heroin use as a covariate, the difference between the aripiprazole and placebo groups was slightly reduced (HR=0.31, 95% CI = 0.04-2.08, $p = 0.22$). We did not calculate Bayes factors for relapse because our clonidine study did not provide a basis for a hypothesis.

Results from this point on are reported only for the "as treated" sample; see the Appendix for more of the ITT results.

Longest duration of cocaine abstinence, and overall proportions of negative urines

Findings were similarly suggestive for duration of cocaine abstinence, measured as the longest run of cocaine-negative urine samples throughout the induction and intervention phase (weeks 13-26): aripiprazole did not significantly increase it (aripiprazole, M = 22.63, SEM = 4.73; placebo, M = 16.13, SEM = 4.54, $p = 0.34$), but the Bayes factor (using the relevant prior result from our clonidine study) was 1.67, again indicating that the result was inconclusive rather than strongly supportive of the null.

The overall percentage of cocaine-negative urine samples did not differ between groups from the beginning of induction through the end of intervention (weeks 13-26) (aripiprazole, M = 54%, SEM = 11%; placebo, M = 51%, SEM = 12%, $p = 0.89$). We did not calculate a Bayes factor because we had not specifically hypothesized a difference.

Self-reported Cocaine Craving (EMA)

During the aripiprazole/placebo intervention phase, when assessed at random moments in daily life via EMA, participants in the aripiprazole group reported cocaine craving ("yes??" or "YES!!") at least as frequently as those in the placebo group (adjusted percentages from Glimmix model: 1.89% of prompts, 95% CI = 1.32 – 2.70%, versus 1.16% of prompts, 95% CI = 1.32 – 1.92%), $F(1,13) = 2.91$, $p = 0.11$, $r_{effect} = .43$, 95% CI = –.08 - .76) (Figure 5). Most participants in the placebo group never reported craving during the intervention phase; almost all participants in the aripiprazole group reported craving at least once (Fisher exact p for group difference in "never" versus "ever" reported craving = .026) (Figure 5). There did not appear to be a relationship between dose and incidence of craving. Both the participant

with the greatest percentage of craving reports (7.6% of random prompts) and the participant who did not report any craving received the 5 mg dose for the majority of the intervention phase.

These findings did not change appreciably when we controlled for the group difference in years of heroin use (data not shown).

Self-reported Mood (EMA)

During the aripiprazole/placebo intervention phase, participants in the aripiprazole group gave lower ratings of sadness, annoyance, boredom, relaxation, excitement, and stress than those in the placebo group [sadness, $F(1,13) = 6.28$, $p<0.05$; annoyance, $F(1,13) = 24.4$, $p<0.0005$; boredom, $F(1,13) = 17.15$, $p<0.005$; relaxation, $F(1,13) = 27.0$, $p<0.0005$; excitement, $F(1,13) = 7.33$, $p<0.05$; stress, $F(1,13) = 13.86$, $p<0.005$]. Ratings of tension, tiredness, and happiness did not differ between groups.

Adverse Events

Of the expected adverse effects of aripiprazole, the one most commonly reported (in 3 participants) was agitation/restlessness. One of the 3 participants reporting agitation/restlessness (who tested positive for cocaine throughout the study) had aripiprazole dosing discontinued after one week of the 15 mg dose. For the other 2, the symptoms resolved when the dosage was reduced from 15 to 5 mg. Three of the other aripiprazole participants were given dose decreases to 5 mg due to reports of tremor (n = 1), paresthesia (n = 1), or suicidal ideation (n = 1). In the placebo group, one participant requested a dose decrease due to irritability. Another participant in the placebo group reported muscle spasms, which resolved within a week; the participant did not request a dose decrease. There was no significant difference between treatment groups in the number of adverse events, nor in the number of participants who reported any adverse events or any serious adverse events.

Discussion

This study raises two interesting issues—one issue arising from the results, the other issue arising from an unexpected difficulty in implementation.

The first issue concerns a possible paradox in the effects of aripiprazole. Although we cannot conclude that aripiprazole protected against cocaine lapse or relapse (in fact, most of our participants lapsed during the first 16 weeks after randomization), the survival curves (Figures 3 and 4) suggest that it did. The Bayes factors we calculated for these measures do not allow us to rule out a beneficial effect. Allowing, for the moment, that aripiprazole *may* have increased the latency to lapse or relapse, any inference of benefit is complicated by our EMA data on cocaine craving. Participants randomized to aripiprazole reported cocaine craving at least as frequently as those randomized to placebo. The absolute rates of craving were low in both groups (1.87% versus 1.01% of random prompts), and the difference did not reach statistical significance, but the effect size was large (equivalent to a Cohen d of .95), and there was a significant difference across groups in the proportion of participants who never reported craving (Figure 5).

If we had simply found that aripiprazole exacerbated cocaine craving and use, we could liken it to the increase in ongoing amphetamine misuse that was seen in a prior human study (Tiihonen et al., 2007). If we had found an increase in use with no increase in craving, we could liken it to the results of a prior human laboratory study in which cocaine self-administration (but not craving) increased as a seemingly compensatory response to blunting of cocaine's acute affects (Haney et al., 2011). We found, instead, a tendency toward an increase in craving, accompanied by either no increase in lapse or relapse or, possibly, a protective effect against lapse and relapse. This combination of effects raises questions about the dissociability of daily-life craving from use. It also raises the question of whether a medication with this behavioral profile would be clinically acceptable. In our sample, no participants spontaneously reported that aripiprazole was exacerbating their craving for cocaine—but because we had not expected it to do so, we also did not probe for it.

It is conceivable that, given its partial-agonist activity at D_2 receptors, aripiprazole could prime stimulant craving. However, there is no indication that the subjective effects of aripiprazole are stimulant-like (Haney et al., 2001; Lile et al., 2005; Stoops et al., 2006, 2013). In humans trained to discriminate amphetamine or methamphetamine from placebo, aripiprazole was consistently identified as placebo (Lile et al., 2005; Sevak et al., 2011).

The ambiguities in our results are due largely to the smallness of the sample size—and this brings us to the second issue. We had much more difficulty than we expected in helping cocaine-using methadone-maintenance patients stop using cocaine for two weeks, even with voucher-based contingency management. In our identically designed study that targeted opiate relapse rather than cocaine relapse (Kowalczyk et al., 2015), enrollees achieved initial opiate abstinence at such a high rate during a pilot study that we shortened the baseline from 10 to 4 weeks before running the full study. In the current study, we had the opposite experience: after a pilot study, we lengthened the baseline from 4 to 10 weeks, but we still could not randomize most of our enrollees to a relapse-prevention group. It is not surprising that cocaine abstinence was more of a challenge than opiate abstinence during buprenorphine maintenance—but we did not anticipate the size of the challenge. We have not been alone in making statements such as: “it is usually much easier to stop using cocaine than it is to stay permanently stopped. The challenge during this stage is...to avoid relapse” (Washton & Stone-Washton, 1993). We must now conclude that even though relapse prevention is exceedingly important, and even though clinical trials need to be designed specifically to examine it, we cannot assume that initial cessation of cocaine use is only a small hurdle. In non-research settings, where inpatient stays are not widely available and where the most effective forms of contingency management are rarely used, a medication that primarily acts to prevent relapse to cocaine use is unlikely to be a good standalone treatment.

In our sample, participants who achieved the abstinence criterion for randomization tended to be older and more educated (though they also had lower incomes) than those who did not. These factors may be important to keep in mind in recruiting participants for future clinical trials using relapse-prevention designs.

Like our successful relapse-prevention trial with clonidine as an adjunct to buprenorphine (Kowalczyk et al., 2015), we designed the current trial to translate findings from the rat reinstatement model of relapse (Davies et al., 2004; Feltenstein et al., 2007; Feltenstein et al., 2009). Our results with aripiprazole cannot be taken as clear evidence for the predictive validity of the reinstatement model, but cross-species comparison is stymied by the seeming dissociation we found between craving and use, which has no parallel in the reinstatement procedure. It might be possible to speculate on drug-specific mechanisms for our findings' having diverged from the predictions of the reinstatement model (e.g., complexities arising from the partial-agonist actions of aripiprazole), but we have no data bearing on that. Also, due to our small sample size, we cannot delve into our EMA data to address mechanistic questions at the behavioral level, as we did with our clonidine study (Kowalczyk et al., 2015) —for example, we do not have enough EMA data to examine craving as a function of the presence of cocaine-related cues.

Our EMA data did show that participants randomized to aripiprazole tended to rate both positive and negative moods lower than participants randomized to placebo, especially when we included EMA data from the post-aripiprazole maintenance phase. This might reflect long-term mood-stabilizing effects of aripiprazole (Rybakowski, 2008).

In summary, the present results suggest that in former cocaine users who have achieved abstinence, aripiprazole may slightly increase daily-life cocaine craving, but are inconclusive regarding its effect on lapse or relapse. Clarification of these unexpected findings will require additional relapse-prevention trials that are not hampered by low rates of initial abstinence from cocaine.

Acknowledgments

Source of Funding: Support for this study was provided by the Intramural Research Program of the National Institute on Drug Abuse.

Appendix

Intent to Treat sample

The Intent to Treat sample included 9 participants in the aripiprazole group and 9 participants in the placebo group. One placebo group participant left the study before providing any EMA data; therefore N=17 for the EMA analyses below.

Table A1

Demographics and baseline data in nonrandomized enrollees and randomized (intent-to-treat) sample

	Nonrandomized (n = 22)		ITT (n = 18)		Comparison
	Mean	SD	Mean	SD	
Age (years)	40.7	7.2	45.0	7.6	t = −1.84, p = .07
Years of education	11.2	1.4	12.3	1.7	t = −2.20, p = .03

	Nonrandomized (n = 22)		ITT (n = 18)		Comparison
	Mean	SD	Mean	SD	
Heroin use, past month (days)	24.2	9.8	20.3	11.6	t = 1.17, p = .25
Cocaine use, past month(days)	15.0	9.6	12.9	11.1	t = 0.61, p = .54
Lifetime years of heroin use	12.6	7.9	16.9	10.5	t = −1.50, p = .14
Lifetime years of cocaine use	11.8	8.4	12.4	8.4	t = −0.24, p = .82
	N	%	N	%	
Sex					exact p = .054
Male	15	68%	17	94%	
Female	7	32%	1	6%	
Race					exact p = .10
African American	11	50%	13	72%	
European American	11	50%	4	22%	
Asian	0	0%	1	6%	
Employed					exact p = .03
Yes	9	41%	14	78%	
No	13	59%	4	22%	
Heroin route of administration[1]					exact p = 1.0
Intravenous	12	57%	10	56%	
Intranasal	9	43%	8	44%	
Cocaine route of admin.					exact p = .31
Smoked or intravenous	21	95%	15	83%	
Intranasal	1	5%	3	17%	

[1] One participant in the nonrandomized group used prescription opiates orally.

Longest duration of cocaine abstinence, and overall proportions of negative urines

Aripiprazole did not significantly increase the duration of cocaine abstinence, measured as the longest run of cocaine-negative urine samples throughout the induction and intervention phase (weeks 13-26) (aripiprazole, n = 9, M = 20.11, SEM = 4.87; placebo, n = 9, M = 14.89, SEM = 4.19, $p = 0.43$), but the Bayes factor (using the relevant prior result from our clonidine study) was 0.63, indicating that the result was inconclusive rather than strongly supportive of the null hypothesis.

The overall percentage of cocaine-negative urine samples did not differ between groups from the beginning of induction through the end of intervention (weeks 13-26) (aripiprazole, n = 9, M = 48%, SEM = 12%; placebo, n = 9, M = 55%, SEM = 11%, $p = 0.66$). We did not calculate a Bayes factor because we had not specifically hypothesized a difference.

Self-reported Cocaine Craving (EMA)

During the aripiprazole/placebo intervention phase, when assessed at random moments in daily life via EMA, participants in the aripiprazole group (n = 9) reported cocaine craving ("yes??" or "YES!!") more frequently (adjusted percentages from Glimmix model: 3.01% of

prompts, 95% CI = 2.29 – 3.95%) than those in the placebo group (n = 8; 0.93% of prompts, 95% CI = 0.53 – 1.63%), $F(1,14) = 18.28$, $p < 0.001$, $r_{effect} = .75$, 95% CI = .42 - .90). This difference was partly driven by the presence of one or two especially frequent cravers in the aripiprazole group, but it did not disappear when the three highest cravers (readily discernible in Figure A1) were removed from the analysis, $F(1,11) = 2.34$, $p = .15$, $r_{effect} = .42$, 95% CI = –.24 - .81 (the p value was no longer below .05, but the confidence interval remained mostly above 0).

The greater frequency of craving in the aripiprazole group began to dissipate after discontinuation of aripiprazole: when the intervention and post-aripiprazole maintenance phases were analyzed together, the group difference was smaller: 2.76% (95% CI = 2.06 – 3.68%) versus 1.92% (95% CI = 1.32 – 2.77%), $F(1,14) = 3.38$, $p = 0.09$, $r_{effect} = .44$, 95% CI = –. 05. - 76.

These findings did not change appreciably when we controlled for the group difference in years of heroin use (data not shown).

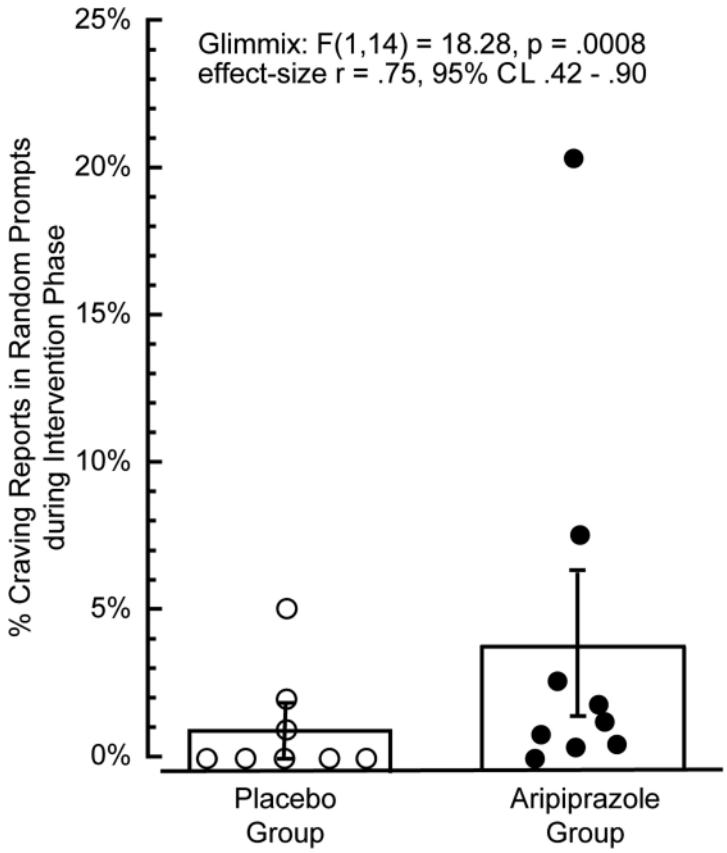

Figure A1.

Self-reported Mood (EMA)

During the aripiprazole/placebo intervention phase, participants in the aripiprazole group (n = 9) gave lower ratings of annoyance, boredom, and relaxation than those in the placebo group [n = 8; annoyed: F (1,14) = 6.78, p < 0.05; bored: F (1,14) = 5.41, p<0.05; relaxed, F

(1,14) = 33.81, p<0.001]. Ratings of stress, sadness, tension, tiredness, excitement, and happiness did not differ significantly between groups.

References

Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989; 154:672–6. [PubMed: 2574607]

Brandon TH, Vidrine JI, Litvin EB. Relapse and relapse prevention. Annu Rev Clin Psychol. 2007; 3:257–84. [PubMed: 17716056]

Davies MA, Sheffler DJ, Roth BL. Aripiprazole: a novel atypical antipsychotic drug with a uniquely robust pharmacology. CNS Drug Rev. 2004; 10:317–36. [PubMed: 15592581]

Dienes Z. Using Bayes to get the most out of non-significant results. Front Psychol. 2014; 5:781. [PubMed: 25120503]

Feltenstein MW, Altar CA, See RE. Aripiprazole blocks reinstatement of cocaine seeking in an animal model of relapse. Biol Psychiatry. 2007; 61:582–90. [PubMed: 16806092]

Feltenstein MW, Do PH, See RE. Repeated aripiprazole administration attenuates cocaine seeking in a rat model of relapse. Psychopharmacology. 2009; 207:401–11. [PubMed: 19779699]

Guy, W. ECDEU Assessment Manual for Psychopharmacology, revised edition. Department of Health, Education, and Welfare; Washington, DC: 1976.

Haney M, Rubin E, Foltin RW. Aripiprazole maintenance increases smoked cocaine self-administration in humans. Psychopharmacology. 2011; 216:379–87. [PubMed: 21373790]

Kishi T, Matsuda Y, Iwata N, Correll CU. Antipsychotics for cocaine or psychostimulant dependence: systematic review and meta-analysis of randomized, placebo-controlled trials. J Clin Psychiatry. 2013; 74:e1169–80. [PubMed: 24434105]

Kowalczyk WJ, Phillips KA, Jobes ML, Kennedy AP, Ghitza UE, Agage DA, Schmittner JP, Epstein DH, Preston KL. Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: A randomized controlled trial with ecological momentary assessment. Am J Psychiatry. 2015; 172:760–7. [PubMed: 25783757]

Lile JA, Stoops WW, Vansickel AR, Glaser PE, Hays LR, Rush CR. Aripiprazole attenuates the discriminative-stimulus and subject-rated effects of D-amphetamine in humans. Neuropsychopharmacology. 2005; 30:2103–14. [PubMed: 15988473]

Lile JA, Stoops WW, Hays LR, Rush CR. The safety, tolerability, and subject-rated effects of acute intranasal cocaine administration during aripiprazole maintenance II: increased aripipirazole dose and maintenance period. Am J Drug Alcohol Abuse. 2008; 34:721–9. [PubMed: 18855244]

Lofwall MR, Nuzzo PA, Campbell C, Walsh SL. Aripiprazole effects on self-administration and pharmacodynamics of intravenous cocaine and cigarette smoking in humans. Exp Clin Psychopharmacol. 2014; 22:238–47. [PubMed: 24467369]

Rosnow RL, Rosenthal R, Rubin DB. Contrasts and correlations in effect-size estimation. Psychol Sci. 2000; 11:446–53. [PubMed: 11202488]

Rybakowski JK. Aripiprazole joins the family of second-generation mood stabilizers. J Clin Psychiatry. 2008; 69:862–3.

Sevak RJ, Vansickel AR, Stoops WW, Glaser PE, Hays LR, Rush CR. Discriminative-stimulus, subject-ratd, and physiological effects of methamphetamine in humans pretreated with aripiprazole. J Clin Psychopharmacol. 2011; 31:470–80. [PubMed: 21694622]

Shaham Y, Shalev U, Lu L, de Wit H, Stewart J. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology. 2003; 168:3–20. [PubMed: 12402102]

Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970; 212:11–9. [PubMed: 4917967]

Stoops WW, Lile JA, Glaser PE, Rush CR. A low dose of aripiprazole attenuates the subject-rated effects of d-amphetamine. Drug Alcohol Depend. 2006; 84:206–9. [PubMed: 16540264]

Stoops WW, Bennett JA, Lile JA, Sevak RJ, Rush CR. Influence of aripiprazole pretreatment on the reinforcing effects of methamphetamine in humans. Prog Neuropsychopharmacol Biol Psychiatry. 2013; 47:111–7. [PubMed: 23994622]

Thomsen M, Fink-Jensen A, Woldbye DP, Wortwein G, Sager TN, Holm R, Pepe LM, Caine SB. Effects of acute and chronic aripiprazole treatment on choice between cocaine self-administration and food under a concurrent schedule of reinforcement in rats. Psychopharmacology. 2008; 201:43–53. [PubMed: 18612628]

Tiihonen J, Kuoppasalmi K, Fohr J, Tuomola P, Kuikanmaki O, Vorma H, Sokero P, Haukka J, Meririnne E. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. Am J Psychiatry. 2007; 164:160–2. [PubMed: 17202560]

Washton AM, Stone-Washton N. Outpatient treatment of cocaine and crack addiction: a clinical perspective. NIDA Res Monogr. 1993; 135:15–30. [PubMed: 8289894]

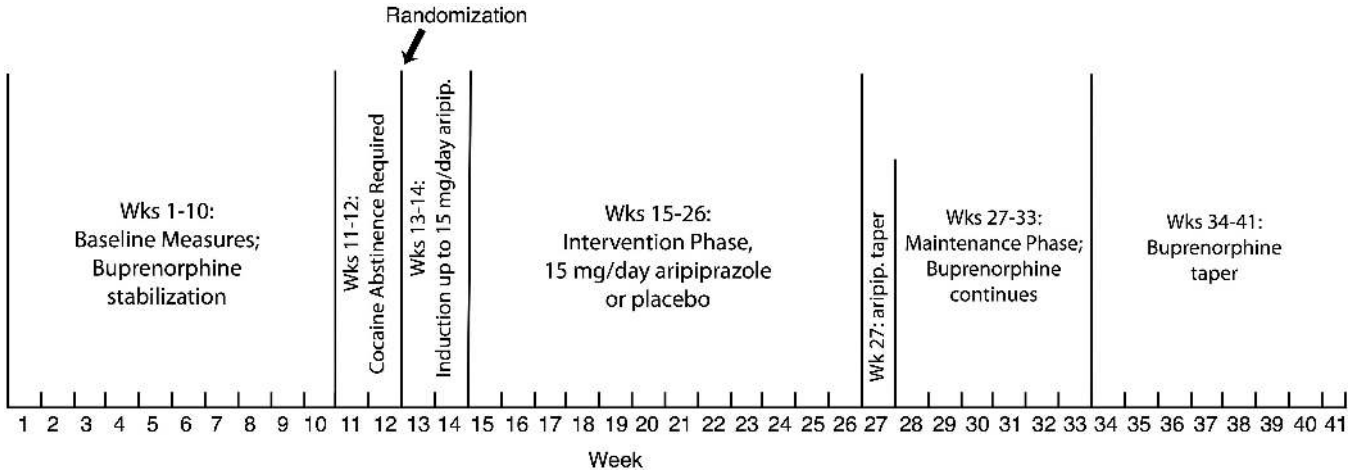

Figure 1.
Study timeline.

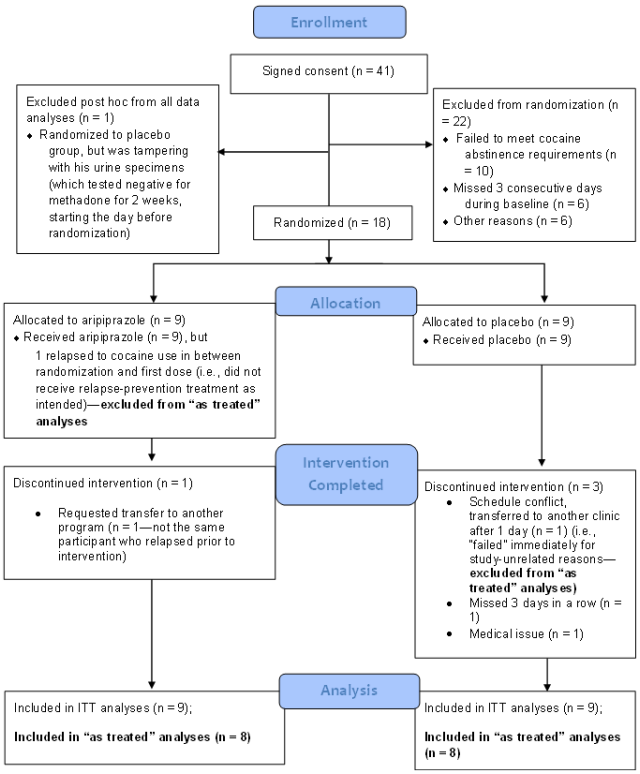

Figure 2.
Study flow diagram.

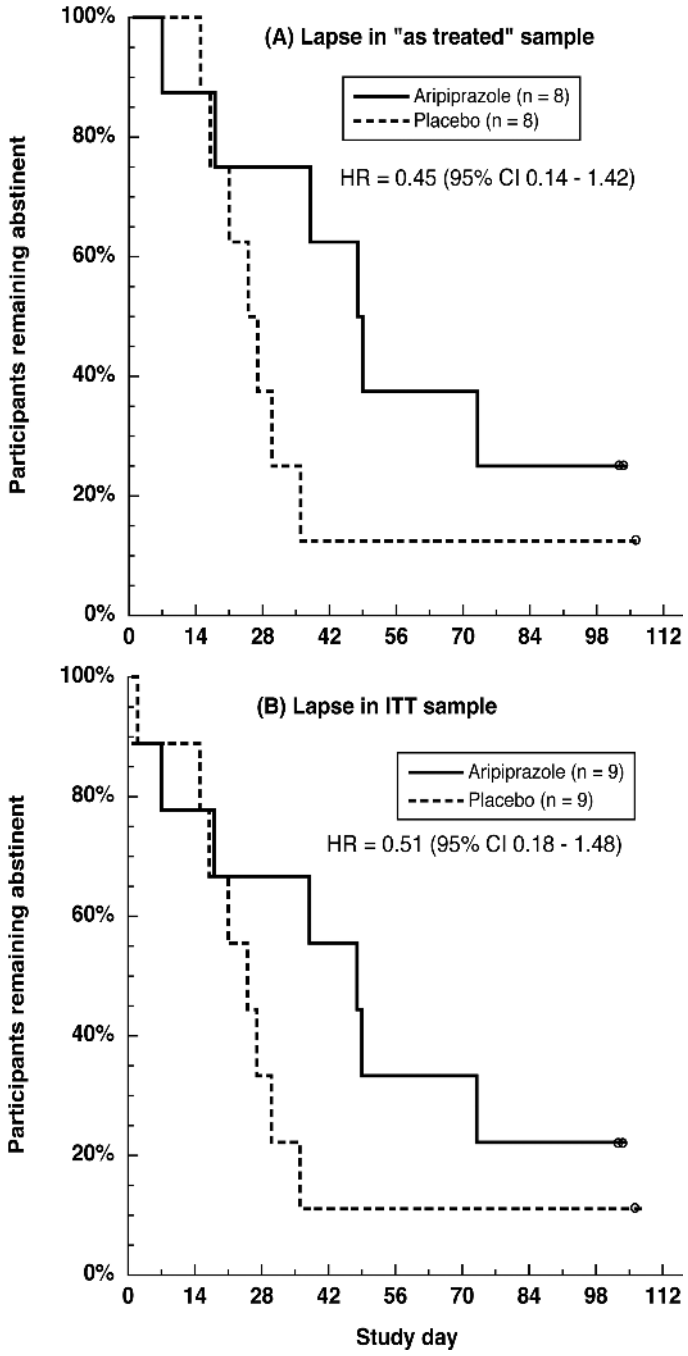

Figure 3.

(A) In the "as treated" sample, aripiprazole appeared to increase the time to initial cocaine lapse, but the effect was not significant (p=0.17). (B) Lapse results were similar in the intent-to-treat (ITT) sample (p = 0.21).

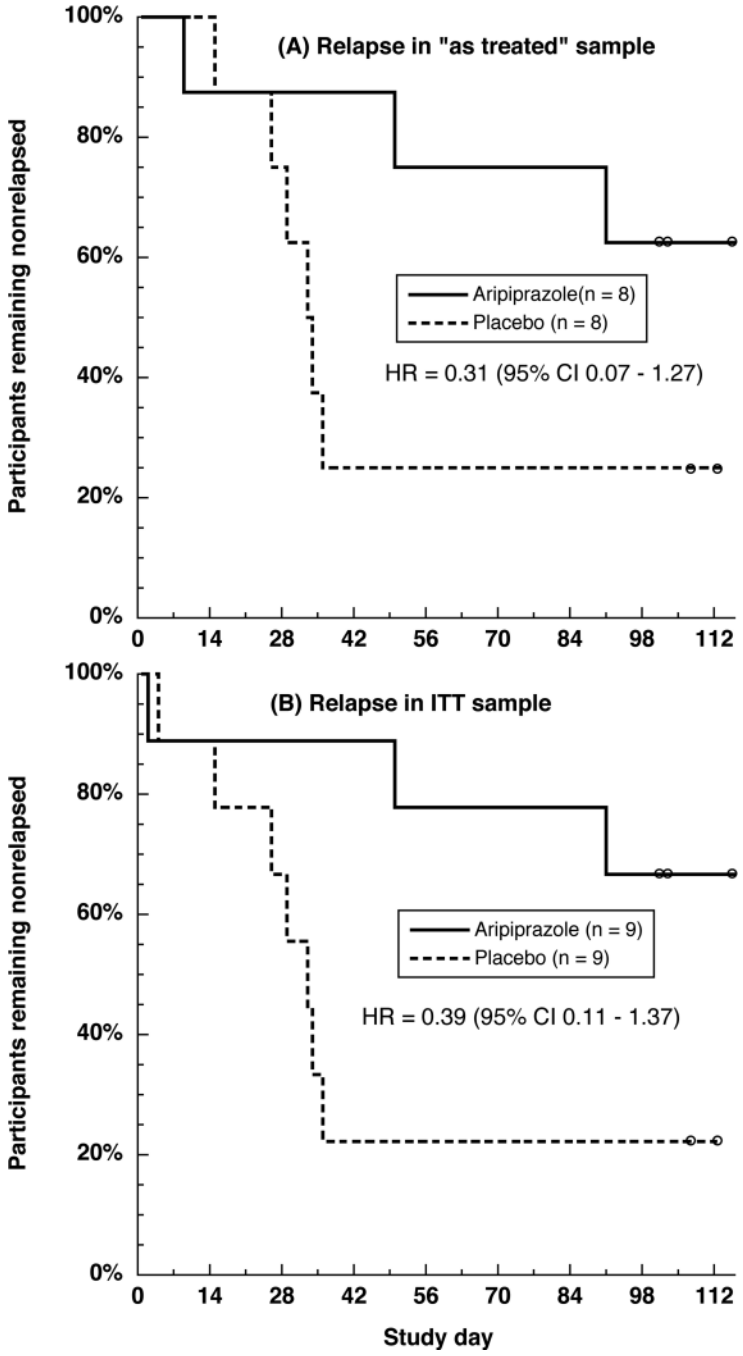

Figure 4.

(A) In the "as treated" sample, aripiprazole appeared to increase the time to cocaine relapse, but the effect was not significant ($p = 0.10$). (B) Relapse results were similar in the ITT sample ($p = 0.14$).

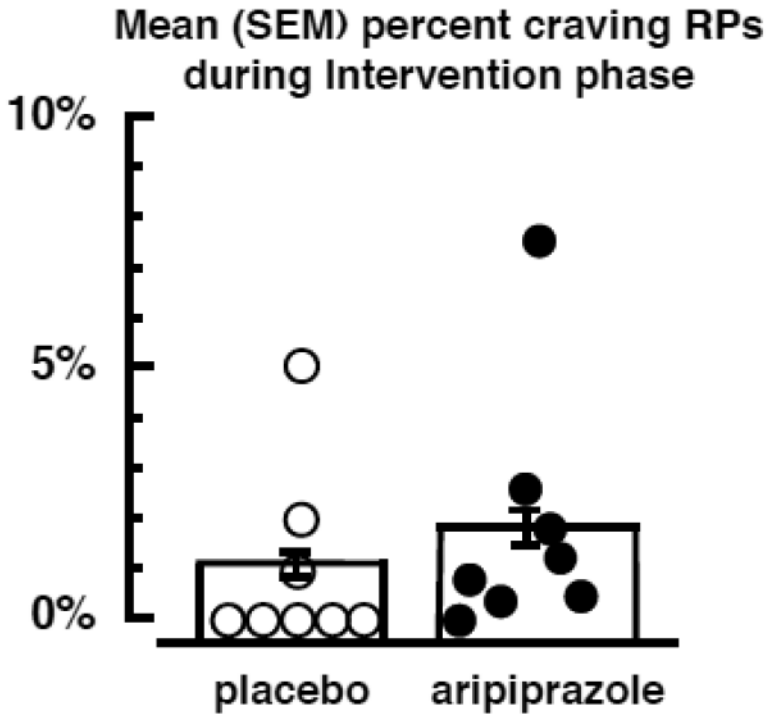

Figure 5.

Cocaine craving in randomly prompted EMA entries was not reported frequently in either group, but tended to be reported more often in the aripiprazole group, $F(1,13) = 2.91$, $p = 0.11$, $r_{effect} = .43$, 95% CI = −.08 - .76. Almost all participants in the aripiprazole group reported craving at least once (Fisher exact p for group difference in "never" versus "ever" reported craving = .026).

Table 1

Demographics and baseline data in "as treated" sample (N = 16)

	Aripiprazole (n = 8)		Placebo (n = 8)		Comparison
	Mean	**SD**	**Mean**	**SD**	
Age (years)	49.4	7.2	42.3	6.1	t = 2.13, p = .052
Years of education	12.6	2.0	12.4	1.1	t = .31, p = .76
Heroin use, past month (days)	16.4	12.8	24.4	9.7	t = −1.41, p = .18
Cocaine use, past month(days)	11.9	10.2	14.8	13.5	t = −.48, p = .64
Lifetime years of heroin use	22.9	10.0	12.5	9.5	t = 2.13, p = .052
Lifetime years of cocaine use	14.5	6.9	9.1	9.9	t = 1.27, p = .23
	N	%	N	%	
Sex					exact p = 1.0
Male	7	88%	8	100%	
Female	1	12%	0	0%	
Race					exact p = .20
African American	8	100%	5	63%	
European American	0	0%	2	25%	
Asian	0	0%	1	12%	
Employed					exact p = 1.0
Yes	7	88%	7	88%	
No	1	12%	1	12%	
Heroin route of administration					exact p = 1.0
Intravenous	4	50%	4	40%	
Intranasal	4	50%	4	50%	
Cocaine route of administration					exact p = 1.0
Smoked or intravenous	7	88%	7	88%	
Intranasal	1	12%	1	12%	