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Effects of Aripiprazole on Subjective and Physiological Responses to Alcohol

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Abstract

Background—Aripiprazole is an atypical antipsychotic with partial agonist activity at D₂ receptors, which could reduce the reinforcing effects of alcohol. The present study examined whether aripiprazole modifies the behavioral and physiological effects of a moderate dose of alcohol in a group of social drinkers.

Methods—18 healthy subjects (9 men; mean age = 27.6 years) completed a double-blind, within-subject study with three experimental sessions in a randomized sequence, during which they received no medication, aripiprazole 2.5 mg, or aripiprazole 10 mg on the day prior to the laboratory session. During the session, subjects consumed alcohol that was served as three standardized drinks (i.e., a total of 0.8 g/kg for men and 0.7 g/kg for women). Breath alcohol concentration (BrAC), heart rate, blood pressure, static ataxia, and subjective effects were measured regularly throughout the laboratory sessions.

Results—Alcohol consumption produced physiological and subjective responses that were consistent with the literature on its effects. Pre-treatment with aripiprazole was generally well tolerated, with tiredness being the most commonly reported adverse event. The medication was associated with modest physiological effects. It also significantly and dose-dependently increased the sedative effects of alcohol and, to a lesser degree, decreased the euphoric effects of alcohol.

Conclusions—These findings require replication in a larger subject sample that includes heavy drinkers and in a study that employs a placebo session. Based on its capacity to increase the sedative effects and decrease the euphoric effects of alcohol, aripiprazole could be of value in the treatment of heavy drinking.

Keywords

Aripiprazole; Alcohol Administration; Subjective Effects of Alcohol; Physiological Effects of Alcohol; Human Laboratory Study

INTRODUCTION

Aripiprazole is an atypical antipsychotic whose unique receptor binding profile combines partial agonist activity at D₂ and 5-HT_{1A} receptors with potent antagonism at 5-HT_{2A} receptors (Inoue et al., 1996; Burris et al., 2002; Jordan et al., 2002; McQuade et al., 2002). The drug is efficacious for the treatment of bipolar disorder (Keck et al., 2006; Sachs et al.,

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2006) and the positive and negative symptoms of schizophrenia (Kane et al., 2002; Marder et al., 2003; Pigott et al., 2003), but does not induce significant extrapyramidal symptoms or metabolic side effects. As a partial agonist, aripiprazole acts as a functional antagonist at D₂ receptors under hyperdopaminergic conditions, yet exhibits functional D₂ agonist properties under hypodopaminergic conditions (Kikuchi et al., 1995). This action of aripiprazole at D₂ receptors suggests that the drug could reduce the reinforcing effects of alcohol, as dopaminergic neurotransmission has been implicated in ethanol-induced reward (Kornetsky et al., 1988; Koob et al., 1994; Nevo and Hamon, 1995) and the D₂ receptor appears to modulate drinking behavior (McBride and Li, 1998; Myers and Robinson, 1999; Li, 2000). Kenna (2003) observed that aripiprazole has potential utility in the treatment of alcohol dependence.

Although Modell et al. (1993) found that pretreatment of alcohol-dependent individuals with the D₂ antagonist haloperidol decreased craving for alcohol elicited by a priming dose, adverse effects of chronic treatment with first-generation D₂ antagonists (e.g., extrapyramidal side effects, dysphoria, apathy) have limited their use in the treatment of alcohol dependence. Atypical antipsychotics, which are better tolerated, particularly among alcoholics, may be more useful for alcohol treatment. Alcohol-dependent individuals treated with olanzapine, compared with placebo, reported decreased craving for alcohol and fewer drinks per drinking day (Hutchison et al., 2001; 2006). A placebo-controlled study of quetiapine showed the drug to increase significantly the mean number of days abstinent in a sample of alcohol-dependent veterans (Monnelly et al., 2004). In a second study of quetiapine, the drug yielded a significantly higher rate of complete abstinence from alcohol than placebo treatment in a sample of alcohol-dependent patients, with evidence that it was most useful among patients with an earlier onset and greater severity of their disorder (Kampman et al., 2007). In a series of 20 outpatients with bipolar or schizoaffective disorder and comorbid substance abuse whose antipsychotic medication was switched to open-label aripiprazole there was a marked improvement in symptoms of both mania and depression, with no change in adverse effects (Brown et al., 2005). Notably, in this sample, among the patients with co-morbid alcohol dependence, there was a statistically significant reduction in alcohol craving and money spent on alcohol.

Based on the evidence that aripiprazole reduces alcohol consumption in high-alcohol-drinking mice (Ingman et al., 2006) and an open-label trial of the drug that showed potential efficacy in reducing alcohol intake in humans (Warsi et al., 2005), Anton et al. (in press) conducted a 12-week multi-center study of the efficacy of aripiprazole for treatment of alcohol dependence. In that study, 295 patients were randomly assigned to receive treatment with aripiprazole (initiated at 2 mg/day, titrated to 30 mg/day at Day 28), or placebo following an initial period of alcohol abstinence. More aripiprazole-treated patients discontinued the study (40.3 vs. 26.7%) and reported treatment-related adverse events (82.8 vs. 63.6%). There were no medication effects on the mean percentage of abstinent days, the percentage of subjects without a heavy drinking day, and the time to first drinking day, although the aripiprazole group had fewer drinks per drinking day and a larger decrease in percent carbohydrate-deficient transferrin, a biomarker of heavy alcohol consumption. At study endpoint, aripiprazole-treated subjects reported more positive subjective treatment effects and less overall severity of alcohol dependence than placebo-treated subjects. A recent fMRI study of non-treatment seeking alcoholics also showed that aripiprazole produced a complete blockade of alcohol cue-induced activation in the nucleus accumbens, indicating its potential to limit the rewarding and reinforcing effects of alcohol (Myrick et al., 2006). As a partial D₂ agonist that can reduce alcohol reinforcement and craving, without producing substantial extrapyramidal adverse effects, aripiprazole could be of value in alcohol treatment.

A recent, open-label, 16-week study in 13 detoxified alcohol-dependent patients suggested that a flexible dosage of aripiprazole (5–15 mg) is useful in this population (Martinotti et al., 2007). Overall, in the study, there was a progressive decrease in alcohol craving and significant reductions of the SCL-90 R General Severity Index. Interestingly, the effect most commonly reported by subjects was a pleasurable or euphoric feeling in the first week of aripiprazole treatment, suggesting that the medication may affect the neural “reward” component of craving, initially by stimulating it and then subsequently by dampening it, consistent with the effects of a dopamine partial agonist.

The present study examined whether aripiprazole modifies the behavioral and physiological effects of a moderate dose of alcohol in a group of healthy social drinkers. Based on the drug’s pharmacological profile, we hypothesized that aripiprazole would reduce the rewarding, stimulating, and anxiolytic effects of alcohol without altering alcohol’s effects on blood pressure or heart rate.

METHODS

Subjects

Eighteen healthy subjects (9 men) between the ages of 21 and 45 were recruited from the Greater Hartford, CT area by advertisement, and were paid for their participation. All subjects gave written informed consent to participate in the protocol, as approved by the University of Connecticut Health Center Institutional Review Board.

Following an initial telephone interview to screen for eligibility, the psychiatric history of each subject was evaluated using the Structured Clinical Interview for DSM-IV (First et al., 1995). The Timeline Follow-back Interview (Sobell and Sobell, 1992) was used to quantify recent alcohol and drug use during the 90 days prior to enrollment. Information on family history of alcoholism was obtained using the Family History Assessment Module (Janca et al., 1997).

Individuals who were eligible for study participation based on these assessments underwent a medical history and physical examination with routine laboratory tests (complete blood count, liver and renal function tests, blood glucose and electrolyte concentration, toxicology screen, and a serum pregnancy test among women).

Subjects were included in the study if they reported moderate drinking (a minimum of three drinks per week and at least three drinks on one occasion in the past month) and had a body mass index of 18.5–30 kg/m². They were excluded if they ever met the DSM-IV criteria for substance abuse or dependence or another major psychiatric disorder, had a previous hypersensitivity reaction to aripiprazole or evidence of liver dysfunction, were currently using benzodiazepines or other psychotropic medications, or were pregnant or nursing. In order to avoid confounding effects of variation in alcohol effects related to ovarian cycle, women were included only if they reported having regular menstrual cycles, were not using oral contraceptives, and had no history of endocrine or reproductive abnormalities.

Study Design

The study utilized a double-blinded, within-subject design, in which each subject served as his or her own control over three experimental sessions that took place two weeks apart, in a randomized sequence. Subjects were assigned to receive in random order 1) no medication, 2) a low dose of aripiprazole (i.e., 2.5 mg), or 3) a higher dose of aripiprazole (i.e., 10 mg) on the day prior to each alcohol laboratory session. This dosage was based on the recommended starting dosage of aripiprazole for treatment of schizophrenia, which is 10–15

mg/day (<http://www.abilify.com>), with the higher dosage chosen to ensure tolerability by the healthy participants and to avoid adverse effects confounding the evaluation of the impact of the medication on the effects of alcohol. The lower dosage of aripiprazole served as an active control for the effects of the higher dosage, so that although some effects of the medication would be evident, those effects would be differentiable from the effects of the higher dosage.

Aripiprazole tablets were administered under double-blind conditions. Although the subject was not blind to the no-medication session, the personnel conducting the laboratory procedure were blind to whether or not medication was administered. Alcohol was served as three standardized drinks, with the dosage chosen to ensure a quantifiable subjective effect (Holdstock and de Wit, 1998) and adjusted for sex differences in pharmacokinetics (i.e., after three drinks a total of 0.8 g/kg for men and 0.7 g/kg for women).

Physiological & Subjective Effects

Breath alcohol concentration (BrAC), heart rate, and blood pressure were measured regularly (at approximately 40 min intervals) throughout the lab session. The gross psychomotor effects of alcohol were quantified using a test of static ataxia in which body sway was recorded using a BalanceCheck Platform Posturography system (Micromedical Technologies, Inc Chatham, IL) as the subject stood as steady as possible for ten seconds with hands at his or her sides. Balance was challenged during this task through the reduction of visual and tactile inputs by instructing subjects to close their eyes, and by placing a four-inch foam pad under their feet. To prevent falls, a support harness secured each subject. Stability was calculated as the sway area traversed over a 30-second period. Subjects' stability measurements were recorded under four conditions: eyes open or closed and with or without tactile perturbation. Analysis of the differences in body sway focused on differences between subjects' performance during eyes closed with tactile perturbation and eyes open without tactile perturbation. This was intended to provide the most sensitive measure of the effects of alcohol and aripiprazole on static ataxia, since of the conditions that were examined these were the two most extreme. Further, 98% of the differences were negative, indicating that, as expected, subjects' stability was worse when they had neither visual nor tactile inputs.

Subjective effects were measured using self-report questionnaires listed below, which were administered on a computer using SPSS data Builder version 3.0. A monitor was placed in front of the subject approximately 22 inches away at normal viewing level. Subjects were instructed to read each question carefully and to answer it to the best of their ability based on how they felt at the time. Subjects used a computer mouse to click on their responses and to scroll down the screen, answering the self-report questions until they reached the end. Study personnel monitored their progress.

1. *Biphasic Alcohol Effect Scale* (BAES; Martin et al., 1993) is a 14-item unipolar adjective rating scale used to measure both the stimulant and sedative effects of alcohol. Subjects were asked to rate on a scale of 0 (not at all) to 10 (extremely) the extent to which they experienced "alcohol-like" feelings.
2. *Addiction Research Center Inventory* (ARCI; Martin et al., 1971) is a 49-item true-false questionnaire with five empirically derived scales that are sensitive to the effects of several classes of abused substances. Items from the drug-induced euphoria Morphine-Benzodrine Group (MBG) scale measure mood state, while the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scale measures sedative-like effects.

3. *Medication Questionnaire & Adverse Effects Questionnaire* were completed to determine if the medication blind had been penetrated or if the subject experienced any adverse side effects that led them to believe they had received the active drug.

Laboratory Procedures

Since aripiprazole reaches peak plasma concentrations 3–5 hours after an oral dose, and has an elimination half-life of 48–68 hours (DeLeon et al., 2004), subjects were administered study medication (0, 2.5, or 10 mg of aripiprazole) 20 hours prior to initiation of the session. This was intended to provide a balance between adverse effects and those effects that were hypothesized to relate directly to the intoxicating effects of alcohol. Subjects were instructed to fast from solid foods for 8 hours before the session. At the time the study medication was administered, a limited assessment (LA) was conducted, including the measurement of vital signs and BrAC and completion by the subject of the ARCI. A full assessment (FA), during which the subject also completed the BAES, was administered repeatedly during the laboratory sessions.

On the day of each laboratory session, subjects arrived at 0900 hours. As shown in Figure 1, an FA was administered 1 hour prior to the first drink ($t = -60$ min); this was followed by a light breakfast (without caffeine). The dose of alcohol was divided into three equal portions, which were served at $t = 0, 10,$ and 20 min, allowing subjects 10 min to consume each drink. Vital signs and BrAC were measured each time a drink (1/3 of the total dose) was consumed. From 30 min to 4.5 hours after the first drink was administered, subjects underwent an FA, which included the BAES, every 40 minutes until 2.5 hours after the first drink and then every 60 minutes until 4.5 hours after the first drink.

Data Analysis

Mixed-effects models were used to detect the effect of aripiprazole on BrAC, three vital signs measurements, stability differences, and four subjective responses, including the BAES stimulant and sedative subscales, and the MBG and PCAG scales of the ARCI. Demographic characteristics such as sex and race (White, Non-White), as well as linear, quadratic, and cubic time effects, were adjusted for in the analyses, when significant at the 5% level. Seven time points were included in the analysis relative to the first alcohol drink: $-60, +30, +70, +110, +150, +210,$ and $+270$ min. The time of the first assessment (-60 min) was recoded for statistical analysis as 0 min to represent the pre-alcohol condition. All interaction effects were examined for statistical significance. When modeling static ataxia, vital signs measures, and subjective responses, BrAC was considered as a potential covariate, both as a main effect and in its interaction with other predictors.

RESULTS

Subjects

A total of 31 subjects were enrolled in the study. Of the 18 participants who completed all three of the laboratory sessions and are the focus of this report, 9 (50%) were male, 13 (72%) were European-American, 4 (22%) were Hispanic, and 1 (6%) was Asian. The average age of the subjects was 27.6 years ($SD = 6.5$). Subjects' mean (SD) body mass index was 24.2 kg/m^2 (2.8). They were well educated, with 94% having completed college. Subjects' drinking was moderate during the 90 days prior to study enrollment, with a mean (SD) of 19.5 (17.2) days of drinking and 1.8 (3.2) days of heavy drinking (i.e., ≥ 5 standard drinks in a day for men and ≥ 4 standard drinks for women), and a total of 47.8 (46.1) standard drinks consumed.

Laboratory Sessions

Adverse Effects—There were no serious adverse events in this study. Of the 31 subjects who participated in at least one laboratory session, six individuals (19.4%) experienced an adverse reaction that led to their withdrawal from the study. Of this number five experienced nausea and vomiting attributable to alcohol consumption (three during the no-medication session and two during the 2.5-mg aripiprazole session), and one experienced heartburn and chest pain during the no-medication session. Two individuals (6.5%) attributed study discontinuation to adverse medication effects: one cited difficulty sleeping at the 2.5-mg dosage and one reported nausea, fainting, and drowsiness at the 10-mg dosage. In addition, two subjects were excluded from the analysis due to a pharmacy error and three subjects discontinued their participation due to time constraints or were lost to follow-up.

Among the 18 subjects who completed the study, the most commonly reported adverse event was the sensation of tiredness, reported by 14 subjects (77.8%) at the 10-mg aripiprazole dosage and seven subjects (38.9%) at the 2.5-mg dosage. Nausea also varied as a function of dosage, with six subjects (33.3%) reporting this symptom at the 10-mg dosage and three subjects (16.7%) reporting it at the 2.5-mg dosage. Neither tiredness nor nausea was reported for the no-medication session. Other adverse effects included sleepiness (33.3% at 10-mg dosage, 50.0% at 2.5-mg dosage, and 33.3% with no medication), headache (27.8% at 10-mg dosage, 22.2% at 2.5-mg dosage, and 22.2% with no medication), and difficulty sleeping (11.1% at 10-mg dosage, 22.2% at 2.5-mg dosage, and 0% with no medication).

Physiological effects

Breath Alcohol Concentration: There were significant main effects on BrAC of sex ($p = 0.025$), race ($p = 0.006$), linear time ($p < 0.001$), quadratic time ($p < 0.001$), and cubic time ($p < 0.001$), and interactions of sex by linear time ($p = 0.007$), sex by quadratic time ($p = 0.012$), race by quadratic time ($p < 0.001$), sex by cubic time ($p = 0.033$), and race by cubic time ($p < 0.001$). Figure 2 shows the fitted curve of BrAC as a function of time, race, and sex. BrAC ascended steeply, peaking at approximately 0.06g/L at 60–120 min after the initiation of drinking, after which it descended slowly to approximately 0.02g/L at 270 min. As illustrated in the figure, at all time points, males had a higher BrAC than females. During the ascending limb, whites had a higher BrAC than non-whites. However, whites' BrAC decreased faster than non-whites, such that during the descending limb, non-whites had a higher BrAC than whites. There was no effect of medication on BrAC.

Heart Rate: There were significant main effects of BrAC ($p = 0.001$) and medication ($p = 0.034$), and interaction effects of sex by medication ($p = 0.004$), race by medication ($p < 0.001$), and linear time by medication ($p = 0.046$) on heart rate. After adjusting for the effects of sex, race, and linear time, heart rate increased as the dosage of aripiprazole increased [estimated coefficient (B) = 39.93, standard error (SE) = 12.27]. The significant interaction effects indicated that the change in heart rate associated with the dosage of aripiprazole depended on both sex and race. In particular, for each mg increase in aripiprazole dosage, the heart rate among white men increased by 0.54 bpm (SE = 0.71), while among non-white men heart rate increased by 4.04 bpm (SE = 0.86). Among white women, heart rate decreased by 1.60 bpm (SE = 0.68), while among non-white women heart rate increased by 1.90 bpm (SE = 0.92).

Systolic Blood Pressure: There were significant main effects of sex ($p < 0.001$), quadratic time ($p < 0.001$) and cubic time ($p < 0.001$), and a significant sex by medication interaction ($p = 0.002$) on systolic blood pressure. After adjusting for time effects, on average, men had higher systolic blood pressure than women [B = 18.80, SE = 4.07]; for each mg increase in

aripiprazole dosage, systolic blood pressure among men decreased by 1.13 torr (SE = 0.67), whereas among women it increased by 1.83 torr (SE = 0.67).

Diastolic Blood Pressure: There was a significant main effect of BrAC ($p = 0.044$), and linear time ($p = 0.017$), and a significant race by medication interaction ($p = 0.027$) on diastolic blood pressure. After adjusting for the linear time effect, subjects' diastolic blood pressure increased with increasing BrAC [$B = 24.48$, $SE = 12.09$], though it did so differentially by race. Among whites, for each mg increase in aripiprazole dosage, diastolic blood pressure increased by 1.63 torr (SE = 0.43), whereas among non-whites it decreased by 0.17 torr (SE = 0.69).

Static Ataxia: There were significant main effects of race ($p = 0.014$) and BrAC ($p = 0.023$), and a significant race by quadratic time interaction ($p = 0.010$) on the difference in ataxia between the conditions involving neither visual nor tactile inputs and both visual and tactile inputs. Non-white subjects showed greater static ataxia than whites, which varied over time. After adjusting for race and time effects, as would be expected, stability decreased as BrAC increased.

Subjective effects

BAES Stimulant subscale: There were significant effects of linear time ($p < 0.001$), and BrAC ($p < 0.001$) on this subscale score. After adjusting for the effects of time, subjects' stimulant subscale score increased as BrAC increased. Figure 3a shows the changes in sample mean score over time by medication condition. Although the effect of medication did not reach significance, the 10-mg aripiprazole dosage was associated with somewhat lower stimulant subscale scores during the ascending limb of the BrAC curve. This apparent difference, however, disappears during the descending limb of the BrAC curve.

BAES Sedative subscale: There were significant effects of medication ($p = 0.013$) and BrAC ($p < 0.001$) on this subscale score. After controlling for dosage of medication, sedative effects increased as BrAC increased. Also, after controlling for the BrAC effect, sedative effects increased as the dosage of aripiprazole increased. In particular, for each mg increase in aripiprazole, the sedative effect increased by approximately 1.04 units [standard error (SE) = 0.42]. Figure 3b shows the change in sample mean score over time by medication condition. It can be seen there that the effects of medication dosage were greater during the ascending limb of the BrAC, with the differences disappearing at 150 min after the initiation of drinking.

ARCI MBG scale: There were significant main effects of linear time ($p = 0.006$), BrAC ($p < 0.001$), and medication ($p = 0.010$), and significant interaction effects of sex by linear time ($p = 0.010$), sex by quadratic time ($p = 0.008$), and sex by cubic time ($p = 0.044$) on this subscale score. After adjusting for the sex and time effects, subjects' MBG scale score increased as BrAC increased, but it decreased as the dosage of aripiprazole increased. Specifically, for each mg increase in aripiprazole dosage, the MBG score decreased by 0.40 units (SE = 0.16). Figure 4a shows the changes in sample mean score over time by medication condition. It can be seen there that the 10-mg aripiprazole dosage was associated with lower MBG scores during the ascending limb of the BrAC curve. This effect, however, diminished during the descending limb of the BrAC curve.

ARCI PCAG scale: As shown in Figure 4b, there were significant main effects of medication ($p < 0.001$) and BrAC ($p < 0.001$), and a significant interaction effect of race by linear time ($p = 0.019$) on this subscale score. After adjusting for the effects of race and time, subjects' PCAG scale score increased with both BrAC and the dosage of aripiprazole.

Specifically, for each mg increase in aripiprazole dosage, the PCAG score increased by 0.54 units (SE = 0.13). Figure 6 shows the changes in sample mean score over time by medication condition. Although the higher dosage of aripiprazole was associated with significantly higher PCAG subscale scores during the ascending limb of the BrAC curve, this effect diminished beginning at 150 min after the initiation of drinking.

DISCUSSION

In this study, both sex and race moderated the BrAC curve, with men showing higher BrACs than women at all time points following the initiation of drinking. White subjects showed a significantly earlier increase in and peak BrAC than non-whites, though this difference was no longer evident by about 150 min following the initiation of drinking. Increasing BrAC was also associated with increases in heart rate, diastolic blood pressure, and static ataxia. With respect to subjective effects, controlling for the effects of sex and race, alcohol dose-dependently produced stimulatory and euphoric effects, as reflected by greater scores on the stimulant subscale of the BAES and the MBG scale of the ARCI. The subjective effects also showed higher order time effects, particularly quadratic effects, which reflected an increase during the ascending limb and a decrease during the descending limb of the BrAC curve. Alcohol also dose-dependently increased scores on the sedation subscale of the BAES and on the PCAG scale of the ARCI, which reflect increased sedation or decreased physical energy. These effects are consistent with a large literature on the physiological and subjective effects of ethanol (Holdstock et al., 2000; Davidson et al., 2002; Söderpalm and de Wit, 2002). Some of the adverse events that resulted in subjects prematurely discontinuing their study participation were also consistent with effects associated in the literature with alcohol consumption.

Treatment with aripiprazole was associated with modest physiological effects. Specifically, the dosage of aripiprazole directly increased heart rate, particularly in men and non-white subjects. Interaction effects of aripiprazole were also noted on blood pressure, with the medication increasing systolic pressure (among women) and diastolic pressure (among whites). However, there were no effects of the medication on static ataxia.

With respect to subjective effects, as hypothesized, the higher dosage of aripiprazole decreased some of the reinforcing effects of alcohol, while increasing its sedative effects. Specifically, aripiprazole 10 mg decreased the euphoric effects of alcohol relative to the no-medication and 2.5 mg dosage of the drug, as measured by the ARCI MBG scale score. Although it failed to reach statistical significance, aripiprazole 10 mg also decreased scores on the BAES stimulation subscale. As was anticipated given the sedative effects of aripiprazole, the 10-mg dosage of the medication increased scores on both the sedative subscale of the BAES and the PCAG scale of the ARCI.

Given the finding that aripiprazole decreased the euphoric effects of alcohol, while increasing its sedative effects, the medication could be of utility in the treatment of heavy drinking. This conclusion is based on evidence that the sedative effects of alcohol are negatively correlated with drinking practices, and as such may be considered aversive (Martin et al., 1993; O'Malley and Maisto, 1984). Further, compared with lighter drinkers, heavy drinkers report greater stimulation in response to an alcohol challenge, and may experience less sedation than social drinkers (King et al., 2002; Thomas et al., 2004). Although the data reported here require replication in a larger sample that includes heavy drinkers, the effects of aripiprazole observed here suggest that the medication could be of value in reducing drinking behavior.

Although the results of a multi-center study of aripiprazole for treatment of alcohol dependence failed to show an advantage for the medication on the primary outcome measure of percent drinking days, the medication was associated with reduced drinking intensity (Anton et al., in press). The profile of effects shown by the medication in the present study are consistent with these findings, in that they suggest that the medication may be useful in reducing drinking by reducing alcohol's positive effects and increasing its negative effects.

These results must be considered in the context of the study's limitations. In particular, the lack of a placebo-control meant that subjects were not blind to the no-medication session, which may have influenced their responses. It should be noted, however, that the 2.5-mg dosage of aripiprazole was in nearly all respects similar to the no-medication condition (except with respect to the likelihood of adverse effects), suggesting that the impact of the 10-mg dosage on the euphoric and sedating effects of alcohol were pharmacological effects, rather than being simply a function of subjects' expectations of the medication's effects. The lack of a placebo alcohol condition also limits conclusions concerning the effects of aripiprazole in the absence of both the expectancies and the pharmacological effects of alcohol. Given the small sample size, it was not possible to stratify the findings by either sex or race. Finally, the study involved only an acute dose of aripiprazole and included only healthy social drinkers, so that a study in which the medication is administered chronically, and in which heavy drinkers participate, may be useful in evaluating the utility of aripiprazole for use in alcohol treatment. It is possible that, since heavy drinkers are more sensitive to the positive stimulant-like effects of ethanol and less sensitive to the sedative effects of alcohol (King et al. 2002), aripiprazole may dampen the stimulating effects more and be better tolerated in a sample of heavy drinkers. Although in the present study involving healthy subjects, it did not seem warranted to include a measure of craving, such a measure could be of value in a study of heavy drinkers. Despite limitations in the study, the results obtained here suggest that additional research on the effects of aripiprazole on the subjective effects of alcohol is warranted.

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Figure 1. Study and assessment timeline

LA, limited assessment; FA, full assessment; D1, first alcoholic drink; D2, second alcoholic drink; D3, third alcoholic drink; BrAC, breath alcohol concentration measurement

Figure 2. Fitted breath alcohol concentration curve by race and sex
BrAC, breath alcohol concentration

Figure 3. Mean BAES Stimulant (a) and Sedative (b) subscale scores by medication condition
BAES, Biphasic Alcohol Effects Scale

Figure 4. Mean ARCI MBG (a) and PCAG (b) scale scores by treatment condition
 ARCI, Addiction Research Center Inventory; MBG, Morphine-Benzedrine Group; PCAG, Pentobarbital-Chlorpromazine-Alcohol Group