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Aripiprazole effects on self-administration and pharmacodynamics of intravenous cocaine and cigarette smoking in humans

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Abstract

Aripiprazole is a partial agonist at dopamine D2 and serotonin 5-HT_{1a} receptors and antagonist at 5-HT₂ receptors. Because both dopamine and serotonin systems are involved in the action of cocaine, this study aimed to determine if aripiprazole could diminish the reinforcing efficacy of cocaine. Secondary aims evaluated aripiprazole effects on *ad lib* cigarette smoking and a novel 40-hour cigarette smoking abstinence procedure. Healthy adults with regular cocaine and cigarette use completed this ~30-day inpatient double blind, randomized, placebo-controlled mixed-design study. An oral placebo lead-in period was followed by randomization to oral aripiprazole (0, 2 or 10 mg daily; n=7 completed/group). Three sets of test sessions, each consisting of three cocaine sample-choice (i.e., self-administration) sessions and one dose-response session, were conducted (during the lead-in period and after randomization before and after achieving aripiprazole steady state). Sample-choice sessions tested three cocaine doses (0, 20, and 40 mg/70 kg, i.v.) with one dose (random order) administered in each sample session; subjective, observer-rated and physiologic outcomes were collected repeatedly before and after cocaine administration. Later that day, participants chose between receiving the sample dose from that morning or descending amounts of money for seven trials (\$19, 16, 13, 10, 7, 4, 1). Dose response sessions administered the three cocaine doses in ascending order for pharmacodynamic and potential pharmacokinetic assessment. A set of two cigarette smoking topography sessions were conducted during placebo lead-in and after randomization; one with and one without 40-hours of cigarette smoking abstinence. Number of *ad lib* cigarettes smoked during non-session days was also collected. Cocaine produced prototypic pharmacodynamic effects and self-administration; neither were significantly altered by aripiprazole. The 40-hour smoking abstinence procedure reliably produced nicotine withdrawal and craving and increased smoking modestly. Aripiprazole did not significantly alter smoking outcomes. These data do not support the further investigation of aripiprazole for the treatment of cocaine or tobacco use disorders.

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Keywords

self-administration; intravenous; cocaine; aripiprazole; cigarette smoking

Introduction

Cocaine use continues to be a significant public health problem in the United States associated with significant morbidity and mortality (e.g., infectious diseases, cardiovascular adverse events). The National Survey on Drug Use and Health reported that in 2011 there were approximately 746,000 new users of cocaine (including crack), 1.4 million persons currently using cocaine, and 0.8 million persons meeting diagnostic criteria for cocaine abuse or dependence (SAMHSA, 2012). The Drug Abuse Warning Network reported that cocaine accounted for 40% of all emergency room department visits involving illicit drugs in 2011 (SAMHSA, 2013). Despite significant efforts, there remain no efficacious pharmacologic treatments for cocaine use disorders.

Cocaine exerts an array of mixed central nervous system actions believed to be involved in the development and maintenance of compulsive drug use, including blockade of reuptake of dopamine, serotonin, and norepinephrine and, less potently, induction of release of these neurotransmitters (Rothman & Baumann, 2003). While it has been well-established that the reinforcing action of cocaine is due, in large part, to its ability to enhance mesolimbic-cortical dopamine activity (Di Chiara & Imperato, 1988), Volkow and colleagues have also shown that there is dopamine hypofunction in other cortical areas, such as the orbital-frontal cortex that is critical to the regulation of drive that may underlie compulsive drug-seeking and conditioned responses (Volkow & Fowler, 2000; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). In addition, there is a growing literature supporting a modulatory role of serotonin in cocaine action and dysregulation of serotonin receptors in cocaine abusers during acute withdrawal and after cocaine overdose (Filip, Alenina, Bader, & Przegalinski, 2010; Huang, Liang, Lee, Wu, & Hsu, 2009; Jacobsen et al., 2000; Mash, Staley, Izenwasser, Basile, & Rutenber, 2000). Given the complex pharmacologic action of cocaine and mechanistic changes occurring with repeated cocaine use, it is logical to evaluate agents with more heterogeneous actions that may target multiple aspects of dysfunction within the addicted brain.

Aripiprazole is a unique atypical antipsychotic because it was the first developed that was not a D2 receptor antagonist, but rather a partial agonist at D2 receptor sites (Burris et al., 2002; Inoue, Domae, Yamada, & Furukawa, 1996; Kikuchi et al., 1995; Lawler et al., 1999). For example, preclinical studies demonstrated that it functioned as an agonist in hypodopaminergic states decreasing dopamine accumulation in reserpine and butylactone-treated animals and acted as a functional antagonist in hyperdopaminergic states blocking apomorphine-induced stereotypy and locomotion (Kikuchi et al., 1995). This action combined with its partial agonist activity at the 5-HT_{1a} receptor and antagonist action at the 5-HT_{2a} receptor led to its conceptualization as a “dopamine serotonin stabilizer” (Jordan et al., 2002). Given these combined receptor actions, it was hypothesized that aripiprazole may be able to decrease cocaine use through blockade of the acute effects of cocaine and through

restoration of neural homeostasis of dopamine and serotonin systems dysregulated by chronic cocaine use. Earlier clinical work supported this hypothesis as acute doses of aripiprazole (20 mg) attenuated the discriminative stimulus properties, cardiovascular effects and liking of d-amphetamine in stimulant abusers (Lile et al., 2005). Also, a small (n=7) 12-week outpatient clinical trial of cocaine-dependent adults treated with 5 mg or 10 mg/daily of aripiprazole showed a reduction in cocaine-positive urine samples (Gonzalez et al., 2005).

More recent clinical studies, reported while the present study was underway, have examined repeated aripiprazole dose administration (10 and 15 mg/day tested) and reported a lack of efficacy in diminishing the reinforcing and subjective effects of intranasal (Lile, Stoops, Hays, & Rush, 2008; Stoops, Lile, Lofwall, & Rush, 2007) and smoked cocaine (Haney, Rubin, & Foltin, 2011). However, no studies to date have reported on the effects of aripiprazole on the reinforcing effects of intravenous cocaine.

Thus, this inpatient study aimed to evaluate the effects of two aripiprazole doses, under both acute and steady state conditions, on the reinforcing effects of cocaine over a range of intravenous cocaine doses using a well-characterized self-administration procedure that employs alternative reinforcers (i.e., money). Multi-dimensional pharmacodynamic assessments of cocaine were also collected. In addition, earlier preliminary data suggest that atypical antipsychotics may reduce cigarette smoking among psychiatric patients switching from typical antipsychotics (George, Sernyak, Ziedonis, & Woods, 1995; George et al., 2000; McEvoy, Freudenreich, & Wilson, 1999) and that D2 receptor agonists and antagonists may affect cigarette smoking behavior among non-psychiatric patients (Brauer, Cramblett, Paxton, & Rose, 2001; Caskey, Jarvik, & Wirshing, 1999; Caskey et al., 2002). Thus, a secondary aim was to examine directly the effects of aripiprazole on *ad lib* smoking behavior compared to placebo and also under conditions of smoking abstinence (i.e., 40 hours of abstinence) versus satiety. If results demonstrate signals of decreased smoking, smoking craving or nicotine withdrawal in this sample of otherwise healthy cocaine users, then aripiprazole, or similar mixed action agents, may warrant further evaluation as smoking cessation medications.

Methods

Participants

Participants were recruited through local advertising and word-of-mouth. Participants were required to be age 21 to 45 years old and within 20% of ideal body weight (approximates BMI but is adjusted for gender). They had to self-report using IV or smoked cocaine approximately 2-3 times per week and smoking cigarettes daily, provide a positive urine drug screen for cocaine metabolite and breath sample for carbon monoxide, and not be seeking drug abuse or smoking cessation treatment. Outpatient screening assessments included the Beck Depression Inventory (Beck & Steer, 1984), Symptom Checklist 90 (Derogatis, Rickels, & Rock, 1976), and Fagerstrom Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). A medical history and physical examination, 12-lead electrocardiogram, and laboratory testing (urine drug screen, pregnancy testing, urinalysis, hemogram, lipid profile, complete metabolic profile) also were completed in order to ensure that all participants were healthy. Volunteers were excluded if

they were pregnant, breastfeeding, had an abnormal ECG, abnormal screening laboratory results (e.g., dyslipidemia, liver function tests three times the upper limits of normal), current medical or psychiatric illness (e.g., hypertension or schizophrenia), or physiologic drug dependence requiring medical management. All participants gave written informed consent and were paid for study participation. The University of Kentucky (UK) Institutional Review Board approved this study, which was conducted in accordance with the Helsinki guidelines for ethical conduct of research. A Certificate of Confidentiality was obtained from the National Institute on Drug Abuse.

Drugs

Using aseptic technique under a laminar flow hood, cocaine powder (Mallinckrodt, Inc., St. Louis, MO) was weighed, dissolved in sterile saline (Hospira, Lake Forest, IL) and filtered through a 0.22 micron Millex-GS filter in order to prepare each IV cocaine dose (10, 20, and 40 mg/70 kg) in 1 ml of solution for injection. IV placebo contained 1 ml of sterile saline. During every cocaine session, normal saline was administered IV in order to keep the peripheral vein open. IV cocaine doses were administered through a peripheral catheter port over 1 min followed by a 10 ml saline flush. Aripiprazole tablets (1 and 5 mg; Otsuka America Pharmaceutical, Rockville, MD) and matched placebo (corn starch) were over-encapsulated in size 0 gelatin capsules in order to maintain the study blind. The study was conducted under IND #75,330.

Study Design and Setting

This 1-month study (mean: 32.3 days) employed a double blind, placebo-controlled, randomized mixed-design with participants residing as inpatients in the UK hospital research unit under 24-hour nursing supervision. They were maintained on a caffeine-free diet and provided daily urine samples that were tested for drugs of abuse; all test results indicated no unauthorized drug use during study participation. Females had weekly urine pregnancy testing; all results were negative. Participants were allowed to smoke their desired brand of cigarettes, provided at no cost, *ad lib* under supervision outdoors when not in session, but not during the required 40-h cigarette smoking abstinence periods (see smoking session section for more details).

After admission, all participants were familiarized with study measures that primarily were collected on a Macintosh computer system and participated in an initial cocaine safety session. In this session, a physician (MRL) administered four IV cocaine doses (0, 10, 20, and 40 mg/70 kg) in ascending order 30 minutes apart. Only those participants who did not exhibit idiosyncratic reactions to cocaine or exceed pre-specified cardiovascular safety parameters proceeded in the study (Walsh, Geter-Douglas, Strain, & Bigelow, 2001). After this session, participants began three sequential phases of twice daily oral aripiprazole dosing (at 1000 and 2200 hrs): 1) a single-blind placebo lead-in (mean days = 10.2); 2) acute (i.e., pre-steady state) dosing (mean days = 7.8); and 3) steady-state dosing (mean days = 11.8). After the placebo lead-in, participants were randomized, stratified by gender, race (white, black, or other), and smoking (< 10 vs. 10 cigarettes/day), to one of three groups: placebo or aripiprazole 2 or 10 mg daily (given as two divided doses) for the remainder of the study. The last seven participants were also stratified by weight (<160 vs. 160 pounds)

as weight-based dosing was used for cocaine and the group mean weights were unevenly skewed. The 10 mg dose was chosen because it is an effective clinical dose to treat schizophrenia, and a PET study demonstrated that, after 14 days of dosing in healthy non-schizophrenic adults, approximately 85% of D2 and D3 receptors in the caudate and putamen were occupied (Yokoi et al., 2002). The 2 mg dose was selected as a lower dose that occupied approximately 61-82% of these receptors in these regions. Experimental cocaine sessions occurred during each phase. Smoking sessions occurred during the placebo lead-in and steady-state phases only and at least 48 hours after any cocaine session. Figure 1 displays the study timeline.

Experimental Cocaine Sessions and Outcome Measures

During each dosing phase, participants participated in two types of cocaine sessions: 1) sample-choice (i.e., self-administration) and 2) dose-response. The first cocaine session in the steady-state dosing phase occurred after a minimum of 13 days of acute dosing in order to achieve approximate steady state concentrations of aripiprazole ($T_{1/2} \sim 75$ hours) and its primary active metabolite dehydro-aripiprazole ($T_{1/2} \sim 94$ hours) (Otsuka Pharmaceutical Co, 2012; Kubo, Koue, Maune, Fukuda, & Azuma, 2007). There were three paired sample-choice sessions during each phase to evaluate the reinforcing effects of cocaine (0, 20, and 40 mg/70 kg, i.v.; randomized order). In the morning, participants had a 1.5-hour sample session wherein they received one cocaine dose (at 0900 hours) and were told to remember its effects because later that day (at 1300 hours), during the 2.5-hour choice session, they could choose between receiving that morning's sample cocaine dose or descending amounts of money (\$19, 16, 13, 10, 7, 4, 1) on each of seven trials with an inter-trial interval of 15 min (Donny, Bigelow, & Walsh, 2004). Primary outcomes from the choice sessions included mean number of injections chosen, dollar value of first injection chosen, and total money earned.

Primary outcomes from the sample sessions included participant- and observer-rated measures and physiologic data. Physiological measures collected every minute included heart rate and blood pressure (Dinamap Pro 1000V3 Monitor, GE Medical Systems, Tampa, FL). Pupil diameter and respiratory rate were assessed at baseline and at 5, 10, 15, 30, and 45 min after drug administration. Pupil diameter initially was measured using a Polaroid camera with a two-fold magnification, but camera film production was discontinued before study completion, and a pupillometer (Neuroptics, San Clemente, CA) was used thereafter. Participant and observer-rated stimulant adjective items were rated on a 5-point scale from 0 (no effect) to 4 (maximum effect) and assessed at baseline and at 10, 30 and 45 min after drug administration. There were 37 participant-rated items (i.e., drug effect, nervous, stimulated, excited, feeling of power, fearful, thirsty, craving for cocaine, sad/depressed, confused, stomach upset/nausea, headache, agitated, abdominal cramps, restless, tired, down, anxious, sleepy, feel a thrill, happy, dizzy/light-headed, dry mouth, weak, drowsy, jittery, tremor, sweating, fidgety, hungry, difficulty concentrating, stuffy nose, seeing or hearing things, irritable, numbness, tingling, suspiciousness) and 9 observer-rated items (i.e., drug effect, difficulty concentrating, fidgety, talkative, positive vocalizations, tremor/shaky, sweating, edgy/irritable, and moody). Participants also rated the street value of each injection and six visual analog scale (VAS) items that included "Any Drug Effect," "Rush,"

“Good Effects,” “Bad Effects,” “Liking,” and “Desire for Cocaine.” Participants clicked along a 100 mm line anchored by “none” at one end (scored 0) and “extremely” at the other end (scored 100) for all VAS items; these were collected at baseline, every minute for the first 10 min and at 15, 30, and 45 after injection.

The dose-response sessions lasted 3.5 hours and tested three ascending doses of IV cocaine (0, 20, and 40 mg/70 kg) at 1-hour intervals to capture the complete time action curve for each dose. The primary purpose of the cocaine dose response sessions was to collect serial peripheral blood samples, drawn through an indwelling catheter inserted into the arm opposite that used for the cocaine administration for later assay of cocaine, aripiprazole and metabolites if results demonstrated that aripiprazole was efficacious. In addition, the same subjective and observer-rated measures and physiologic data that were collected during sample sessions were collected in dose-response sessions.

Cigarette Smoking Experimental Sessions and Naturalistic Smoking Assessment

Two types of smoking topography sessions were completed during the placebo lead-in and steady-state dosing phases: 1) one session was conducted after 40 hours of smoking abstinence and 2) one session was conducted after *ad lib* smoking (i.e., sated). Order of session type (i.e., sated or abstinent) was counterbalanced across participants and aripiprazole doses. Sessions started at noon, lasted 2.5 hours, and never occurred the day after a cocaine session. Participants smoked cigarettes using the Clinical Research Support System (CReSSmicro) device (Plowshare Technologies Inc, Baltimore, MD). Topography outcomes were collected only during the first cigarette smoked and included puff volume (ml), average flow (ml/sec), peak flow (ml/sec), puff duration (ms), inter-puff interval (ms), and total puffs. The total number of cigarettes smoked during each session was recorded. At baseline and after each cigarette smoked, carbon monoxide levels were measured with a piCO+ Smokerlyzer (Covita, Haddonfield, NJ) along with the following participant-rated assessments: 1) revised 9-item Minnesota Nicotine Withdrawal Scale (irritability, anxiousness, depression, difficulty concentrating, insomnia, restless, impatient, excessive hunger and craving cigarettes) with each item rated on a scale from 0-3 (none, mild, moderate, severe) (Etter, Ussher, & Hughes, 2013; Hughes, 2007) and summed to give a total score; 2) the brief Questionnaire for Smoking Urges (QSU-brief) that forms two subscales, Factor 1 and Factor 2, reflecting the positive and negative reinforcing effects of smoking, respectively (Cox, Tiffany, & Christen, 2001; Tiffany & Drobes, 1991); 3) Shiffman and Jarvik Scale, which gives four subscales (craving, psychological, physical, stimulation) describing symptoms experienced during smoking abstinence (Shiffman & Jarvik, 1976); 4) a cigarette satisfaction item that asked “Please rate your satisfaction with the cigarette you just smoked” on a scale from 1 (not at all satisfied) to 10 (extremely satisfied); 5) five VAS smoking effect items, which included “Do you: feel any effect from this cigarette; good effects from the cigarette; bad effects from the cigarette; like the effect from the cigarette; and dislike the effect of the cigarette?”; 6) five VAS cigarette craving items, which asked “How: pleasant would a cigarette be right now; much of an urge or desire do you have to smoke right now; much do you want to smoke just for the pleasure of smoking; much do you need to smoke right now, just for relief; and much do you want to

smoke right now?" VAS items were presented on a 100-mm line anchored on the left with "not at all (scored 0)" and on the right with "extremely" (scored 100).

Naturalistic smoking behavior during *ad lib* smoking days (i.e., excluding study session days and days with 40 h smoking abstinence) was assessed through nursing and volunteer self-report of number of cigarettes smoked per day.

Assessment of Aripiprazole Adverse Effects

Weight was assessed at admission, at the start of the acute (i.e., pre-steady state) and steady-state phases, and at the end of the steady-state phase. The corrected QT interval (ms) and serum alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase levels (IU/L) were assessed at screening and discharge. Serum glucose and lipid levels were assessed at admission and discharge, but due to variable discharge times, not all results were completed under fasting conditions. Participants rated the severity (not at all, mild, moderate, severe, and very severe) of 11 possible side effects of aripiprazole (i.e., agitated, constipation, headache, insomnia, lightheaded, nausea, restlessness, sweating, trouble swallowing, and vomiting) weekly. The Abnormal Involuntary Movement Scale (AIMS) and Barnes Akathisia Scale were completed daily (Barnes, 1989; Guy, 1976).

Analyses

Participant demographic and baseline substance use characteristics were compared between Groups (i.e., aripiprazole 0, 2, and 10 mg) using 1-factor models. For physiologic and participant- and observer-rated outcomes collected repeatedly in cocaine dose-response and sample sessions, peak maximum scores were calculated after each dose. In order to ensure that randomization was successful, placebo lead-in data (prior to random assignment) were evaluated for all Cocaine session data using 2-factor (Group, Cocaine Dose) models. If there were no significant Group effects (i.e., no significant main effects or interactions involving Group) during the placebo lead-in, effects of aripiprazole on cocaine outcomes then were evaluated with 3-factor models [Phase (acute and steady state), Group, and Cocaine Dose].

Placebo lead-in smoking session data first were analyzed using 3-factor models for Group, Session Type (sated versus 40 h abstinent), and Time (baseline before first cigarette smoked versus after first cigarette smoked). If there were no significant Group differences, placebo lead-in analyses alone were repeated (without Group as a factor) to evaluate the effects of the 40-hour abstinent smoking procedure on smoking outcomes. Steady state data were then evaluated using 3-factor models (Group, Session Type, and Time). Change from placebo lead-in scores were calculated and used for subsequent analyses evaluating acute and steady state outcomes if there were any significant Group effects detected during the placebo lead-in for cocaine or smoking sessions.

Naturalistic smoking was evaluated by calculating the average number of cigarettes smoked on *ad lib* smoking days during each phase. In order to ensure no baseline differences between groups prior to randomization, 1-factor models (Group) evaluated smoking during the placebo lead-in. Subsequently, 2-factor models (Group, Phase) evaluated smoking during the acute and steady state phases. Change from admission to discharge in serum

laboratory measures and ECG QTc intervals were calculated and evaluated with 1-factor models (Group). Weight was evaluated with a 2-factor model (Group and Time). All models were run with Proc Mixed in SAS 9.3 (SAS Institute, Inc., Cary, NC). Tukey post-hoc comparisons were completed to explore detected significant main effects and interactions. Other side effect measures are described descriptively. Data are presented as means (standard errors) unless otherwise noted. Statistical significance was set at $p < 0.05$.

Results

Participants

Twenty-one participants (19 males, 2 females) completed the study ($n=7/\text{group}$). Table 1 displays their demographic and substance use characteristics. Non-completers ($n=13$; 10 males, 3 females) discontinued the protocol for the following reasons: five left for personal reasons (e.g., decided wanted treatment, missing family); four were insensitive to the subjective and/or reinforcing effects of cocaine either during the safety session or during cocaine sessions in the placebo lead-in phase; one violated unit rules; one was discharged due to blood pressure exceeding safety parameters after cocaine administration; one was discharged due to poor venous access (required for blood sampling); and one was unable to understand study tasks.

Experimental Cocaine Sessions

Placebo lead-in analyses from the self-administration sessions showed no significant Group effects as expected. Analyses of acute (i.e., pre-steady state) and steady-state self-administration session data showed a main effect of Cocaine for all outcomes (all F values > 50 and p values < 0.0001) without significant Group effects. There was a main effect of Phase for dollar value of the first injection ($F: 6.970$, $p=0.017$) and money earned (8.780 , $p=0.008$) whereby dollar value for cocaine doses tended to increase in both active aripiprazole groups between the acute to the steady-state phase. The result for number of injections chosen is displayed in Figure 2 and is illustrative of the other self-administration outcomes (data not shown).

Sample and dose response session analyses evaluated the same pharmacodynamic outcomes and had similar results. Thus, only sample session results are reported. Placebo lead-in analyses showed five outcomes with unexpected Group effects (hungry, irritable, nervous, numbness and heart rate); however, no group differences in the acute and steady-state analyses were observed after correction for these baseline differences.

Acute and steady-state sample session analyses typically showed a lack of Group effects. There were prototypical and statistically significant Cocaine Dose effects on most participant- and observer-rated outcomes and physiologic measures (e.g., feeling stimulated and excited, appearing fidgety and sweating, and having greater maximum pupil diameter, and higher peak maximum heart rate and systolic and diastolic blood pressure). “Liking” is shown in Figure 3; similar results were found for “Good Effects” and “Rush” whereby all showed Cocaine Dose-related increases in ratings (all F values > 58 and p values < 0.0001). “Liking” also showed a significant Group $\times$ Cocaine Dose interaction ($F: 4.440$, $p=0.005$).

whereby it appeared that those receiving aripiprazole 2 mg reported greater liking of the highest cocaine dose compared to those receiving placebo or aripiprazole 10 mg. However, post-hoc Group comparisons among each cocaine dose were not significant. Only four other measures showed significant main effects of Group or interactions of Group with Cocaine Dose and/or Phase (i.e., participant ratings of feeling of power, thirsty, and abdominal cramps and observer-rated difficulty concentrating). However, these four items had low peak ratings within each group after each cocaine dose (less than 1.0).

Cigarette Smoking Experimental Sessions

Placebo lead-in analyses showed that the 40-hour abstinence procedure produced lower CO levels ($F: 27.660, p < 0.0001$), higher MNWS scores ($F: 15.720, p = 0.001$), and higher ratings of craving on several measures (e.g., QSU Factors 1 and 2, Shiffman Craving subscale, and all Craving VAS items) compared to sated sessions without significant Group effects. This is illustrated in Figure 4. Results also demonstrated that CO levels significantly increased in both session types after smoking the first cigarette, while MNWS scores and craving decreased significantly after smoking the first cigarette in the abstinent session. Participants smoked 3.0 (0.2) cigarettes in the abstinent session versus 2.6 (0.2) cigarettes in the sated session ($F: 2.900, p = 0.009$). Topography measure outcomes and VAS smoking effect scores were not significantly different between sated and abstinent sessions (data not shown). Significant Group main effects were detected on the Schiffman Craving subscale ($F: 4.250, p = 0.031$) and Craving VAS pleasant item ($F: 3.930, p = 0.038$) whereby there were lower craving scores [0 mg: 21.4 (1.6), 2 mg: 15.3 (1.6)] and higher pleasant scores [0 mg: 38.6 (6.8), 2 mg: 66.5 (6.6)] among those who later would be randomized to the 2 mg group than to the placebo group. The VAS good effects from smoking item showed a significant Group $\times$ Time interaction ($F: 4.500, p = 0.026$) without significant post-hoc comparisons.

Evaluation of steady-state smoking session data revealed that all participants smoked at least one cigarette during each smoking session (maximum=6); however, there was no effect of aripiprazole on the number of cigarettes smoked, CO level, craving measures, or smoking topography outcomes. “Any Effects” from smoking showed a significant Group effect ($F: 4.850, p = 0.021$) whereby after smoking the first cigarette in both session types, “Any Effects” ratings were highest for the 2 mg dose [(34.6 (7.7))] and lowest for the 10 mg dose [(13.6 (4.4))]. However, post-hoc tests showed that these were not significantly different compared to placebo [26.2 (6.4)], and no other VAS smoking effect item showed significant Group effects. There was a main effect of Group ($F: 3.930, p = 0.038$) on the Shiffman Physical Symptoms subscale with the 10 mg group [14.4 (0.6)] having significantly lower scores than placebo [17.3 (0.5)] across both session types. This appears attributable to significantly lower scores on the Physical Symptom subscale item “Do you have fluttery feelings in your chest right now?” in the 10 mg group [4.7 (0.3)] compared to placebo group [6.0 (0.2)] because it was the only physical subscale item with a significant Group effect. Notably, a score of 5 indicates “probably not” and score of 6 indicates “definitely not” showing that fluttery feelings were not common in either group. On the MNWS (group $F: 3.590, p = 0.049$), the 10 mg group had significantly higher total withdrawal scores [3.1(0.5)] than placebo across both session types [1.5 (0.4)]. These are low total MNWS scores for both groups, and there were no individual MNWS items with significant Group effects.

Naturalistic Cigarette Smoking Assessment

During the placebo lead-in, there were no significant Group differences in the number of cigarettes smoked per day as evaluated by nursing [10.2 (1.1)] or participant self-report [10.4 (1.1)]. After randomization, number of cigarettes smoked/day did not differ among ARP doses by phase. However, there was a significant Group $\times$ Phase interaction on cigarette smoking. Post-hoc comparisons demonstrated that smoking increased among those receiving aripiprazole 2 mg from 12.5 (2.2) during the acute (i.e., pre-steady state) phase to 17.7 (3.1) cigarettes/day during the maintenance phase as measured by self-report (Figure 5); nursing report showed similar results (data not shown).

Aripiprazole Adverse Effects

There were no significant effects of Group on liver function tests, glucose and lipid values, QTc intervals, or weight. Participants in all groups gained an average of 17.1 (2.3) lbs during study participation. There were no abnormal involuntary movements and no reports of restlessness that caused discomfort in any participant post-randomization. All side effects were rated as mild or moderate. The most common side effects reported were insomnia, headache and constipation.

Discussion

This inpatient mixed design, double-blind, randomized placebo controlled study evaluated the efficacy of aripiprazole (2 and 10 mg daily) in attenuating the pharmacodynamic effects and self-administration of intravenous cocaine and cigarette smoking. It also evaluated the effects of a novel 40-hour cigarette smoking abstinence procedure. The results indicate that aripiprazole was not efficacious in diminishing intravenous cocaine use or the positive reinforcing subjective effects of cocaine. Similarly, aripiprazole did not provide a signal of attenuating nicotine withdrawal and craving or cigarette smoking under abstinent or sated smoking conditions. However, the 40-hour cigarette smoking abstinence procedure produced nicotine withdrawal and craving and lower CO values demonstrating that this procedure is a sensitive, reliable and valid model for inducing modest levels of nicotine withdrawal.

A strength of the study is that it evaluated two doses of aripiprazole and conducted experimental cocaine sessions twice; once soon after initiating aripiprazole dosing, before steady state could be reached, and again after at least 13 days of dosing, approximating when steady state should be reached. This is important because several effective pharmacotherapies for substance use disorders, such as buprenorphine and methadone for opioid dependence treatment, do not provide signals of reduced opioid use or blockade of the pharmacodynamics effects of illicit opioids used immediately. The lack of any signal suggesting that aripiprazole may be a helpful cocaine pharmacotherapy also was not due to insensitive experimental cocaine procedures because the demonstrated rates of cocaine self-administration and pharmacodynamic effects of cocaine clearly were sensitive to cocaine dose manipulations. For example, cocaine self-administration increased (see Figure 2) and choices for money decreased as the available dose of cocaine increased, replicating previous

work and demonstrating the utility of this self-administration method (Donny, Bigelow, & Walsh, 2003; Walsh et al., 2001).

Notably, aripiprazole was safe and well tolerated, and in combination with placebo cocaine, produced no signal of abuse liability among cocaine users. Interestingly, participants gained an average of 17 pounds over the course of this 1-month study. Weight gain has been observed among participants in other inpatient studies and is likely due to increased access to food and decreased physical activity. There were several non-completers in this study (but none related to aripiprazole side effects), which resulted in a small sample size that may have limited power to detect aripiprazole effects. However, it is unlikely that a larger sample would have resulted in substantially different results given the negative results from other clinical studies evaluating the effects of aripiprazole on the reinforcing effects of intranasal or smoked cocaine (Haney, Rubin, & Foltin, 2011; Lile, Stoops, Hays, & Rush, 2008; Stoops, Lile, Lofwall, & Rush, 2007), and recent randomized clinical trials have also shown negative results for aripiprazole as a treatment for methamphetamine dependence (Coffin et al., 2013; Sulaiman et al., 2013). This study now extends these negative findings to intravenous cocaine.

Interestingly, Haney and colleagues' study actually reported an increase in self-administered smoked cocaine (12 and 25 mg doses) with aripiprazole 15 mg/day. While our study showed no evidence of aripiprazole increasing cocaine self-administration, it did suggest that the 2 mg group experienced more liking for the 40mg/70 kg cocaine dose than the placebo and 10 mg groups during steady state. Interestingly, this 2 mg group also increased their cigarette smoking from pre-steady state to steady state phases, but the number of cigarettes smoked daily did not surpass the number of cigarettes smoked per day while outpatient prior to study admission, and ad lib smoking outcomes did not differ between groups.

There was no evidence that aripiprazole decreased cigarette craving, decreased smoking (in session and during naturalistic ad lib conditions), or alleviated nicotine withdrawal in this sample of cocaine users that also smoked cigarettes daily. Notably, cigarette smoking decreased after admission to the hospital during the placebo lead-in phase. This may be due to the inpatient environment lacking their natural environmental smoking cues and a response cost associated with smoking in the hospital (i.e., can smoke only in a designated smoking area that is under staff supervision) as has been suggested and observed in inpatient opioid dependent cigarette smokers. Aripiprazole 10 mg increased MNWS total scores compared to placebo in the current study, although these scores were relatively low overall, which may reflect the sample's relatively modest level of nicotine dependence (see Table 1: in each group, mean Fagerstrom scores were 4-5). Previous work evaluating aripiprazole's effect on cigarette smoking are limited and mixed. For instance, in both heavy and light smokers without other substance or psychiatric disorders, a single 10 mg dose worsened nicotine withdrawal (Liu et al., 2009) while repeated aripiprazole dosing at 10 mg/day for 2 weeks in heavy smokers did not worsen nicotine withdrawal compared to placebo (Liu et al., 2010).

In summary, repeated dosing of aripiprazole at doses of 2 and 10 mg/day did not attenuate the reinforcing efficacy of intravenous cocaine and did not relieve nicotine withdrawal,

cigarette craving, or decrease cigarette smoking. These results do not support aripiprazole as a treatment for cocaine use disorders or as a cigarette smoking cessation treatment.

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Figure 1.

Study timeline. The first cocaine sample-choice session during the steady-state dosing phase occurred after a minimum of 13 days of dosing.

Figure 2.

Effects of aripiprazole on number of cocaine injections self-administered. Three-factor ANOVA (Group, Cocaine Dose, Phase) showed significant main effects of Cocaine Dose. Post-hoc tests revealed no modulatory effects of Group on Cocaine Dose in either acute (i.e., pre-steady state) or steady-state phases (i.e., no significant results for Group $\times$ Phase $\times$ Cocaine Dose or Group $\times$ Cocaine Dose post-hoc comparisons).

Figure 3.

Effects of aripiprazole on peak participant-rated drug liking scores during cocaine sample sessions. Three-factor ANOVA (Group, Cocaine Dose, Phase) showed significant main effects of Cocaine Dose. There was a significant Group $\times$ Cocaine Dose interaction for Like; however, post-hoc testing revealed no significant comparisons.

Figure 4.

Abstinence versus sated cigarette-smoking sessions during placebo lead-in. There were significant main effects of session type and time for all outcomes shown. BL = baseline time point. Filled symbols denote significant difference compared to BL time point within that session type. * Significant difference between session types at that time point.

Figure 5.

Participant self-report of number of cigarettes smoked. BL = Baseline self-report during outpatient screening. There was no main effect of Group during the inpatient study. However, there was a significant Group $\times$ Phase interaction whereby post-hoc comparisons demonstrated that smoking increased among those receiving aripiprazole 2 mg from 12.5 (2.2) during the acute phase to 17.7 (3.1) cigarettes/day during the maintenance phase.

Table 1

Demographic and substance use characteristics.

Characteristic	Aripiprazole Dose		
	0 mg (n=7)	2 mg (n=7)	10 mg (n=7)
Age in years	32.6 (3.1)	34.0 (2.5)	38.1 (1.4)
Years of completed education	11.3 (0.9)	11.3 (0.8)	11.4 (0.2)
Male gender, n (%)	7 (100%)	6 (85.7%)	6 (85.7%)
Weight in lbs	157.7 (5.9)	154.8 (9.0)	174.7 (10.4)
Race, n (%):			
African American	5 (71.4%)	5 (71.4%)	5 (71.4%)
Caucasian	2 (28.6%)	2 (28.6%)	2 (28.6%)
Current primary route of cocaine use, n (%):			
Smoked	7 (100%)	6 (85.7%)	7 (100%)
Intravenous	0 (0%)	1 (14.3%)	0 (0%)
Number of days in the last 30 days use of:			
Cocaine	19.4 (3.4)	13.6 (3.3)	21.1 (2.8)
Benzodiazepines	0.3 (0.2)	0.3 (0.3)	0.6 (0.4)
Alcohol	7.9 (3.4)	8.3 (2.5)	17.0 (3.8)
Heroin	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Prescription Opiates	1.0 (0.4)	0.9 (0.7)	1.6 (1.4)
Number of cigarettes smoked/day	12.3 (2.1)	20.4 (3.0)	18.0 (2.6)
Fagerstrom score	3.6 (1.0)	5.3 (0.8)	4.1 (1.1)

Data are means (S.E.) unless otherwise indicated. There were no statistical differences among the three randomized groups.