Published in final edited form as:

J Addict Med. 2012 December ; 6(4): 265–273. doi:10.1097/ADM.0b013e31826b767f.

Safety of Atomoxetine in Combination with Intravenous Cocaine in Cocaine- Experienced Participants

Louis Cantilena, M.D., Ph.D.^a, Roberta Kahn, M.D.^b, Connie C. Duncan, Ph.D.^c, Shou-Hua Li, Ph.D.^b, Ann Anderson, M.D.^b, and Ahmed Elkashef, M.D.^b

^aDivision of Clinical Pharmacology and Medical Toxicology, Uniformed Services University of Health Sciences, Bethesda, MD 20814

^bMedical/Clinical Branch, Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20892

^cDepartment of Psychiatry, Uniformed Services University of Health Sciences, Bethesda, MD 20892

Abstract

Objectives—Atomoxetine has been considered as an agonist replacement therapy for cocaine. We investigated the safety of the interaction of atomoxetine with cocaine, and also whether cognitive function was affected by atomoxetine during short-term administration.

Methods—In a double-blind placebo-controlled inpatient study of 20 cocaine-dependent volunteers, participants received atomoxetine 80 mg daily followed by 100 mg daily for 5 days each. On the fourth and fifth day at each dose, cocaine (20 mg and 40 mg) was infused intravenously in sequential daily sessions.

Results—Pre-infusion mean systolic pressures showed a small but statistically significant difference between placebo and both doses of atomoxetine. Pre-infusion mean diastolic pressures were significant between placebo and atomoxetine 80 mg only. The diastolic pressure response to 40 mg cocaine was statistically significant only between the 80 mg and 100 mg atomoxetine doses. All ECG parameters were unchanged. VAS scores for “bad effect” in the atomoxetine group were significantly higher at baseline, then declined, and for “likely to use” declined with atomoxetine treatment. On the ARCI the atomoxetine group scored significantly lower on amphetamine, euphoria and energy subscales ($p < 0.0001$). Other VAS descriptors, BSCS, POMS, and BPRS showed no differences. Atomoxetine did not affect cocaine pharmacokinetics. In tests of working memory, sustained attention, cognitive flexibility, and decision-making, atomoxetine improved performance on the visual n-back task. There were no differences in any pharmacokinetic parameters for cocaine with atomoxetine.

Conclusions—Atomoxetine was tolerated safely by all participants. Certain cognitive improvements and a dampening effect on VAS scores after cocaine were observed, but should be weighed against small but significant differences in hemodynamic responses after atomoxetine.

Keywords

atomoxetine; cocaine; interaction; pharmacokinetics; cognitive; safety

Introduction

Atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter (NET) and increases both dopamine and norepinephrine in the prefrontal cortex (Bymaster et al., 2002; Swanson et al., 2006), and is an accepted therapy for attention deficit/hyperactivity disorder (ADHD) with a recognized lower abuse potential compared to methylphenidate (Jasinski, 2008; Heil, 2002). A recent study with methylphenidate suggested that improvement of symptoms of ADHD contributes to the likelihood of use-reduction of cocaine, a common comorbidity of ADHD. Since atomoxetine is an effective therapeutic for ADHD, it may therefore present a safer alternative agonist treatment for cocaine abuse compared to methylphenidate and other stimulants. Atomoxetine has also been shown to have beneficial effects on short-term attention span, concentration, and daytime alertness after a variety of neuropathologies (Carroll et al., 1993; Levin et al., 1998). By improving cognitive performance in short-term use, atomoxetine could possibly benefit cocaine addicts early in their treatment by improving their retention of psychosocial therapy aimed at reforming drug-seeking behavior.

We hypothesized that atomoxetine and cocaine could be safely co-administered to cocaine-experienced adult participants in a controlled clinical environment, and that atomoxetine had no effect on the expected pharmacokinetics of cocaine. We conducted an inpatient double-blind placebo-controlled multiple dose study in cocaine-experienced volunteers to evaluate the safety of co-administration of intravenous cocaine and atomoxetine by recording cardiovascular changes, subjective responses to cocaine administration, and adverse events (AEs), using two doses of atomoxetine known to be safe and effective for the treatment of ADHD. We also evaluated whether atomoxetine altered the PK of intravenous cocaine or its major metabolite, benzoylecgonine (BE), and whether peak and trough pharmacokinetics (PK) of atomoxetine were affected by cocaine. The possible effects of atomoxetine on craving for cocaine, mood, cognitive function, and memory were also evaluated.

Participants and Methods

The study was a double-blind placebo-controlled, parallel group trial conducted in the inpatient Clinical Pharmacology Unit of the Uniformed Services University of Health Sciences (USUHS), and was reviewed and approved by the USUHS institutional review board, and by the Data Safety Monitoring Board of the National Institute on Drug Abuse (NIDA). It was conducted in accordance with the Declaration of Helsinki and was registered with clinicaltrials.gov under NCT00265265. All the participants provided written informed consent.

Eligible participants were experienced cocaine users between the ages 18 to 45, not seeking treatment at the time of the study, within 20% of ideal body weight, weighed at least 45 kg, and met the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for cocaine abuse or dependence. Participants were documented to have used cocaine by the smoked or intravenous route within the 6 weeks prior to enrollment and provided a positive urine test for BE within 30 days prior to entering the study. Female participants were required to have a negative pregnancy test within 72 hours prior to receiving the first screening infusion, and agreed to use a form of birth control during the study period, unless they had a history of surgical sterilization or were postmenopausal. Qualified participants were, by history and physical examination, free of any clinically significant medical contraindications, and were judged by the investigator to be able to comply with protocol requirements, and the rules and regulations of the Clinical Pharmacology Unit.

Potential subjects were excluded from the study if they had a current or past history of seizure disorder from any cause, including alcohol- or drug-related seizure, significant family history of seizure disorder, or a history of any medically adverse reaction to cocaine. Candidates were also excluded if they met the DSM-IV criteria of major psychiatric illness other than ADHD, as determined by structured clinical interview (SCID), were dependent on drugs of abuse besides cocaine or nicotine, or required medical detoxification for alcohol dependence. Other exclusions were: prior history of liver disease, current elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceeding the upper limit of normal, personal or family history of significant cardiovascular disease; positive serology for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) type 1; diagnosis of adult asthma or chronic obstructive pulmonary disease; and any illness, condition, or use of medications, that in the opinion of the Principal Investigator and the admitting physician, would preclude safe completion of the study. Candidates were also excluded if they had donated a unit of blood, participated in any other clinical investigation involving cocaine administration within 4 weeks of enrollment in this trial, used illicit drugs besides cocaine and marijuana; or used any prescription drugs within 14 days of the start of the study or non-prescription drugs within 7 days of the start of the study.

There were 45 days allotted for pre-intake outpatient screening. After admission up to 7 days were allowed for the participants' urine to become negative for cocaine (Days -15 to -9), 2 days of inpatient screening (Days -8 and -7), and 1 day of screening cocaine infusions of saline, 20 mg and 40 mg cocaine (Day -6) intravenously (IV) to evaluate the cardiovascular effects of cocaine. At least 3 days after the screening infusions (Days -5 through -3) and when urine BE was negative, participants were randomized in a 1:1 ratio to receive either saline followed 1 hour later by cocaine or cocaine followed 1 hour later by saline. Both the investigator and subject were unaware of the order of infusion. These sessions are denoted as "baseline" cocaine infusions and were delivered on 2 consecutive days (Days -2 and -1). 20 mg of cocaine was administered IV on Day -2 and 40 mg on Day -1. If the subject was unable to distinguish between a 20 mg and a 40 mg dose of IV cocaine during baseline infusions, as manifested by a higher score on VAS and an observed increase in heart rate after 40 mg of cocaine compared to 20 mg, they were excused from further participation.

On the next day (Day 0) participants were randomly assigned to receive either atomoxetine or matched placebo orally at 20 mg once daily for 2 days (Days 0-1), 40 mg daily for 2 days (Days 2-3), 80 mg daily for 5 days (Days 4-8), and 100 mg daily for 5 days (Days 9-13). During the last 2 days of the 80 mg and 100 mg atomoxetine/placebo doses, participants received IV cocaine and saline in sessions identical in design to Days -2 and -1.

During cocaine infusion sessions the participants were maintained in the recumbent position with continuous real-time monitoring of electrocardiogram, pulse oximetry, and automated systemic pressure. The cocaine dose or an equivalent volume of saline was administered over one minute into a free-flowing intravenous line in the antecubital vein. The cocaine 20 mg/saline session was always conducted on the day before the cocaine 40mg/saline session, but the investigator was blinded to the order of saline or cocaine administration in each session. Vital signs were taken at -15, -10, -5, minutes before the dose, then every 2 minutes to +10 minutes, then every 5 minutes to +55 minutes after each cocaine dose. At 60 minutes after the second cocaine/saline dose vital signs were continued every 30 minutes for 3 hours, then hourly for 2 more hours. 12-lead electrocardiograms (ECG) were obtained at -10, +4, +40 minutes relative to each cocaine/saline dose.

Blood samples were collected for pharmacokinetics after the 40 mg dose of cocaine on 0 mg, 80 mg and 100 mg of atomoxetine, and placebo. Additionally a morning blood sample was drawn daily for the trough concentration of atomoxetine.

Subjective effects of cocaine were assessed by Visual Analog Scale (VAS). The effect of atomoxetine on craving for cocaine was assessed by the Brief Substance Craving Scale (BSCS). Mood and personality were assessed using the Brief Psychiatric Rating Scale (BPRS) and Profile of Moods State (POMS). The abuse liability of atomoxetine was assessed using the Addiction Research Center Inventory (ARCI).

Cognitive function was evaluated using a battery of computer- and experimenter-administered tests. The following tests were conducted on Day -7 and Day 11: n-back test, Anagram Test, Trail-Making Tests A and B, Stroop Color-Word Interference test, Controlled Oral-Word Association test, and Continuous Performance Test (CPT). The Wisconsin Card Sorting Test and the Iowa Gambling Task were administered on Day 11 only. Participants were discharged 4 days after the last cocaine infusion session and returned for follow up 2 weeks after discharge. Adverse events were collected daily throughout the inpatient period and at the follow up visit.

Statistical Methods

The pre-infusion value of each variable was taken as the mean of 15 minutes of measurement after all monitoring equipment and intravenous lines were placed. The baseline value is defined as the entire observation period before randomization.

The maximum value was obtained for each vital sign (HR, SBP, DBP) on each participant for atomoxetine or placebo dosage (0, 80 or 100 mg), infusion type (cocaine or saline), and infusion dosage. From these data, the change in maximum value between baseline (0 mg) and each of the other two dosages (80 mg and 100 mg) was calculated for each participant for each of these combinations.

Each change score was regressed on pharmacotherapy (atomoxetine or placebo), infusion type (cocaine or saline) and their interaction using generalized estimating equations (GEE) (Liang and Zeger, 1986) separately for each combination of vital sign, infusion dosage and pharmacotherapy dosage. From these fitted models, we estimated the mean difference between atomoxetine and placebo (pharmacotherapy main effect) and the interaction between pharmacotherapy and infusion type. A statistically significant interaction suggests that the difference between atomoxetine and placebo depends upon whether the infusion is cocaine or saline. Sequential Bonferroni adjustment (Holm, 1979) permitted correction for multiple comparisons. To examine the effectiveness of randomization, GEE was also used to test for differences at baseline (0 mg of pharmacotherapy) mean of each vital sign between pharmacotherapy and infusion type, separately for each infusion dosage.

For subjective assessments: VAS, ARCI, BPRS, and BSCS variables were analyzed by mixed effect ANOVA. For each of the ARCI subscales- amphetamine, energy, euphoria, dysphoria, and sedation- a mixed model ANOVA was also performed.

For the cognitive battery, statistical analysis of group differences in demographics, the attention inventory, and results of tests administered once (Wisconsin Card Sorting Test and Iowa Gambling Task) were carried out with univariate ANOVA and chi-square. Performance on the battery of cognitive tests and IQ subtests was analyzed by means of mixed design repeated-measures ANOVA, with group (atomoxetine, placebo) as a between-participants factor and session (baseline, treatment) as a within-participant factor. An interaction of group by session was considered evidence of a drug effect.

Demographics

99 participants gave informed consent, 63 were screen failures, 7 declined to participate, 8 dropped out after admission but before randomization. The most common reason for screen

failure was having an illness or medication that would preclude participation. The next most common reason was that the history or physical examination showed a contraindication. The third common reason included a family history of early cardiovascular disease. 21 were randomized 1:1 to receive either atomoxetine or placebo, and 16 completed the study. Of the remaining 5 randomized participants, 1 withdrew before receiving study medication and 4 received at least one dose of the study medication. These four were included in the safety analysis.

Table 1 describes the demographic distribution of the participants who completed the trial. The only 2 female participants were in the placebo group. Most participants were between 31 and 45 years old. All participants except one were African-American. There were no differences between the two groups for alcohol dependence or use of other substances of abuse. There were also no baseline differences between groups on cognitive tests.

Results

Tables 2a and 2b summarize the mean heart rate, systolic pressure and diastolic pressure responses to cocaine infusions, for 20 mg and 40 mg respectively.

The atomoxetine group was found to have a significantly higher mean systolic pressure compared to the placebo group at pre-infusion for all doses of atomoxetine, including 0 mg, on the cocaine 20 mg infusion days. On the 40 mg infusion days, the mean pre-infusion systolic pressure was significantly higher than placebo on the atomoxetine 100 mg dose only. All peak heart rate and pressure responses were not significantly different from placebo. Because of the unexpected finding of higher baseline systolic pressures in the atomoxetine group, the change of each vital sign variable from baseline to peak response was compared for significance between doses of atomoxetine. These pair-wise comparisons are summarized in Table 3.

A clinically small but statistically significant difference for diastolic pressures between the atomoxetine 80 mg and 100 mg doses was found after cocaine 40 mg. Comparisons of the differences between atomoxetine and placebo groups are not shown because they were not significant.

Heart Rate

Mean heart rates in both groups were similar at pre-infusion and peak response on all infusion days for all doses of atomoxetine. All responses to cocaine were small in magnitude and the peak response was reduced as the atomoxetine dose increased. The highest maximum differences were seen after cocaine on atomoxetine 0 mg. Peak response differences between 0 mg: 80 mg atomoxetine, 0 mg: 100 mg, and 80 mg: 100 mg were not significant.

Systolic pressure

As already noted, the atomoxetine group had a higher mean systolic pressure at inpatient baseline on both Day -2 and -1 compared to the placebo group. However, peak systolic pressures were not significantly different after both doses of cocaine. As with heart rate, the effect of atomoxetine on mean systolic pressure responses was reduced as the dose was increased. No differences in means of peak systolic pressure response were significant in pairwise comparisons of doses.

Diastolic pressure

The atomoxetine group had a higher mean pre-infusion diastolic pressure, on the 80 mg dose only, on both infusion days. After 40 mg cocaine the peak diastolic pressures observed between 80: 100 mg atomoxetine was small but significant (6.5 ± 4.2 , $p = 0.003$).

Electrocardiogram

Atomoxetine had no significant effects on the electrocardiogram. PR intervals were significantly reduced at 4 minutes post cocaine infusion on Day -1 only, and returned to baseline at 40 minutes post infusion. RR intervals were significantly shortened, reflecting post cocaine infusion tachycardia, on all infusion days. There were no significant differences between the groups for PR, RR, QRS, and QTc intervals, calculated using the Fredericia correction.

Psychological effects

VAS—Pre infusion VAS scores were zero or close to zero in both groups. “Bad effects” scores were significantly higher at baseline, cocaine 40 mg, in participants randomized to atomoxetine compared to placebo. The “Bad effect” score in the atomoxetine group decreased significantly over the treatment period ($p = 0.003$). Ratings of “likely to use” were scored significantly lower in the atomoxetine group at doses of 80 and 100 mg, compared to the placebo group ($p = 0.03$). Composite scores were computed per individual and were also analyzed by mixed effect analysis of variance. The “composite: good” scale is the sum of the ratings for “good effects”, “high” and “stimulated”, and the “composite: bad” scale is the sum of the ratings for “bad effects”, “depressed”, and “anxious”. There were no significant effects on the “composite: good” scores. Atomoxetine group ratings for “composite: bad” after cocaine were significantly lower compared to the placebo group ($p = 0.003$). Figures 1 and 2 illustrate VAS scores for “Likely to use” and “Bad effects”.

The ARCI was administered once daily on all non-infusion days between Day -5 and Day 17. On Days 2 through 17, the atomoxetine group scored significantly lower on the amphetamine, energy, and euphoria subscales, ($p < 0.0001$). There were no significant differences between groups for the dysphoria and sedation subscales.

The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire (Mezinskas, et al., 1998). Participants completed the questionnaire every other day starting on Day -7 until the study ended. Craving for cocaine was highest in both groups on Day -5, which represents the day after participants received their baseline screening session of 20 and 40 mg cocaine. There were no significant differences between the atomoxetine and placebo groups on any days of assessment.

The BPRS total score ratings serve as indicators of psychiatric co-morbidity in drug-dependent participants. Participants started the measure at baseline and were administered this interview daily during treatment with atomoxetine and within 1 hour of the completion of all cocaine infusions, to identify possible acute psychotic effects of cocaine. Mean values of 3.0 were observed for all subscales in both groups before and after cocaine infusions, with no differences. The highest mean score of 3.4 was observed for anxiety/depression after cocaine on Day -2.

Cognitive

Figure 3 illustrates the salient improvements to the performance of the n-back task after atomoxetine treatment.

Performance on the n-back task varies with the memory load (“n”). As expected, greater memory load was associated with more errors, reflecting the increased demands on working memory. As the task became more difficult, misses increased from baseline to treatment for the placebo group but decreased for the atomoxetine group (Group x Session x Memory load, $p = .038$). The number of misses on the 3-back did not differ between groups in the baseline session but was reduced significantly after treatment with atomoxetine ($p = .048$).

No statistically significant effects were seen on hits or commission errors on the visual CPT. On auditory versions of the CPT, the variability of reaction time did not change across sessions in the placebo group, but decreased significantly post-treatment in the atomoxetine group ($p = .052$). That is, the drug appeared to “normalize” performance on this measure of auditory sustained attention.

In the Wisconsin Card Sorting Test, “failure to maintain a set,” showed a significant difference between groups ($p = .03$). The atomoxetine group had a mean of 2.25 failures as compared to 0.88 for the placebo group. Because this test was administered only once following treatment, the effect of atomoxetine in producing this difference in errors cannot be evaluated independently of possible group differences at baseline. For the Anagram Test, Trail Making Test, Stroop Test, Controlled Oral-Word Association Test, and Iowa Gambling Task no statistically significant differences were observed.

Pharmacokinetics

Peak and trough atomoxetine plasma concentrations following doses of 80 mg daily and 100 mg daily were measured. One subject had exceptionally high trough levels compared to the other participants and had a missing data point at Day 6, and was thus excluded from the summary statistics calculations. Mean peak and trough concentrations increased with increasing doses of atomoxetine.

Pharmacokinetic (PK) parameters for cocaine and its metabolites, benzoylecgonine (BE) and ecgonine methylester (EME), were determined using non-compartmental model. C_{max} was the observed maximum plasma concentration and T_{max} was the observed time to reach maximum plasma concentration. The area under the plasma concentration versus time curve (AUC) and half-life ($t_{1/2}$) were estimated using WinNonLin 5.2. $AUC(0-\infty)$ was determined using linear trapezoidal rule from time 0 to the time of the last measurable concentration (C_t) and extrapolated to infinity. The half-life was determined from the terminal-phase of the plasma concentration-time curve. The plasma samples were collected for only 6 hours after a cocaine dose. Due to the long half-lives of cocaine metabolites, the half lives and the AUC values extrapolated to infinity [$AUC(0-\infty)$] could not be obtained for BE and EME. $AUC(0-6 \text{ hours})$ was reported for the metabolites. The pharmacokinetic parameters for cocaine and cocaine metabolites (BE and EME) following the 40 mg cocaine infusion on subjects receiving atomoxetine/placebo are presented in Tables 4 and 5 respectively.

To assess the effect of atomoxetine on the PK of cocaine and cocaine metabolites, an analysis of variance (ANOVA) was performed on T_{max} , half-life and the natural logarithms (LN) of C_{max} and AUC with treatment group as a fixed effect. Comparisons of atomoxetine vs. placebo groups were performed for baseline, Day 8, and Day 13. The data show no differences in any of the PK parameters for either cocaine or metabolites between atomoxetine-dosed and placebo-dosed participants.

Adverse Events

Two participants were withdrawn from the study due to clinically significant abnormalities. One subject in the placebo group had a substantial increase in liver enzymes (AST/ALT)

beginning on Day 6 and was discontinued from treatment on Day 8 when repeat analysis revealed even higher levels. At the 2-week follow-up evaluation, the subject's AST and ALT were within normal limits. One subject in the atomoxetine group was discontinued on treatment day 8 because he experienced ectopic atrial tachycardia after receiving 40 mg of cocaine. The arrhythmia was self-limited. Two other subjects discontinued voluntarily for non-medical reasons, one in each treatment group.

A total of 89 adverse events were reported for the entire group of 20 participants. 53 events occurred in the 10 participants randomized to atomoxetine and 36 events occurred in 7 of 10 participants randomized to placebo. This difference was not statistically significant. There were 6 headaches reported in the atomoxetine group vs. 1 headache in the placebo group ($p=0.06$). Gastrointestinal complaints, including nausea, gastric irritation, and decreased appetite were more frequent in the atomoxetine group ($n=8$) compared to the placebo group ($n=2$) ($p=0.07$). The most frequently reported adverse events with a "definite to possible" relationship to study drug was mild somnolence and fatigue experienced by 9 participants, 6 in the atomoxetine group and 3 in the placebo group. Insomnia was reported in 2 placebo participants and 1 atomoxetine subject. All adverse events were considered mild in severity, with the exception of elevation of liver enzymes in the instance described above, and one report of dyspnea. Both of these were classified as moderate in intensity and both occurred in placebo participants. In the intent-to-treat population somnolence, fatigue, and headache were the most frequently reported treatment-emergent adverse events for both groups. 4 of the 5 treatment-emergent reports of somnolence and 4 treatment-emergent reports of headache occurred in participants randomized to the atomoxetine group. Fatigue developed after the start of study drug in 2 participants in each group. Treatment-emergent chest pain was reported in 2 atomoxetine participants and 1 placebo subject. There were no serious adverse events experienced by any participants.

Discussion

Atomoxetine presents the potential for the treatment of cocaine addicts with and without ADHD without the disadvantages of the abuse liability of other scheduled stimulant medications (Gibson et al., 2006). In this study we demonstrated that the hemodynamic and psychological effects of cocaine are not potentiated by atomoxetine over the course of two weeks. We judged that doses of 80 mg and 100 mg of atomoxetine daily over 13 days would sufficiently replicate the real clinical use of atomoxetine for approved indications. Administration of cocaine as intravenous infusions of 20 mg and 40 mg allows for safe exposure to two doses which are submaximal in hemodynamic effect but allow the subject to distinguish the dose-response induced psychological effects of cocaine. The design of this study follows a paradigm that has been reviewed and approved by the Food and Drug Administration to determine the safety of medications which might be applied in clinical practice for the treatment of cocaine abuse.

In other populations, atomoxetine-treated adult subjects experienced mean increases in systolic (~2.0 mm Hg) and diastolic (~1.0 mm Hg) blood pressures compared with placebo. At a final study visit, 2.2% (11/510) had systolic blood pressure measurements ≥ 150 mm Hg compared with 1.0% (4/393) of placebo subjects (Lilly & Co. 2005). In this trial atomoxetine had a mild, statistically significant effect on systolic blood pressure and no significant effect on heart rate or diastolic pressure. After challenges with cocaine, the group differences between hemodynamic responses were small. Recently, a study of seven cocaine-dependent participants who received atomoxetine at a maximum dose of 80 mg for 3–5 days, followed by self-administration of intranasal cocaine likewise demonstrated that the cardiovascular effects of cocaine were no greater in the presence of atomoxetine than alone (Stoops et al., 2008).

Atomoxetine appeared to blunt the pleasing effects of cocaine, as reflected in VAS scores. Participants who received atomoxetine reported lower scores for ARCI subscales of euphoria, energy and amphetamine. Atomoxetine had no effect on craving as assessed by BSCS, and no mood disturbances were appreciable, as assessed by BPRS. Our findings complement those of a number of reports regarding the effects of agonist replacement therapies for stimulant dependence. It has been shown that dopamine agonists can enhance cognition (Ersche, 2011), or attenuate the subjective effects of cocaine while demonstrating no pharmacokinetic interaction (Baker, 2007). Generally, the more “stimulant-like” the compound, the more apparent are increases in pulse and blood pressure (Rush, 2009).

Chronic stimulant users are known to suffer cognitive deficits. Cocaine users demonstrate impaired performance of attention tasks, executive function, memory, and processing and correction of errors (Briand et al., 2008; Franken et al., 2007; Gooding et al., 2008). These deficits impair the abuser’s ability to maintain quality of life activities as well as obtain potential benefit from behavioral therapy aimed at assisting their abstinence. Like methylphenidate, atomoxetine selectively increases extracellular dopamine and norepinephrine in the prefrontal cortex through adrenergic alpha-2 and dopaminergic D1 receptor stimulation (Berridge et al., 2006; Swanson et al., 2006). Atomoxetine and methylphenidate have also been shown to increase histamine release widely in the cortex (Fox, et al 2002). Through activation of histamine H3 receptor targets, atomoxetine improves spatial learning and memory deficits (Liu et al., 2008). Atomoxetine has been reported to exert beneficial effects on impairments of cognition due to a diversity of causes, including traumatic brain injury (Reid and Hamm, 2008), ADHD (Chamberlain et al., 2007) and schizophrenia (Rao et al., 2007; Friedman et al., 2004). In our study, participants were using cocaine up until shortly prior to admission for the test period and presumably at their functional cognitive “baseline.” Even after a short course of treatment atomoxetine exerted a significant effect on a test of working memory and in the auditory Continuous Performance Task (CPT), which has been specifically shown to be impaired in cocaine users (Gooding et al., 2008). No improvements in the placebo group were noted, excluding the possibility that environmental factors were ameliorative; additionally, all participants continued to receive cocaine during their participation. We are encouraged to expect that atomoxetine may lead to continued cognitive improvement in individuals who discontinue use of cocaine over longer periods of time.

Conclusion

Atomoxetine was generally safe in this small sample of cocaine-experienced participants who received intravenous doses of cocaine. One subject who had received atomoxetine was discontinued from participation after a brief self-limited episode of atrial tachycardia immediately following infusion of 40 mg of cocaine. The effect of an interaction between atomoxetine and cocaine could not be ruled out. Blood pressure interactions between cocaine and atomoxetine were comparable to placebo, or mildly attenuated. The psychoactive effects of cocaine appeared to be mildly counteracted by atomoxetine. However, a small preliminary safety trial of this kind is insufficient to draw any conclusions other than lack of enhancement of euphoric and drug-craving effects. Cognitive improvements in working memory and auditory attention were demonstrated during this short trial of atomoxetine, an encouraging finding for its potential as a treatment medication for cocaine addicts, especially those with comorbid ADHD.

Acknowledgments

This study was funded through grant/cooperative agreement HU0001-04-1-0006 between the National Institute on Drug Abuse (NIDA) and the Henry M Jackson Foundation for the Advancement of Military Medicine. Data

management, pharmacokinetic analysis and plasma drug analyses were supported by NIDA contracts N01DA-05-8864, N01DA-7-8870 and N01DA-3-8829 respectively. The authors thank C. Nora Chiang at NIDA for designing and overseeing the pharmacokinetic portion of the study.

References

- Baker J, Pade P, et al. Acute Cocaine Responses Following Cocaethylene Infusion. *Am J Drug Alcohol Abuse*. 2007; 33:619–625. [PubMed: 17668348]
- Berridge CW, Devilbiss DM, Andrzejewski ME, et al. Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biol Psychiatry*. 2006; 60:1111–1120. [PubMed: 16806100]
- Briand LA, Gross JP, Robinson TE. Impaired object recognition following prolonged withdrawal from extended-access cocaine self-administration. *Neuroscience*. 2008; 155:1–6. [PubMed: 18590801]
- Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology*. 2002; 27:699–711. [PubMed: 12431845]
- Carroll KM, Rounsaville BJ. History and significance of childhood attention deficit disorder in treatment-seeking cocaine abusers. *Compr Psychiatry*. 1993; 34:75–82. [PubMed: 8485984]
- Chamberlain SR, del Campo N, Dowson J, et al. Atomoxetine improved response inhibition in adults with Attention Deficit/Hyperactivity Disorder. *Biol Psychiatry*. 2007; 62:977–984. [PubMed: 17644072]
- Ersche KD, Roiser JP, Lucas M, et al. Peripheral biomarkers of cognitive response to dopamine receptor agonist treatment. *Psychopharmacology*. 2011; 214:779–789. [PubMed: 21088959]
- Fox GB, Pan JB, Esbenshade TA, et al. Effects of histamine H3 receptor ligands GT-2331 and ciprofloxacin in a repeated acquisition avoidance response in the spontaneously hypertensive rat pup. *Behav Brain Res*. 2002; 131:151–161. [PubMed: 11844582]
- Franken IHA, van Strein JW, Franzek EJ, et al. Error-processing deficits in patients with cocaine dependence. *Biological Psychol*. 2007; 75:45–51.
- Friedman JI, Stewart DG, Gorman JM. Potential noradrenergic targets for cognitive enhancement in schizophrenia. *CNS Spectr*. 2004; 9:350–355. [PubMed: 15115947]
- Gibson AP, Bettinger TL, Patel NC, et al. Atomoxetine versus stimulants for treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother*. 2006; 40:1134–1142. [PubMed: 16735655]
- Gooding DC, Burroughs S, Boutros NN. Attention deficits in cocaine dependent patients: Converging behavioral and electrophysiological evidence. *Psychiatry Res*. 2008; 160:145–154. [PubMed: 18555537]
- Heil SH, Holmes HW, Bickel WK, et al. Comparison of the subjective, physiological, and psychomotor effects of atomoxetine and methylphenidate in light drug users. *Drug Alcohol Depend*. 2002; 67:149–156. [PubMed: 12095664]
- Holm S. A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*. 1979; 6:65–70.
- Jasinski DR, Faries DE, Moore RJ, et al. Abuse liability assessment of atomoxetine in a drug-abusing population. *Drug Alcohol Depend*. 2008; 95:140–146. [PubMed: 18328639]
- Levin FR, Evans SM, Kleber HD. Prevalence of adult attention-deficit hyperactivity disorder among cocaine abusers seeking treatment. *Drug Alcohol Depend*. 1998; 52:15–25. [PubMed: 9788002]
- Liang K-Y, Zeger SL. Longitudinal analysis using generalized linear models. *Biometrika*. 1986; 73:3–22.
- Lilly & Co, Eli. STRATTERA® (atomoxetine) Capsules, FDA Approved Labeling-Revised. Eli Lilly and Company; Indianapolis, IN: Feb 1. 2005
- Liu LL, Yang J, Lei F, et al. Atomoxetine increases histamine release and improves learning deficits in an animal model of Attention-Deficit Hyperactivity Disorder: the spontaneously hypertensive rat. *Basic & Clinical Pharmacology and Toxicology*. 2008; 102:527–532. [PubMed: 18346050]
- Mezinskis J, Dryenforth S, Goldsmith R, Cohen M, Somoza E. Craving and withdrawal symptoms for various drugs of abuse. *Psychiatric Annals*. 1998; 28:577–583.

- Rao NP, Venkatasubramanian G, Gangadhar BN. Treatment of cognitive deficits in schizophrenia with atomoxetine: a case report. *J Clin Psychiatry*. 2007; 68:1998–1999.
- Reid WM, Hamm RJ. Post-injury atomoxetine treatment improves cognition following experimental traumatic brain injury. *J Neurotrauma*. 2008; 25:248–256. [PubMed: 18352838]
- Rush CR, Stoops WW, Hays LR. Cocaine effects during d-amphetamine maintenance: A human laboratory analysis of safety, tolerability and efficacy. *Drug Alcohol Depend*. 2009; 99:261–271. [PubMed: 18926645]
- Stoops WW, Blackburn JW, Hudson DA, et al. Safety, tolerability and subject-rated effects of acute intranasal cocaine administration during atomoxetine maintenance. *Drug Alcohol Depend*. 2008; 92:282–285. [PubMed: 17719727]
- Swanson CJ, Perry KW, Koch-Krueger S, et al. Effect of the attention deficit/hyperactivity disorder drug atomoxetine on extracellular concentrations of norepinephrine and dopamine in several brain regions of the rat. *Neuropharmacology*. 2006; 50:755–760. [PubMed: 16427661]

Figure 1.

VAS: Score of “likely to use” by treatment group and study day, after Cocaine infusion.

Cocaine 20mg given Days -2, 7 & 12. Cocaine 40mg given Days -1, 8 & 13.

Figure 2.

VAS: Score of “bad effects” by treatment group and study day, after Cocaine infusion.

Cocaine 20mg given Days -2, 7 & 12. Cocaine 40mg given Days -1, 8 & 13.

Figure 3. Comparison between groups for n-back test, number of misses, before and after treatment.

Table 1

Subject Demographics

	Atomoxetine (n=10)	Placebo (n=10)	Total (n=20)
Age (yrs)	39.7 (4.3)	40.2 (5.9)	40.0 (5.0)
Height (cm) Mean (SD)	69.6 (3.1)	68.8 (1.6)	69.2 (2.4)
Weight (kg) Mean (SD)	76.8 (13.3)	73.1 (11.5)	74.9 (12.2)
Gender:			
Male	10	8	18
Female	0	2	2
Education (years)	13.1 (1.4)	12.4 (1.3)	12.8 (1.3)
DMS-IV (SCID) Diagnosis at screening:			
Alcohol abuse	5 (50)	4 (40)	9 (45)
Alcohol dependence	1 (10)	0 (0)	1 (5)
Cannabis abuse	4 (40)	5 (50)	9 (45)
Cannabis dependence	0 (0)	1 (10)	1 (5)
Cocaine abuse	2 (20)	0 (0)	2 (10)
Cocaine dependence	8 (80)	10 (100)	18 (90)
Wender Utah rating Scale	15.2 (6.8)	19.4 (18.3)	17.3(12.6)
Digit Symbol-coding	8.5 (1.9)	10.2 (2.6)	9.4 (2.3)

Table 2a

Summary of the pre-infusion means and standard deviations and post-infusion maximal values after cocaine 20 mg and saline.

					Vital Signs					
					Heart Rate			Systolic Pressure		
					N	Mean	SD	N	Mean	SD
Infusion Dose	Study Day	Treatment Dose	Treatment Assignment	Infusion Period						
20	-2	0	Atomoxetine	Pre-infusion *	8	76.00	4.80	8	130.7	10.2
				Saline	8	86.00	6.72	8	137.9	10.6
				Cocaine	8	100.0	12.1	8	155.9	16.8
			Placebo	Pre-infusion	8	76.00	11.5	8	116.4	7.93
				Saline	8	84.00	10.2	8	128.0	6.82
				Cocaine	8	98.38	16.6	8	139.0	11.4
	7	80	Atomoxetine	Pre-infusion *#	8	78.46	7.34	8	135.8	10.2
				Saline	8	96.75	10.3	8	147.3	13.1
				Cocaine	8	95.75	10.7	8	155.3	12.6
			Placebo	Pre-infusion	8	77.75	12.6	8	123.9	9.15
				Saline	8	85.00	10.7	8	128.1	11.4
				Cocaine	8	102.1	22.6	8	145.4	16.7
	12	100	Atomoxetine	Pre-infusion *	8	81.38	7.82	8	131.6	5.66
				Saline	8	94.88	6.03	8	147.9	8.13
				Cocaine	8	102.4	7.41	8	151.9	9.08
			Placebo	Pre-infusion	8	78.71	10.6	8	120.5	8.98
				Saline	8	86.63	15.6	8	129.9	2.85
				Cocaine	8	106.0	23.2	8	145.0	12.5

* preinfusion mean systolic pressures: atomoxetine all doses vs. placebo, $p < 0.05$

preinfusion mean diastolic pressure: atomoxetine 80 mg vs. placebo $p < 0.05$

Table 2b

Summary of the pre-infusion means and standard deviations and post-infusion maximal values after cocaine 40 mg and saline.

					Vital Signs					
Infusion Dose	Study Day	Treatment Dose	Treatment Assignment	Infusion Period	Heart Rate		Systolic Pressure		Diastolic Pressure	
					N	Mean	N	Mean	N	SD
40	-1	0	Atomoxetine	Pre-infusion	8	76.17	8	131.3	8	74.29
				Saline	8	83.13	8	142.6	8	85.38
				Cocaine	8	107.8	8	159.3	8	88.13
		Placebo	Placebo	Pre-infusion	8	73.92	8	120.0	8	67.79
				Saline	8	83.63	8	130.3	8	78.13
				Cocaine	8	110.0	8	152.9	8	89.13
	8	80	Atomoxetine	Pre-infusion [#]	8	81.25	8	132.8	8	74.25
				Saline	8	99.38	8	145.4	8	83.63
				Cocaine	8	107.8	8	152.1	8	86.63
		Placebo	Placebo	Pre-infusion	8	75.25	8	123.1	8	66.67
				Saline	8	88.25	8	131.0	8	80.00
				Cocaine	8	112.3	8	153.5	8	97.50
	13	100	Atomoxetine	Pre-infusion [*]	8	81.96	8	136.8	8	78.83
				Saline	8	98.25	8	150.1	8	87.75
				Cocaine	8	106.0	8	159.0	8	93.13
		Placebo	Placebo	Pre-infusion	8	77.29	8	125.5	8	75.50
				Saline	8	88.38	8	133.6	8	90.50
				Cocaine	8	109.9	8	153.1	8	92.00

* Preinfusion mean systolic pressure atomoxetine 100 mg vs. placebo, $p < 0.05$

Preinfusion mean diastolic pressure atomoxetine 80 mg vs. placebo, $p < 0.05$

\$watermark-text

\$watermark-text

\$watermark-text

Table 4
Summary (Mean $\pm$ Standard Deviation) of Cocaine PK Parameters Following an Intravenous Infusion of 40 mg Cocaine

Parameter	Baseline		Day 8 -Atomoxetine 80 mg daily		Day 13 -Atomoxetine 100 mg daily	
	Atomoxetine	Placebo	Atomoxetine	Placebo	Atomoxetine	Placebo
C _{max} (ng/mL)	243.5 $\pm$ 21.2	288 $\pm$ 102.7	298 $\pm$ 79.0	301.6 $\pm$ 73.8	276 $\pm$ 76.4	312.9 $\pm$ 112.2
T _{max} (hr)	0.14 $\pm$ 0.11	0.12 $\pm$ 0.06	0.085 $\pm$ 0.067	0.13 $\pm$ 0.065	0.12 $\pm$ 0.16	0.125 $\pm$ 0.062
AUC(0-inf) (ng*hr/mL)	355.6 $\pm$ 45.5	364.8 $\pm$ 78.0	358 $\pm$ 32.2	401.1 $\pm$ 92.7	365.1 $\pm$ 50.3	411 $\pm$ 139.4
t _{1/2} (hr)	1.47 $\pm$ 0.27	1.56 $\pm$ 0.16	1.34 $\pm$ 0.18	1.36 $\pm$ 0.10	1.51 $\pm$ 0.34	1.36 $\pm$ 0.16
Clearance(L/hr)	114.1 $\pm$ 14.0	114.3 $\pm$ 25.9	112.5 $\pm$ 10.4	103.9 $\pm$ 21.2	111.4 $\pm$ 15.1	106 $\pm$ 30.6

Table 5

Summary (Mean $\pm$ Standard Deviation) of PK parameters for Cocaine Metabolites Following an Intravenous Infusion of 40 mg Cocaine

Parameter	Baseline		Day 8 -Atomoxetine 80 mg daily		Day 13 -Atomoxetine 100 mg daily	
	Atomoxetine	Placebo	Atomoxetine	Placebo	Atomoxetine	Placebo
Benzoylcegonine						
C _{max} (ng/mL)	248.5 $\pm$ 36.2	254.9 $\pm$ 34.7	268.6 $\pm$ 77.9	267.2 $\pm$ 56.1	262.5 $\pm$ 44.9	261.6 $\pm$ 38.9
T _{max} (hr)	2.38 $\pm$ 0.88	1.34 $\pm$ 0.38	2.69 $\pm$ 1.22	1.57 $\pm$ 0.49	2.25 $\pm$ 0.46	2.19 $\pm$ 0.51
AUC(0–6 hr) (ng [*] hr/mL)	1253 $\pm$ 162	1266 $\pm$ 185.0	1336 $\pm$ 320	1317 $\pm$ 244	1334 $\pm$ 233	1293 $\pm$ 198
Ecgonine methyl ester						
C _{max} (ng/mL)	26.9 $\pm$ 6.1	26.2 $\pm$ 4.1	27 $\pm$ 5.4	26.9 $\pm$ 3.3	27.7 $\pm$ 7.7	26.4 $\pm$ 3.7
T _{max} (hr)	1.63 $\pm$ 0.43	1.64 $\pm$ 0.69	2.04 $\pm$ 1.32	1.35 $\pm$ 0.48	1.71 $\pm$ 0.41	1.66 $\pm$ 0.42
AUC(0–6 hr) (ng [*] hr/mL)	128.9 $\pm$ 28.8	123.3 $\pm$ 23.6	126.8 $\pm$ 29.4	124.4 $\pm$ 15.4	131.1 $\pm$ 29.3	122.2 $\pm$ 15.8