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Atomoxetine in abstinent cocaine users: cognitive, subjective and cardiovascular effects

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Abstract

No pharmacotherapies are approved for the treatment of cocaine use disorders (CUD). Behavioral treatments for CUD are efficacious for some individuals, but recovery rates from CUD remain low. Cognitive impairments in CUD have been linked with poorer clinical outcomes. Cognitive enhancing pharmacotherapies have been proposed as promising treatments for CUD. Atomoxetine, a norepinephrine transporter inhibitor, shows potential as a treatment for CUD based on its efficacy as a cognitive enhancer in other clinical populations and impact on addictive processes in preclinical and human laboratory studies.

In this randomized, double-blind, crossover study, abstinent individuals with CUD (N=39) received placebo, 40 and 80 mg atomoxetine, over three sessions. Measures of attention, response inhibition and working memory; subjective medication effects and mood; and cardiovascular effects were collected. Analyses assessed acute, dose-dependent effects of atomoxetine. In addition, preliminary analyses investigating the modulation of atomoxetine dose effects by sex were performed.

Atomoxetine increased heart rate and blood pressure, was rated as having positive and negative subjective drug effects, and had only modest effects on mood and cognitive enhancement.

Keywords

Atomoxetine; norepinephrine; cocaine; cognition; addiction

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Declaration of interest

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1. Introduction

Cognitive deficits are seen as a particular challenge for treatment seeking cocaine users or abstinent individuals with CUD who require intact cognitive functioning to engage in treatment or learn new behavioral strategies to inhibit ongoing drug use or avoid relapse following abstinence. Chronic cocaine use is associated with cognitive deficits across a wide range of cognitive domains including response inhibition, working memory, and attention (e.g. [1, 2]). Cognitive impairments in CUD may arise as a result of cocaine withdrawal, cocaine-related damage to relevant neural systems, or pre-existing vulnerability factors for CUD and other comorbid disorders like ADHD. Although withdrawal-related cognitive impairments may improve across prolonged abstinence [3], they may not be fully ameliorated [4, 5]. Importantly, cognitive impairments in CUD may persist during abstinence and continue to pose a challenge for relapse prevention. In fact, recent cocaine use may even mask cognitive impairments, which may become more pronounced during abstinence [6]. As such, medications targeting cognitive function may represent a promising treatment strategy for CUD to aid in initiation of abstinence or relapse prevention in abstinent individuals with CUD [7].

Atomoxetine, a cognitive enhancer, is marketed for ADHD and has been shown to be a generally well-tolerated and efficacious treatment for ADHD across prolonged treatment (e.g. [8, 9]). It is a selective inhibitor of the norepinephrine transporter, which regulates norepinephrine neurotransmission by facilitating reuptake of norepinephrine into presynaptic nerve terminals. Inhibition of the norepinephrine transporter with atomoxetine increases extracellular levels of norepinephrine and dopamine in the prefrontal cortex but not the striatum [10] consistent with its cognitive enhancing effects and limited abuse potential.

Atomoxetine has also been considered as a potential treatment for CUD. A 12-week double-blind, placebo-controlled trial of atomoxetine (80–100mg/day) in active cocaine users (atomoxetine: 25 randomized, 16 completers; placebo: 25 randomized, 12 completers) found no significant effect of atomoxetine on cocaine use outcomes [11]. In a 12-week open-label trial of atomoxetine (80–100mg/day) in individuals with comorbid cocaine use disorders and ADHD (N=20; 19 men, 1 woman), self-reported ADHD symptoms were reduced, but cocaine use did not change across the trial (although the authors note substantial drop-out as a limitation [12]). Although preliminary and limited by small sample size, these studies did not support the potential use of atomoxetine for the pharmacotherapy of CUD in active cocaine users. What has not been addressed is whether atomoxetine will function as a cognitive enhancer in abstinent individuals with CUD who do not have ongoing cocaine use. This remains an important clinical consideration given the suggestions from pre-clinical research that atomoxetine may show promise as a relapse prevention aid [13–17] and human laboratory studies suggesting that atomoxetine may diminish the acute effects of cocaine [18, 19] or d-amphetamine [20]. Associations between poorer cognitive function and worse treatment engagement or substance use outcomes during or following treatment [21–24], including likelihood of relapse[25], underline the theoretical potential for cognitive improvements to improve substance use outcomes or enhance the efficacy of cognitively demanding behavioral treatments like cognitive behavioral therapy.

As a potential cognitive enhancer to be used in addition to behavioral therapy, atomoxetine targets cognitive functions that are thought to be critical for addictive processes including response inhibition, sustained attention, and working memory functions. A laboratory study of single doses of atomoxetine in adults with ADHD showed improved response inhibition (SST) and sustained attention (RVP) [26]. However, in healthy males without ADHD, atomoxetine did not improve response inhibition on SST [27]. Regarding cocaine users, in a previous study with male active cocaine users, those randomized to atomoxetine (80 or 100mg; 5 days each) performed better than the placebo group on measures of cognitive function including working memory and sustained attention [18]. To extend these promising findings and to examine the potential use of atomoxetine in individual with CUD, we examined atomoxetine's effects in male and female cocaine users who are in early abstinence and do not have ongoing drug use. Previous studies have shown that early abstinence is associated with greater cognitive deficits in cocaine users [6]. Therefore, it is important to assess its effects on these cognitive domains in individuals with CUDs during early abstinence. To assess the safety and tolerability of atomoxetine in this population, our study also included other measures of drug effects including heart rate, blood pressure, subjective drug effects, and mood. In this within-subject crossover study, we evaluated the acute effects of two doses (40, 80mg) of atomoxetine, relative to placebo. We hypothesized that atomoxetine would be well-tolerated and improve performance in cognitive functions including attention, working memory, and response inhibition in abstinent cocaine users.

2. Material and Methods

2.1 Participants

Thirty-nine abstinent cocaine users were recruited from the New Haven area by word-of-mouth, fliers, and newspaper advertisements. After the initial phone screening, potential subjects underwent a comprehensive evaluation including medical, psychiatric, and drug use histories and physical, psychiatric, and laboratory examinations. Alongside this information, diagnoses of DSM-IV criteria were determined by a psychiatrist, following psychiatric interview with the participant. Participants included English-speaking men and women, aged 21–50 who met the following inclusion criteria: 1) DSM-IV criteria for cocaine dependence in early remission and history of current or past treatment for cocaine dependence; 2) no self-reported cocaine use for the past 30 days (recent cocaine use was ruled out by negative urine toxicology screens at screening and all testing days) with reported cocaine use in past year; 3) no other current dependence or abuse of other drugs of abuse or alcohol (except tobacco); 4) no current medical problems and normal ECG; 5) for women, not pregnant or breast feeding, and using acceptable birth control methods. Participants were excluded if they: 1) met DSM-IV criteria for current major psychiatric illnesses including mood, psychotic, or anxiety disorders; 2) had a history of major medical illnesses including liver disease, heart disease, or other medical conditions that would make it unsafe for study participation; or 3) had a known allergy to atomoxetine. This study was approved by the VA Connecticut Healthcare System Human Subjects Subcommittee, and all subjects signed informed consent forms prior to their entry into the study and were compensated for their participation.

2.2 Procedures

In this randomized, double-blind, placebo-controlled, within-subject crossover study, participants received 40 mg, 80 mg atomoxetine, and placebo treatment, one pill per day, over three test days. To control for the possibility of carryover effects of the medication, test days were each scheduled approximately 6 days apart. Order of treatment condition (across test days) was randomly assigned and counter-balanced across individuals. Participants were informed that this was a study testing a medication that may help their attention, learning and memory. To minimize the effects of food on medication absorption, subjects were asked not to eat after midnight before coming for the session and were provided a standard light breakfast. Subjects were instructed to smoke cigarettes or drink caffeinated beverages as they normally do between session days and on the morning prior to each session, to minimize withdrawal effects. During the sessions, subjects were not permitted to smoke cigarettes or drink caffeinated beverages. Experimental session started around 8:30 a.m. After baseline measures were obtained, subjects received the assigned study medication followed by a light breakfast. For the next four hours, outcome measures were collected as described below.

2.3 Baseline questionnaires

At baseline, participants were evaluated for the presence of depressive symptoms using the 20-item CES-D, a 20-item scale with total score ranging from 0–60 [28]. Presence and severity of childhood trauma was assessed with the 28-item CTQ [29], which contains five subscales (Physical Abuse, Physical Neglect, Emotional Abuse, Emotional Neglect, and Sexual Abuse). CTQ scores are predictive of cocaine relapse outcomes in women, but not in men [30].

2.4 Drugs

Atomoxetine (Strattera ®) was obtained from Eli Lilly (Indianapolis, IN). Atomoxetine was given at 40 mg or 80 mg, as a single oral dose. The typical starting dose of atomoxetine for the treatment of ADHD in adults is 40 mg, while the maintenance dose ranges from 40 to 100 mg/day. Following oral administration, peak plasma atomoxetine levels are reached within two hours. The elimination half-life of atomoxetine is most commonly 5 hours, but ranges up to approximately 24 hours in a small proportion of individuals who are poor metabolizers [9, 31].

2.5 Outcome measures

The outcome measures included physiological, subjective, and cognitive performance measures.

2.5.1 Physiological measures—Heart rate and systolic and diastolic blood pressure were collected prior to pill administration and at 30, 60, 90, 150, and 180 and 240 minutes post-pill administration.

2.5.2 Subjective drug effects and mood measures—Subjective drug effects and mood measures were collected prior to pill administration and at 60, 90, and 150 and 180 minutes post-pill administration.

The ARCI consists of 49 true-or-false questions making five subscales: drug-induced euphoria (Morphine-Benzedrine Group; MBG), stimulant-like effects (Amphetamine; A), intellectual efficiency and energy (Benzedrine Group; BG), dysphoria (Lysergic Acid; LSD), and sedation (Pentobarbital-Chlorpromazine; PCAG) [32].

The DEQ assessed the acute subjective effects of atomoxetine, rating 10 items on a visual analogue scale from 0 (“not at all”) to 10 (“extremely”). Items were used to calculate three factors: Feel Good (mean of “feel good drug effects”, “want more drug” and “like the drug”), Negative (mean of “anxious”, “feel down”, “feel bad drug effects”), and Stimulatory (mean of “stimulated”, “high”, and “feel drug strength”), with one item (“sedated”) not included in any factor [33].

The POMS, widely used in behavioral pharmacology [34], is a 65–item rating scale used to measure the effects of medication treatments on mood using six subscales: Tension, Depression, Anger, Vigor, Fatigue, and Confusion [35].

2.5.3 Cognitive measures—Cognitive Performance was assessed with three computerized tasks, chosen based on cognitive deficits in cocaine users or sensitivity to atomoxetine.

The IMT measures brief attentional capacity and memory, and is influenced by response inhibition capacity [36–38]. Five-digit numbers (e.g. 59213) appear one at a time and participants are instructed to respond when a five-digit number is identical to the one that immediately preceded it. A correct response to a matching set is detection ‘hit’. Non-target stimuli consist of “catch” stimuli, which differ from target by one digit, and “filler” stimuli, which is a random five-digit number. Only responses to ‘catches’ are classified as ‘false alarms’. ‘Hit’ and ‘false alarm’ rates are used to calculate primary signal detection outcome measures: discriminability (d'), which reflects sensitivity to the target, and response bias (Beta), where lower and higher scores respectively indicate liberal versus conservative response biases. Response latency for correct targets was also included as a measure of attention and psychomotor speed.

The CANTAB RVP is a measure of sustained attention with a small working memory component [39]. Digits are rapidly (100/minute) and pseudo-randomly presented for 7 minutes. Subjects are instructed to press when the third digit of a 3-digit target sequence (e.g. 3-5-7) is displayed. Primary outcomes are indices of target discriminability (A') and response bias (B'') and response latency to targets.

The CANTAB SST is a test of response inhibition [40], the ability to stop an already initiated action. Subjects are instructed to press the left button when they see a left-pointing arrow or press the right button when they see a right-pointing arrow, as quickly and accurately as they can but, if they hear an auditory ‘stop’ signal (a beep) following the visual ‘go’ signal, they should withhold their response and not press either button. The timing

between the ‘go’ and ‘stop’ signals is adjusted according to subjects’ responses to converge on approximately 50% success rate of stopping on stop trials. The primary outcome measure is the SSRT, which is the estimated speed of stopping. Additional outcome measures include the mean, median and standard deviation of correct ‘go’ response times.

2.6 Statistical analyses

To assess treatment effects, we used a mixed-effect repeated-measures analysis using JMP (version 11.0). The structure of the analysis included a fixed main effect for treatment (placebo, 40 or 80 mg atomoxetine) and a random effect for participant. When data was collected across multiple time points, all post-pill administration time-points were included in the analyses. To account for possible carryover effects of the medication or learning/test-retest effects across testing days, analyses were re-run including test day (1,2,3) and test day by treatment interactions. If the dose findings (i.e., significance level) remained stable with and without the inclusion of test day and test day by dose, then results are presented from the simpler analysis excluding day. Otherwise, both are reported. Due to the analysis of multiple outcomes within each domain, Bonferroni corrections were applied for the number of outcomes tested within each domain (cardiovascular, subjective drug effect, mood, cognition). All reported results survive these Bonferroni corrections unless otherwise stated.

An exploratory sex analysis considered sex and sex-by-treatment effects in this dataset and is presented in a Data in Brief [41].

3. Results

3.1 Demographics

Baseline and demographics data are reported in full in Table 1. Of the 39 individuals in the study sample (29 men, 10 women), 21 (53.85%) were African-American, and 18 (46.15%) were European American. Three (7.69%) European Americans were of Hispanic ethnicity. The average age was 41.21 years (SD = 7.47). Average Center for Epidemiologic Studies Depression Scale (CES-D) scores were (M = 8.76, SD = 6.73). Thirty-five (89.74%) individuals in the sample reported having at least completed high school (12 years of education) or obtained a high school equivalent degree (e.g., General Education Degree (GED)). Of those, 12 (30.77%) reported some level of college training. The remaining four (10.26%) individuals reported partial completion of high school.

3.2 Treatment condition order and timing of testing days

The average time between each testing day was 5.93 days (SD=2.18 days; range=3–15 days). Inclusion of testing day and testing day by treatment condition interactions in the models did not alter the pattern of significance of dose effects on any outcome measures (physiological, subjective, cognitive). Therefore, results are reported for the simpler model, without testing day.

3.3 Physiological responses

Means and statistics for physiological (as well as subjective drug, mood and cognitive) results are reported in Table 2. Both atomoxetine doses increased heart rate relative to

placebo, with greater increases at 80 than 40 mg atomoxetine. Systolic blood pressure was higher for both atomoxetine doses, relative to placebo. Diastolic blood pressure was only significantly raised by 80 mg atomoxetine relative to placebo.

3.4 Subjective responses and mood

3.4.1 DEQ—Atomoxetine increased reports of all three subjective effects DEQ factors. “Stimulatory” and “negative” factors were rated higher at both doses, relative to placebo. “Feel good” factor was rated higher at the 40 mg atomoxetine dose relative to placebo or 80 mg atomoxetine.

3.4.2 ARCI—The LSD (dysphoria) subscale showed increases at 80 mg atomoxetine, compared to placebo or 40 mg atomoxetine. There were no significant main effects of treatment for other subscales measuring symptoms of euphoria (MBG), stimulant-like effects (A), intellectual efficiency and energy (BG), or sedation (PCAG).

3.4.3 POMS—No significant main effects of dose on ‘depression’, ‘vigor’, ‘anger’ or ‘tension’ were observed. A decrease in ‘Fatigue’ at 40 mg atomoxetine, relative to placebo or 80 mg atomoxetine, did not survive Bonferroni correction for multiple comparisons.

3.5 Cognitive Outcomes

On IMT, both doses, relative to placebo, were associated with improved (increased) discriminability performance (d′), however this effect did not survive Bonferroni correction. There were no significant main effects of treatment on any RVP or SST primary outcome measures.

4. Discussion

In individuals with cocaine dependence in early remission (abstinent more than 30 days, less than one year), atomoxetine increased heart rate and systolic and diastolic blood pressure modestly, consistent with prior findings in healthy controls or individuals with CUD. Atomoxetine at both doses produced stimulatory as well as negative subjective drug effects on the DEQ, while the higher dose (80 mg) produced dysphoric effects on the ARCI and no significant positive effects on the DEQ, supporting minimal abuse liability. Findings did not provide strong support for cognitive enhancing effects of acute atomoxetine in this sample. While both atomoxetine doses improved discriminability performance on IMT relative to placebo, these results did not survive corrections for multiple comparisons, and atomoxetine doses did not significantly impact other cognitive outcomes.

Atomoxetine increased heart rate and systolic and diastolic blood pressure. Consistent with prior research in different clinical samples and healthy controls, increases in heart rate and blood pressure were of small enough magnitude that they would be of limited clinical significance [42]. In a previous clinical trial with cocaine users, atomoxetine treatment increased the systolic and diastolic blood pressure by about 4mmHg [11]. Further, in previous human laboratory studies, atomoxetine treatment did not enhance the heart rate and blood pressure increases produced by cocaine [19, 27]. However, the cardiovascular effects of atomoxetine may still be clinically relevant to consider prior to prescription of

atomoxetine in someone with existing hypertension or cardiovascular disease, which are found in higher rates in people with CUDs [43, 44], although cardiac risk factors may dissipate over abstinence [45].

Dysphoric subjective effects on the ARCI (LSD subscale) were only observed at the higher dose (80 mg), subjective 'negative' and 'stimulatory' effects on the DEQ were observed at both doses, while 'feel good' DEQ effects were observed only at 40 mg dose. These findings are consistent with previous findings from cocaine users and other samples and point to relatively low abuse potential of atomoxetine [27].

Atomoxetine showed modest effects on improving performance on a measure of discriminability (IMT d′), which taps into processes of attention, response inhibition and memory, although this finding did not survive correction for multiple comparisons. In a prior study, individuals with CUDs relative to healthy controls, showed impairments in d′ in difficult (but not easy) versions of a continuous performance task, without group differences on response bias (Beta) or response speed, a pattern interpreted as arising from deficits in visual information processing, rather than motor disinhibition [46]. In the current study, atomoxetine modestly improved discriminability (d′) in a difficult condition with heavier memory load and heavier visual processing load (IMT d′ but not RVP A″), with no significant effects on measures tapping response inhibition (SSRT) or response bias (IMT Beta or RVP B′) and no main effects of dose on response speed or variability. Impaired IMT d′ in individuals with CUD has been associated with diminished white matter integrity in regions important for prefrontal cortical connectivity [47]. Contrary to our expectations, atomoxetine did not improve RVP or SST performance in our sample. In prior studies, acute doses of atomoxetine (60mg) improved SST in a mixed-sex sample of adults with ADHD [26], but not in healthy men without ADHD [27]. In a previous study, with only male cocaine users in the medication condition, atomoxetine improved performance on the n-back, a task of working memory and sustained attention, and speeded corrected responses on a continuous performance task, without affecting the performance on other measures of cognitive control (Stroop), psychomotor speed and cognitive flexibility/set-shifting (Trails) [18].

There were several limitations with the study and directions for future research arising from these findings. The sample size was modest (N=39), particularly for an exploratory analysis of sex (29 men, 10 women; presented separately in a Data in Brief [41]). Therefore, findings should be considered preliminary and require replication. It is possible that cognitive impairment or response to atomoxetine dose would differ based on severity of cocaine dependence or duration of abstinence, but these variables were not available within the current sample. Although diagnosis of cocaine dependence in early remission was confirmed by psychiatric interview with an experienced clinician, the specific symptoms endorsed by each subject were not systematically recorded in research records. Therefore, it was not possible to compile a 'severity score' based on symptom count. Furthermore, while duration of abstinence was required to be greater than 30 days and less than one year to meet this diagnostic criterion, the precise last date of cocaine use was not available for most subjects so a 'days of abstinence' variable could not be reliably computed. Single doses of 40 and 80 mg were tested on separate days, so these findings reflect acute effects of atomoxetine only.

Although this study and prior studies (e.g. [26]) have found effects of atomoxetine from a single dose, the subjective, cardiovascular and cognitive-enhancing effects of atomoxetine may differ between single dose and prolonged maintenance on the medication. For example, prior clinical trials suggested that, within individuals with ADHD who remained in treatment as long as 24 weeks, incremental increases in treatment response were observed across that time period [31]. Therefore, it would remain important to test the longer-term efficacy and tolerability of atomoxetine to treat CUDs, and modulation of these effects by sex. Subjects were abstinent for at least the past 30 days, so the clinical application of the current findings would be in the context of atomoxetine as a relapse prevention treatment in individuals who have achieved abstinence. In theory, if a cognitive enhancing pharmacotherapy were found to be safe and effective in CUD, one logical application of such a treatment would be as an adjunct to behavioral treatments (e.g., cognitive behavioral therapy), with a view to facilitating treatment engagement or treatment-related cognitive skills. However, it is important to note that the current findings in abstinent CUDs may not apply equally to CUDs in a treatment setting, since they may be more likely to be still using cocaine intermittently. Atomoxetine may differentially affect cognition, mood, and cardiovascular and subjective effects during periods of intermittent cocaine use or more recent abstinence.

5. Conclusions

In summary, atomoxetine may have a favorable tolerability and abuse potential profile in individuals with CUDs who are currently in early abstinence from cocaine but only showed very modest evidence of cognitive enhancing effects, and the cognitive findings did not survive correction for multiple comparisons. It remains important to assess the effects of atomoxetine in abstinent men and women with CUDs within a larger sample in a longer-term trial to characterize the tolerability and efficacy of sustained use of atomoxetine within individuals working to maintain abstinence from cocaine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADHD Attention Deficit Hyperactivity Disorder

ARCI	Addiction Research Center Inventory
CES-D	Center for Epidemiologic Studies Depression Scale
CTQ	Childhood Trauma Questionnaire
CUD	Cocaine Use Disorder
DEQ	Drug Effects Questionnaire
IMT	Immediate Memory Task
POMS	Profile of Mood States
RVP	Rapid Visual Information Processing Task
SSRT	Stop Signal Reaction Time
SST	Stop Signal Task

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Highlights

- Atomoxetine has been proposed as a pharmacotherapy for cocaine use disorder (CUD)
- This human laboratory study tests two atomoxetine doses versus placebo in abstinent CUD
- Atomoxetine had modest subjective, cardiovascular, mood and cognitive effects

Table 1

Baseline measures for entire study sample

Measures	Total Sample (N=39)	
	N	*(%)*
Demographics		
Race		
African American/Black	21	53.85%
Not of Hispanic Origin	21	53.85%
Hispanic Origin	0	0.00%
European American	18	46.15%
Not of Hispanic Origin	15	38.46%
Hispanic Origin	3	7.69%
Highest Level of Completed Education		
College/University graduate	1	2.56%
Partial college training	11	28.21%
High School graduate/GED	23	58.97%
Partial high school	4	10.26%
Marital Status		
Never Married	22	56.41%
Married	6	15.38%
Separated	4	10.26%
Divorced	7	17.95%
Employment Status		
Full-time (35 or more hours per week)	7	17.95%
Unemployed less than one month	4	10.26%
Unemployed greater than one month	28	71.79%
Sex		
Male	29	74.36%
Female	10	25.64%
	Mean	*(SD)*
Age, years	41.21	7.47
Self-reported Measures at Baseline		
CES-D Summary Score	8.76	6.73
CTQ		
Physical Abuse	8.47	4.72
Physical Neglect	8.26	3.61
Emotional Abuse	8.85	4.59
Emotional Neglect	10.24	5.28
Sexual Abuse	7.23	4.81

CES-D: Center for Epidemiologic Studies Depression Scale; CTQ: Childhood Trauma Questionnaire; SD: Standard Deviation.

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Table 2

Effects of atomoxetine dose on cardiovascular, subjective drug effects, mood and cognitive measures

Measure	Subscales	Full Sample (N=39)						Statistics (for Dose Effects)
		Placebo Session		40 mg ATX Session		80 mg ATX Session		Dose
		Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F(p)*
Cardiovascular								
	Heart Rate**	72.20	10.27	75.48	11.22	77.10	12.63	**38.50 (<0.0001); 80ATX > 40ATX > PLA**
	Systolic BP**	119.55	10.82	123.00	12.43	123.37	11.82	**13.92 (<0.0001); 40, 80ATX > PLA**
	Diastolic BP**	71.24	8.69	72.58	10.42	73.41	9.62	**6.75 (0.001); 80ATX > PLA**
Subjective Drug Effects								
ARCI								
	Sedation (PCAG)	3.60	2.68	3.36	2.36	3.73	2.90	-
	Dysphoria (LSD)**	2.62	1.51	2.82	1.64	3.20	2.02	**5.68 (0.004); 80ATX > PLA,40ATX**
	Euphoria (MBG)	5.99	4.78	5.98	4.69	5.73	4.39	-
	Stimulant-Like Effects (A)	4.05	2.54	4.20	2.54	4.10	2.44	-
	Intellectual Efficiency and Energy (BG)	6.78	2.45	6.77	2.30	6.52	2.57	-
DEQ								
	Feel Good Factor**	0.67	1.02	1.05	1.26	0.81	0.97	**9.47 (<0.0001); 40ATX > PLA,80ATX**
	Negative Factor**	0.60	0.76	0.82	0.87	0.73	0.84	**8.05 (0.0004); 40,80ATX > PLA**
	Stimulatory Factor**	0.81	1.09	1.22	1.51	1.10	1.11	**10.15 (<0.0001); 40,80ATX > PLA**
Mood								
POMS								
	Anger	1.94	1.65	2.29	2.17	2.24	2.35	-
	Depression	3.46	2.48	3.37	2.31	3.63	2.52	-
	Fatigue*	5.95	3.28	5.50	3.29	5.82	3.04	4.50 (0.012); PLA, 80ATX > 40ATX
	Confusion	4.55	1.16	4.77	1.29	4.66	1.42	-
	Tension	5.09	2.16	5.16	2.27	5.25	2.18	-
	Vigor	2.53	1.82	2.72	2.21	2.90	2.19	-
Cognitive								

Measure	Subscales	Full Sample (N=39)						Statistics (for Dose Effects)
		Placebo Session		40 mg ATX Session		80 mg ATX Session		Dose
		Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F(p)*
IMT								
	Discriminability (d′)*	1.04	0.77	1.14	0.96	1.14	0.88	3.27 (0.044); 40,80ATX > PLA
	Response Bias (Beta)	1.15	0.45	1.34	1.25	1.11	0.59	-
	Mean Correct RT	542.69	81.50	529.79	82.10	533.42	82.07	-
RVP								
	Discriminability (A′)	0.87	0.09	0.88	0.06	0.89	0.07	-
	Response Bias (B″)	0.82	0.22	0.87	0.14	0.86	0.16	-
	Mean Correct RT	464.44	113.07	446.70	106.84	452.64	133.22	-
SST								
	SSRT	226.96	102.81	221.55	110.78	219.83	115.41	-
	Median correct RT on GO trials	665.64	184.72	656.53	199.12	638.07	188.24	-
	Mean correct RT on GO trials	737.30	224.73	723.42	237.78	688.46	200.71	-
	SD correct RT on GO trials	404.79	367.16	386.61	297.03	298.71	210.20	-

Raw means and standard deviations are presented for the whole sample by dose. Results from analyses of atomoxetine dose (PLA: placebo; 40ATX: 40 mg atomoxetine; 80ATX: 80 mg atomoxetine) are presented as F(p). When results reach statistical significance (p≤0.05), direction of the effect is reported within the table. ATX: atomoxetine; PLA: placebo; W: women; M: men; NS: non-significant (p>0.05); DEQ: Drug Effects Questionnaire; ARCI: Addiction Research Center Inventory; POMS: Profile of Mood States; IMT: Immediate Memory Task; RVP: Rapid Visual Processing; SST: Stop Signal Task; SSRT: Stop Signal Reaction Time; RT: response time; SD: standard deviation; BP: Blood Pressure.

Missing data: Placebo Visit (N=5 missing from DEQ, ARCI, POMS, Physiological; N=4 missing from RVP, SST; N=3 missing from IMT); 40ATX visit (N=1 missing from SST, RVP, IMT); 80ATX visit (N=2 missing from DEQ, ARCI, POMS, Physiological, IMT, RVP, SST).

** Indicates dose effect reached bonferroni-corrected statistical significance level, correcting for number of variables per domain ('subjective effects'=3DEQ + 5 ARCI variables=0.05/8=corrected p threshold <0.006; 6 POMS Mood variables (corrected p threshold <0.008); 3 physiological variables (corrected p threshold<0.017); 10 cognitive variables (corrected p threshold <0.005)

* Indicates dose effect reached uncorrected statistical significance level of p<.05. Statistics that did not reach at least significance level of p<.05 are not reported (indicated by '−')