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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.

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. Fillmore and Rush, 2002; Jovanovski et al., 2005). 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 (Coffey et al., 2000), they may not be fully ameliorated (Bolla et al., 1999; Bolla et al., 2000). 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 (Woicik et al., 2009). 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 (Sofuoglu, 2010).

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. Fredriksen et al., 2013; Simpson and Plosker, 2004). 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 (Bymaster et al., 2002) 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

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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(80–100 mg/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 (Walsh et al., 2013). In a 12-week open-label trial of atomoxetine (80–100 mg/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 (Levin et al., 2009)). 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 preclinical research that atomoxetine may show promise as a relapse prevention aid (Brenhouse et al., 2010; Broos et al., 2015; Economidou et al., 2011; Jordan et al., 2014; Zlebnik and Carroll, 2015) and human laboratory studies suggesting that atomoxetine may diminish the acute effects of cocaine (Cantilena et al., 2012; Stoops et al., 2008) or d-amphetamine (Sofuoglu et al., 2009). Associations between poorer cognitive function and worse treatment engagement or substance use outcomes during or following treatment (Carroll et al., 2011; Kiluk et al., 2011; Streeter et al., 2008; Teichner et al., 2001), including likelihood of relapse (Fox et al., 2009), 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) (Chamberlain et al., 2007). However, in healthy males without ADHD, atomoxetine did not improve response inhibition on SST (Nandam et al., 2011). Regarding cocaine users, in a previous study with male active cocaine users, those randomized to atomoxetine (80 or 100 mg; 5 days each) performed better than the placebo group on measures of cognitive function including working memory and sustained attention (Cantilena et al., 2012). 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 (Woicik et al., 2009). 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, 80 mg) 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 4 h, 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 to 60 (Radloff, 1977). Presence and severity of childhood trauma was assessed with the 28-item CTQ (Bernstein et al., 1994), 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 (Hyman et al., 2008).

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 2 h. The elimination half-life of atomoxetine is most commonly 5 h, but ranges up to approximately 24 h in a small proportion of individuals who are poor metabolizers (Simpson and Plosker, 2004; Clemow and Bushe, 2015).

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