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Atomoxetine does not alter cocaine use in cocaine dependent individuals: A double blind randomized trial

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ABSTRACT

Background: Cocaine abuse continues to be a significant public health problem associated with morbidity and mortality. To date, no pharmacotherapeutic approach has proven effective for treating cocaine use disorders. Preclinical and clinical evidence suggests that noradrenergic activity may play a role in mediating some effects of cocaine and may be a rational target for treatment.
Methods: This double blind, placebo-controlled randomized, parallel group, 12-week outpatient clinical trial enrolled cocaine dependent individuals seeking treatment to examine the potential efficacy of the selective norepinephrine reuptake inhibitor, atomoxetine (80 mg/day; p.o.; $n = 25$), compared to placebo ($n = 25$). Subjects were initially stratified on cocaine use (<15 days or ≥15 days of the last 30), age and race using urn randomization. Attendance, medication adherence and study compliance were reinforced with contingency management, and weekly counseling was offered. An array of measures (vital signs, laboratory chemistries, cognitive and psychomotor tests, cocaine craving and urine samples for drug testing) was collected throughout the study and at follow-up.
Results: Survival analysis revealed no differences in study retention between the two groups, with approximately 56% of subjects completing the 12-week study (Cox analysis $\chi^2 = .72$; $p = .40$; Hazard Ratio 1.48 [95% CI 0.62–3.39]). GEE analysis of the proportion of urine samples positive for benzoylecgonine, a cocaine metabolite, revealed no differences between the atomoxetine and placebo groups ($\chi^2 = 0.2$, $p = .66$; OR = 0.89 [95% CI 0.41–1.74]). Atomoxetine was generally well tolerated in this population.
Conclusions: These data provide no support for the utility of atomoxetine in the treatment of cocaine dependence.

1. Introduction

Cocaine abuse and dependence are associated with increased morbidity and mortality arising from adverse cardiovascular effects, increased transmission of blood-borne illnesses, and increased risks in pregnancy and birth outcomes. Recent estimates suggest that there are 1.5 million current cocaine users in the United States (U.S.; SAMHSA, 2011). According to the DAWN reporting system, cocaine is the most common illicit drug involved in U.S. emergency department visits, which numbered 488,101 in 2010 alone (SAMHSA, 2012). Despite efforts aimed at the development of effective pharmacotherapies for the treatment of cocaine dependence, no agents have demonstrated sufficient efficacy to warrant approval by the Food and Drug Administration.

Cocaine acts in the central nervous system to inhibit monoamine transporters, including dopamine, serotonin and norepinephrine (e.g., see review by Rothman and Baumann, 2003) and it possesses other pharmacological properties. Perhaps it is this complex pharmacological profile that has led to the difficulty in finding an effective pharmacotherapy to treat cocaine dependence. Despite its interaction with multiple central and peripheral targets, the rewarding effects of cocaine are thought to arise primarily from its inhibition of dopamine reuptake, resulting in an increase in synaptic dopamine concentrations in the mesolimbic dopamine

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system (Di Chiara and Imperato, 1988; Ritz et al., 1987). Moreover, it has been postulated that long-term changes in dopaminergic neurophysiology at the level of the cortex, specifically the orbitofrontal cortex, may underlie cocaine withdrawal symptoms, persistent states of craving, and compulsive drug-seeking behavior (for review see Volkow and Fowler, 2000). Therefore, numerous studies have evaluated agents with dopaminergic activity for efficacy against cocaine in controlled pharmacotherapy trials, including dopamine agonists, such as pergolide (Malcolm et al., 2000), bromocriptine (Handelsman et al., 1997), mazindol (Stine et al., 1995) and levo-dopa (Mooney et al., 2007; Schmitz et al., 2008) and dopamine antagonist-like compounds, such as risperidone (Grabowski et al., 2000, 2004a; Loebl et al., 2008) and the dopamine depleting agent, reserpine (Winhusen et al., 2007). The vast majority of these studies have reported no supportive evidence for efficacy, although a few studies of robust stimulant compounds, such as d-amphetamine (Grabowski et al., 2001, 2004b; Shearer et al., 2003) and methamphetamine (Mooney et al., 2009) have produced statistically significant signals of efficacy. While preclinical studies suggest a critical role for the serotonergic actions of cocaine (Walsh and Cunningham, 1997), randomized clinical trials of serotonergic agents in primary cocaine dependent individuals, including fluoxetine (Batki et al., 1996; Grabowski et al., 1995; Schmitz et al., 2001; Winstanley et al., 2011), tryptophan (Jones et al., 2004), ritanserin (Johnson et al., 1997), ondansetron (Johnson et al., 2006) and others have largely failed to demonstrate efficacy.

There is preclinical evidence suggesting that targeting the noradrenergic action of cocaine may be a rational approach (Sofuoglu and Sewell, 2009; Weinshenker and Schroeder, 2007). However, only a few clinical trials have been conducted to examine noradrenergic agents for cocaine dependence (for review see Sofuoglu and Sewell, 2009). Atomoxetine is a potent norepinephrine reuptake inhibitor with little action at dopamine and serotonin transporters (Bolden-Watson and Richelson, 1993; Wong et al., 1982). It is marketed for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults (Simpson and Plosker, 2004), but, unlike other therapies for ADHD, atomoxetine does not act as a stimulant and does not appear to have abuse potential (Gasior et al., 2005; Jasinski et al., 2008; Lile et al., 2006; Wee and Woolverton, 2004). Furthermore, while atomoxetine does not increase extracellular dopamine concentrations in brain regions involved in reward and reinforcement (e.g., nucleus accumbens), it does increase extracellular dopamine in brain regions thought to be involved in craving and compulsive drug seeking (e.g., prefrontal cortex; Bymaster et al., 2002). A recent study in rats demonstrated that treatment with acute atomoxetine (1 mg/kg) decreased cue-induced cocaine seeking and relapse to cocaine seeking after abstinence, with minimal effects on sucrose responding and locomotor activity (Economidou et al., 2011). Few human studies have examined atomoxetine for potential efficacy against cocaine. One laboratory study reported that chronic treatment with atomoxetine was safely tolerated but produced minimal attenuation of the subjective effects of acute intranasal cocaine (Stoops et al., 2008). A small ($n = 20$) open-label clinical trial was conducted to study the efficacy of atomoxetine in ADHD patients who also had comorbid cocaine dependence. While modest improvements were observed on attention-related behaviors, atomoxetine did not significantly decrease cocaine use over the course of the 12-week trial (Levin et al., 2009); however, this trial used an open-label design and the co-morbid study population had a high drop-out rate (75%). Thus, the purpose of this study was to conduct a double blind, placebo-controlled, outpatient clinical trial to examine the safety and efficacy of atomoxetine for the treatment of cocaine dependence in a cohort of individuals with primary cocaine dependence.

2. Methods

2.1. Subject recruitment and screening

Adult volunteers ages 18–60 reporting cocaine use in the preceding 30 days who met DSM-IV criteria for and were seeking treatment for cocaine dependence were recruited through advertisements and word-of-mouth. Exclusion criteria included dependence on any drug requiring detoxification (i.e., benzodiazepines, barbiturates, alcohol or opioids), current Axis I disorder other than substance use, significant ongoing medical problems (e.g., seizure disorders, uncontrolled hypertension, abnormal ECG), pregnant or lactating females, and recent use of CYP2D6 inhibitors/inducers, MAO-inhibitors or selective serotonin reuptake inhibitors. Individuals enrolled in other drug treatment programs or required to provide urine samples for parole/probation were excluded. The study took place at the Robert Straus Behavioral Research Science Building in Lexington, KY. This study was conducted in accordance with the Helsinki guidelines for ethical human research and was approved by the University of Kentucky (UK) Institutional Review Board. A Certificate of Confidentiality was obtained from the National Institutes of Health, and all subjects gave written informed consent. The study was registered at www.clinicaltrials.gov (NCT00617201).

Screening lasted up to 2 weeks (a minimum of 4 clinic visits were required separated by $\geq$48 h) during which study eligibility was determined. At each visit, breath alcohol level (Alcomate Prestige; AK Solutions, Palisades Park, NJ, U.S.A.) and vital signs were obtained. Observed urine samples were collected and tested for the presence of drugs (methamphetamine, cocaine, tetrahydrocannabinol, methadone, benzodiazepines, barbiturates, morphine-like opioids, phencyclidine, oxycodone, methylenedioxymethamphetamine; Redwood Toxicology Laboratory, Santa Rosa, CA). To qualify, subjects were required to provide at least one urine sample positive for cocaine during screening but were not informed of the enrollment criteria. Urine pregnancy tests were conducted weekly. Subjects were paid $15 for each visit except the day of their physical examination when they received $25.

An extensive medical and psychiatric evaluation was completed that included substance use and drug abuse treatment history, licit medication usage, electrocardiogram (ECG), blood and urine chemistries (including pregnancy testing for females), physical exam, and structured interviews including the Addiction Severity Index (ASI; McLellan et al., 1992) and Structured Clinical Interview for DSM-IV diagnoses (First et al., 1996). Additional assessments included weight, demographics, the NEO personality inventory (Costa and McCrae, 1985), the Beck Depression Inventory (Beck et al., 1961), the Profile of Mood States (McNair et al., 1971), the Conners Adult ADHD Rating Scale Short Version (CAARS-S:S; Connors et al., 1999), a cocaine-use timeline follow-back (TLFB; adapted from Sobell and Sobell, 1992) and a Cocaine Craving Scale (Sussner et al., 2006). The TLFB used a calendar to record the days subjects used cocaine, how much cocaine was used, how much time and money was spent using cocaine and the route of cocaine administration. The Cocaine Craving Scale asked subjects to rate the following statements on a 7-point scale: "I want cocaine so bad I can almost taste it." "I have an urge for cocaine." "I am going to use cocaine as soon as possible." "I think that I could resist using 'coke' now." "I crave 'coke' right now." "All I want to use now is cocaine." "I have no desire for cocaine right now." "Using cocaine now would make things seem just perfect." "I will use cocaine as soon as I get the chance." "Nothing would be better than using 'coke' right now."

Because atomoxetine is approved for the treatment of ADHD, four psychomotor/cognitive tasks were incorporated into the trial. During screening, these were administered on each of four visits for practice and to establish baseline responding. They included a