Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2014 April 3; 50: 44–52. doi:10.1016/j.pnpbp.2013.11.013.

Assessment of Safety, Cardiovascular and Subjective Effects After Intravenous Cocaine and Lofexidine

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Abstract

The primary objective of this study was to determine the safety of lofexidine, an α_2 receptor agonist, alone and concurrent with cocaine in non-treatment seeking cocaine-dependent or cocaine-abusing participants. After screening, eligible participants received double-blind, randomized infusions of saline and 20 mg of cocaine on Day 1, and saline and 40 mg of cocaine on Day 2. Subjects were randomized and started receiving daily administration of placebo (N=4) or lofexidine on Day 3 and continued on this schedule until Day 7. Two dosing regimens for lofexidine were investigated: 0.8 QID (N=3) and 0.2 mg QID (N=11). On Days 6 and 7, subjects received double-blind infusions of saline and 20 mg of cocaine on Day 6, and saline and 40 mg of cocaine on Day 7. The data reveal a notable incidence of hemodynamic-related AEs over the course of the study. Two of the three participants at the 0.8 mg dose level discontinued, and five of 11 participants at the 0.2 mg dose level were withdrawn (or voluntarily discontinued) after hemodynamic AEs. Subjective effects and cardiovascular data were derived from all participants who were eligible to receive infusions (i.e., did not meet stopping criteria) on Days 6 and 7 (6 received lofexidine 0.2 mg, QID and 4 received placebo, QID). As expected, cocaine significantly increased heart rate and blood pressure, as well as several positive subjective effects. There was a trend for lofexidine to decrease cocaine-induced cardiovascular changes and cocaine-induced ratings for "Any Drug Effect", "Good Effects", and "Desire Cocaine", but sample size issues limit

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Author Disclosures

Contributors: Authors De La Garza, Galloway, Newton, Mendelson, Mojsiak, Lao, Anderson and Kahn designed the study and wrote the protocol. Authors De La Garza, Newton, Haile and Mahoney managed the literature searches and summaries of previous related work. Authors De La Garza, Galloway and Lao undertook the statistical analysis, and author De La Garza wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest: None of the authors have any conflicts of interest to report.

the conclusions that can be drawn. Despite the trends to reduce cocaine-induced subjective effects, cardiovascular AEs may limit future utility of lofexidine as a treatment for this population.

Keywords

Norepinephrine; Cocaine; Lofexidine; Addiction; Treatment

Introduction

Cocaine is a highly addictive stimulant. National Survey on Drug Use and Health statistics from 2011 revealed that 670,000 persons used cocaine or crack cocaine for the first time (equal to ~1,835 initiates/day), 1.4 million people self-reported using cocaine at least once during the last month, and 800,000 persons were classified with dependence on or abuse of cocaine. Moreover, data from the Treatment Episode Data Set for 1998–2008 suggested that 17% of all patients who entered drug treatment programs in the USA did so for the treatment of stimulant addiction (SAMHSA 2010). A variety of neuropharmacological strategies and targets are being pursued as treatments for cocaine addiction. Some of these strategies include blocking cocaine's positive subjective effects, reducing cocaine craving, treating underlying co-morbid conditions that may predispose individuals to developing dependence, and stress reduction to prevent relapse (Haile & Kosten 2013; Haile et al. 2012b; Verrico et al. 2013).

Research has primarily focused on dopamine (DA), yet genetic and pharmacological evidence have implicated noradrenergic mechanisms in mediating the effects of cocaine and other stimulants (Haile et al. 2012b; Weinshenker & Schroeder 2007). For example, our group has shown that the anti-hypertensive medication, perindopril, an angiotensin converting enzyme inhibitor that modulates norepinephrine (NE) neurotransmission reduced the positive subjective effects produced by methamphetamine in methamphetamine-dependent participants (Newton et al. 2009). In animal models, noradrenergic α -1 receptor (α -1R) knockout mice are insensitive to the locomotor activating effects of cocaine (Drouin et al. 2002), and treatment with the short-acting α -1R antagonist prazosin blocked stimulant-induced locomotor activation (Blanc et al. 1994; Snoddy & Tessel 1985) and drug-induced reinstatement of cocaine-seeking in rats (Zhang & Kosten 2005). Most recently, our group showed that treatment with the long-acting α -1R antagonist doxazosin significantly attenuated the subjective effects "stimulated", "like cocaine", and "likely to use cocaine if had access" in cocaine-dependent participants (Newton et al. 2012).

Cocaine increases central and peripheral NE levels (Rothman et al. 2001; Sofuoglu et al. 2001). Medications that target NE attenuate stimulant-induced positive subjective drug effects, decrease drug use, and attenuate withdrawal symptoms (Colfax et al. 2011; Cruickshank et al. 2008; Gaval-Cruz & Weinshenker 2009; Haile et al. 2012a; Newton et al. 2012; Newton et al. 2009). The importance of developing pharmacotherapies that target NE is underscored by experience using the medication disulfiram. Disulfiram is indicated for the treatment of alcohol dependence but has been shown to block reinstatement of cocaine seeking behavior in an animal model of relapse and decrease cocaine use in numerous

clinical trials (Haile et al. 2012a; Schroeder et al. 2010). Disulfiram and its metabolite, diethyldithiocarbamate, chelate copper and inhibit the copper-dependent enzyme dopamine β -hydroxylase (D β H) that is responsible for the conversion of DA to NE thereby decreasing the synthesis of NE. Decreasing central levels of NE appears to be responsible for disulfiram's effects on cocaine use in humans. Although disulfiram has shown efficacy as a treatment for cocaine dependence, potentially dangerous interactions with alcohol preclude it from becoming a first-line pharmacotherapy (Roache et al. 2011).

Like disulfiram, α -2 autoreceptor agonists (α -2R) also decrease NE levels but do so through a different mechanism. α -2R agonists reduce the activity of noradrenergic neurons and reduce NE release (Aghajanian & VanderMaelen 1982). The prototypical α -2R agonist clonidine blocks cocaine-induced activation, reinstatement of cocaine-seeking and stress-induced increases in craving measures in dependent individuals (Carey et al. 2008; Jobes et al. 2011). A newer α -2R agonist, lofexidine, also attenuates stress-induced reinstatement of cocaine-seeking in rats (Erb et al. 2000; Highfield et al. 2001) and decreases drug withdrawal and stress-induced craving in humans (Sinha et al. 2007; Yu et al. 2008). Recently, acute treatment with lofexidine was shown to significantly reduced cocaine self-administration in rhesus monkeys, however, chronic treatment produced a leftward shift in the cocaine self-administration dose-effect curve (Kohut et al. 2013). Taken together, available evidence appears to support the notion that lofexidine may attenuate cocaine's effects in humans. Therefore, we conducted the first study assessing the impact of lofexidine in combination with cocaine in non-treatment seeking cocaine-dependent or cocaine-abusing participants.

Methods

Selection of Participants

Each individual underwent an extensive medical history and physical examination. For inclusion into the study, participants were 1) required to meet Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV-TR) criteria for cocaine abuse or dependence, 2) not be seeking treatment at the time of the study, 3) between 18 and 50 years of age, inclusive, 4) a current cocaine user (confirmed by a positive urine test for cocaine metabolites (benzoylecgonine: BE) once within the outpatient screening period), 5) self-reported use of cocaine by the smoked or intravenous (IV) route in the past 6 weeks, and 6) able to verbalize understanding of the consent form and provide written informed consent.

Participants were excluded if they demonstrated any clinically significant contraindication(s) for participating in the study such as 1) vital signs outside specified normal ranges, 2) clinically significant abnormal ECG, 3) current or past history of a seizure disorder, 4) current diagnosis of major psychiatric illness (e.g., schizophrenia, bipolar disorder, major depression, or other psychiatric condition that required medication), or 5) any illness, condition, or use of medications, that in the opinion of the principal investigator and the admitting physician, would preclude safe or successful completion of the study. Importantly, exclusion criteria also included that the subjects must not have been dependent on any drugs other than cocaine or nicotine.

This study was in compliance with applicable Food and Drug Administration laws and regulations, the World Medical Association Declaration of Helsinki (1989), and the International Conference for Harmonization Harmonized Tripartite Guideline for Good Clinical Practice. The Institutional Review Boards (IRBs) at the California Pacific Medical Center (CPMC), University of California San Francisco, Baylor College of Medicine (BCM), and Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) approved the study. Prior to undergoing any study procedures, participants provided written informed consent.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study (Figure 1) designed to assess the effects of lofexidine vs. placebo on the subjective effects produced by IV infusions of cocaine (20 mg and 40 mg) and saline in volunteers who met criteria for cocaine abuse or dependence. Placebo (given four times daily (QID)) and two dosing regimens for lofexidine were investigated: daily oral doses of 3.2 mg (N=3) given in divided doses of 0.8 mg QID, and daily oral doses of 0.8 mg (N=11) given in divided doses of 0.2 mg, QID. A total of 16 subjects were to be randomized 3:1 to receive either lofexidine or matched placebo, but adverse events (AEs) precluded enrollment of the intended sample size (see stopping criteria below).

Participants who provided informed consent were screened for eligibility. Outpatient screening assessments were completed during Study Days -30 to -3, during which time the subject provided one urine specimen positive for BE and completed all other outpatient screening measures. If still eligible, participants underwent clinic intake procedures on Day -2 and inpatient screening. Participants provided a negative urine specimen for BE at this time for admission into the study (a requirement to assure that all participants had been cocaine-free for at least 3–5 days before exposure to cocaine in the laboratory). Inpatient screening included a single-blind screening infusion (Infusion Session #1) of sequential IV infusions of 20 mg cocaine, followed by saline, followed by 40 mg of cocaine given 1 hour apart on Study Day -1 (~24 hours before baseline infusion sessions). Visual analog scale (VAS) scores from “I feel HIGH” and “I LIKE cocaine” were used. The highest score within the first 10 minutes of injection of saline or the two doses of cocaine was used for each of these questions to discriminate those individuals who could discern differences between saline and cocaine infusions. A 10 mm increase (on a scale of 0–100) in the VAS scale for these questions was considered a significant subjective response to cocaine, and participants who met these criteria continued to be housed in the inpatient unit for an additional 9 days (Study Days 1 to 9).

Once an individual met all criteria to participate in the study, s/he received double-blind baseline infusions of saline and 20 mg of cocaine on Day 1 (Baseline Infusion Session #2), and saline and 40 mg of cocaine on Day 2 (Baseline Infusion Session #3), in randomized order. Subjective effects, blood pressure (BP), heart rate (HR), and electrocardiogram (ECG) measures were taken repeatedly during these sessions. On Day 3, participants were randomized in a 3:1 ratio to receive lofexidine or matched placebo until Day 7. On Day 7, only two doses (the 0700 and 1200 doses) of lofexidine/placebo were administered.

Participants received double-blind infusions of saline and 20 mg of cocaine on Day 6 (Infusion Session #4), and saline and 40 mg of cocaine on Day 7 (Infusion Session #5). The order of the saline and cocaine infusions for Sessions #4 and #5 was the same as that randomized for Sessions #2 and #3, respectively. Cardiovascular and subjective effects data were recorded using the same schedule as during the baseline infusions. Clinic discharge occurred on Day 9, approximately 48 hours after the last dose of lofexidine/placebo. Participants were asked to return for a follow-up visit ~7 days after clinic discharge.

Drugs

Cocaine hydrochloride was manufactured by Murty Pharmaceuticals for NIDA and was supplied in aqueous solution. Cocaine is a potent inhibitor of monoamine transporters, including DA, serotonin, and NE transporters (Fleckenstein et al. 2000; Miller et al. 2001). Cocaine binds at the DA transporter and inhibits neurotransmitter reuptake, leading to a build-up of extracellular DA levels and potentiation of mesolimbocortical pathways (Haile et al. 2012b; Verrico et al. 2013). The distribution half-life of cocaine from an IV dose is about 10 min and the elimination $T_{1/2}$ of cocaine is ~1 hour (50–80 min). Doses used for IV cocaine administration in this study have been successfully utilized in several laboratory-based clinical studies and have proven safe (Johnson et al. 1998; Newton et al. 2012; Newton et al. 2005; Roache et al. 2011; Walsh et al. 1994). All subjects received cocaine infusions on five days: Days –1, 1, 2, 6, and 7 (as described above). Cocaine or saline was administered by IV push over 60 seconds by a study physician. Lofexidine hydrochloride 0.2 mg tablets, and matching placebo, were manufactured by US WorldMeds (Louisville, KY, USA).

Lofexidine hydrochloride is an orally active imidazoline adrenergic α -2-receptor agonist and has a similar mechanism of action to clonidine (reducing the release of NE); however, lofexidine has a higher affinity for 2A receptor subtypes, possibly resulting in less antihypertensive activity. A study in healthy male participants was conducted to characterize the clinical pharmacokinetic profile of oral lofexidine (single dose and multi-dose) (Al-Ghananeem 2009). In the single doses tested (1.2 mg and 2.0 mg dose), the average time to maximum concentration was observed at ~3 hours. In the multi-dose study (0.4 mg twice daily (BID) on Day 9, 0.8 mg BID on Days 10–15, and 0.6 mg BID on Day 16), steady state levels of lofexidine were achieved on the second day of dosing. The average C_{max} observed after the first dose of 0.4 mg was comparable to the results in the single dose study.

Stopping Criteria

Before each dose of lofexidine/placebo, the subject had bedside cardiovascular assessments consisting of a recumbent ECG, systolic and diastolic BP, and HR, followed by a repeated systolic and diastolic BP, and HR measurements following 3 minutes of standing, to elicit orthostatic changes to BP and/or orthostatic symptoms such as dizziness or faintness.

The dose of lofexidine/placebo was withheld if recumbent vital signs did not meet the following criteria: Systolic BP > 105 mmHg, Diastolic BP > 65 mmHg; HR > 60 bpm; ECG, sinus rhythm: QT <450 msec/QTc <470 msec. In addition, the dose of lofexidine/placebo was withheld if the above vital signs criteria were satisfied but after standing

upright, any of the following criteria were met: Systolic BP fell by >20% or >20 mmHg from recumbent pressure; Diastolic BP fell by >20% or >10 mmHg from recumbent pressure; HR fell to <60 bpm, corroborated on ECG and palpation, or any symptom of orthostasis occurred (dizziness, nausea, lightheadedness, confusion, or syncope) regardless of the absolute value of the vital signs.

If the subject received the scheduled dose of lofexidine, he/she was assessed hourly for 4 hours after the dose for BP, HR, and ECG, using the same order of assessment as before the dose, and was asked about symptoms consistent with orthostasis or hypotension. Each episode of hypotension or orthostasis that met criteria for holding a dose of lofexidine, or hypotension/orthostasis that required treatment at any time between doses of lofexidine was recorded as an AE.

Individual Subject Stopping Criteria

A record of total daily doses was kept for each subject. Any subject was discontinued from participation for any of the following reasons: 1) Missed two scheduled doses within a 24-hour period - on the basis of vital signs changes or refused a dose because of subjective intolerance, 2) Missed a cumulative total of three scheduled doses at any time for the same reasons, 3) Systolic BP < 80 mmHg, 4) Diastolic BP < 40 mmHg, 5) 20% fall of systolic BP or diastolic BP post-dose, 6) Experiences orthostatic symptoms, 7) HR < 45 bpm on ECG, 8) QTc > 450 msec for males or > 480 msec for females, 9) QT interval increase > 30 msec compared to baseline, or 10) Syncope.

Adverse Events

AEs were assessed by clinical staff, a nurse, or physician starting as soon as the subject signed the informed consent. If an AE was reported that required medical attention, it was reported to a study physician immediately. The investigator or study physician assessed subjects for any medical or psychiatric side effects. All AEs were recorded on an AE case report form completed weekly and reviewed by the principal investigator.

Cardiovascular Assessments

HR and BP were assessed prior to and 1 hour following each lofexidine/placebo dose. On the last several days of the inpatient stay, subjects had HR and BP checked and recorded four times daily for evidence of rebound hypertension. If subject had any evidence of rebound hypertension or hypotension, they were monitored hourly for 4 hours, then every 4 hours until their HR and BP returned to within 10% of screening/baseline values. After stable HR and BP were observed over four consecutive readings, the subject was eligible for discharge.

On Days 6 and 7, continuous bedside monitoring of ECG was performed starting 15 min before the first infusion and up to one hour after the last infusion. 12-lead ECGs were recorded 15 min before the first infusion of the day and at 4, 6, 12, 30, and 55 min after each infusion. In addition, 12-lead ECGs were recorded prior to and 1 hour following each lofexidine/placebo dose.

Before and after each IV infusion on Days 6 and 7, physiologic responses were closely monitored using repeated HR, BP, and ECG readings. HR and BP were taken 5 min prior to the start and at 5, 10, 15, 20, 25, 30, and 45 min after each infusion.

Subjective Effects

During and after the infusions, subjective responses were recorded. Specifically, computerized VAS was administered 15 min before, and 5, 10, 15, 20, 25, 30, and 45 min after each infusion. On a continuous scale digitized between 0 to 100, participants reported the degree to which they felt “any drug effect”, “high”, “good effects”, “bad effects”, “like cocaine”, “desire for cocaine”, “depressed”, “anxious”, “stimulated”, and “likely to use”. Participants also answered “How much do you think this infusion is worth in dollars?”

Data Analyses

AE data were compiled for all groups and analyzed by Fisher's Exact Test. In order to quantify lofexidine's “within subjects” effect on ECG, the baseline post-infusion maximum (for ventricular rate, and QRS and QTcF intervals) or minimum (for RR, PR, and QT intervals) was calculated for each infusion. For each subject and period (baseline or interaction) the post-saline maximum/minimum was subtracted from the post-cocaine maximum/minimum, and this new difference was analyzed by one-way repeated measures ANOVA for each treatment group and cocaine challenge.

Post-randomization (Days 6 and 7) cardiovascular (HR and BP) and subjective effects data were analyzed using repeated-measures ANOVA as a function of Lofexidine dose (0 or 0.8 mg), Cocaine dose (0, 20 or 40 mg) and Time (5, 10, 15, 20, 25, 30 and 45 min). These data were also analyzed with respect to peak effects (maximum change from baseline) using one-way ANOVA. All values reflect within-session change from baseline. For all measures, statistical significance was set at $p < 0.05$.

Results

Subject Disposition

Figure 2 provides a summary of the subject outcomes following informed consent. Of the 70 subjects who consented, 18 subjects were randomized to the treatment groups (lofexidine or placebo) and 11 completed the study. Ten individuals completed the protocol at the BCM site and one participant completed the protocol at the CPMC site. Of the seven subjects who did not complete the study after inpatient admission, six were discontinued by investigators, including the first two subjects who received 0.8 mg QID of lofexidine and experienced orthostatic hypotension, and four subjects who received 0.2 QID of lofexidine, and experienced hypotension and bradycardia. Another subject at 0.2 QID voluntarily withdrew due to hemodynamic-related AEs.

Adverse Events and ECG

Seventeen out of 18 subjects experienced at least one AE, including all patients in the placebo and lofexidine 0.8 mg QID groups. A total of 64 AEs were reported for the entire group of 18 subjects, which included 13 events occurring in the lofexidine 0.8 mg QID

group, 45 events in the lofexidine 0.2 mg QID group, and 6 events occurring in the placebo group. The most frequently reported treatment-related AEs were bradycardia (4 subjects), dry mouth (4 subjects), hypotension (4 subjects), orthostatic hypotension (3 subjects), and lethargy (3 subjects, all at the 0.8 mg dose level). The frequency of dizziness and lethargy were significantly greater with lofexidine than placebo at the 5% significance level (Table 1).

Detailed outputs of all ECG outputs are available by request. In brief, lofexidine had statistically significant effects on ECG measurements, such as the average post-infusion ventricular rate (-15.1 bpm or -15.5% with 0.8 mg lofexidine and 40 mg cocaine), maximum post-infusion QTcF interval (13.1 msec with 0.2 mg lofexidine and 20 mg cocaine), and RR interval ($+87.1$ msec or $+12.6\%$ with 0.8 mg lofexidine and 40 mg cocaine). In some cases, there was a statistically significant interaction between cocaine and lofexidine, indicating that the lofexidine effect varied with cocaine dose.

Demographics and Drug Use

Table 2 summarizes the demographic and drug use characteristics by study group for the 12 individuals who received cocaine infusions on Days 6 and 7. The majority of participants were Black males who were ~40 years of age, and used cocaine for ~ 12 of the previous 30 days.

Cardiovascular Effects

For Heart Rate time-course (Figure 3A), there was no main effect of Lofexidine ($F_{1,144}=2.26$, $p=0.146$), a significant main effect for Cocaine ($F_{2,144}=6.54$, $p=0.005$) and Time ($F_{6,144}=19.95$, $p<0.0001$), but no significant Lofexidine $\times$ Cocaine $\times$ Time interaction ($F_{12,144}=0.83$, $p=0.616$). For Heart Rate peak effects (Figure 3B), there was no main effect of Lofexidine ($F_{1,24}=0.51$, $p=0.483$), a significant main effect for Cocaine ($F_{2,24}=6.17$, $p=0.007$), but no significant Lofexidine $\times$ Cocaine interaction ($F_{2,24}=2.66$, $p=0.096$).

For Systolic BP time-course (Figure 3C), there was no main effect of Lofexidine ($F_{1,144}=3.26$, $p=0.084$), a significant main effect for Cocaine ($F_{2,144}=4.36$, $p=0.024$) and Time ($F_{6,144}=8.96$, $p<0.0001$), and a significant Lofexidine $\times$ Cocaine $\times$ Time interaction ($F_{12,144}=0.83$, $p=0.019$). For Systolic BP peak effects (Figure 3D), there was no main effect of Lofexidine ($F_{1,24}=1.58$, $p=0.220$), no main effect for Cocaine ($F_{2,24}=2.57$, $p=0.097$), and no significant Lofexidine $\times$ Cocaine interaction ($F_{2,24}=0.38$, $p=0.688$).

For Diastolic BP time-course (Figure 3E), there was no main effect of Lofexidine ($F_{1,144}=0.008$, $p=0.993$), no main effect for Cocaine ($F_{2,144}=1.69$, $p=0.205$), a significant effect for Time ($F_{6,144}=4.48$, $p=0.0003$), but no Lofexidine $\times$ Cocaine $\times$ Time interaction ($F_{12,144}=0.168$, $p=0.078$). For Diastolic BP peak effects (Figure 3F), there was no main effect of Lofexidine ($F_{1,24}=0.34$, $p=0.566$), no main effect for Cocaine ($F_{2,24}=1.73$, $p=0.199$), and no significant Lofexidine $\times$ Cocaine interaction ($F_{2,24}=0.44$, $p=0.649$).

Subjective Effects

Detailed outputs of all subjective effects outputs are available by request. The most intriguing are presented here. For “Any Drug Effect” time-course (Figure 4A), there was no main effect of Lofexidine ($F_{1,144}=4.15$, $p=0.053$), a significant main effect for Cocaine ($F_{2,144}=13.34$, $p<0.0001$) and Time ($F_{6,144}=19.06$, $p<0.0001$), but no significant Lofexidine $\times$ Cocaine $\times$ Time interaction ($F_{12,144}=0.67$, $p=0.776$). For “Any Drug Effect” peak effects (Figure 4B), there was no main effect of Lofexidine ($F_{1,24}=2.89$, $p=0.102$), a significant main effect for Cocaine ($F_{2,24}=17.22$, $p<0.0001$), but there was no significant Lofexidine $\times$ Cocaine interaction ($F_{2,24}=1.19$, $p=0.322$).

For “Good Effects” time-course (Figure 4C), there was a significant main effect of Lofexidine ($F_{1,144}=6.57$, $p=0.017$), Cocaine ($F_{2,144}=9.87$, $p=0.0007$) and Time ($F_{6,144}=9.45$, $p<0.0001$), but no significant Lofexidine $\times$ Cocaine $\times$ Time interaction ($F_{12,144}=0.64$, $p=0.807$). For “Good Effects” peak effects (Figure 4D), there was no main effect of Lofexidine ($F_{1,24}=2.22$, $p=0.149$), a significant main effect for Cocaine ($F_{2,24}=11.03$, $p=0.0004$), but no significant Lofexidine $\times$ Cocaine interaction ($F_{2,24}=0.97$, $p=0.395$).

For “Desire Cocaine” time-course (Figure 4E), there was no main effect of Lofexidine ($F_{1,144}=0.47$, $p=0.129$), a significant main effect for Cocaine ($F_{2,144}=8.96$, $p=0.001$) and Time ($F_{6,144}=15.38$, $p<0.0001$), but no significant Lofexidine $\times$ Cocaine $\times$ Time interaction ($F_{12,144}=0.744$, $p=0.707$). For “Desire Cocaine” peak effects (Figure 4F), there was no main effect of Lofexidine ($F_{1,24}=3.60$, $p=0.07$), a significant main effect for Cocaine ($F_{2,24}=14.15$, $p<0.001$), but there was no significant Lofexidine $\times$ Cocaine interaction ($F_{2,24}=0.29$, $p=0.753$).

Discussion

The current laboratory-based study demonstrated a trend for lofexidine to decrease cocaine-induced cardiovascular changes and cocaine-induced subjective effects, but sample size issues limit the conclusions that can be drawn. These data are largely in accordance with our primary hypothesis and a growing literature demonstrating a critical role for NE in the subjective and reinforcing effects produced by cocaine in humans (although the population in this report was small and highly selective - making it difficult to generalize). However, numerous safety concerns, including hypotension and changes in ECG measures, may limit future utility of lofexidine as a treatment for cocaine dependence. The small sample size is a concrete limitation of this study, but stopping enrollment was necessary to assure participant safety - it was not a lack of conducting an appropriate power analysis for sample size. Another limitation of this study was the paucity of information about use of cocaine and other drugs (e.g., nicotine, alcohol). The absence of that information makes comparing these data to others where participant characteristics are better known problematic, and does not allow assessment of whether something about the participant's drug use influenced study outcomes. Notwithstanding, the current data serve as proof-of-concept and set the stage for the development and testing of noradrenergic compounds with similar pharmacological profiles and mechanisms of action, but that possess less deleterious effects on hemodynamic parameters.

Lofexidine and clonidine are relatively non-selective, binding both α -2 adrenergic receptors and imidazoline receptors (Bousquet 2000). It is known that imidazoline receptor activation results in hypotension. That lofexidine targets imidazoline receptors and decreases presynaptic noradrenergic release and subsequent sympathetic drive may account for the prominence of this AE in the present study. A more specific α -2 adrenergic receptor agonist, such as guanfacine, may be worth evaluating since it is less sedating, better tolerated, has a longer half-life, and has more selectivity for α -2 adrenergic receptors found in prefrontal cortex (Nami et al. 1983; Ramos et al. 2006; Spiegel & DeVos 1980). Of particular interest, a recent study in 20 cocaine-dependent individuals showed that guanfacine lowered stress- and cue-induced nicotine craving and cue-induced cocaine craving, anxiety and arousal (Fox et al. 2012); suggesting that guanfacine warrants further study. Other drugs that reduce NE are also likely to be good candidate medications for cocaine dependence. Among these, the D β H inhibitor nopicastat is especially enticing. In particular, Weinshenker and colleagues have shown that nopicastat significantly attenuates reinstatement of cocaine self-administration in rodents under several distinct challenge conditions (Schroeder et al. 2013). Importantly, a phase-I safety and preliminary efficacy study in humans showed that nopicastat was well tolerated and reduced some positive subjective effects produced by cocaine in the laboratory (Cunningham et al. 2010), and continued testing of nopicastat is ongoing (Clinical Trials #01704196).

Acknowledgments

Role of Funding Source: Funding for this study was derived from a contract to R. De La Garza and G. Galloway from the National Institutes on Drug Abuse, and also included use of NIH-funded GCRC resources at BCM (RR 00188). This publication was supported in part by the National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH, through UCSF-CTSI Grant Number UL1 RR024131. Part of this work was conducted at, and supported by, the MEDVAMC, Houston, TX.

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Highlights

1. This study determined the safety of lofexidine concurrent with cocaine.
2. Two dosing regimens for lofexidine were investigated: 0.8 and 0.2 mg QID.
3. The data reveal a notable incidence of hemodynamic-related AEs.
4. There was a trend for lofexidine to decrease cocaine-induced subjective effects.
5. Cardiovascular AEs may limit future utility of lofexidine as a treatment.

Figure 1.
Study Schema

Figure 2.
Subject disposition after enrollment.

Figure 3.

Cardiovascular responses to Lofexedine and Cocaine are shown as the full time-course (panels A,C,E) and peak effects (panels B,D,F). All data reflect change from baseline (given time-point minus T=-5 min) and are displayed as mean $\pm$ S.E.M.

Figure 4.

Subjective Effects responses to Lofexedine and Cocaine are shown as the full time-course (panels A,C,E) and peak effects (panels B,D,F). All data reflect change from baseline (given time-point minus T=-15 min) and are displayed as mean $\pm$ S.E.M.

Table 1
Subjects Experiencing Treatment-Related Adverse Events by MedDRA SOC/PT, and Treatment Group

MedDRA System Organ Class	MedDRA Preferred Term	Lofexidine 0.8 mg (N=3)	Lofexidine 0.2 mg (N=11)	Placebo (N=4)	Fisher's Exact Test P-value (2-Tail)
Cardiac disorders	Bradycardia	0	4	0	0.407
	Dry mouth	2	2	0	0.126
Gastrointestinal disorders	Dizziness	2*	0	0	0.020
	Lethargy	3*	0	0	0.001
	Sedation	0	1	0	1.000
	Hypotension	0	4	0	0.407
Vascular disorders	Orthostatic hypertension	0	1	0	1.000
	Orthostatic hypotension	2	1	0	0.083
Total		3*	7	0	0.020

Table 2

Participant Demographics

Category	Lofexidine (N=6)	Placebo (N=4)
Age (years)	46.9 ± 2.3	41.6 ± 9.4
Gender		
Female	2	2
Male	4	2
Race		
Black	5	3
White	1	1
Ethnicity		
Hispanic or Latino	1	1
Not Hispanic or Latino	5	3
Education (years)	13.4 ± 2.2	11.3 ± 1.0
DSM Cocaine Dependence	6 (100%)	4 (100%)
Cocaine Use (last 30 days)	14.2 ± 8.0	14.5 ± 3.9

Data are shown as percentages or Mean ± S.D.