STUDY #: NIDA-CPU-Atomoxetine-0001

PHASE 1, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTIPLE DOSE ASSESSMENT OF POTENTIAL INTERACTIONS BETWEEN INTRAVENOUS COCAINE AND ATOMOXETINE

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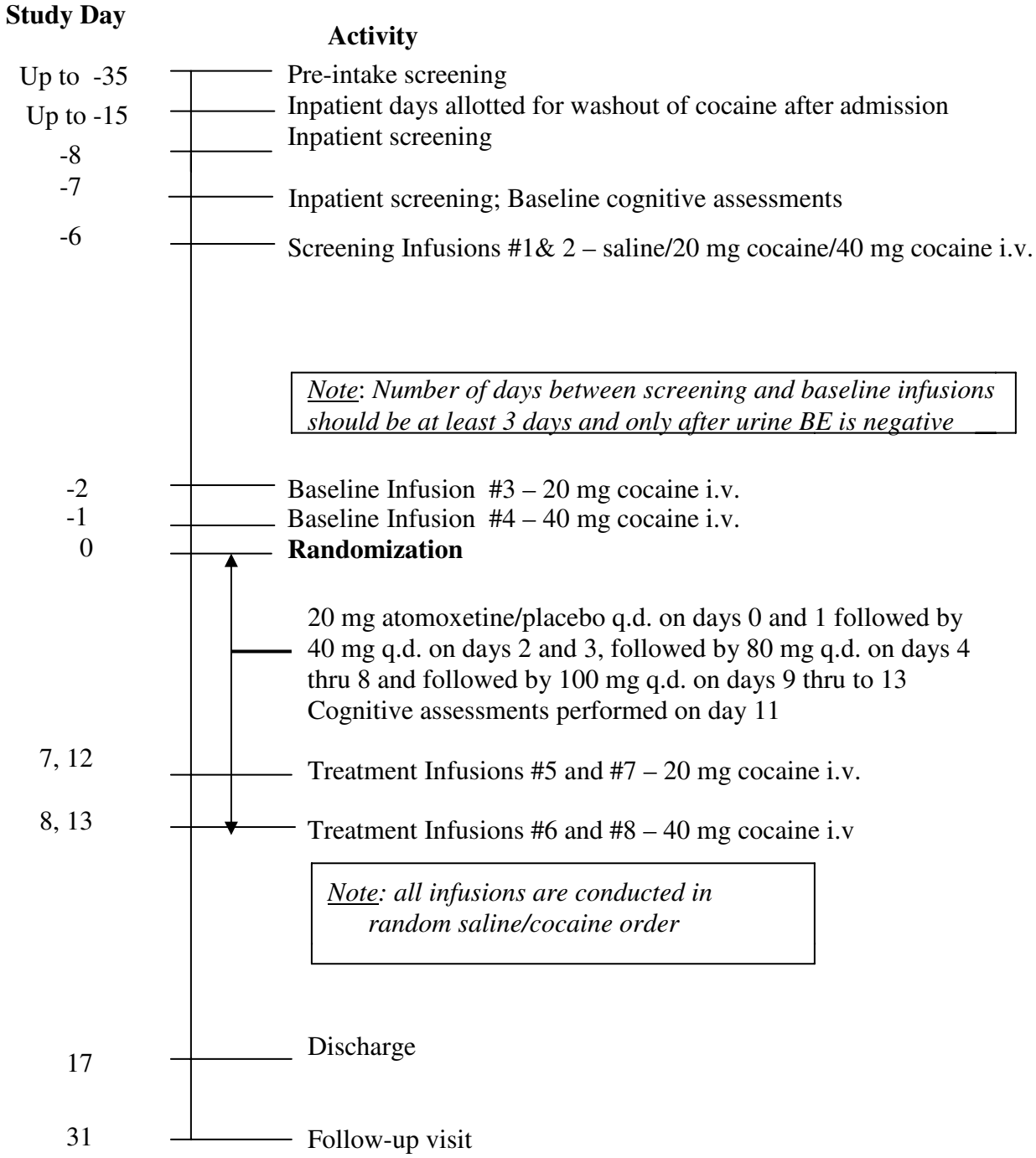
1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	attention deficit hyperactivity disorder
AE	adverse event
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANOVA	analysis of variance
ARCI	Addiction Research Center Inventory
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the blood concentration-time curve
BE	benzoylecgonine
BP	Blood Pressure
BPRS	Brief Psychiatric Rating Scale
BSCS	Brief Substance Craving Scale
BUN	blood urea nitrogen
CAP	College of American Pathologists
CBT	cognitive behavioral therapy
CLIA	Clinical Laboratory Improvement Amendment of 1988
COPD	chronic obstructive pulmonary disease
CRF	Case Report Form
CPK	creatinine phosphokinase
CPT	Continuous Performance Tests
CPU	Clinical Pharmacology Unit
DHHS	Department of Health and Human Services
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSMB	Data and Safety Monitoring Board
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
GCP	good clinical practices
HIV	human immunodeficiency virus
HR	heart rate
IRB	Institutional Review Board
i.v.	intravenous(ly)
LDH	lactate dehydrogenase
MAO	monoamine oxidase
mg	milligrams
mL	milliliter
NDA	New Drug Application
NIDA	National Institute on Drug Abuse
PK	pharmacokinetic(s)
POMS	Profile of Mood States

Abbreviation	Definition
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SERT	serotonin transporter
USUHS	Uniformed Services University of the Health Sciences
VAS	Visual Analog Scale
WCST	Wisconsin Card Sorting Task

2 MODEL STUDY SCHEMA



3 ABSTRACT

STUDY OBJECTIVES: This is a human laboratory clinical pharmacology study to assess potential interactions between intravenous (i.v.) cocaine and atomoxetine (Strattera) administered orally in four escalating doses.

Primary: The primary objective of this study is to determine the safety of coadministration of atomoxetine in therapeutic doses concurrent with i.v. cocaine infusions of 20 and 40 mg by measuring adverse events and cardiovascular responses [heart rate (HR), blood pressure (BP), and electrocardiogram (ECG)].

Secondary:

1. To determine safety, tolerance and PK of atomoxetine at the dosing schedule demonstrated to be safe and effective for the treatment of attention deficit hyperactivity disorder (ADHD).
2. To evaluate whether administration of atomoxetine alters the pharmacokinetics (PK) of cocaine or its major metabolite, benzoylecgonine (BE).
3. To evaluate whether atomoxetine treatment alters the subjective effects of cocaine measured by Visual Analog Scale (VAS) and craving measured by Brief Substance Craving Scale (BSCS).
4. To assess the effects of atomoxetine on mood and personality using BPRS and POMS assessments and on the abuse liability using ARCI.
5. To assess the effects of atomoxetine on cognitive function using a battery of computer- and experimenter-administered tests.

STUDY DESIGN: This is a dose escalating, double-blind, placebo-controlled inpatient study in 16 cocaine-experienced volunteers. To ensure that volunteers safely tolerate the cardiovascular effects of cocaine, screening infusions of 20 mg and 40 mg cocaine i.v. will be administered on day -6. At least three days after the screening cocaine infusions, to allow for the urine assay to become negative for BE, all subjects will receive baseline cocaine infusions of 20 mg and 40 mg i.v. on two consecutive days (days -2 and -1) and will be randomized (1:1) the next day (day 0) to receive atomoxetine by oral administration (8 subjects), or matched placebo (8 subjects). The subjects will receive atomoxetine 20 mg once daily (q.d.) for 2 days, 40 mg q.d. for 2 days, 80 mg q.d. for 5 days and 100 mg q.d. for 5 days orally or matched placebo. After beginning daily treatment with either atomoxetine or placebo, subjects will receive treatment cocaine infusions of 20 mg and 40 mg i.v. on the two last days of 80 mg and 100 mg atomoxetine dosage levels. Each cocaine infusion will be preceded or followed by saline i.v. infusion in random order; cocaine and saline infusions will be administered 60 minutes apart. The subjects will be discharged 4 days after the last infusion of cocaine (day 17). Subjects will be requested to return for follow-up 2 weeks after the day of discharge.

STUDY DURATION: Subjects will have up to 30 days for outpatient screening. The inpatient period will include up to seven days allotted for cocaine washout after admission (days -15 to -9), two days of inpatient screening (days -8 and -7), one day of screening cocaine infusions

(day -6), at least three days between screening and baseline infusions (days -5 thru -3), two days of baseline cocaine infusions (days -2 and -1), 14 days of treatment with atomoxetine or placebo (days 0 thru 13) and four days of inpatient washout until discharge on day 17. Subjects will be requested to return for follow-up 14 days after the day of discharge.

SAMPLE SIZE: Subjects will continue to be screened until 16 subjects have completed. Study subjects who complete the inpatient phase of the study will be considered completed subjects. Subjects who receive at least one dose of the study drug will be evaluated as intent-to-treat subjects.

POPULATION: Volunteer experienced cocaine users, 18-to-45 years of age, who have used cocaine by the smoked or i.v. route in the past six weeks and provided a positive urine test for cocaine within 30 days prior to entering the study.

TREATMENTS: All subjects will receive atomoxetine in an escalating dose schedule of 20 mg q.d. for 2 days, 40 mg q.d. for 2 days, 80 mg q.d. for 5 days and 100 mg q.d. for 5 days orally or matched placebo.

ASSESSMENTS: The primary outcome measure is safety. Safety of cocaine administration in atomoxetine dosed subjects will be measured by recording adverse events, BP, and HR, and by recorded ECGs. Secondary outcome measures include pharmacokinetic parameters, psychological assessments, and cognitive assessments. Potential pharmacokinetic interactions between cocaine and atomoxetine will be assessed by blood sampling for cocaine and BE and for peak and trough levels of atomoxetine during cocaine treatment infusions (sessions #6 and #8). The effect of atomoxetine on cocaine craving will be assessed by BSCS; other psychological assessments include POMS**,** VAS, ARCI and BPRS**.** Cognitive tests will be performed at baseline and at steady state of atomoxetine at the highest 100 mg q.d. dose level (day 11).

4 INTRODUCTION AND RATIONALE

4.1 Therapeutic Strategies for Treating Cocaine Abuse

A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for cocaine abuse. These include: 1) blocking cocaine's effects, 2) restoration of central nervous system homeostasis, 3) reducing craving or enhancing the addict's ability to manage his/her response to craving, 4) treating underlying comorbid conditions that may predispose targeted subpopulations toward dependence, and 5) stress reduction to prevent relapse.

4.1.1 Use of Dopaminergic and Serotonergic Agents to Treat Cocaine Dependency

In the mid-90s, after the earlier pharmacologic trials of tricyclic antidepressants to treat cocaine dependence (Gawin, 1986; Giannini *et al.,* 1986), the search for an effective pharmacotherapy for cocaine addiction was focused on dopaminergic agents (bromocriptine, bupropion, cabergoline) with direct or indirect agonist activity at dopamine receptors (Johanson and Schuster, 1995). Cocaine binds at the dopamine transporter and inhibits neurotransmitter

reuptake, which sustains elevated extracellular dopamine levels and potentiation of dopaminergic neurotransmission in mesolimbocortical pathways (Kuhar *et al*., 1991). A combination of theory and experimental data suggest that chronic cocaine use depletes brain dopamine, which is experienced as increased cocaine craving.

The lack of success in finding an effective pharmacological treatment for cocaine abuse thus far, may in part, is due to the cocaine's apparent action on multiple neurotransmitter systems. Cocaine is a potent inhibitor of not only the DAT, but of serotonin and norepinephrine transporters (SERT and NET, respectively) (Fleckenstein *et al.,* 2000; Miller *et al.,* 2001). Single gene knockouts in mice of DAT, SERT and NET indicated that any one of these transporters might be able to mediate cocaine reward in the other's absence (Sora *et al.,* 1998; Xu *et al.,* 2000). This hypothesis was recently confirmed by a NIDA research team headed by Dr. George Uhl, which studied genetically altered (double knockout) mice that were missing one or both copies of DAT and SERT genes (Sora *et al.,* 2001). They found that cocaine reward depends on both DAT and SERT blockade and that serotonin, as well as dopamine, plays a critical role in the development of cocaine addiction. The effects of transporter gene copy numbers on the cocaine place preference test indicated a greater role for DAT than SERT in cocaine reward/reinforcement in mice, consistent with previous pharmacological studies. Thus, mice with even a single DAT gene copy and no SERT copies still experienced reward/reinforcement behavior following cocaine administration, while cocaine-induced reward/reinforcement behavior was totally blocked in mice with no DAT gene and either half-normal or absent SERT. It is obvious that previously held views that DAT blockade is the sole site for cocaine reward have been replaced by a broader picture of multi-transporter involvement (DAT, SERT and NET) in cocaine's hedonic effects (Lin and Uhl, 2002; Uhl *et al.,* 2002).

As cocaine was generally considered to exert its locomotor and rewarding effects exclusively through an increased dopaminergic transmission in the nucleus accumbens;, much attention has been paid to the alterations in the regulation of DAT and DA receptors that result from long-term exposure to cocaine. Far less attention has been paid, however, to the role of noradrenergic systems as mediators of the acute and chronic actions of cocaine, although cocaine accumulates in high concentrations in NE-rich brain regions of non-human primates, such as locus coeruleus, hippocampus and amygdala (Madras and Kaufman, 1994) and dose dependently increases extracellular NE in the rat hippocampus, prefrontal cortex and nucleus accumbens (Florin *et al.,* 1994; Li *et al.,* 1996). The recently reported interactions between central noradrenergic and dopaminergic systems (adrenergic excitation of DA neurons or adrenergic potentiation of central dopaminergic neurotransmission) implicate noradrenergic transmission in the behavioral effects of stimulants, including cocaine (Darracq et al., 1998; Auclair *et al.,* 2002). Importantly, the involvement of the dopaminergic system in the cardiovascular effects of psychostimulant drugs that have been traditionally associated with their noradrenergic effects has been also demonstrated (Volkow *et al*., 2003). This cross-talk between noradrenergic and dopaminergic systems indicates the potential importance of agents that affect both systems as a medication for stimulant abuse. From this point of view, atomoxetine (Strattera), may have a potential for the treatment of cocaine dependence.

4.1.2 Atomoxetine as a Potential Cocaine Dependency Medication

The present study will evaluate the safety of atomoxetine (Strattera), a selective norepinephrine reuptake inhibitor, compared to placebo, concurrent with i.v. cocaine infusions.

Atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter that has been approved by FDA in November of 2002 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children, adolescents and adults. It is the first non-stimulant medication approved for the treatment of ADHD and the first medication approved for the treatment of adult ADHD. The safety and effectiveness of atomoxetine (Strattera) has been established in several double-blind, placebo-controlled short-term and long-term clinical trials in children, adolescents and adults who met DSM-IV criteria for ADHD. In all these studies, ADHD symptoms, such as inattentiveness and hyperactivity/impulsivity, were statistically significantly improved by atomoxetine (Strattera) (Package Insert, 2002). Atomoxetine (Strattera) increases both DA and NE in frontal cortex and may thereby enhance cognitive functioning in ADHD patients (Stahl, 2003).

It has been observed that a relatively high percentage of cocaine abusing or dependent individuals have a current diagnosis of ADD or a past history of ADHD. For example, in one sample of 281 cocaine abusers seeking treatment, 12% of the individuals met DSM-IV criteria for childhood ADHD, and 10% for adult ADD (Levin *et al.,* 1998). In another report, 35% of 298 treatment-seeking cocaine abusers met DSM-III-R criteria for childhood ADHD (Carroll *et al.,* 1993). Compared to those who did not have a childhood ADHD diagnosis, those that did, reported more severe substance use, earlier onset of cocaine abuse, and more frequent and intense cocaine use. Other studies assessing the prevalence of ADD in individuals seeking treatment for cocaine abuse or dependence, as well as those assessing the prevalence of cocaine use in subjects seeking treatment for ADD, and evaluating the adult status of children who were treated for ADHD, support the association between ADD and cocaine use. It is possible that cocaine use by some individuals with ADD/ADHD may be an attempt to self-medicate for the disorder.

In summary, the rationale for studying atomoxetine (Strattera) as a potential medication to treat cocaine dependence is based on several mechanisms. First of all, atomoxetine (Strattera) may act as a substitution/agonist medication and thus reduce cocaine dependency. Secondly, it is important that atomoxetine (Strattera) is proved to be effective in patients with ADHD, which is common among cocaine abusers. Based on that fact, it may be useful for treatment of cocaine dependence in an indirect way by improving cognitive functions of cocaine-dependent subjects by sharpening short-term attention span and improving concentration and daytime alertness and thus allowing them to benefit from cognitive behavioral therapy (CBT) and other treatment compliance-enhancing forms of psychosocial therapy aimed at reforming drug-seeking behavior.

4.2 Cocaine

Pharmacology. Cocaine is a potent inhibitor of monoamine transporters including dopamine, serotonin, and norepinephrine transporters (Fleckenstein *et al.,* 2000; Miller *et al.,* 2001). Cocaine binds at the dopamine transporter and inhibits neurotransmitter reuptake, leading to a build-up of extracellular dopamine levels and potentiation of mesolimbocortical pathways

(Kuhar *et al*., 1991). Neuroimaging (positron emission tomography) studies of human volunteers who regularly abuse cocaine indicate that doses used by cocaine abusers lead to a significant brain dopamine transporter blockade, which is associated with subjective effects of cocaine (self-reported "high") (Volkow *et al*., 1997). Single gene knockout studies in mice of dopamine, serotonin or norepinephrine transporters indicated that any one of these transporters might be able to mediate cocaine reward in the other's absence (Sora *et al.,* 1998; Xu *et al.,* 2000).

Cocaine affects nearly every organ and system, with the most dramatic changes being observed in the cardiovascular system and the brain. An important factor of cocaine-induced toxicity is vasoconstriction of coronary arteries and cerebral blood vessels combined with increased platelet aggregation, which can lead to focal or general ischemic episodes and myocardial and cerebral infarctions. In the cardiovascular system, tachycardia, hypertension, arrhythmias, and arteriosclerotic lesions are typical complications of cocaine abuse that often precede myocardial ischemia and infarction (Karch, 1993). Chronic use of cocaine can result in serious neuropathies, including optic nerve neuropathy, and can lead to seizures, cerebral infarction, cerebral hemorrhage, multifocal cerebral ischemia, and cerebral atrophy (Majewska *et al*.,1996). Psychiatric impairments associated with cocaine abuse include cognitive deficits, particularly in attention, problem solving, abstraction, arithmetic performance and short-term memory (Majewska *et al.,*1996). The most significant psychopathologies observed in cocaine addicts include anhedonia, anxiety, anergy, paranoia, depression, and bipolar mood disorder, which may predispose to suicide and are believed to contribute to cocaine craving and relapse. Cocaine seems to be hepatotoxic in humans (Marks and Chapple, 1967); this hepatotoxicity is enhanced by drugs such as barbiturates, alcohol and cocaine adulterants. Cocaine also induces pulmonary disorders, which are particularly severe in cocaine smokers. These disorders include barotrauma, inflammation and lung infections, pulmonary congestion, edema, hypertrophy of pulmonary arteries, and pulmonary necrosis (Karch, 1993).

Cocaine Pharmacokinetics. The distribution half-life of cocaine from an intravenous (i.v.) dose is about 10 min and the elimination half-life of cocaine is about 1 hour (50-80 min) (Jeffcoat *et al.,* 1989).

Cocaine Metabolism. Cocaine is primarily metabolized by esterases in the plasma and liver (Stewart *et al.,* 1977; Dean *et al.,* 1991) to inactive metabolites, benzoylecgonine (BE), ecgonine methyl ester and ecgonine. A very small portion of cocaine is metabolized by hepatic microsomal enzymes to an active metabolite, norcocaine (N-demethyl metabolite). In the presence of ethanol, liver carboxylesterase catalyzes the ethyl transesterification of cocaine to form cocaethylene plus methanol (Dean *et al.,* 1991).

Cocaine Dose Justification. Intravenous cocaine administration spanning the doses proposed for use in this study (20 mg and 40 mg) have been previously investigated in human laboratory clinical trials (Johnson *et al.,* 1998; Walsh *et al.,* 1994). Johnson and colleagues conducted continuous non-invasive cardiovascular monitoring in eight healthy cocaine addicts receiving intravenous doses of cocaine 0.325 mg/Kg or 0.650 mg/Kg. They demonstrated dose dependent increases in pulse and mean arterial pressure following cocaine administration that peaked 5 min post-cocaine infusion with a maximal responses being sustained for a further 15 and 35 min afterwards, respectively. Cocaine administration had no significant effect on peripheral

oxyhemoglobin saturation, and no clinical abnormalities of rhythm or conductivity were seen on ECG. These doses of cocaine (20 mg and 40 mg) and the method of single-dose i.v. cocaine administration as well as procedures for cardiovascular monitoring appear to be relatively safe for laboratory studies of healthy cocaine addicts with no pre-existing cardiovascular disease. Importantly, in a phase 1 clinical trial study of fluoxetine, intravenous cocaine doses of 20 mg and 40 mg did not produce any adverse physiological or subjective reactions in 5 healthy adult male volunteers with histories of cocaine abuse (Walsh *et al.,* 1994).

4.3 Atomoxetine

4.3.1 Chemistry

Atomoxetine (Strattera) has a chemical name of (-)-N-methyl-3-phenyl-3-(*o*-tolyloxy)-propylamine hydrochloride. The molecular formula is $C_{17}H_{21}NO.HCl$, which corresponds to a molecular weight of 291.82. It is a white to practically white solid, which has a solubility of 27.8 mg/mL in water. Atomoxetine (Strattera) is manufactured by Eli Lilly & Co. (Indianapolis, Ind.) as capsules for oral use only, in strengths of 10, 18, 25, 40, and 60 mg.

4.3.2 Pharmacology

Atomoxetine (Strattera) is metabolized via cytochrome P450 (CYP)-2D6 pathway; at least one metabolite is active. Peak plasma concentrations of atomoxetine (Strattera) are reached in 1 to 2 hours after oral administration. Accumulation of atomoxetine (Strattera) is seen during multiple dose therapy in poor (but not extensive) metabolizers; in extensive metabolizers (most subjects), half-life of atomoxetine (Strattera) is about 4 hours, whereas in poor metabolizers (less than 1% of population) the half-life is about 22 hours (Package Insert, 2002).

Single-dose and steady-state PK of atomoxetine (Strattera) was evaluated in pediatric patients with ADHD (N=21) (Witcher *et al.,* 2003). Plasma concentrations of atomoxetine, 4-hydroxyatomoxetine and N-desmethylatomoxetine were estimated in CYP450 2D6 extensive metabolizer patients with ADHD (N=21). The results of this study indicate that atomoxetine was rapidly absorbed with peak plasma concentrations occurring 1 to 2 hours after dosing, and half-life averaged 3.12 and 3.28 hours after a single dose and at steady state respectively ((Witcher *et al.,* 2003).

4.3.3 Previous Human Experience

Atomoxetine (Strattera) is approved for the treatment of ADHD in children and adolescents, ages 6 to 18, and in adults (Package Insert, 2002). Atomoxetine (Strattera) has been studied in several double-blind placebo-controlled clinical trials of patients with ADHD and its safety is well established.

4.3.4 Dose Justification.

The doses of atomoxetine (Strattera) to be used in this study (20 mg q.d, 40 mg q.d, 80 mg q.d, and 100 mg q.d.) are within the dose range recommended for the treatment of ADHD patients. The maximum recommended total daily dose of atomoxetine (Strattera) in children and adolescents over 70 kg and in adults is 100 mg (Package Insert, 2002).

Atomoxetine (Strattera) can be taken once or twice daily with or without food. Atomoxetine (Strattera) capsules should never be broken; they must be taken as a whole at the same time every day to keep on schedule. If a dose is missed it should be taken as soon as possible; the prescribed total daily dose should not be exceeded in any 24-hour period.

4.3.5 Atomoxetine Safety

The safety and tolerability of atomoxetine (Strattera) has been established in premarketing clinical studies involving more than 4,000 patients with ADHD, the majority of which were treated for 6-10 weeks while 526 patients were treated for over 6 months and 169 patients were treated for longer than 1 year (Package Information, 2002; Kratochvil *et al.,* 2003)). In general, atomoxetine (Strattera) has been used as a once or twice daily oral tablet in the range of 60 to 120 mg/day; the mean dose being 95-100 mg/day (Package Insert, 2002). At these doses, atomoxetine (Strattera) is well tolerated and AEs possibly associated with atomoxetine (Strattera) are short-lived and mild or moderate in severity. Adverse events associated with atomoxetine (Strattera) (incidence of 2% or greater) include the following:

- Abdominal pain
- Constipation
- Dyspepsia
- Vomiting
- Dry mouth
- Nausea
- Decreased appetite
- Weight decrease
- Sinus headaches
- Irritability
- Mood swings
- Insomnia
- Difficulty urinating
- Decreased libido
- Erectile dysfunction
- Dysmenorrhea

Short-term and long-term cardiovascular safety studies of atomoxetine (Strattera) indicate that it was not associated with QTc interval prolongation and that its effects on increases in pulse and blood pressure were small and of little, if any, clinical importance (Wernicke *et al.,* 2003). However, atomoxetine (Strattera) should be used with caution in patients with hypertension, tachycardia or cardiovascular disease because it can increase blood pressure and heart rate.

The effects of overdose greater than the maximum recommended daily dose in humans are unknown, and no specific information is available on the treatment of overdose.

4.3.6 Potential Drug Interactions

The potential for metabolism-mediated drug-drug interactions with atomoxetine has been studied. Biotransformation of atomoxetine is carried out by the CYP2D6 enzymatic pathway,

and coadministration with CYP 2D6 inhibitors may result in a substantial increase in atomoxetine plasma exposure. Thus, atomoxetine (Strattera) should not be taken with inhibitors of CYP2D6, such as quinidine and antidepressants including fluoxetine (Prozac) and paroxetine (Paxil). Atomoxetine (Strattera) should not be taken with monoamine oxidase inhibitors (MAOI), such as Nardil or Parnate or within 14 days of stopping MAOI. Atomoxetine (Strattera) should not be taken with albuterol as it has been shown to potentiate albuterol-induced increases in heart pressure and heart rate (Package Insert, 2002).

Cocaine is primarily metabolized by esterases in the plasma and liver to inactive metabolites, benzoylecgonine (BE), ecgonine methyl ester, and ecgonine (Stewart *et al.,* 1977; Kloss *et al.,* 1984; Dean *et al.,* 1991) with a very small portion of cocaine being oxidized to an active metabolite norcocaine by CYP3A pathway (Ladona *et al.,* 2000). Thus, theoretically the metabolic pathways of atomoxetine (Strattera) and cocaine do not overlap. This Phase 1 human laboratory study will evaluate whether there may be an interaction between atomoxetine and cocaine.

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of this study is to determine if there are significant interactions between atomoxetine treatment concurrent with i.v. cocaine infusions of 20 and 40 mg by measuring adverse events and cardiovascular responses [heart rate (HR), blood pressure (BP), and electrocardiogram (ECG)]. Note: A significant interaction is defined as: more than 50% of the subjects treated with atomoxetine experience a pharmacodynamic interaction when challenged with cocaine, which brings the stopping criteria (section 11.4.5) into effect.

5.2 Secondary Objective

1. To determine safety, tolerance and PK of atomoxetine at the dosing schedule demonstrated to be safe and effective for the treatment of attention deficit hyperactivity disorder (ADHD).
2. To evaluate whether administration of atomoxetine alters the pharmacokinetics (PK) of cocaine or its major metabolite, benzoylecgonine (BE).
3. To evaluate whether atomoxetine treatment alters the subjective effects of cocaine measured by VAS and craving measured by BSCS.
4. To assess the effects of atomoxetine on mood and personality using BPRS and POMS assessments and on the abuse liability using ARCI.
5. To assess the effects of short-term treatment with atomoxetine on cognitive function using a battery of computer- and experimenter-administered tests.

6 STUDY DESIGN

This is a dose escalating, double-blind, placebo-controlled inpatient study in 16 cocaine-experienced volunteers. To ensure that volunteers safely tolerate the cardiovascular effects of cocaine, screening infusions of 20 mg and 40 mg cocaine i.v. will be administered on day -6. At least three days after the screening cocaine infusions, to allow for the urine assay to become negative for BE, all subjects will receive baseline cocaine infusions of 20 mg and 40 mg i.v. on

two consecutive days (days -2 and -1) and will be randomized (1:1) the next day (day 0) to receive atomoxetine by oral administration (8 subjects), or matched placebo (8 subjects). The subjects will receive atomoxetine 20 mg once daily (q.d.) for 2 days, 40 mg q.d. for 2 days, 80 mg q.d. for 5 days and 100 mg q.d. for 5 days orally or matched placebo. After beginning daily treatment with either atomoxetine or placebo, subjects will receive treatment cocaine infusions of 20 mg and 40 mg i.v. on the two last days of 80 mg and 100 mg atomoxetine dosage levels. Each cocaine infusion will be preceded or followed by saline i.v. infusion in random order; cocaine and saline infusions will be administered 60 minutes apart. The subjects will be discharged 4 days after the last infusion of cocaine (day 17). Subjects will be requested to return for follow-up 2 weeks after the day of discharge.

Subjects who receive at least one dose of the study drug will be evaluated as intent-to-treat subjects. Study subjects who complete the inpatient phase of the study will be considered completed subjects. Subjects will continue to be screened until 16 subjects have completed.

7 STUDY SITE

The study will be conducted at the Uniformed Services University of the Health Sciences (USUHS). On admission, subjects with positive urine drug toxicology will be allowed a washout period of up to seven days before the first cocaine infusion.

8 SUBJECT SELECTION

8.1 Inclusion Criteria

In order to participate in the study, subjects must:

1. Be volunteers who are not seeking treatment at the time of the study.

2. Be between 18 and 45 years of age and within 20% of ideal body weight according to the Metropolitan Height and Weight Chart, and weigh at least 45 kg.

3. Meet DSM-IV criteria for cocaine abuse or dependence.

4. Must currently use cocaine by the smoked or intravenous route, and this use must be confirmed by a positive BE urine test once within 30 days prior to entering the study.

5. Be able to verbalize understanding of the consent form, provide written informed consent, and verbalize willingness to complete study procedures.

6. If female, have a negative pregnancy test within 72 hours prior to receiving the first screening infusion, or be postmenopausal, or have had a hysterectomy, or have been sterilized, or agree to use one of the following methods of birth control during the study:

a. patch
b. double barrier contraception techniques, such as diaphragm and condom (by the partner), intrauterine device and condom, or sponge and condom
c. complete abstinence from sexual intercourse

7. Have a history and brief physical examination that demonstrate no clinically significant contraindication for participating in the study.

8. Be able to comply with protocol requirements, Clinical Pharmacology Unit (CPU) rules and regulations and be likely to complete all the study treatments.

8.2 Exclusion criteria

In order to participate in the study, subjects must not:

1. Have a current or past history of seizure disorder, including alcohol- or stimulant-related seizure, febrile seizure, or significant family history of idiopathic seizure disorder.

2. Have any previous medically adverse reaction to cocaine, including loss of consciousness, chest pain, or seizure.

3. According to DSM-IV criteria as determined by structured clinical interview (SCID), have any history of major psychiatric illness other than ADHD, drug dependence or disorders secondary to drug use.

4. Be pregnant or lactating.

5. Have a history of liver disease or current elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceeding the upper limit of normal.

6. Have donated a unit of blood or participated in any other clinical investigation involving cocaine administration within 4 weeks of enrolling on the study.

7. Have a history of any illness, or a family history of early significant cardiovascular disease, or a history of behavior, that in the opinion of the investigator might confound the results of the study or pose additional risk in administering the investigational agents to the subject.

8. Be seropositive for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) type 1.

9. Have a diagnosis of adult (i.e., 21 years or older) asthma, or chronic obstructive pulmonary disease (COPD), including those with a history of acute asthma within the past two years, and those with current or recent (past 2 years) treatment with inhaled or oral beta-agonist.

10. Have any illness, condition, and use of medications, that in the opinion of the Principal Investigator and the admitting physician, would preclude safe and/or successful completion of the study.

11. Currently use illicit drugs besides cocaine and marijuana.

12. Have 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.

13. Be unable to distinguish between a 20 mg and 40 mg dose of cocaine intravenously during the administration of baseline infusions as manifested by a higher score on Visual Analog Scale and increase in heart rate after the 40 mg dose of cocaine compared to the 20 mg dose. Note: During the first 35 minutes after cocaine infusion, the average of the highest response to VAS question #2 ("feel high") plus the highest response to VAS question #9 ("feel stimulated") should be higher on 40 mg than on 20 mg i.v. cocaine; also, during the first 10 minutes after i.v. cocaine, the HR response to either 20 mg or 40 mg i.v. cocaine should be at least 10 bpm more than the basal HR measured 5 minutes before infusion.

14. Be physiologically dependent on alcohol requiring medical detoxification.

9 INVESTIGATIONAL AGENTS

9.1 Atomoxetine

Atomoxetine will be supplied as 20 mg, 40 mg and 60 mg capsules.

Atomoxetine capsules: each capsule contains atomoxetine hydrochloride and pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate and other inactive ingredients as well as one or more of the following: FD&C Blue No.2, synthetic yellow iron oxide, titanium oxide. The capsules are imprinted with edible black ink.
Placebo capsules will be supplied as an exact match of atomoxetine.

It is recommended that atomoxetine capsules and the matching placebo capsules be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

9.2 Cocaine

Cocaine hydrochloride solutions, 10 mg/mL in 2 mL ampoule (20 mg dose) and 20 mg/mL in 2 mL ampoule (40 mg dose), will be manufactured by Murty Pharmaceuticals for NIDA. The Cocaine hydrochloride solutions should be stored in the pharmacy vault under refrigerated conditions. Standard controlled substance procedures will govern access to the drug. Cocaine will be administered by i.v. infusion over 60 seconds by the study physician. Any unused drug will be disposed according to standard practices.

10 TREATMENT PLAN

10.1 Atomoxetine and Placebo

Each subject in the active treatment group will receive 20 mg of atomoxetine q.d. on study days 0 and 1, 40 mg q.d. of atomoxetine on study days 2 and 3, 80 mg atomoxetine q.d. on study days

4 thru 8 and 100 mg q.d. atomoxetine on study days 9 thru 13. Each subject in the placebo treatment group will receive matched placebo capsules q.d. on study days 0 thru 13 on the same dosage schedule used in the atomoxetine group.

Subjects will be instructed to take the dose of atomoxetine or placebo with approximately 250 mL of water once a day at 8:00 a.m., and the research nurse will ensure the medication has been ingested by visually examining their oral cavity. Note: The first dose of atomoxetine or placebo on day 0 will be given immediately after randomization.

Subjects will take one 20 mg atomoxetine capsule q.d. on days 0 and 1, one 40 mg atomoxetine capsule q.d. on days 2 and 3, two 40 mg atomoxetine capsules q.d. on days 4 thru 8 and one 40 mg atomoxetine capsule with one 60 mg atomoxetine capsule q.d. on days 9 thru 13.

10.2 Cocaine

All subjects will receive cocaine infusions on 7 days: days -6, -2, -1, 7, 8, 12 and 13. Cocaine will be administered by i.v. push over 60 seconds by the study physician. Subjects will receive 20 mg cocaine i.v. on days -6, -2, 7 and 12, and 40 mg cocaine i.v. on days -6, -1, 8 and 13. For screening (day -1), subjects will receive saline infusion at 8:00 a.m. followed by 20 mg cocaine infusion at 9:00 a.m. and 40 mg cocaine infusion at 10:00 a.m. For each baseline and treatment session, subjects will be randomly assigned (1:1 ratio) to receive either saline at 9:00 a.m. followed one hour later at 10:00 a.m. by cocaine or cocaine at 9:00 a.m. followed one hour later at 10:00 a.m. by saline in a double-blind fashion (subjects and research staff will be blinded).

10.3 Prior and Concomitant Medication(s)

No prescription medication for 14 days and non-prescription medications (including dietary health food supplements) for 7 days are to be taken by subjects prior to the start of the study. Female subjects must not use oral contraceptives, Depo-Provera, Norplant or intrauterine progesterone contraceptive system 30 days prior to study participation and during the study. Addition of any medication during the course of the study must be discussed with the NIDA medical monitor prior to administration. Should there be a clinical indication for any additional medication during the course of the study, the name of the drug, dosage, reason for administration, and duration of administration must be recorded on the appropriate case report form (CRF). One multivitamin per day that does not exceed 100% of the recommended daily allowance (RDA) for each component is permitted for ingestion by each subject except during inpatient periods.

10.4 Dietary, Physical Activity, and Other Restrictions

Diet. On cocaine infusion days, subjects must not consume any food or drink except water for 1 hour prior and 2 hours after infusion. Food and drink must be provided by the site (USUHS).

Exercise. Subjects will be instructed to refrain from participation in contact sports and weight lifting from 48 hours before inpatient period until completion of the study.

Tobacco Products. Subjects will be allowed to smoke during the study in designated areas and accompanied by site staff at scheduled times according to the rules of the site (USUHS). Smoking is not permitted from one (1) hour prior to until two (2) hours after drug administration. Smoking is not permitted 1 hour prior to cocaine infusion.

Alcohol. Subjects will be questioned about their estimated daily intake of alcohol during the pre-study evaluation of eligibility. Any subject who shows physiological dependence on alcohol requiring medical detoxification will be excluded. Alcoholic beverages are not permitted from 48 hours before the inpatient period until the discharge from the study. Subjects will have a breath analyzer test on admission; if a subject is found to test positive for alcohol, the investigator or his designee may, at his discretion, decide if the subject should be rescheduled.

11 STUDY PROCEDURES

Appendix I provides a detailed table of the timing of study activities.

11.1 Screening

(Subjects will have up to 30 days for screening. Up to seven days after admission (days -15 through -9) are allotted for the subjects' urine to become negative for cocaine. Day -8 and -7 are the days of inpatient screening.)

Interested candidates between the ages of 18 and 45 who have been determined during the telephone screening process to have used cocaine by the smoked or i.v. route, are not seeking treatment, and are available to participate in an inpatient study for 21 days will meet with the investigator and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the local site's Institutional Review Board *(*IRB). After providing informed consent, the subject will proceed to the screening/baseline assessments phase of the study.

Screening of subjects to establish eligibility will occur initially before clinic intake and be completed after intake. Assessments performed before intake include collection of demographic information and completion of a subject locator form, a timeline follow back interview for cocaine use for the past 30 days, medical history, a 12-lead ECG, and physical examination including vital signs (HR and BP). Blood will be collected for complete blood count, chemistries, including liver function tests, hepatitis serology and HIV type 1 antibody test, pregnancy test and alcohol assessments. Urine will be collected for routine urinalysis.

A urine drug toxicology screen will also be conducted for drugs of abuse. With the exception of cocaine, cocaine metabolites, and marijuana, the urine drug toxicology screen must be negative to enroll in the study. Candidates deemed eligible based on the screening assessments mentioned above will be administered a structured clinical interview (SCID) by a trained mental health professional, to determine if there are any underlining psychiatric conditions that might exclude the potential subject from participation. These assessments must be completed within 30 days before clinic intake.

Subjects will be instructed that no prescription/non-prescription medications are to be taken within 14 and 7 days of the intake, respectively. Subjects will also be instructed to refrain from using any alcohol from 48 hours before clinic intake until discharge from the study. Subjects will also be instructed to refrain from participation in contact sports and weight lifting from 48 hours before the inpatient period until study completion.

Subjects must be informed of the unknown risks of becoming pregnant and must agree not to become pregnant during the time they are participating in this study. Women of childbearing potential can be enrolled; however, appropriate contraception must be used throughout the study. No oral contraceptives, Depo-Provera, Norplant and intrauterine progesterone contraceptive system are to be taken or used within 30 days of the intake. Abstinence (starting at least 14 days prior to study) or double barrier contraception techniques, such as diaphragm and condom (by the partner), intrauterine device and condom, or sponge and condom must be used during the study. If there is any question that a female subject will not be reliable in the use of these double-barrier contraceptive methods, she will not be entered into the study.

Women participating in the study will be tested for serum beta-human chorionic gonadotropin (ß-HCG) to detect pregnancy at outpatient screening and at intake screening within 72 hours prior to receiving the first cocaine infusion. In the case of a positive or borderline serum ß-HCG pregnancy test at the intake screening, the subject will be excluded from the study. Subjects will again be tested prior to discharge from the study. In the case of a positive or borderline test at the end of the inpatient period, the NIDA clinical monitor will be contacted and the pregnancy will be recorded as an adverse event. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been terminated or completed. The outcome of the pregnancy will be reported to the NIDA clinical monitor without delay within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The result of each pregnancy test will be recorded on a CRF.

All drug-abusing applicants for study participation will receive counseling about drug dependence and be advised that treatment for drug abuse is indicated and available. Applicants not participating in the study will receive treatment referral information as appropriate. At the completion of their participation, study participants will again be advised that treatment is indicated and available, and will be given treatment referral information and assistance.

11.2 Intake Screening

Potential candidates whose screening assessment results do not exclude them from study participation will complete intake procedures and reside full-time as inpatients until discharge or completion of the study. Screening procedures after intake will be completed on days -8 or -7 and will include brief physical exam, vital signs, 12-lead ECG, urine drug toxicology screen, a ß-HCG (pregnancy test), a breath alcohol analyzer test, BSCS, BPRS, POMS, ASI-Lite, VAS, ARCI and cognitive assessments. Subjects with positive urine BE after intake will be allowed a washout period of up to seven (7) days before the first screening cocaine infusion (session #1).

11.3 Enrollment and Randomization

A prospective subject who meets all of the study inclusion criteria and does not meet any of the exclusion criteria may be enrolled onto the study. Note: The enrollment is to be the first day that subject receives any study drug, including cocaine (day -6). After completing baseline cocaine infusions (sessions #3 and #4) and if still eligible for participation in the study, subjects will be randomized (day 0) to receive either placebo (8 subjects) or atomoxetine (8 subjects).

The data-coordinating center will supply the Research Pharmacist with pre-coded envelopes with treatment assignments. On study day 0, the investigator or study coordinator will obtain the treatment assignment from the Research Pharmacist. The Research Pharmacist will dispense the coded bottle of investigational agent for the subject to the investigator. It is recommended that if a subject is terminated before completing all of the cocaine infusion sessions, a replacement subject will be randomized until 16 subjects have completed the study.

11.4 Cocaine Infusion Sessions

11.4.1 Schedule

Intravenous cocaine infusions will be conducted according to the schedule shown in Table 1. For screening, subjects will receive saline infusion at 8:00 a.m. followed by 20 mg cocaine infusion at 9:00 a.m. and 40 mg cocaine infusion at 10:00 a.m. For each baseline and treatment session, subjects will be randomly assigned (1:1 ratio) to receive either saline at 9:00 a.m. followed one hour later at 10:00 a.m. by cocaine or cocaine at 9:00 a.m. followed one hour later at 10:00 a.m. by saline in a double-blind fashion (subjects and research staff will be blinded). Each series of repeated administrations (baseline and treatment) will consist of two infusion sessions over two consecutive days and will be conducted in a random saline/cocaine order (Table 1). During the screening and baseline infusion assessments, the subject's responses to cocaine without concomitant atomoxetine or placebo administration will be assessed. During the treatment infusion sessions, the subject's responses to cocaine with concomitant atomoxetine or placebo administration will be assessed. Each baseline and treatment infusion session will be on different days. The fixed ascending sequence each week is a safety precaution.

Table 1. Cocaine Infusion Session Schedule

Study Phase	Session Number	Study Day	Infusion
Screening	Sessions 1 and 2	-6	Saline infusion, followed by 20 mg cocaine 1 hr later and followed by 40 mg cocaine 1 hr later
Baseline	Session 3	-2	Saline/20 mg cocaine followed by 20 mg cocaine/saline 1 hr later
Baseline	Session 4	-1	Saline/40 mg cocaine followed by 40 mg cocaine/saline 1 hr later
Treatment (dose 80 mg)	Session 5	7	Atomoxetine/placebo followed by saline/ 20 mg cocaine 1 hr later and followed by 20 mg cocaine/saline 1 hr later
Treatment (dose 80 mg)	Session 6	8	Atomoxetine/placebo followed by saline/ 40 mg cocaine 1 hr later and followed by 40 mg cocaine/saline 1 hr later
Treatment (dose 100 mg)	Session 7	12	Atomoxetine/placebo followed by saline/ 20 mg cocaine 1 hr later and followed by 20 mg cocaine/saline 1 hr later
Treatment (dose 100 mg)	Session 8	13	Atomoxetine/placebo followed by saline/ 40 mg cocaine 1 hr later and followed by 40 mg cocaine/saline 1 hr later

11.4.2 Conduct of Cocaine/Saline Infusion Sessions

All subjects will receive cocaine infusions on 7 days: days -6, -2, -1, 7, 8, 12 and 13. Cocaine will be administered by i.v. push over 60 seconds by the study physician. Subjects will receive 20 mg cocaine i.v. on days -6, -2, 7 and 12, and 40 mg cocaine i.v. on days -6, -1, 8 and 13. A study physician will administer each i.v. infusion dose over 1 minute duration. For screening, subjects will receive saline infusion at 8:00 a.m. followed by 20 mg cocaine infusion at 9:00 a.m. and 40 mg cocaine infusion at 10:00 a.m. For each baseline and treatment session, subjects will be randomly assigned (1:1 ratio) to receive either saline at 9:00 a.m. followed one hour later at 10:00 a.m. by cocaine or cocaine at 9:00 a.m. followed one hour later at 10:00 a.m. by saline in a double-blind fashion (subjects and research staff will be blinded). During the treatment infusions (sessions #5-8), the subjects will take atomoxetine or placebo at 8:00 a.m., and after that will get the infusions at 9:00 a.m. and 10:00 a.m. (Tables 1 and 2).

For a subject to receive the first screening cocaine infusions (session #1 and 2), s/he must have a drug toxicology screening that shows negative urine drug/metabolite levels for drugs of abuse (except marijuana). Subjects with positive urine drug toxicologies will be allowed a washout period of up to seven days before the screening cocaine infusion session. The screening infusions are administered to ensure that volunteers safely tolerate the cardiovascular effects of the cocaine test doses.

The baseline cocaine infusions of 20 and 40 mg i.v. (sessions #3 and #4) are performed at least 3 days after screening cocaine infusion session and when urine is negative for cocaine. The baseline infusions provide cardiovascular and psychological response data in the absence of the investigational agent atomoxetine. Only subjects safely tolerating both 20 mg and 40 mg of cocaine and who can distinguish between the cardiovascular, as assessed by HR, and psychoactive effects, as assessed by VAS, of these two doses, will continue in the study. Specifically, during the first 35 minutes after cocaine infusion, the average of the highest response to VAS question #2 ("feel high") plus the highest response to VAS question #9 ("feel stimulated") should be higher on 40 mg than on 20 mg i.v. cocaine; also, during the first 10 minutes after i.v. cocaine, the HR response to either 20 mg or 40 mg i.v. cocaine should be at least 10 bpm more than the basal HR measured 5 minutes before infusion.

Before and after each i.v. infusion, the subjects' physiologic responses will be closely monitored using repeated HR, BP, and ECG readings. During infusion sessions #1-8, BP and HR will be recorded at the following time points relative to the first infusion of the day: -15, -10, -5, 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 62, 64, 66, 68, 70, 75, 80, 85, 90, 95, 100, 110, 115, 120 minutes and then every 30 minutes for the next 4 hours. ECG and HR will be monitored continuously beginning 10 minutes before the first infusion until 4 hours after the second infusion. Subjects will be placed on telemetry for monitoring until the completion of 24 hours after the first infusion. 12-lead ECG will be performed at -10 minute and at 4, 40, 64, and 100 minutes after the first infusion. Subjects will be monitored for at least 1 hour after second infusion by study personnel and staff. Thereafter, nursing staff will monitor participants and take vital signs for 4 hours and until vital signs revert to being within 10% of the baseline.

The VAS for psychoactive response to cocaine, will be administered before and at 5, 15, 25 and 35 minutes after each cocaine/saline infusion, and will be continued every 30 minutes for as long as the symptoms remain.

11.4.3 Safety Precautions

A physician will perform the infusions and will be present for at least 1 hour after the completion of the infusions. Thereafter, the physician will remain on the medical campus and be available by pager for prompt response, if needed, for at least four hours post-infusion. If a subject demonstrates a significant adverse reaction to cocaine, the cocaine administration will be halted, appropriate medical response will be implemented, and the subject will be discontinued from the remainder of the study. The BPRS will be performed within 1 hour of the completion of each infusion to assess possible acute psychosis due to cocaine.

11.4.4 Stopping Criteria for Further Cocaine Infusion

Cocaine intravenous administration will be discontinued if any of the following events occurs:

1. Systolic BP > 165 mm Hg;
2. Diastolic BP > 100 mm Hg;
3. HR > 130 bpm;
4. Behavioral manifestation of cocaine toxicity, e.g., agitation, psychosis, inability to cooperate with study procedures.

11.5 Stopping Criteria for Further Study Participation

Further participation of the subject is stopped if any of the following events occur:

1. Acute chest pain, shortness of breath;
2. Systolic BP > 180 mm Hg sustained for 5 minutes or more;
3. Diastolic BP > 120 mm Hg sustained for 5 minutes or more;
4. Heart rate > (220 - age x 0.85) bpm sustained for 5 minutes or more;
5. Neurological or psychiatric events (e.g., panic or psychosis);
6. A clinically significant ECG abnormality, such as:
    - ST segment elevations in two or more continuous leads of greater than 0.1 mV.
    - ST segment depression of greater than 1 mm that are flat or down-sloping at 80 msec after the J point.
    - New bundle branch block.
    - Mobitz II 2^0 or 3^0 heart block.
    - Atrial fibrillation or atrial flutter or activation of any non-sinus tachyarrhythmia for greater than 10 seconds.
    - Three or more consecutive ectopic ventricular complexes at a rate of greater than 100 per minute.
7. Any condition that in the clinical judgment of the investigator is of sufficient magnitude to present a danger to the subject.

11.6 Volunteer Discontinuation

Subjects will be excluded or discharged if their behavior is disruptive, non-compliant with study procedures, or otherwise not consistent with remaining in the hospital.

11.7 Subject Discharge and Follow-Up

The subjects will be discharged from the hospital on day 17, four days after the last dose of atomoxetine and the last infusion of cocaine (session #8). Subjects will be requested to return for follow-up at 14 days after the day of discharge.

11.8 Subject Payment

Subject payment will consist of payment for screening procedures, payment for all in-patient procedures, and final payment at the completion of the outpatient visit. Schedule of payments should provide incentive for subjects to complete the outpatient follow-up.

12 CLINICAL AND LABORATORY EVALUATIONS

A table summarizing the timing of the clinical and laboratory assessments to be conducted over the entire study period is shown in Appendix I.

12.1 Screening

Screening evaluations will be performed initially before clinic intake and then in the inpatient setting.

Screening Assessments before Intake. The following evaluations will be performed before clinic intake and must be performed within 30 days prior to intake:

1. Informed Consent;
2. Locator Form;
3. Demographics Information;
4. Cocaine use for prior 30 days using timeline follow back method;
5. Urine drug toxicology screen;
6. Medical history;
7. Physical examination and vital signs (BP and HR);
8. 12-lead ECG;
9. Hematology;
10. Blood chemistry, including liver function tests;
11. Hepatitis serology and HIV 1 antibody test;
12. Serum ß-HCG (pregnancy test);
13. Plasma alcohol;
14. Routine urinalysis;
15. SCID;
16. Adverse events.

Inpatient Screening Assessments. The following evaluations will be performed after intake before the first cocaine infusion:

1. Vital signs (BP and HR);
2. 12-lead ECG;
3. Blood chemistry, including liver function tests;
4. Urine drug toxicology screen;
5. Breath alcohol analyzer test;
6. Serum ß-HCG (pregnancy test);
7. BPRS and POMS;
8. ASI-Lite;
9. BSCS;
10. VAS, ARCI;
11. Adverse events daily;
12. Brief physical examination;
13. Cognitive assessments.

12.2 Evaluations Performed While Inpatient

1. Adverse events will be monitored daily starting as soon as the subject signs the Informed Consent;
2. Blood chemistry, including liver function tests will be performed on days 6 and 13;
3. POMS and BSCS will be performed every other day;
4. ARCI will be performed on all non-infusion days;
5. Cognitive assessments will be performed during intake screening (day -7), before screening cocaine infusions, and when the steady state of the highest 100 mg dose level of atomoxetine is reached (day 11).

12.3 Evaluations Performed During Infusion Sessions

Table 2 shows the series of activities that occur on days when cocaine infusion sessions are scheduled. Refer to Table 1 for the timing of the infusion sessions according to the study day. Note that not all activities occur at each infusion session. Those activities that do not occur at each infusion session are noted. The starting time point may not be exactly at 7:55 a.m.; however, all other time points should be relative to the actual starting time.

Table 2. Cocaine Infusion Sessions Daily Schedule

Time-point	**Activity (occurs at all sessions unless otherwise indicated)**
7:30 a.m.	Breakfast
7:55 a.m.	Draw blood for atomoxetine assay (sessions #6, 8)
8:00 a.m.	**Administer atomoxetine/placebo (sessions #5-8)**
8:05 a.m.	POMS, BSCS
8:30 a.m.	Insert catheters (catheter for blood may already be in place)
8:40 a.m.	Draw blood for cocaine assay (sessions # 4, 6, 8)
-15 min	VAS BP, HR
-10 min (8:50 a.m.)	**Start continuous monitoring of ECG and HR** 12-lead ECG BP, HR
-5 min	BP, HR
Time 0 (9:00 a.m.)	**Inject saline/cocaine i.v. 1 min push**
2 min	BP, HR
3 min	Draw blood for cocaine assay (sessions # 4, 6, 8)
4 min	12-lead ECG BP, HR
5 min	VAS
6 min	BP, HR
8 min	BP, HR
10 min	BP, HR Draw blood for cocaine assay (sessions # 4, 6, 8)
15 min	VAS BP, HR
20 min	BP, HR Draw blood for cocaine assay (sessions # 4, 6, 8)
25 min	VAS BP, HR
30 min	Draw blood for cocaine assay (sessions # 4, 6, 8) BP, HR
35 min	VAS BP, HR
40 min	12-lead ECG BP, HR
45 min	VAS BP, HR BPRS
50 min	BP, HR
55 min.	BP, HR
58 min	Draw blood for cocaine assay (sessions # 4, 6, 8)
60 min (10:00 a.m.)	**Inject cocaine/saline i.v. 1 min push**

Time-point	Activity (occurs at all sessions unless otherwise indicated)
62 min	BP, HR
63 min	Draw blood for cocaine assay (sessions # 4, 6, 8)
64 min	12-lead ECG BP, HR
65 min	VAS
66 min	BP, HR
68 min	BP, HR
70 min	Draw blood for cocaine assay (sessions # 4, 6, 8) BP, HR
75 min	VAS BP, HR
80 min	Draw blood for cocaine assay (sessions # 4, 6, 8) BP, HR
85 min	VAS BP, HR
90 min	Draw blood for cocaine assay (sessions # 4, 6, 8) BP, HR
95 min	VAS BP, HR
100 min	12-lead ECG BP, HR
105 min	BPRS Draw blood for cocaine assay (sessions # 4, 6, 8) Draw blood for atomoxetine assay (sessions #6, 8)
110, 115 min	BP, HR
120 min (1:00 p.m.)	Draw blood for cocaine assay (sessions # 4, 6, 8) BP, HR
150 min	BP, HR
180 min	BP, HR. Draw blood for cocaine assay (sessions # 4, 6, 8)
210, 240, 270 min	BP, HR
300 min (4:00 p.m.)	**Stop continuous ECG monitoring** BP, HR Draw blood for cocaine assay (sessions # 4, 6, 8)
360 min	BP, HR
420 min	Draw blood for cocaine assay (sessions # 4, 6, 8)

12.4 Evaluations of Cognitive Function

Subjects will be asked to perform a series of computerized and pen and paper tasks designed to assess cognitive flexibility, decision-making, and working memory during intake screening (day -7), before screening cocaine infusions. The assessment tools have been validated in drug abusing and non-abusing subjects. Each testing session is estimated to occupy 60-90 minutes. The testing sessions will be repeated on day 11 when the steady state for the highest 100 mg dose

of atomoxetine is reached. The computerized and experimenter-administered cognitive tests to be performed include: (1) an auditory and (2) a visual version of the Continuous Performance Test (CPT), (3) the Iowa Gambling Task, (4) the N-Back Working Memory Test, (5) the Anagram Task (pen and paper), and (6) the Wisconsin Card Sorting Test (WCST). The first five tests will be administered twice and the WCST will be administered only once (day -7). The battery of cognitive tests will require 1-2 hours to administer in the Clinical Pharmacology Unit of USUHS. A separate protocol detailing these testing procedures is provided by Drs. Frances Gabbay and Connie Duncan, Clinical Psychophysiology and Psychopharmacology Laboratory, Department of Psychiatry, USUHS (see Appendix V).

12.5 Evaluations at Discharge and Follow-up

The subjects will be discharged from the hospital 4 days after the last infusion of cocaine (session #8) on day 17. Subjects will return for follow-up visit at 14 days after discharge (day 31).

The following evaluations will be performed at time of discharge and during the follow-up visit. The same evaluations will be performed in the case of early study discontinuation:

1. Vital signs (BP and HR);
2. Hematology;
3. Blood chemistries, including liver function tests;
4. 12-lead ECG;
5. Serum ß-HCG (pregnancy test);
6. Urine drug toxicology screen;
7. Adverse events;
8. Brief physical exam at discharge; complete physical exam at follow-up.

12.5 Clinical and Laboratory Assessment Methods

The following describes the methods to be used for collection of clinical and laboratory evaluations.

12.5.1 Intake Assessments

A variety of standardized psychosocial assessments and information will be collected during screening and intake in order to describe fully the characteristics of participants and in order to facilitate future contact for follow-up. Study personnel who will administer the questionnaires and interviews are extensively trained and experienced in working with a drug abusing population.

12.5.1.1 Addiction Severity Index (ASI)-Lite CF Version

The ASI-Lite CF version will be administered by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the principal investigator. The ASI-Lite is the interviewer's estimate of the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological). Composite scores will be calculated according to the procedures described by McGahan *et al*. (1982) and Carroll *et al*. (1994). The Lite version is a shorter version of the

ASI that still retains all questions used to calculate the ASI composite scores. The ASI-Lite will be completed after intake.

12.5.1.2 Cocaine Use by Timeline Follow Back Method

Detailed histories of cocaine use over the past 30 days prior to screening will be obtained using the timeline follow-back method. The timeline follow-back method was described and validated by Sobell *et al.,* (1986) for reporting alcohol use. It has also been found to be a reliable method for assessing the history of psychoactive substance use in drug-abusing populations (Fals-Stewart *et al.,* 2000).

12.5.1.3 SCID

This instrument will be administered during screening and serves to determine whether the subject meets the DSM-IV criteria for drug dependence and to rule out any major psychiatric disorders (e.g., affective disorders, schizophrenia).

12.5.1.4 Breath Alcohol Analyzer Test

The breath alcohol analyzer test will be administered at intake to assess recent alcohol use.

12.5.2 Medical Assessments

12.5.2.1 Physical Exam

A physical exam of the oral cavity, head, eyes, ears nose and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed during screening, discharge from the inpatient phase, and at follow-up. Height and weight will be recorded.

12.5.2.2 Medical History

To monitor the health of all potential study subjects, health profiles and medical history will be collected during screening.

12.5.2.3 Vital Signs

Vital signs to be assessed at intake include oral temperature, sitting blood pressure, pulse rate, and respiratory rate.

12.5.3 Eligibility Checklist

The Eligibility Checklist must be completed prior to randomization and enrollment. This information will be used to determine whether the patient may be enrolled in the study. This form will document final eligibility and, if applicable, the reason the subject was not enrolled in the study.

12.5.4 Urine Toxicology

Urine toxicology for marijuana, opiates, cocaine, and amphetamines will be monitored once daily (8 a.m.), as documented by a qualitative urine test that detects all these compounds, during outpatient and inpatient screening. Up to 7 inpatient days after admission (days -15 through -9)

will be allotted for washout to document when subject's urine becomes negative for cocaine. This test will be also performed at the time of discharge and at the follow-up visit.

12.5.5 Laboratory Tests

12.5.5.1 Hematology

Blood will be collected in anticoagulant containing vacutainer tubes for hematologic assessments. Analysis of hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, differential white blood cell count and platelet count will be performed. Analyses will be performed in the local clinical laboratory. The laboratory performing these assessments will be either directly regulated by the College of Pathologists (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification. Hematologic assessments will occur during screening, at discharge and at follow-up.

12.5.5.2 Blood Chemistries/Liver Function Tests

Blood will be collected in serum separation vacutainer tubes and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: creatinine, blood urea nitrogen (BUN), glucose, creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), and electrolytes (Na, K, Cl, HCO_3). Liver function tests will include total bilirubin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), and alkaline phosphatase (ALP). The laboratory performing these assessments will be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification. The blood chemistry/liver function tests will be conducted at outpatient and inpatient screening, on days 6 and 13, at discharge (day 17) and at follow-up (day 31).

12.5.5.3 Pregnancy Test

A blood-based pregnancy test designed to measure human chorionic gonadotropin will be performed during outpatient screening, at inpatient screening within 72 hours before first screening cocaine infusion (session #1), at discharge and at follow-up.

12.5.5.4 Infectious Disease Panel

Blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed during screening for the following analytes: hepatitis B surface antigen, hepatitis C virus antibody and HIV type 1 antibody.

12.5.6 Methods for Assessment of Primary Outcome Measures

12.5.6.1 Primary Outcome Measures

The primary outcome measures are adverse events and cardiovascular responses (HR, BP, ECG measurements).

12.5.6.2 Adverse Events (AEs)

AEs will be assessed daily by an investigative staff nurse or physician starting as soon as the subject has signed the informed consent. If an AE is reported to a nurse that requires medical attention, it should be reported to a study physician immediately. The investigator or study physician will assess subjects for any medical or psychiatric side effects. All AEs will be recorded on an AE CRF that is completed weekly.

12.5.6.3 Cardiovascular Assessments

Before and after each i.v. infusion, the subjects' physiologic responses will be closely monitored using repeated HR, BP, and ECG readings. During infusion sessions #1-8, BP and HR will be recorded at the following time points relative to the first infusion of the day: -15, -10, -5, 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 62, 64, 66, 68, 70, 75, 80, 85, 90, 95, 100, 110, 115, 120 minutes and then every 30 minutes for the next four hours. ECG and HR will be monitored continuously beginning 10 minutes before the first infusion until 4 hours after the second infusion. Subjects will be placed on telemetry for monitoring until the completion of 24 hours after the first infusion. 12-lead ECG will be performed at -10 minute and at 4, 40, 64, and 100 minutes after the first infusion. Subjects will be monitored for at least 1 hour after second infusion by study personnel and staff. Thereafter, nursing staff will monitor participants and take vital signs for 4 hours and until vital signs revert to being within 10% of the baseline (Table 2).

12.5.7 Methods for Assessment of Secondary Outcome Measures

12.5.7.1 Secondary Outcome Measures

The secondary outcome measures include PK of study agent atomoxetine, PK of cocaine and BE, craving for cocaine assessed using BSCS, psychological and mood and personality tests including BPRS, POMS, VAS, abuse liability assessment of atomoxetine using ARCI, and cognitive assessments.

12.5.7.2 Blood Sample Collections for Pharmacokinetic Determinations

A schedule of blood collections and volumes is provided in Appendix II including collection of samples for cocaine and atomoxetine blood levels for pharmacokinetic calculations.
Samples for cocaine PK will be collected during 40 mg i.v cocaine infusion at baseline (day -1) and during 40 mg i.v cocaine treatment infusions on days 8 and 13. Blood for cocaine/BE PK determinations will be collected at the following time points: 20 minutes prior to and 3, 10, 20, 30, 58, 63, 70, 80, 90, 105, 120, 180, 300 and 420 minutes post 40 mg infusions (sessions 4, 6, and 8).

Atomoxetine peak and trough levels will be measured by blood sampling 5 minutes before atomoxetine/placebo and 170 minutes after dose on days 6, 8, 11 and 13.

An intravenous catheter will be inserted for each infusion session, and can be maintained in place for the two days of infusion sessions in one week, if the subject wishes. Two intravenous catheters will be placed for infusion sessions that involve repeated blood draws on days -1, 8, and 13; one will be for cocaine administration, the other for blood sample collection.

Samples will be collected for cocaine pharmacokinetics in Vacutainer™ tubes containing sodium fluoride and potassium oxalate. In order to assess atomoxetine peak and trough levels, blood will be collected in heparin-containing Vacutainers™. Total blood loss during the study will be approximately 390 mL.

Blood drawn from all subjects should be considered infectious and extreme caution should be used to avoid needle sticks and direct contact with blood or plasma. Using appropriate Vacutainers:

a. Draw blood and invert tube 8-10 times.
b. Centrifuge the blood (3000 x g for 15 min.) immediately to prevent hemolysis.
c. Using a disposable pipet, immediately transfer the plasma from the tubes to a single plastic plasma storage vial and secure the cap tightly.
d. Label the vial as described below.
e. Freeze sample at -20°C immediately after transferring to shipping vial. Store in an upright position. Keep frozen until shipment.

12.5.7.3 Subjective Responses (VAS and ARCI)

During and after the saline and cocaine infusions subjects' subjective responses will be closely monitored. VAS will be administered 15 minutes before, and at 5, 15, 25 and 35 minutes after each i.v. infusion. For this scale, subjects will report the degree to which they feel “any drug effect”, "high", “good effects”, “bad effects”, “like cocaine”, "desire for cocaine", "depressed", "anxious", “stimulated”, and “likely to use” on a continuous scale digitized between 0 to 100 for computing a score. In addition, they will be asked to answer the question: “How much do you think this is worth in dollars?”

ARCI will be administered at baseline and on all non-infusion days once a day. The ARCI consists of 49 statements in a true/false. For training purposes, VAS and ARCI will be also administered once a day on days -10 and -9.

12.5.7.4 Brief Substance Craving Scale (BSCS)

The BSCS is a self-administered assessment that asks the subject to rate his or her craving for cocaine. The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire (Mezinskis *et al.*, 1998). If the subject is unable to self-administer this assessment (e.g. physical handicap, poor reading skills) study personnel can assist by reading the questions out loud to the subject and/or marking the subject's response on the CRF. However, study personnel are not to offer interpretations of the questions. Subjects will start the measure at baseline and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.5.7.5 Profile of Mood States (POMS)

The POMS is a questionnaire that measures dimensions of affect or mood. It consists of 65 adjectives to which the client responds according to a 5-point scale ranging from “not at all” to “extremely”. Subjects will start the measure at baseline and continue to complete this questionnaire on an every other day basis, until the end of the study.

12.5.7.6 Brief Psychiatric Rating Scale (BPRS)

The BPRS is an interview that may be administered by a trained research nurse and conducted either by remote video or in face-to-face format to evaluate the severity of subject's psychopathology, including anxiety, depression and symptoms of schizophrenia. The BPRS may be dichotomized into subjective items based on patients' verbal reports and objective items based on visual observation of patients' behavior. The BPRS total score ratings serve as indicators of psychiatric comorbidity in drug-dependent subjects and as predictors of mental health services utilization. Subjects will start the measure at baseline, will be administered this interview daily during treatment with atomoxetine to assess possible effects of atomoxetine and also on the days of all cocaine infusions (sessions #1-8) within one hour of the completion of infusions, as an indicator of possible acute psychotic effects of cocaine.

12.5.8 Concomitant Medications

Concomitant medications will be assessed once per week by an investigative staff member. Any medications to be taken during the study must be approved by the site principal investigator/study physician.

12.5.9 Discharge Form

The Discharge CRF will document all data relevant to subject discharge: reason for discharge; date of discharge; and study day of discharge.

13 REGULATORY AND REPORTING REQUIREMENTS

13.1 Good Clinical Practices

This study will be conducted in accordance with the most current version of the International Conference on Harmonization Guide for Good Clinical Practices (GCP). An Operations Manual will be provided to all investigational sites as a study quality assurance tool.

13.2 FDA Form 1572

The investigator agrees to sign and submit a Statement of Investigator (FDA Form 1572) to the sponsor prior to initiating this study.

13.3 IRB Approval

Prior to initiating the study, the investigator will obtain written IRB approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the investigator for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials given to the subject. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

The investigator will ensure that a duly constituted IRB at the study site that conforms with FDA regulations (21 CFR part 56) will review the protocol and the volunteer informed consent form. Each investigator will follow IRB and FDA guidance regarding reporting of adverse events.

Each investigator will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human subjects or others and will not make any changes in the protocol without IRB approval, except where necessary to eliminate immediate hazards to human subjects. Following procedures outlined by the IRB, each investigator will describe the study, its risks and benefits, to each subject and ensure that each subject understands the study prior to obtaining the subject's signature. A copy of the consent form will be given to the subject.

13.4 Informed Consent

All potential candidates for the study will be given a current copy of the Informed Consent Form to read. The investigator or other study physician will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

13.5 Risks and Benefit Assessment

The primary risks of this study are those of possible adverse reaction to the study drugs, cocaine and atomoxetine. There is extensive experience with these cocaine infusion procedures and they appear to be safe. The doses used are modest, the exposure periods to the agents are brief, the safety screening and monitoring are appropriate, and there have been no significant prior adverse events with these procedures. Atomoxetine is an FDA approved medication with a known risk profile, including effects on the cardiovascular system, such as mild tachycardia and 3 mm mean increase in BP, and effects on other body systems such as abdominal pain, constipation, dyspepsia, vomiting, dry mouth, nausea, decreased appetite, weight decrease, sinus headaches, irritability, mood swings, insomnia, difficulty urinating, decreased libido, erectile dysfunction, and dysmenorrhea.

It is possible that the pharmacologic activities of cocaine and atomoxetine might be additive or potentiated when they are administered together. The ascending order of cocaine doses is one protection against this risk. Also, following dosing with atomoxetine, subjects' behavior will be closely monitored to detect changes such as agitation, paranoia or hallucinations. There is the risk of a breach of confidentiality regarding study records, but this is unlikely, since staff is well trained and experienced in this area.

The study does not offer direct therapeutic benefit to participants. Because it is directed toward the identification and development of effective treatment for cocaine abuse, it does offer the potential of future benefit to this same population group.

Overall, we believe that the risks are modest, that appropriate precautions have been taken, that there is potential societal health benefit, and that therefore the risk/benefit ratio is favorable.

13.6 Drug Accountability

Upon receipt, the investigator/pharmacist or a licensed designate is responsible for taking inventory of the investigational agents. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agents shall be returned to the study sponsor.

13.7 Outside Monitoring

Compliance With NIDA Policy On Monitoring Plans: In June 2000, the National Institutes of Health (NIH) issued a policy that extended the requirement for inclusion of monitoring plans to phase 1 and 2 clinical trials. (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html) That Further Guidance followed the policy issued in June 1998 on data and safety monitoring (http://grants.nih.gov/grants/guide/notice-files/not98-084.html), which required the establishment of Data and Safety Monitoring Boards (DSMBs) for all NIH-supported or -conducted multi-site clinical trials involving interventions that entail potential risk to the participants. NIH requires each Institute to have a system of oversight of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data.

This protocol is in compliance with that policy. The procedures for reporting Serious Adverse Events (SAEs) to NIDA, the IRB and FDA are contained under section 13.8. A DSMB will be reviewing the data and safety information from this trial.

Medical Monitor: A medical monitor will be appointed for the study. The medical monitor will be responsible for establishing concurrence with the investigator on the severity of any SAEs, the relatedness to the study treatments, and for determining if the SAE should be reported to the FDA in a 7 or 15 day expedited report or an annual report. The medical monitor will also be responsible for tracking and assessing trends in the SAEs reported.

Clinical Monitors: All investigators will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all source documents for each subject. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational agents are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by GCP guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and compliance with good clinical practice guidelines and FDA regulations, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the sponsor's representatives will be scheduled at appropriate intervals but more frequently at the beginning of the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study they will advise on storage of study records and return of unused study

medication. The site should anticipate visits by sponsor, sponsor's representatives, NIDA, and the FDA.

13.8 Adverse Events Reporting.

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the principal investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix III.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication-related or clinically significant**.** For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution. AEs should be reported up to 4 weeks following completion of, or termination from treatment.

13.9 Serious Adverse Events

Each adverse event or reaction will be classified by the study investigator as serious or non-serious. Based on the seriousness of the adverse event or reaction appropriate reporting procedures will be followed. The International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration defines serious adverse event (SAE) or reaction as any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening; *(NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure.

Any SAEs due to any cause that occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24-hours by telephone to: the Study Medical Monitor and the IND sponsor. The telephone report is to be followed by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Attached to the SAE Form should be photocopies of the AE Form, the Concomitant Medication Form, and the Medical History Form from the subject's CRFs. All serious medical events are also to be reported to the responsible IRB according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the sponsor.

Any fatal or life-threatening SAE that is investigational agent related and unexpected must be reported by the sponsor initially to the FDA within 7 calendar days via telephone, facsimile or e-mail. A follow-up written report must be submitted in 8 days to the FDA. All AEs that are both serious and unexpected but not life threatening or lethal must be reported to the FDA, in writing, within 15 calendar days of notification of the sponsor of the SAE. All other SAEs will be reported in an annual report or more frequently as necessary. Any additional clinical information that is obtained must be reported to the FDA, as it becomes available in the form of an information amendment. The sponsor will inform NIDA of all SAEs that occur during the study.

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to the sponsor in order that the sponsor can comply with these regulations.

If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of a SAE, the subject must have appropriate follow-up medical monitoring. If the subject is hospitalized, medical monitoring will consist of not less than daily evaluation by physical examination, vital signs, laboratory evaluations, and if applicable, ECG monitoring for significant treatment-emergent abnormalities. Monitoring will continue for no less than 30 days, to determine whether the problem prompting hospitalization has resolved or stabilized with no further change expected, or is discovered to be clearly unrelated to study medication, or progresses to death.

14 ANALYTICAL PLAN

14.1 Outcome Measures

14.2 Primary Outcome Measures

The primary outcome measures are adverse events and cardiovascular responses (HR, BP, ECG).

14.3 Secondary Outcome Measures

Secondary outcome measures are intended to determine if there are any changes in atomoxetine or cocaine pharmacokinetics and to assess the effects of atomoxetine on a variety of psychological and cognitive measures and its abuse liability. Secondary outcome measures include:

1. PK parameters of cocaine and BE including:

AUC_{0-24}	Area under the plasma concentration time-curve from 0 to 24 hours at steady state
C_{max}	Maximum observed concentration
T_{max}	Time for maximum concentration
k_e	Elimination rate constant (if data permit)
$t_{1/2}$	Elimination half-life (0.693/(z))
CL/F	Clearance of the study agent determined by the formula CL=Dose/AUC_{0-24} (if data permit)
V_d/F	Volume of distribution (if data permit)

2. PK of study agent atomoxetine (peak and trough levels)
3. Craving for cocaine, assessed using BSCS
4. Psychological effects of cocaine using VAS
5. Abuse liability using ARCI
6. Mood and personality assessments (BPRS and POMS)
7. Cognitive assessments.

14.4 Analysis Plan

14.4.1 Primary Outcome Measures

HR and BP measures during saline infusions will be compared to HR and BP after each cocaine infusion (20 mg and 40 mg doses). Changes in HR and BP induced by cocaine infusion along with atomoxetine will be compared to those without atomoxetine, by cocaine dose level (20 mg and 40 mg doses), using repeated measures analysis of variance (ANOVA).

Changes in ECG readings during saline infusion as compared to those taken during cocaine infusions will be reported as summary statistics.

Adverse event data will be compiled for atomoxetine and placebo cohorts and presented as summary statistics.

14.4.2 Secondary Outcome Measures

Plasma concentration-time profiles of cocaine after the baseline 40 mg cocaine infusion (session #4) will be analyzed to obtain pharmacokinetic parameter estimates of cocaine (T_{max}, $T_{max,}$ AUC_{0-24}, apparent $t_{½}$, CL/F, V_d/F, and k_e) by individual and the means computed (between subjects comparison) will be compared with data from the post-atomoxetine treatment cocaine infusions (sessions #6 and 8) being averaged by subject. Blood for cocaine/BE PK determinations will be collected at the following time points: 20 minutes prior to and 3, 10, 20,

30, 58, 63, 70, 80, 90, 105, 120, 180, 300 and 420 minutes post 40 mg infusions (sessions #4, 6, 8).

PK parameters determined for treatment infusions will be compared by *t*-tests. Confidence intervals (90%) for each parameter will be determined. To be certain that there are no inherent differences between the pharmacokinetics of cocaine between the atomoxetine and placebo cohorts, pharmacokinetic parameters between these two cohorts will also be compared during the baseline 40 mg i.v. cocaine infusion.

Blood for atomoxetine PK determination will be collected 5 minutes before and 170 minutes after the dose on days 6, 8, 11 and 13. Pharmacokinetics (peak and trough levels) of atomoxetine during treatment at a dose of 80 mg q.d. (day 6) and 100 mg q.d. (day 11) will be determined. These data will be compared to PK of atomoxetine obtained during the treatment cocaine infusions for these dose levels, i.e., session #6 for 80 mg q.d. (day 8) and session #8 for 100 mg q.d. (day 13), by t-tests.

Psychological outcome measure (VAS) obtained during saline infusions will be compared between atomoxetine and placebo cohorts to those during cocaine infusions by cocaine dose level to determine the extent to which these measures are modified by the administration of atomoxetine using repeated measures ANOVA.

Changes in BSCS, POMS and BPRS scores will be compared before and after atomoxetine administration using repeated measures ANOVA or generalized estimating equations.

Population demographics for both subjects treated with atomoxetine and placebo will be presented in a tabular form.

15 DATA MANAGEMENT AND CASE REPORT FORMS

15.1 Data Collection

Data will be collected at the study sites on source documents that will be entered at the site into electronic case report forms (eCRFs). eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. eCRFs should be completed according to the instructions in the study operations manual. The principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The principal investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

15.2 Data Editing and Control

Data received at the data-coordinating center will be reviewed. If incomplete or inaccurate data are found a data clarification request will be forwarded to the site for a response. The site will resolve data inconsistencies and errors prior to returning data to the data-coordinating center. All corrections and changes to the data will be reviewed prior to being entered into the main study database.

Participating investigators agree to routine data audits by the sponsor's designated staff. Monitors will routinely visit the site to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that study agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented, all essential documents required by GCP regulations are on file, and the site is conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using the established procedures specified in the study Operations Manual.

15.3 Data Entry, Processing, and Analyses

Data will be collected at the study sites on source documents that will be entered into CRFs. When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, statistical analysis of the data will be performed by the data coordinating center's statisticians in accordance with the analytical plan section of this protocol.

15.4 Study Documentation and Records Retention

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approved consent form and signed subject consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, patient diaries, biopsy reports, ultrasound photographs, patient progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of two years after discontinuation of the IND or 2 years after the approval of a New Drug Application (NDA).

15.5 Confidentiality

15.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that proprietary

information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

15.5.2 Confidentiality of Patient Records

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored securely. Only research staff and sponsor or sponsor's representative will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA or sponsor. Upon approval of the study by an IRB, an application will be filed with NIDA for a certificate of confidentiality.

By signing the protocol the investigator agrees that within local regulatory restrictions and ethical considerations, the sponsor or any regulatory agency may consult and/or copy study documents in order to verify case report form data.

The procedure for applying for a certificate of confidentiality is provided in Appendix IV.

16 PUBLICATIONS OF THE STUDY RESULTS

Publications derived from this study will include input from the principal investigator, his or her colleagues, and sponsor personnel. Such input should be reflected in publication authorship, and agreement regarding order of authors should be established before writing a manuscript. Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this study 60 days prior to submission for presentation.

17 SIGNATURES

SPONSOR REPRESENTATIVES

Typed Name	Signature	Date
Ann Anderson, M.D. NIDA Medical Monitor	_____	_____
Nora Chiang, Ph.D. NIDA Investigator	_____	_____
Ahmed Elkashef, M.D. NIDA Investigator	_____	_____
Steven Grant, Ph.D. NIDA Investigator	_____	_____
Roberta Kahn, M.D. NIDA Investigator	_____	_____
Jurij Mojsiak, M.S. NIDA Investigator	_____	_____

INVESTIGATOR (S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 13.8 of this protocol.

Typed Name	Signature	Date
Louis Cantilena, Jr., M.D., Ph.D Principal Investigator	_____	_____
Connie Duncan, Ph.D. Sub-investigator	_____	_____
Frances Gabbay, Ph.D. Sub-investigator	_____	_____

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Appendix I: Time and Events Schedule

Study Phase	**Pre-intake Screening**	**Intake Screening**	**Screening Infusions**	**Baseline Infusions**		**Treatment Infusions**				**Dis-charge**	**Follow-up**
Study day	**Up to -35**	**-15* to -9**	**-6**	**-2**	**-1**	**7**	**8**	**12**	**13**	**17**	**31**
Informed consent	X										
Locator form/Demographics	X										
Cocaine use by timeline follow-back	X										
Breathalyzer test		X									
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X
SCID	X										
Medical History	X										
Physical Exam (complete)	X										X
Physical Exam (brief)		X								X	
ASI-Lite		X									
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Chemistries plus liver function tests**	X	X							X	X	X
Hematology	X									X	X
Pregnancy Test***	X	X								X	X
Infectious disease serology	X										
Plasma alcohol	X										
Urine toxicology screen	X	X								X	X
POMS, BSCS		X[a]									
Cognitive assessments****											
Atomoxetine or placebo						X[b]					
Atomoxetine blood levels							X[f]		X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Cocaine Infusion Session #			**1&2**	**3**	**4**	**5**	**6**	**7**	**8**		
Saline/20 mg cocaine/40 mg cocaine i.v. 20 mg cocaine i.v.			X	X		X		X			
40 mg cocaine i.v.					X		X		X		
VAS		X[c]	X	X	X	X	X	X	X		
ARCI		X[d]									
Continuous BP, HR, ECG monitoring			X	X	X	X	X	X	X		
BPRS		X[e]	X	X	X	X	X	X	X		
Cocaine Blood PK					X		X		X		

*Days -15 through -9 are allotted for washout of cocaine after admission. Subjects' urine will be tested daily to document when it becomes negative for cocaine.

** Blood chemistries, including liver function tests, will be performed at outpatient and inpatient screening, on days 6 and 13, at discharge (day 17) and at follow-up (day 31).

*** Pregnancy test at intake screening should be done within 72 hours before the first screening cocaine infusion.

**** Cognitive assessments will be performed on day -7 and on day 11.

X[a] - POMS, BSCS will be performed at intake and then every other day.
X[b] - atomoxetine will be administered at 20 mg q.d. on days 0 and 1, 40 mg q.d. on days 2 and 3, 80 mg q.d. on days 4-8 and 100 mg q.d. on days 9-13.
X[c] - VAS will be performed on days -10, -9, and on all infusion days.
X[d] - ARCI will be performed on days -10, -9, and on all non-infusion days.
X[e]- BPRS will be administered on baseline, every day during treatment with atomoxetine and on the days of all cocaine infusions.
X[f] - atomoxetine blood levels will be determined on days 6, 8, 11 and 13.

APPENDIX II: Schedule of Blood Collections

Analysis	**Volume Per Sample**	**Type[a]**	**Number of Samples per Day[b]**											**Total Volume**
Study Day			Screening	D-8	D-1	D1	D2	D3	D6	D8	D11	D13	D17	D31	
Chemistries plus liver function tests	10 mL	S	1	1					1			1	1	1	60 mL
Hematology	10 mL	P	1										1	1	30 mL
Infectious disease serology	10 mL	S	1												10 mL
PK Samples for cocaine	5 mL	P			15					15		15			225 mL
PK Samples for Atomoxetine	5 mL	P							2	2	2	2			40 mL
Pregnancy Test	5 mL	S	1	1									1	1	20 mL
Alcohol Test	5 mL	P	1												5 mL
Total															**390 mL**

[a]S = serum, P = plasma; [b]D = day

APPENDIX III: Instructions For Evaluating and Reporting Adverse Events and Serious Adverse Events

A. GENERAL INSTRUCTIONS

1. Report the severity of the event following the guidance in section B below.

2. Report the relatedness of the event to the study agent administration according to the guidance in section C.

B. DEFINITIONS – SEVERITY OF EVENTS

Mild: Awareness of symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

Severe: Incapacitating with inability to work or do usual activity.

C. DEFINITIONS – RELATEDNESS OF EVENTS

The investigator is responsible for defining, in his/her best judgment, the relationship of the AE/SAE to the study drug/placebo. The degree of certainty for which the AE/SAE is attributed to the study drug or alternative causes (e.g. natural history of the underlying disease, concomitant therapies, etc.) should be determined by how well the experience can be understood in terms of one or more of the following:

- ***Exposure:*** Is there evidence that the subject was actually exposed to the drug/placebo?

- ***Timing of the study drug/placebo:*** Did the AE/SAE follow in a reasonable temporal sequence from administration of the drug test?

- ***Consistency with study drug profile:*** Known pharmacology and toxicology of the study drug in animals and man; reaction of similar nature having been previously described with the study drug.

- ***Alternative explanations*** for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.

- ***Response to discontinuation*** of the study drug/placebo.

Terms and definitions to be used in assessing the study agent relationship to the AE/SAE are:

- ***Unknown:***
  Use this category only if the cause of the AE/SAE is not possible to determine

- ***Definitely Not Related:***
  The subject did not receive the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE/SAE.

- ***Remotely Related:***
  There is evidence of exposure to the test drug or there is another more likely cause of the AE/SAE.

- ***Possibly Related:***
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, but the AE/SAE could have been due to another equally likely cause.

- ***Probably Related:***
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, and the AE/SAE is more likely explained by the test drug than by any other cause.

- ***Definitely Related:***
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, the AE/SAE is more likely explained by the test drug than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the test drug or test drug class.

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

A laboratory or ECG AE is any clinically significant worsening in a test variable that occurs during the course of the study, whether or not considered to be study agent related. For each such change, provide the information requested on date of test, severity, likelihood of a relationship to investigational agent, change in investigational agent dosage due to the AE, and treatment required.

All laboratory AEs should be specified as an increased or decreased test result (e.g. “increased glucose”, “decreased potassium”) or as a term that implies an abnormality (e.g., hypercalcemia, azotemia).

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the study drug/placebo, must be reported ***within 24 hours*** to the Medical Monitor and the IND sponsor.

The following information must be provided with the initial report of an SAE or unexpected AE:

- Name of person reporting the SAE/unexpected AE
- Subject's I.D. number
- Name of the principal investigator and institution
- Description of the SAE/unexpected AE
- Date and time of Onset
- Date/time of administration of last dose of study agent/placebo prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to study drug (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the study drug, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

3-day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the Medical Monitor/Alternate and the IND sponsor within 3 days of reporting the event. Required documents that must be submitted include the following:

- SAE Form
- Concomitant Medication CRF pages
- Adverse Events CRF pages
- Copies of source documents pertinent to the event (lab reports, ECG tracings, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the investigator's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor/Alternate

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed for 30 days or until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended inpatient period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected

adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported.

The investigator is required to provide the Medical Monitor/Alternate and the IND sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug/placebo.

Reporting to the FDA

The IND sponsor is required to report SAEs to the FDA:

- in 7 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the study agent, with a followup written report in 8 days;

- in 15 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), but not immediately life-threatening; and

- in an annual report in all other cases.

APPENDIX IV: Procedure for Applying for a Certificate of Confidentiality

The only people who will know the identity of the subjects are members of the research team and, if appropriate the physicians and nurses. No information about the subjects, or provided by the subjects during the research, will be disclosed to others without the subjects' written permission, except:

- if necessary to protect subjects' rights or welfare, or
- if required by law.

When the results of the research are published or discussed in conferences, no information will be included that would reveal subjects' identity. Authorized representatives of the FDA and NIDA study monitors may need to review records of individual subjects. As a result, they may know subjects' names, but they are bound by rules of confidentiality not to reveal their identity to others. The results of this study including laboratory results and clinical information collected during this study will be submitted to the FDA and may be used for research purposes. The results of this study may be published but will not personally identify any subjects. All records will be kept in locked storage locations that will be accessible only to authorized study personnel.

Applying for a Certificate of Confidentiality

A Certificate of Confidentiality helps researchers protect the privacy of subjects in health research projects against compulsory legal demands (e.g., court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. The certificate was developed to protect against the involuntary release of personally identified research information of a sensitive nature sought through any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. This authority was granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law No. 91-513, Section 3(a).

Investigators will obtain a certificate to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

"The Secretary [of the Department of Health and Human Services] may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, and on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals" (Public Health Service Act 301 (d), 42 U. S. C. 241 (d), as amended by Public Law No. 100-607, Section 163 (November 4, 1988))."

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

The Investigator will submit the application, as outlined in the Confidentiality Certificate Application Instructions (http://www.nida.nih.gov/Funding/ConfidentialityInstruct.html), along with IRB review documentation and a copy of the informed consent/assent forms to be used in the study. The Principal Investigator must sign the application and submit everything to:

Ms. Jacqueline R. Porter
NIDA Certificate of Confidentiality Coordinator
or
Ms. Sandra Solomon,
Certificate of Confidentiality Assistant

Office of Extramural Affairs
6001 Executive Boulevard, Room 3158, MSC 9547
Bethesda, Maryland 20852-9547
Rockville, MD 20852 (courier or express mail)
TEL: 301-443-2755
FAX: 301-443-0538
E-MAIL: jporter@nida.nih.gov or ssolomo1@nida.nih.gov

Since a certificate is generally issued to a sponsoring research institution, the application and its assurances, must be signed by a faculty member or a senior official. The principal investigator, or their staff, will not represent the issuance of a Certificate to potential participants as an endorsement of the research project by DHHS or use it in a coercive manner for recruitment of subjects. The investigator must use the authority of the Certificate to resist compulsory disclosure of individually identifiable research data.

The study subjects should be informed that a Certificate is in effect, and be given a fair and clear explanation of the protection it affords, including the limitations and exceptions. This information will be included in the informed consent. Please see below some suggested wording:

"We have received a Certificate of Confidentiality from the National Institute on Drug Abuse, which will help us protect your privacy. The Certificate protects against the involuntary release of information about your participation in this study. The researchers involved in this project cannot be forced to disclose your identity or your participation in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests disclosure of your participation, the researchers will provide research data. The Certificate does not protect against that voluntary disclosure.

Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or a Food and Drug Administration request under the Food, Drug and Cosmetics Act."

or

"A Certificate of Confidentiality has been obtained from the Federal Government for this study to help insure your privacy. This Certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we see [learn] something that would immediately endanger you, your child, or others, we may discuss it with you, if possible, or seek help."

Study subjects will be notified that a Certificate has expired if they are recruited to the study after the expiration date of the Certificate and an extension of the Certificate's coverage has not been granted.

If the research scope of a project covered by a Certificate should change substantially, the PI will request an amendment to the Certificate; however, the NIDA Certificate Coordinator may require a new Certificate depending on the extent of the change in scope. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate, as research information collected after the expiration of a Certificate is not protected from compelled release.

A Certificate of Confidentiality is a legal defense against a subpoena or court order, and is to be used by the researcher to resist disclosure. The researcher should seek legal counsel from his or her institution if legal action is brought to release personally identifying information protected by a certificate. The Office of General Counsel for DHHS is willing to discuss the regulations with the researcher's attorney.

APPENDIX V: Cognitive Assessment Battery

Atomoxetine and Cocaine:

Preliminary Study of Cognitive Effects in a Phase I Clinical Trial

Cognitive Assessment Battery

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Connie C. Duncan

Clinical Psychophysiology and Psychopharmacology Laboratory

Department of Psychiatry, USUHS

During intake screening, before the first cocaine infusion (day -7), participants will be asked to perform a 1-2 hour battery of computer- and experimenter-administered tasks designed to assess a variety of cognitive functions, including cognitive flexibility, decision-making, working memory, sustained attention, and response inhibition. These tests have been validated in healthy men and women, as well as in individuals with drug abuse and other disorders. The cognitive battery will be repeated on day 11, when the steady state for the highest dose (100 mg) of atomoxetine is reached (with the exception of the Wisconsin Card Sorting Test, which will be administered only at baseline on day -7).

The battery comprises:

Continuous Performance Test (CPT). The CPT is recognized as a sensitive test of sustained attention and response inhibition. In this task, a series of stimuli is presented one at a

time. In one version, the series comprises a stream of alternating "X"s and "Y"s. Each alternating letter defines a target. Periodic "lures," in which the stimuli do not alternate (i.e., the second of two identical, successively presented stimuli), require the participant to inhibit a response. Participants will be instructed to respond as quickly as possible by pressing a button when, and only when, a target is presented. Auditory and visual versions of the CPT will be included in the battery.

The task yields the following measures of performance: (a) reaction time to targets, (b) variance of reaction time to targets, (c) failures to respond to target stimuli ("omission errors"), which reflect deficits in *sustained attention*, and (d) responses to non-target (repeated) stimuli ("commission errors"), which reflect *failures of inhibition*. Reaction time of commission errors can be calculated if the number of such responses is adequate.

Iowa Gambling Task. In this task, which was developed to assess the ability to evaluate immediate and delayed rewards and losses, participants will select from four decks of cards offering different monetary rewards and punishments. Two of the decks will offer high immediate gains but would be poor choices over the long run, in that selections from those decks would eventually result in net losses of money. The other two decks will represent good choices, offering smaller immediate rewards but yielding modest long-term gains. Performance on the Iowa Gambling Task is measured by a global outcome score, calculated by summing the number of cards chosen from the high yield decks minus the number chosen from the low yield decks. Low scores reflect poor performance; negative scores indicate a relative preference for choices from the low yield decks.

N-Back Working Memory Test. The *n*-back task is similar to other working memory tasks in that it requires the maintenance of stimulus identity and serial position information. The task is unique, however, in that it requires the dynamic comparison of serially-presented stimuli. In this task, participants are presented with a sequence of stimuli, and asked to judge whether the current stimulus matches the stimulus that preceded it by *n* places in the sequence. For example, in a 3-back task with the sequence of letters *B*, *Q*, *D*, *P*, *Q*, participants should respond positively to the second *Q* because it matches the letter that appeared three letters earlier.

Anagram Task. This task involves unscrambling a series of letters to form as many words as possible, using all the letters in the series. Performance will be quantified by summing the total number of legitimate words found in the anagrams.

Wisconsin Card Sorting Task (WCST). The Wisconsin Card Sorting Task (WCST) has been used to evaluate the ability to form abstract concepts and to shift from established response sets (i.e., *cognitive flexibility*). In this task, the participant is presented with four sample cards, each with geometric designs that vary along three stimulus dimensions: color (red, green, yellow, blue), number (1-4), and shape (triangle, star, cross, circle). The participant is asked to match test cards to reference cards according to the color, shape, or number of stimuli on the cards. Feedback is provided after each match, enabling the participant to acquire the correct rule of classification. After a fixed number of correct matches, the rule is changed without notice, and the participant must shift to a new mode of classification.