

**Study Title: Impact of Sustained Release d-Amphetamine on Choice Between Cocaine and a Non-Drug Reinforcer**

**NCT number: NCT02383043**

**Version date: 12/17/17**

## 1. BACKGROUND

Cocaine-use disorders continue to be a significant public health concern, yet no effective pharmacological treatments have been identified. This project is founded on the proposition that translational research on the development of cocaine pharmacotherapies will benefit from the use of coordinated and homologous procedures in animals and humans to study effects of candidate medications on choice between cocaine and a non-drug reinforcer. The present application describes the human laboratory side of the project; the non-human primate research will be conducted by our colleagues at Virginia Commonwealth University. Despite the relative strengths of human and non-human primate approaches, translational research has been hampered by the use of widely different self-administration procedures and medication treatment regimens. The proposed project seeks to harmonize rhesus monkey and human procedures used to screen medications by establishing parallel self-administration methods that will employ the same cocaine doses, route of cocaine (i.e., intravenous) administration and schedule of reinforcement, as well as a species-specific alternative reinforcer that effectively reduces drug taking. Self-administration procedures will be used in this project because the reinforcing effects of drugs are central to their abuse and the development of dependence. An alternative reinforcer to cocaine will be offered because the choice to use cocaine to the exclusion of other behaviors is a hallmark of dependence, and an effective medication should assist patients in reducing drug use and reallocating behavior from drug use to more responsible and productive activities. Maintenance treatment studies are proposed to more closely model a clinical scenario. Achieving the aims of this project will exert a sustained and powerful impact by establishing a research platform for cocaine medication screening that will tightly link animal and human approaches thereby accelerating translational research on medications development.

## 2. OBJECTIVES

The primary objective of this study is to assess self-administration of cocaine vs. a non-drug reinforcer during maintenance on an indirect dopamine agonist, d-amphetamine, in an effort to equilibrate cross-species sensitivity and to provide a comparator for effects of other, non-dopaminergic candidate medications examined in future studies. Multiple d-amphetamine doses will be tested to ensure the functional equivalence of the cocaine and alternative reinforcer magnitudes, which can be further refined, if necessary, prior to testing novel compounds. d-Amphetamine was chosen as a standard because the effects of cocaine have been attributed primarily to blockade of dopamine uptake, and dopaminergic agonists alter laboratory cocaine self-administration in a predictable manner.

## 3. STUDY DESIGN

A double blind, placebo-controlled, within-subjects design will be used. Each subject will be enrolled as an inpatient for 33 days and participate in 12 experimental sessions in which the reinforcing effects of various doses of IV cocaine (0, 3, 10 and 30 mg/70 kg) and an alternative monetary reinforcer (\$6.00) will be determined on a concurrent PR schedule choice procedure during maintenance on oral d-amphetamine SR (0, 30 and 60 mg/day).

## 4. STUDY POPULATION

We intend to enroll eighteen (6 female, 12 male) completers into this study. These individuals must be English-speaking, English-reading volunteers 18-55 years of age of varying ethnic backgrounds. Enrollment in this study will occur between January 1, 2015 and December 31, 2017. Volunteers will be required to provide legal proof of age.

### *Inclusion Criteria:*

- Recent cocaine use via the smoked or intravenous route, verified by a cocaine-positive urine sample.
- Otherwise healthy, without contraindications to cocaine.
- Meet Cocaine Dependence or Abuse criteria, verified by Structured Clinical Interview for DSM-IV (SCID).

-Use of an effective form of birth control (e.g., birth control pills, surgical sterilization, IUD, cervical cap with a spermicide, condoms or abstinence; females only). A urine pregnancy test will be conducted before the start of each session to ensure that female subjects do not continue in the study if pregnant.

*Exclusion Criteria:*

- Chemistry values or screening outcomes including outside normal ranges that are deemed by the study physician to be clinically significant. Lipid levels, which have not typically been included in our screening tests, are included in this protocol as an additional check for cardiovascular health.
- Hypertension  $\geq 140/90$  mmHg during screening or before dosing on the medical safety session
- BMI  $\geq 30$ .
- Electrocardiogram abnormalities, including:
  - Atrial premature beats ( $\geq 2$  consecutive)
  - Ventricular premature beats (Lown's Grade 3 or higher;  $\geq 2$  consecutive beats, multiform)
  - Heartblock (2<sup>nd</sup> or 3<sup>rd</sup> degree AV block or bundle branch block)
  - Pre-excitation syndromes (Wolff-Parkinson-White or Lown-Ganong-Levine)
- History of serious physical disease, current physical disease, impaired cardiovascular functioning, chronic obstructive pulmonary disease, history of seizure, or current or past histories of serious psychiatric disorder that in the opinion of the study physician would interfere with study participation.
- First degree family member with significant premature cardiac comorbidity.
- Current or past histories of substance abuse or dependence that are deemed by the study physician to interfere with study completion.

Screening procedures for all subjects will include a medical history questionnaire, laboratory chemistries (blood chemistry screen, complete blood count, ECG and urinalysis) and a brief psychiatric examination. These procedures will be conducted under our lab's screening protocol (03-0509). All study participants will be judged by the study physicians, Drs. Lon Hays, Abner Rayapati, Kevin Hatton, or their representative, to be healthy.

During the initial screening interview, potential volunteers will be asked to provide a urine specimen that will be screened for the presence of recent use of amphetamine, benzodiazepines, barbiturates, cocaine, tetrahydrocannabinol (THC) and opiates. In order to continue participation once experimental sessions have begun after admittance to the hospital, volunteers must provide a urine negative for amphetamines, benzodiazepines, barbiturates and opiates on each day of their participation. Volunteers will be allowed to continue if they test positive for cocaine. Volunteers will be maintained on a caffeine free diet and will have to abstain from alcohol for the duration of their participation.

## **5. SUBJECT RECRUITMENT METHODS AND PRIVACY**

Volunteers are recruited primarily through formal advertisement (i.e., regular newspaper advertisements placed generally in free newspapers), local flyers posted in public areas (e.g., bars, marketplaces) and by word-of-mouth. These advertisements are approved under our screening protocol (IRB # 03-0509). Volunteers will make initial contact by phone with one of our recruiters who have completed the research training and HIPAA compliance web-based teaching models. If the volunteer self-discloses information that would make him/her potentially eligible for the study, they will be invited to come in for a screening appointment. Screening is completed by one of our research assistants at the UK Laboratory of Human Behavioral Pharmacology (LHBP). Study investigators may interact with volunteers in this setting and appropriate cautions are in place to ensure privacy during the intake process.

## **6. INFORMED CONSENT PROCESS**

All potential subjects that are identified using the subject recruitment methods noted above will provide informed consent prior to participating in the protocol. Subjects that meet the eligibility criteria noted above will come to the LHBP and will undergo a field sobriety test and provide an expired air sample that will be tested for the presence of alcohol. If the subject passes the field sobriety test (walk and turn, one-leg balance [timed], finger-to-nose and backwards-counting tasks) and the expired air sample is negative, he or she will then be

given a copy of the approved informed consent document to read and sign. After reading the consent document, the PI or one of the Co-Is on this protocol will address any questions the subject may have in order to assess the subject's understanding of the protocol. After this, the subject will receive a copy of the informed consent document and will sign a form indicating that they have received a copy of the form they read and signed.

## 7. RESEARCH PROCEDURES

*General Procedures.* Volunteers that meet the inclusion criteria will participate as inpatients at the University of Kentucky Clinical Research Unit (CRU). Volunteers will be discharged upon completion of the entire protocol.

This experiment will require each volunteer to participate for 33 days. Sessions will be conducted as outlined in Table 1 (see below). Please note three important points relating to the table below: 1) The sequence of maintenance conditions and the cocaine and d-amphetamine maintenance doses are illustrative. The order of d-amphetamine SR maintenance will be random, with one exception. The lower active d-amphetamine SR maintenance condition will be tested prior to the higher active condition. The cocaine dose order available for self-administration will be randomly determined. 2) Please also note that participation will require a minimum of three additional sessions to avoid experimental testing on weekends. More than three additional sessions might be required depending on the day of the week that a subject is admitted to the unit. 3) If subjects leave the protocol for a reason unrelated to study procedures (e.g., a family emergency or dental problems), they may be re-admitted with physician approval to complete the remainder of the protocol, picking up with the next maintenance condition after the last one completed. Thus, they may not complete the protocol over one approximately 33-day admission.

To confirm equivalent maintenance dosing across species, blood will be drawn from the indwelling catheter used for drug administration on the first and last of the four experimental sessions during each maintenance phase in order to determine plasma levels of d-amphetamine. If necessary due to trouble with the catheter, the blood sample will be drawn directly with a needle and syringe. Samples will be processed and stored by the BAL/CCTS and then shipped to the ARUP laboratories at the University of Utah for analysis using liquid chromatography / mass spectroscopy (LC/MS). Samples submitted for analysis will not contain any PHI.

Day	Table 1
1	Admission to the CRU and practice session.
2	Medical Safety Session. Start d-amphetamine maintenance in PM.
3-11	d-Amphetamine SR maintenance (30 mg daily). Oral dose administered twice daily (0700 and 1900 h) in escalating fashion, based on clinical dosing recommendations, up to target daily dose (i.e., doses 1-3 = 5 mg, doses 4&5 = 10 mg, remaining doses = 15 mg).
8-11	Self-administration sessions. Subjects complete 1 sample and 9 choice trials to receive cocaine (0, 3, 10 and 30 mg/70 kg) or money (\$6.00) by responding on the concurrent PR schedule.
12-20	d-Amphetamine SR maintenance (placebo; 0 mg administered twice daily).
17-20	Self-administration sessions. Details are the same as Days 10-13.
21-29	d-Amphetamine SR maintenance (60 mg daily). Oral dose administered twice daily (0700 and 1900 h) in escalating fashion up to target daily dose (i.e., doses 1-3 = 5 mg, doses 4&5 = 10 mg, doses 6&7 = 20 mg, remaining doses = 30 mg).
26-29	Self-administration sessions. Details are the same as Days 10-13.
30	Discharge from the CRU.

During their participation in the research protocol, volunteers will not be allowed to leave the CRU, nor will visitors be allowed. Research volunteers will be allowed to make local telephone calls. After completing the

research protocol, interested volunteers will be offered a referral to an appropriate drug abuse treatment program.

All volunteers will provide urine and expired air samples daily during study participation once experimental sessions have been initiated. The presence of non-nicotine, non-cannabinoid drugs of abuse or alcohol not administered experimentally in the research protocol will result in immediate termination from the research study.

This experiment will consist of 12 experimental sessions across approximately 33 days and conducted according to the timeline in Table 1 (see above). On the day of admission, volunteers will be allowed to acclimate to the CRU. During this time, volunteers will be maintained on a caffeine-free diet, receive instructions concerning the details of the daily research procedures and general rules of the inpatient research unit and complete a "practice" session to familiarize them with the experimental routine and tasks. The practice session will follow the session timeline with the exception that no drug or response-contingent money will be available and no maintenance dose will be administered. On the day after the practice session, subjects will participate in a medical safety session in which they will receive each of the doses IV cocaine that will be available in subsequent sessions (i.e., 1 infusion of 0, 3, 10 and 30 mg/70kg cocaine) administered in ascending order and separated by 30-min intervals; subjects exceeding the predetermined cardiovascular parameters will be excluded from further participation.

Cardiovascular hypersensitivity is defined as heart rate  $> (220 - \text{subject age}) \times 0.85$ , systolic pressure  $> 180$  mm Hg or diastolic pressure  $> 120$  mm Hg. ECG. If vital signs are elevated above these criteria, the nurse or physician will re-assess using the automated machine at minute intervals for 5 total readings. If vital signs remain above these criteria for all 5 readings, a manual reading will be taken. If vital signs are still elevated, a subject will not receive further doses, will be followed until symptom resolution, and will be excluded from further research participation. These criteria have been recommended by Michelle Lofwall, M.D., who served as an advisor in the preparation of this protocol, and used in previous studies of intravenous cocaine self-administration in humans (e.g., Walsh et al., 2010). Cardiovascular hypersensitivity also includes prolonged abnormal heart rhythmicity assessed via 3-lead telemetry. Abnormal heart rhythmicity during experimental sessions is defined as ventricular arrhythmias that occur at a frequency greater than 5 per minute, are multifocal, or occur as couplets (2 consecutive beats) or salvos (3 or more consecutive beats), and persist for greater than 15 min. A cardiovascular emergency will be managed using UK medical center procedures (i.e., response from a code blue team). In Dr. Lofwall's previous study at the CRU that guided the medical safety monitoring parameters for the present protocol, subjects were administered up to 320 mg/70 kg intravenous cocaine across an experimental session (i.e., maximum of 8 administrations of 40 mg/70 kg). Important to note is that none of the subjects (N=22) were discharged due to exceeding the cardiovascular threshold criteria. One subject experienced premature ventricular contraction after receiving placebo and active cocaine, and was subsequently discharged. Cocaine produced expected increases in heart rate and blood pressure, but there were no clinically significant changes that required cessation of cocaine dosing or protocol discharge. Likewise, no subjects have been discharged from the ongoing protocol in which subjects self-administer various doses of IV cocaine (0, 3, 10 and 30 mg/70 kg) due to cardiovascular adverse events.

Maintenance dosing with d-amphetamine will begin on the evening of the medical safety session according to the dose escalation procedure described in Table 1. Maintenance medications will not be administered if a subject's heart rate is  $\geq 100$  bpm, systolic pressure is  $\geq 150$  mmHg or diastolic pressure is  $\geq 100$  mmHg. In addition, the UKU side effects scale will be completed daily to monitor for the emergence of side effects and HR/BP will be taken every two hours while subjects are awake. The timeline for daily activities on maintenance days is shown in Table 2.

Time	Table 2-Daily Activities for Maintenance Days
0700	Patient awakened. Vital signs recorded. Medication administered if vitals are within range. Subject eats breakfast.
1200	Lunch is served.
1300	UKU completed.
1900	Dinner is served. Vital signs recorded. Medication administered if vitals are within range and no indication of sedation or withdrawal.
2300	Lights out.

Prior to each experimental session, subjects will be allowed to eat a standard, fat-free breakfast. Breakfast must be consumed by 0800 (a minimum of 2 hours prior to the first scheduled dose at 1000). Table 3 (below) outlines the experimental session activities. Sessions will begin at 0900 hours and will last approximately 6 hours. At 0900 hours, volunteers will complete the pre-drug measures and cardiovascular monitoring will begin. The first intravenous drug administration (Sampling Dose) will occur at 1000 h and subjects will be informed of the alternative reinforcer available that session. A behavioral assessment battery (subjective questionnaires) will be completed immediately before and 15 min after dosing. At 1030 subjects will be offered the opportunity to complete the first ratio on the concurrent PR task to receive the cocaine dose sampled previously or the money value available that session. A dose earned will be provided immediately after completion of the response requirement. Subjects will have the opportunity to request that items not available on the UK CRU be purchased for them using money earned. Nine total choice trials will occur at 30-min intervals (i.e., 1030, 1100, 1130, 1200, 1230, 1300, 1330, 1400 and 1430 h). The behavioral assessment battery will be completed prior to each choice trial. No experimental activities will be scheduled for the remainder of the day. Volunteers will be free to engage in recreational activities (e.g., watch television, read, listen to music, arts and crafts, play video or board games). Research volunteers will be required to be in bed with the lights out by 2300 hours.

Heart rate and blood pressure will be recorded prior to cocaine administration and at frequent intervals (i.e., every 2 minutes) afterwards for the duration of the session. Prior to cocaine administration, subjects must have a heart rate of < 130 bpm, systolic blood pressure < 165 mm Hg and diastolic blood pressure < 100 mm Hg. Heart rhythmicity will be assessed via 3-lead telemetry continuously during each experimental session, will be printed out and verified as normal prior to dose administration, and will be monitored continuously for a minimum of 15 minutes following each infusion.

Time	Table 3 Experimental Session Timeline
0700	Subject awakened and provided with breakfast. Urine drug testing. Subjects allowed a single tobacco cigarette prior to the start of experimental activities (smoking after session activities permitted).
0900	Session begins. Cardiovascular monitoring initiated (see below for details).
1000	Sample dose of IV cocaine (0, 3, 10 or 30 mg/70 kg) administered; subjects informed of alternative monetary value available that session. Behavioral assessment battery (subjective questionnaires) completed immediately before and 15 min after dosing.
1030	Subjects complete the first ratio on the concurrent PR task to receive the sampled cocaine dose or the money value available that session. A dose earned will be provided immediately after completion of the response requirement. Subjects will also have the opportunity to request that items not available on the UK CRU be purchased for them using these earnings. Nine total choice trials will occur at 30-min intervals (i.e., 1030, 1100, 1130, 1200, 1230, 1300, 1330, 1400 and 1430 h). The assessment battery will be completed prior to each choice trial.
1500	Session ends. Subjects free to engage in various recreational activities.

*Apparatus.* Behavioral testing will be conducted at the CRU. Volunteers will be tested using an individual Macintosh computer that automates behavioral tasks. When not completing behavioral tasks, volunteers will be allowed to engage in sedentary recreational activities (i.e., read or watch television).

*Progressive-Ratio Procedure.* We have used similar PR procedures to assess the reinforcing effects of stimulant drugs, including cocaine (reviewed in Stoops, 2008; Stoops et al., 2010). After sampling the IV cocaine dose (3, 10 and 30 mg/70 kg) and being informed of the money value available in that session, subjects will complete 9 choice trials, separated by 30 min. The initial response requirement for each reinforcer will be 400 responses (i.e., mouse clicks). The completion of a response requirement for a given reinforcer (i.e., cocaine or money) will increase the response requirement for that reinforcer by 100. These response requirements were based on our previous human laboratory studies that have tested various ratio parameters in an effort to maximize drug-maintained responding while minimizing placebo self-administration (Sevak et al., 2011; Stoops et al., 2010). Subjects may choose not to complete a ratio for either reinforcer during a choice trial, but physiological measures and the assessment battery will still be completed as scheduled, and the ratio requirements for each reinforcer will carry forward to the next trial.

*Subject-Rated Drug-Effect Questionnaires.* Two questionnaires used extensively in human behavioral pharmacology research will be used to measure various aspects of mood and drug effect: 1) Adjective-Rating Scale and 2) Drug-Effect Questionnaire. The subjective-effects measures are described in Appendix A.

*Physiological Indices.* Heart rate, blood pressure and heart rhythmicity (*via* ECG) will be recorded using a Dinamap digital monitor (Critikon, Pro 1000, Tampa, FL). These measures will be measured at least three times in the hour before intravenous drug administration and immediately prior to completion of subject-rated measures for the remainder of session. ECG monitoring will be continuously conducted, and will be printed and read immediately before, and 15 minutes after intravenous drug administration, during the experimental session. Telemetry-certified nurses will interpret the results with instructions to contact Drs. Hays, Rayapati or Hatton regarding abnormalities.

*Drug Dose and Administration.* Cocaine and d-amphetamine doses will be administered under double-blind conditions and medical supervision. We currently hold an IND for intranasal cocaine administration and have amended it for IV administration during d-amphetamine maintenance.

Syringes containing the IV cocaine dose for a particular session (i.e., dose in mg/70kg) will be drawn from aseptically prepared stock solutions. Stock solutions are prepared by dissolving cocaine HCl USP (Mallinckrodt, St. Louis, MO) in 0.9% sodium chloride, and filtering the solution through a 0.22  $\mu$ m filter into a sterile, pyrogen-free vial. The doses for administration (3, 10 and 30 mg/70 kg) will be prepared and drawn up into syringes within 24 h of an experimental session and individually labeled for each subject. The 0 mg dose will contain only 0.9% sodium chloride. Each dose will be administered in a standard volume (e.g., 1.0 mL) via a catheter in the non-dominant arm over 30 s. A slow drip of normal saline will be used after initial catheter insertion for the duration of the session to maintain patency and a 10 mL normal saline flush will be administered after each cocaine injection. This method of cocaine preparation has been conducted previously at the UK Investigational Pharmacy, and this procedure for IV administration has been used successfully in our ongoing study.

d-Amphetamine SR doses will be prepared using commercially available tablets and cornstarch placed into size 0 opaque capsules. Placebo capsules will contain only cornstarch, but will be visually identical to active dose capsules. d-Amphetamine maintenance doses will be administered in an escalating fashion up to the target daily dose (e.g., doses 1-3 = 5 mg, doses 4&5 = 10 mg, doses 6-final = 15 mg for the 30 mg/day dose; doses 1-3 = 5 mg, doses 4&5 = 10, doses 6&7 = 20 mg, doses 8-final = 30 mg for the 60 mg/day dose). Target doses are based on clinical dosing recommendations and a 12-h half-life (Spansule® sustained-release d-amphetamine product information), which will result in the attainment of steady-state blood levels prior to initiating cocaine self-administration sessions. We have safely and successfully used this dose escalation procedure in previous protocols (e.g., Pike et al., 2014).

*Data Analysis.* Self-administration data from the 8 subjects who complete the protocol will be analyzed using two-factor repeated-measures ANOVA with Cocaine Dose (0, 3, 10 and 30 mg/70 kg) and d-Amphetamine SR Maintenance Dose (0, 30 and 60 mg/day) as factors. A significant attenuation in the cocaine self-administration dose-effect curve will be inferred if the main effect of d-Amphetamine or an interaction of the

Cocaine and d-Amphetamine factors attains statistical significance in the ANOVA, and the mean square error term will be used to conduct contrast tests to make appropriate pair-wise comparisons between means. Subjective-effects and physiological data from the Sampling Trial will be analyzed in a similar fashion.

## **8. RESOURCES**

This study will take place at the CRU. Experimental sessions will only be conducted on weekdays. All drug administration will take place at the UK CRU in a room equipped with all the necessary physiologic and computer equipment for the study. Dr. Hatton, the responsible medical investigator for this study, is an Associate Professor in the departments of Anesthesiology and Surgery, Chief in the Division of Critical Care Medicine and Medical Director of the UK Healthcare Neurocritical Care Service. Dr. Hays is an adult psychiatrist who has worked extensively with individuals with substance use disorders in both the clinical and research setting. Dr. Rayapati is an adult psychiatrist who has worked with individuals with substance use disorders in both the clinical and research setting. They will be available to attend to medical problems as well as any psychological or psychiatric issues that may arise. Drs. Lile, Rush and Stoops will provide scientific oversight for the study and have safely completed numerous human behavioral pharmacology studies. Overall, the study team and resources described above are well equipped to protect participants and successfully implement, carry out and complete this study protocol.

## **9. POTENTIAL RISKS**

The behavioral and physiological assessment procedures employed in these studies are benign. The risks to the study subjects are those related to the administration of the drugs under study. All of the drugs to be administered in the proposed research have been administered safely to human subjects under controlled-laboratory conditions. The relative safety, as well as the contraindications and possible side effects of these compounds are well known and documented. However, the administration of any drug involves some risks simply because individuals differ in their reactions to drugs.

Common side effects of cocaine include anxiety, restlessness, diuresis, irritability, suppressed appetite, insomnia, gastrointestinal upset, increased heart rate, increased blood pressure, palpitations and arrhythmias. It is likely that subjects will experience one or more of these side effects. More serious side effects following the chronic, unsupervised administration of much higher doses of cocaine have occurred and include psychotic episodes, suppressed breathing, seizures, myocardial infarctions, heart failure and death. It is unlikely that subjects will experience these more serious side effects.

Common side effects of amphetamines include nausea, abdominal pain, loss of appetite, dry mouth, weight loss, changes in mood, headache, tremor, difficulty sleeping, nervousness, restlessness, increases in temperature, changes in heart rate or blood pressure (including irregular heart rate and blood pressure), palpitations, anxiety, dizziness, hallucinations, forgetfulness, sleepiness and performance impairment. More serious side effects could include allergic reaction, chest pain, heart attack or other heart related problems, changes in blood platelet levels, stroke, psychotic episodes, seizures, Tourette's Syndrome and sudden unexplained death.

During catheter placement, there is some risk of bruising, soreness, infection, bleeding, pain and irritation from the insertion of the needle. However, these risks are minimal since standard sterile procedures will be used. There is also a risk of syncope. The likelihood of syncope is uncertain and will vary across subjects; however, all medical staff are prepared to manage the occurrence of syncope.

There is also the risk that a subject's PHI may be seen by others. PHI is considered individually identifiable health information transmitted or maintained in any form (electronic means, on paper, or through oral communication) that relates to the past, present or future physical or mental health or conditions of an individual that may be used or disclosed. The following PHI will be collected as part of this project: names (individual, employer, relatives, etc.), address, telephone number, Social Security number, dates (birth, admission, discharge), medical record numbers, driver's license numbers, mental and physical health history, drug use history, results from mental and physical health screening, results from personality questionnaires and data from experimental measures. This risk will be minimized since all appropriate precautions will be taken to protect subjects' PHI, according to the guidelines established by the HIPAA.

The doses to be administered in the present experiment were chosen to minimize, if not eliminate, the chance of these side effects occurring since these side effects are related to dose. Thus, it is unlikely that subjects will experience side effects during the experimental protocol. All experiments proposed in this application will be conducted at the CRU and under medical supervision. Side effects of the drugs are temporary, usually dissipating in less than 24 hours.

There is some theoretical risk that subjects might choose to seek out illicit sources of drugs they received experimentally and liked. However, this risk is minimal since all drugs are administered under blind conditions and in a setting that is not conducive to the development of dependence.

## 10. SAFETY PRECAUTIONS

Protocol management forms will include prompts for research staff members to record any protocol anomalies, data collection problems, concerns with study subjects, or any unusual events that could impact the safety of the subjects or the integrity of the protocol. In addition, the PI, as well as the study physician or his appointed representative, are available at all times by telephone to respond to any questions or concerns that occur during the study. Furthermore, the PI meets with the project staff on a regular basis in the laboratory or by telephone contact to review the study activities.

As described above, Drs. Hatton, Rayapati and Hays will screen all potential subjects for physical and psychiatric contraindications to participation. Urine samples will be monitored throughout each study to ensure that female subjects are not pregnant and that all subjects are adhering to the drug use restrictions. All subjects in these studies will be thoroughly informed of the various drug side-effects which they might experience and will be appropriately cautioned concerning their activities in the hours after drug administration. However, this should not pose a significant problem because research subjects will be under the direct supervision of the nursing staff on the CRU at all times during drug dosing. Participation is voluntary, so individuals can withdraw at any time if they find the behavioral procedures or drug effects undesirable. The drug doses to be administered in the present experiments were chosen to minimize, if not eliminate, the chance of these side effects occurring. As noted above, Drs. Hatton, Rayapati and Hays will screen all potential research subjects for medical contraindications, and Dr. Gurley will review the ECG, prior to study participation. Drs. Hatton, Rayapati and Hays will monitor research subjects throughout their participation. We anticipate that careful subject selection, dose selection and subject monitoring will greatly reduce, if not eliminate, the occurrence of serious side effects. The assembled team of investigators has been conducting inpatient and outpatient human behavioral pharmacology studies with healthy subjects and subjects with histories of drug abuse for more than 60 years combined and have never observed a serious drug-related unanticipated serious adverse event. To monitor for adverse events/side effects, the Udvalg for Kliniske Undersøgelser (UKU) Side Effects Rating Scale will be completed daily with subjects by CRU nursing staff. Staff observations, subjective-effects drug effects and spontaneous subject report will also be used to monitor for adverse events.

To minimize the risk associated with intravenous cocaine administration, dosing will occur under the supervision of ACLS-certified medical staff (Dr. Hatton and CRU nurses). During the medical safety and experimental sessions, heart rate and blood pressure will be recorded prior to cocaine administration and at frequent intervals (i.e., every 2 minutes) afterwards for the duration of the session. Prior to cocaine administration, subjects must have a heart rate of  $< 130$  bpm, systolic blood pressure  $< 165$  mm Hg and diastolic blood pressure  $< 100$  mm Hg. Heart rhythmicity will be recorded continuously via 3-lead telemetry during each experimental session, and will be monitored continuously for a minimum of 15 minutes following each infusion. Subjects who exhibit hypersensitivity (i.e., HR and BP outside of parameters or abnormal ECG) to the cardiovascular effects of cocaine at any point during these studies will not receive further doses, will be followed until symptom resolution, and will be excluded from further research participation. Cardiovascular hypersensitivity is defined as heart rate  $> (220 - \text{subject age}) \times 0.85$ , systolic pressure  $> 180$  mm Hg or diastolic pressure  $> 120$  mm Hg elevated consistently across a five minute period of monitoring (see above). Cardiovascular hypersensitivity also includes prolonged abnormal heart rhythmicity, which is defined as ventricular arrhythmias that occur at a frequency greater than 5 per minute, are multifocal, or occur as couplets

(2 consecutive beats) or salvos (3 or more consecutive beats), and persist for greater than 15 min. Ischemia or other abnormalities as described in the exclusion criteria would also be cause for discharge. A cardiovascular emergency will be managed using UK medical center procedures (i.e., response from a code blue team).

Subjects will be required to report a history of cocaine use via the smoked or intravenous route to be eligible for study participation. Therefore, subjects who do not have a history of intravenous cocaine use (i.e., those individuals reporting smoked cocaine) will likely be enrolled and receive cocaine by a new route of administration. The National Advisory Council on Drug Abuse guidelines indicate that “a thorough assessment of the risks entailed if participants are to be exposed to...a new route of administration than they would normally encounter by their own choice in their usual circumstance.” We do not feel that the administration of intravenous cocaine to subjects who report no previous experience by this route of administration puts subjects at undue risk for two reasons. First, smoked cocaine administration results in a rapid onset and greater self-reported effects compared to intravenous cocaine at doses that produce comparable blood concentrations, and smoked cocaine was chosen over intravenous cocaine in a self-administration procedure, suggesting that the abuse potential of intravenous cocaine is less than smoked cocaine (Cone, 1995; Foltin and Fischman, 1991, 1992). Second, a study that evaluated cocaine use patterns following investigational intravenous cocaine administration to intravenous-naïve cocaine users did not detect changes in frequency of illicit cocaine use or the adoption of intravenous use after study participation (Kaufman et al. 2000). Furthermore, several investigative teams have published studies in which intravenous cocaine was administered to human subjects with a history of smoked, but not intravenous, cocaine (e.g., Haney et al., 1998; Newton et al., 2001; Walsh et al., 2010), demonstrating that the field finds this practice acceptable from an ethical standpoint. Also worth noting is that some subjects who have participated in our previous research have reported intravenous cocaine use.

Subjects will receive intravenous cocaine during maintenance on oral d-amphetamine, which could further increase the risk for adverse cardiovascular events. However, previous clinical research has demonstrated the safety and tolerability of cocaine administration during d-amphetamine maintenance, suggesting that cardiovascular risk in the proposed studies will be minimal. In a study by Greenwald and colleagues (2010), subjects were maintained on d-amphetamine SR at the doses proposed in this application (i.e., 30 and 60 mg/day). d-Amphetamine modestly, but significantly, elevated baseline heart rate and systolic and diastolic blood pressure readings (an increase of approximately 10 bpm, 12 mmHg and 10 mmHg, respectively); however, a bolus dose of 100 mg intranasal cocaine failed to further increase these cardiovascular parameters. In our previous study in which we administered up to 60 mg of intranasal cocaine during maintenance on 30 mg/day d-amphetamine, baseline heart rate and systolic blood pressure were elevated (approximately 6 bpm and 5 mmHg, respectively) and then further increased by cocaine (Rush et al., 2009). However, maximum heart rate did not exceed 95 bpm or 130 mmHg on average following cocaine administration, and no adverse cardiovascular events occurred. In a second study, up to 30 mg of intranasal cocaine was administered during maintenance on 40 mg/day d-amphetamine (Rush et al., 2010). In that study, cocaine significantly increased systolic and diastolic blood pressure, and d-amphetamine maintenance further increased BP, but only by a maximum of about 5 mmHg, and not to a statistically significant degree. Lastly, a review by Herin and colleagues (2010) evaluated the risk profile of d-amphetamine maintenance on an outpatient basis in treatment seekers and found it favorable. The results of several controlled clinical trials incorporating careful monitoring of side effects, including frequently repeated ECGs, indicated that the effects of d-amphetamine maintenance on blood pressure and heart rate were nominal. Similarly, multiple reports from community-based clinics failed to note serious adverse events in diverse populations.

As noted above, serious side effects of stimulants include seizures. The occurrence of seizures appears to be related to the presence of certain predisposing factors including histories of head trauma, seizures or CNS tumors and the administration of concomitant medications that lower seizure threshold. Subjects that report personal histories of head trauma, seizures or CNS tumors or a first-degree family history of seizures will be excluded from research participation. Most seizures resolve of their own accord and typically, individuals with a history of seizures will be the only ones who require intervention. In the event that a seizure should occur, the standard response is to allow 15 minutes for it to spontaneously resolve. If the seizure has not stopped within the allotted time, diazepam is to be administered by the attending physician or his designee. Because we

exclude individuals with a history or risk of seizures, it is very unlikely that a subject will have a seizure or that we will need to administer diazepam. If a research subject experiences a seizure he/she will be excluded from further research participation.

Potential subjects must meet criteria for cocaine-use disorders to be enrolled in the proposed experiments. It is possible that these subjects will experience abstinence symptoms once admitted to the CRU. As noted above, we have several safeguards in place to monitor for adverse events. If a subject experiences significant symptoms of abstinence following admission to the CRU, he or she will be treated in accordance with the standard practice of the University of Kentucky Hospital and then dismissed from the study.

To avoid potential drug interactions, volunteers taking any prescribed medication chronically, except birth control, will be excluded. The medical personnel on this protocol will determine if it is safe for a potential volunteer to discontinue taking their medication during their participation.

All subject PHI is confidential and will be protected according to the guidelines established by the HIPAA. An "Authorization to use and disclose PHI for research purposes" approved by the UK IRB will be obtained. This allows the investigators on this project to use or share health information with the United States Department of Health and Human Services (DHHS) representatives, the UK IRB, the UK Office of Research Integrity (ORI), UK medical center representatives, other research collaborators or when required by law. In addition, a Certificate of Confidentiality will be obtained from NIDA. All PHI will be protected as described above for safeguarding experimental data and PHI in the Research Materials section.

During the course of participation in the research, a subject could experience dissatisfaction or discomfort with the experimental procedures. A research staff member will be immediately available to address these issues, and the study subjects have telephone contact information to reach both the PI and the study physician. In addition, if individuals become overly distressed or distraught, participation in the study is discontinued immediately and private consultation with the study physician and/or PI is offered immediately.

#### **11. BENEFIT vs. RISK**

The degree of risk to which individual study participants are exposed as a consequence of their research participation is slight. In contrast, the potential and probable benefits to be derived by society in general and by patients as a group appear to be considerable. The major benefits of this study are clinical and scientific ones related to the development of efficient and predictive screening procedures for putative pharmacotherapies for cocaine-use disorders. Individual study participants are expected to benefit personally from the medical and psychiatric evaluations and from referrals for medical and psychiatric treatment that are provided whenever appropriate. Overall, the risk/benefit ratio appears favorable and the conduct of this research seems well justified.

#### **12. AVAILABLE ALTERNATIVE TREATMENTS**

There are no available alternative treatments as this is not a treatment study. If volunteers express the desire for treatment they will be given referrals for treatment and not be allowed to participate in this study.

#### **13. RESEARCH MATERIALS, RECORDS AND PRIVACY**

Urine and blood samples will be collected at screening prior to a subject's participation in the experimental protocol under another IRB approved protocol (Number 03-0509). These urine samples will be tested for the presence of a full range of drugs of abuse. Blood samples will be used for the laboratory chemistries. Females will also be given a pregnancy test at the time of screening (via the urine sample). Urine drug and pregnancy tests will be conducted prior to the conduct of each experimental session. Other data obtained from the subjects will involve the number of self-administered doses of cocaine, subjective effects based on questionnaires, and non-intrusive staff observations and ratings.

#### **14. CONFIDENTIALITY**

Identifying information will be stored in a separate, locked area from all other de-identified data and codes linking the two will be kept under lock and key or on password protected computers. Incidental materials containing subject identifiers will be shredded or incinerated. Identification and access of identified

data/specimens will be available only to study investigators when it is detrimental to subject safety or the conduct of the research protocol. For example, if a subject has an adverse event, we will want to obtain a quantitative drug screen to identify whether there may have been illicit drug use while in the study versus a true adverse event related to the study procedures. In the future, data/specimens may be shared with non-UK affiliations in a HIPAA compliant manner.

#### **15. PAYMENT**

Subjects will be paid \$40 for each day they reside on the CRU and will receive a \$40 completion allowance for these days if they complete the entire experiment (\$2640, based on the schedule provided above). The amount earned by the volunteer will be disbursed to them upon completion of the study. Payments will be disbursed in amounts up to \$500 dollars and will be given every week following discharge until the volunteer is paid in full. When volunteers return on a weekly basis to receive their payments, we will survey them regarding their drug use since being discharged from the study. Subjects can also earn up to \$648.00 by choosing to receive money instead of cocaine doses. Worth noting is that in the previous version of this protocol, subjects chose to receive cocaine instead of money (\$0.01-3.00) under most conditions, suggesting that it is unlikely that they will receive the full \$648.00 in the proposed protocol. A volunteer can earn a maximum of \$3280.00 for participating in this study.

#### **16. COSTS TO SUBJECTS**

There will be no cost to the volunteer for participating. Costs for the screening procedures (i.e., medical history questionnaire, physical examination including laboratory chemistries (blood chemistry screen, complete blood count, urinalysis) and a psychiatric examination will be paid by the Laboratory of Human Behavioral Pharmacology.

#### **17. DATA AND SAFETY MONITORING**

The purpose of this project is to establish a research platform that facilitates animal-to-human translational research on development of medications for treatment of cocaine abuse and dependence. A randomized, double-blind, placebo-controlled, within-subjects design will be employed for the human laboratory experiments proposed in this project. Subjects will be 18 cocaine-using men and women of various race/ethnicity, aged **18-55**, who meet criteria for cocaine-use disorder, but are not seeking treatment for their drug use. All subjects must provide informed consent to participate. This sample will be recruited from the local community and will participate as inpatients at the UK CRU.

This project will establish parallel self-administration methods in humans and non-human primates (studies conducted by our colleagues at Virginia Commonwealth University) that will be used in conjunction as a medications screening tool for cocaine dependence. Intravenous cocaine and species-specific alternative reinforcers are made available on a concurrent progressive-ratio (PR) schedule. In the present study, the sensitivity of cocaine choice in monkeys and humans to pharmacologic treatment will be demonstrated using maintenance on d-amphetamine as a standard.

The Principal Investigator, Joshua A. Lile, will be responsible for monitoring the safety and efficacy of this trial, executing the DSMP, and complying with the reporting requirements. The PI will provide a summary of the DSM report to NIDA on an annual basis as part of the progress report. The DSM report will include the subject sociodemographic characteristics, expected versus actual recruitment rates, retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of serious adverse events (SAEs), and any substantial actions or changes with respect to the protocol. The DSM report to NIDA will also include, if applicable, the results of any data analysis conducted. There are no conflicts of interest.

##### **Data Monitoring Plan**

Data will be collected using a computerized data collection and management system. This system automates the collection of the self-administration, subjective-effect and physiological data, which ensures the accuracy and completeness of data collection. The data are stored in a unique file on the hard-drive of the computer and are printed at the end of each session. In all instances, the data files do not contain the name of

the subject, but instead, each subject is identified by a unique four-digit number. Data files for experimental tasks and physiological measures from each experimental session will be managed and combined into a single electronic spreadsheet by automated macros. Data for all subjects will then be combined into a single electronic spreadsheet and separated by experimental measure for statistical analysis and graphing.

The primary outcome for these experiments will be the break point and number of self-administered cocaine injections from the concurrent progressive-ratio choice procedure during maintenance on d-amphetamine. The secondary outcomes will be the results from the subjective and physiological measures. Data will be analyzed using ANOVA. The alpha level will be set at 5%.

As noted above, data are collected using an automated computer system, which increases the accuracy and completeness of data collection and ensures the validity and integrity of the data. The quality of manipulated data and data analyses will be monitored by random inspection by the PI and/or Co-Investigators. Interim analysis of the data will be conducted when 50% of the sample is accrued. If statistically significant differences are revealed for all outcome measures, the study will be ended.

#### Safety Monitoring Plan

Potential subjects will provide information regarding their drug use history and undergo an extensive physical and psychiatric health screening to determine their eligibility and safety of their participation. Potential subjects must meet DSM IV criteria for abuse of or dependence on cocaine and must present with a urine sample positive for cocaine at the time of screening. Any potential subject with a history of clinically significant physical disease, current physical disease (e.g., impaired cardiovascular functioning, histories of seizure, asthma, diabetes, head trauma or CNS tumors), or current or past histories of psychiatric disorder, other than substance abuse or dependence, will be excluded from research participation. All study subjects will be judged by the medical staff to be psychiatrically and physically healthy. Females must be using an effective form of birth control in order to participate and must not be pregnant.

Methods for monitoring adverse events (AEs) will include observations by the medical and research staff, spontaneous report by the subjects, regular measurement of cardiovascular indices, use of the UKU Side Effects Rating Scale and subjective-effects questionnaires. Subjects will not receive study drug if they have any signs or symptoms that may contraindicate its administration (e.g., HR and BP outside of predetermined range for a prolonged period, development of serious side effects).

All AEs occurring during the course of the study will be collected, documented, and reported to the PI following each occurrence. The occurrence of AEs will be assessed daily for the duration of participation, as needed and follow-up visits will be scheduled as appropriate. The study investigators will follow all AEs to the point of a satisfactory resolution. Subjects may be withdrawn from the study if the investigators determine it is the best decision in order to protect the safety of the subject. All AEs will be assessed to determine if they meet criteria for a serious adverse event (SAE).

Serious adverse events, as defined by the FDA, will be systematically evaluated daily for the duration of participation, as needed and follow-up visits will be scheduled as appropriate. Any SAE, whether or not related to the study drug, will be reported to the IRB, NIDA, and the FDA. In the event that a subject either withdraws from the study or the investigator decides to discontinue a subject due to an SAE, the subject will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to the study drugs, or results in death.

#### **18. SUBJECT COMPLAINTS**

Subjects may at any time ask study personnel questions about the study procedures or make complaints. All staff will be aware to notify Drs. Lile, Rush, Stoops, Hatton, Hays or Rayapati about any subject concern or complaint as it arises. Subjects will be allowed the opportunity to discuss any concerns or questions with an investigator promptly, in person and in confidence. It should be noted, however, that subjects will be told that some concerns and complaints will not be kept private such as an adverse event, protocol deviation or threat to the safety of participants or integrity of the research study. In these cases, all information will be made available to the Principal Investigator in order to determine any further course of action. Dr. Hatton, Hays or

Rayapati will also communicate with the nursing or laboratory staff on at least a weekly basis in order to discuss any concerns regarding particular subjects or with respect to the conduct of the study.

**19. RESEARCH INVOLVING NON-ENGLISH SPEAKING SUBJECTS OR SUBJECTS FROM A FOREIGN CULTURE** Not Applicable.

**20. HIV/AIDS RESEARCH POLICY** Not applicable.

**21. PI SPONSORED FDA-Regulated Research**

Dr. Rush holds an IND for intranasal cocaine (53,164). This IND has been amended to include the administration of intravenous cocaine, and was amended following approval of the previous request to include i.v. cocaine administration during maintenance on d-amphetamine. The IND amendment has been received by the FDA. Dr. Lile has managed the initial submission, amendments and oversight for Dr. Rush's IND for methamphetamine (104,829), as well as the amendments for the administration of i.v. cocaine on the abovementioned IND. Both investigators are aware of the necessary reporting requirements and other responsibilities associate with IND sponsorship. As required by the FDA, Drs. Rush and Lile will submit annual reports on the progress of the IND and will also report serious adverse events in accordance with published guidelines. Dr. Rush and Lile will train all study staff on their responsibilities regarding the IND.