Cover Page
Behavioral Effects of Drugs (Inpatient): 38
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BACKGROUND

Cocaine use disorder is an unrelenting public health concern. Nearly 1 million people met criteria for cocaine use disorder in 2017, a rate that has remained stable for the past decade. Cognitive behavioral therapy (CBT) is a psychosocial treatment that durably reduces cocaine use. However, CBT does not promote cocaine abstinence or eliminate cocaine relapse in all patients. It is also not implemented in many treatment clinics because it requires substantial clinical time commitment. Moreover, the mechanisms underlying the efficacy of CBT are not well understood. Determining the mechanisms that drive the efficacy of CBT will promote refinement and enhancement of CBT methods, and ultimately its implementation, thereby maximizing the impact of CBT on the public health burden posed by cocaine use disorder.

Two primary, interrelated components of CBT are the decisional analysis of positive and negative outcomes resulting from cocaine use and the regulation of cocaine craving. These components target the diminished control over cocaine use despite negative consequences, exacerbated by craving, that characterizes cocaine use disorder. It is believed that the emphasis on the negative consequences of cocaine use and reductions in craving promoted by CBT directly reduces cocaine taking, but this hypothesis has not been tested.

Human laboratory research provides a means of determining the mechanisms underlying effective treatments for drug use disorders. Research with alcohol, cigarettes and methamphetamine has modeled the decisional analysis and craving regulation aspects of CBT by instructing subjects to focus on the positive or negative aspects of drug use when presented with drug cues. Consideration of negative or long-term aspects of substance use reduced craving for those substances. *Preliminary data from our laboratory has extended those findings to show that focusing on the negative aspects of cocaine use reduces cocaine craving.* Whether reduced craving drives reductions in cocaine self-administration remains to be determined.

We have developed human laboratory cocaine self-administration procedures that have strong predictive validity for determining the impact of behavioral manipulations on cocaine taking. For example, we have shown that the availability of mutually exclusive alternative reinforcers reduces cocaine self-administration. This arrangement models another effective psychosocial intervention, contingency management. In this pilot study, our self-administration procedures will be adapted to evaluate the influence of decisional analysis/craving regulation features of CBT on cocaine self-administration, thereby determining how these components contribute to the ability of CBT to promote biologically verified cocaine abstinence.

The specific aim of this project is to demonstrate that the decisional analysis/craving regulation aspects of CBT reduce cocaine self-administration in subjects with cocaine use disorder through diminished craving responses. Thirty non-treatment seeking human subjects meeting diagnostic criteria for cocaine use disorder will complete an outpatient, crossover, placebo-controlled study consisting of 1 practice and 9 experimental sessions. In each experimental session, the reinforcing effects of intranasal cocaine (0, 40 or 80 mg) will be determined under one of three regulation of craving conditions that simulate CBT decisional analysis (i.e., negative instruction, positive instruction or a neutral “look” condition). After sampling the dose of cocaine available in each session, subjects will complete the craving manipulation assigned to that session, they will then rate their craving and finally they will have the opportunity to earn the sampled dose in a progressive-ratio procedure. We hypothesize that focusing on the negative effects of cocaine use will decrease craving and reduce cocaine self-administration relative to the positive and “look” conditions, and that craving will be positively correlated with self-administration outcomes.

2. OBJECTIVES

The primary objective of this study is to determine the influence of a craving manipulation on the reinforcing effects of cocaine.

3. STUDY DESIGN

A double-blind, placebo-controlled, crossover design will be used in this experiment. A completely within-subject design will be used such that each subject will receive all possible dose conditions.

4. STUDY POPULATION

Up to 100 individuals will be screened to participate in this study. We intend to enroll thirty (15 male and 15 female) completers into the study. These individuals must be English-speaking, English-reading subjects 18-55 years of age of varying ethnic backgrounds. Enrollment in this study will occur between January 15, 2019 and January 14, 2020. Subjects will be required to provide legal proof of age. Subjects must be healthy and without contraindications to cocaine. Subjects must also report recent use of cocaine and must meet diagnostic criteria for cocaine use disorder using the Structured Clinical Interview for DSM-5 (SCID). Subjects must provide a cocaine positive urine during screening to verify cocaine use status. 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 (44379). Chemistry values and screening outcomes must be deemed normal. If chemistry values or screening outcomes fall outside normal ranges, a study physician must deem them clinically insignificant for a subject to be enrolled. An electrocardiogram must also be within normal limits. Any potential subject with a 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 will be excluded from participation. Subjects with current or past histories of substance use disorder that are deemed by the doctor to interfere with study completion will also be excluded from participation. Female subjects must be using an effective form of birth control (e.g., birth control pills, surgical sterilization, IUD, cervical cap with a spermicide, condoms, or abstinence) in order to participate. A urine pregnancy test will be conducted before the start of each experimental session to ensure that female subjects do not continue in the study if pregnant. All study subjects will be judged by the study physician, Dr. Lon R. Hays or Dr. Abner O. Rayapati to be healthy.

During the initial screening process, potential subjects 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 opioids. In order to participate in an experimental session, subjects must provide a urine negative for recent use of amphetamine, barbiturates, benzodiazepines, and opioids on each day of their participation. Subjects will be allowed to continue if they test positive for recent use of cocaine or marijuana (THC) if they pass the sobriety test and have vital signs within acceptable limits (see below).

5. SUBJECT RECRUITMENT METHODS AND PRIVACY

Subjects 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, restaurants, stores), and by word-of-mouth. These advertisements are approved under our screening protocol (IRB # 44379). Subjects 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 subject 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) and is covered under our approved screening protocol (IRB # 44379). Study investigators may interact with subjects 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, 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. Subjects that meet the inclusion criteria will participate as outpatients at the University of Kentucky LHBP and Clinical Services Core (CSC). Subjects will be discharged at the end of each day, provided that they meet release criteria.

This experiment will require each subject to complete a total of one practice and nine experimental sessions over approximately two to three weeks. Experimental sessions will be conducted as outlined in the table below. We would like to note that the order of the experimental sessions (i.e., dose tested and craving manipulations) will be randomized across subjects. The practice session will familiarize subjects with the experimental routine and tasks, but no drug will be administered and subjects will receive instructions on each of the craving manipulation conditions (positive, negative, and look [neutral]).

Time	
0800	Arrival at LHBP. Drug and alcohol use restriction compliance verified. Transport to CSC.
0900	Baseline craving, subjective-effect and physiological measures completed.
1000	Subject samples intranasal dose available for that session. Subjective-effect and physiological measures completed at 15-minute intervals for 45 minutes. Commodity purchase tasks completed 15 minutes after sampling dose.
1045	Subject completes regulation of craving manipulation assigned for that session (positive, negative or look) and rates craving.
1050	Subject offered opportunity to work for dose on progressive-ratio schedule.
1100	Dose administered, if earned and physiological measures are within acceptable limits.
1115	Subjective-effects and physiological measures completed.
1130	Craving manipulation, craving measurement, progressive-ratio procedure and subjective-effects and physiological measures sequence completed. Repeats 4 more times at 45-minute intervals.
1530	Discharge from CSC. Return to LHBP for final sobriety testing, payment and release.
Note	Cocaine dose and craving manipulation will be presented in random order. A fully factorial design will be used so that all possible combinations are tested once each over nine sessions.

Subjects will be encouraged to abstain from illicit drugs for the duration of the study and from alcohol for the 12 hours prior to, and following, each experimental session. They must also agree to abstain from solid food and caffeine for 4 hours before each experimental session. Subjects will arrive at the LHBP at approximately 0800 hours. Upon arrival at the LHBP, a breathalyzer and a field sobriety test will be conducted, a urine sample collected, and pre-session paperwork completed. A breathalyzer positive for alcohol or a urine sample positive for recent use of amphetamine, benzodiazepines, barbiturates, or opioids will preclude the subject from participation in the session. If a subject tests positive for recent use of cocaine or marijuana (THC), Dr. Hays or Dr. Rayapati must be notified. Subjects will only be allowed to participate in a session with a marijuana or cocaine positive urine if they pass the sobriety testing and baseline cardiovascular measures are within acceptable limits (i.e., heart rate < 90 bpm, if systolic pressure < 140, or diastolic pressure < 90). Moreover, intranasal cocaine doses may not be administered until two hours following all subjects' arrival, regardless of the outcome of their urinalysis. Subjects will then be provided with a standard, fat- and caffeine-free breakfast. Prior to beginning each experimental session, subjects that report smoking tobacco cigarettes will be allowed to smoke one cigarette.

At 0830, subjects will be transported to the CSC. Physiological measures will be recorded at 15-minute intervals upon arrival at the CSC. At 1000, subjects will sample the dose of intranasal cocaine available that day (0, 40 or 80 mg). After sampling the drug, subjects will complete the subject-rated measures. Subjects will then make 5 choices to self-administer the sampling dose after completing the craving manipulation. Choices will be separated by 45 minutes. Drug administration will be withheld if heart rate > 90 bpm, if systolic pressure > 140 or

diastolic pressure > 90. Subjects will be excluded from further research participation if at any time during an experimental session heart rate increases above 130 bpm, diastolic pressure increases above 110 mmHg or systolic pressure above 180 mmHg.

At approximately 1530, subjects will be transported back to the LHBP and provided lunch. Subjects will then complete post session sobriety testing. If no drug effects are detected and vital signs are within acceptable limits (i.e., heart rate < 100 bpm, if systolic pressure < 150, or diastolic pressure < 100), subjects will be released from the laboratory at approximately 1630 h. At this time, payment for that day's session will be given to the subject. If drug effects are evident at the end of the experimental session, subjects will remain at the laboratory until these effects dissipate. Subjects must agree not to operate a motor vehicle or heavy machinery for 6 hours after leaving the laboratory.

Apparatus. Behavioral testing will be conducted at the LHBP and CSC. Subjects will be tested using an individual laptop computer that automates behavioral tasks.

Regulation of Craving Manipulation. This task was developed based on previous work with cigarettes, methamphetamine and alcohol (Kober et al., 2010a; 2010b; Lopez et al., 2015; Naqvi et al., 2015) and will be essentially identical to what was used in our pilot study (Strickland et al., 2016). At the outset of the practice session, participants will be presented with cocaine images and trained on each of the three strategies (positive, negative, look [neutral]), based on previous work with methamphetamine users (Lopez et al., 2015). During positive trials, participants will be told to focus on positive subjective effects of consuming cocaine (e.g., stimulation, good effects). During negative trials, participants will be told to focus on negative subjective effects of consuming cocaine (e.g., feeling sad the next day, guilt over money spent or damage to personal relationships). During look trials, participants will be told to respond naturally to the cocaine stimulus.

During the actual manipulation in experimental sessions, subjects will be presented 30 trials depicting cocaine images. Each trial will begin with an instruction presentation (i.e., positive, negative, look) followed by 6-second image presentation. The instruction presentation will remain constant within each experimental session. Images will be presented in random order from a bank of 300 images to minimize habituation. After each image offset, subjects will rate craving for cocaine using a 0-10 visual analog scale (0 = Not at All; 10 = Very Much) (Lopez et al., 2015). Craving, averaged across all trials in a session, will be the primary outcome. The manipulation will be repeated prior to each self-administration opportunity.

Progressive-Ratio Procedure. Following a 30-image trial, subjects will be offered the opportunity to earn the sampled cocaine dose on the Progressive-Ratio Procedure. We have a long history of using this procedure to assess the reinforcing effects of stimulant drugs (Stoops, 2008), including cocaine (Stoops et al., 2010a; 2012a). It yields orderly, dose-related self-administration outcomes. Subjects will have a total of five opportunities to earn the dose they sampled at the outset of the session in order to provide multiple replication trials to determine the impact of the craving manipulation on drug self-administration (Ferster and Skinner, 1957; Spiga and Roache, 1997). The initial response requirement for a dose will be 400 mouse clicks. Response requirements will increase by 200 for each subsequent dose. For example, if a subject chooses cocaine at the first trial, earning that dose would require 400 responses. At the second opportunity, if he/she chooses to earn cocaine again, earning that dose would require 600 responses. If he or she elects not to earn cocaine at any given opportunity, the response requirement would not increase for the next opportunity. If a subject were to choose cocaine across all opportunities, the response requirements would be 400, 600, 800, 1000 and 1200 responses. The primary outcome is the number of cocaine doses earned.

Subjective-Effects and Physiological Measures. A subjective-effects questionnaire and physiological measures will also be used to assess cocaine effects and monitor safety.

Subjective-Effects Measures. One subject-rated questionnaire that measure various aspects of mood and drug effect will be used: the Drug-Effect Questionnaire. This questionnaire is sensitive to stimulant drug effects (Rush et al., 2003).

Physiological Measures. Heart rate, blood pressure, heart rhythmicity and oral temperature will be recorded using a digital monitor. These outcomes are sensitive to stimulant drug effects (Stoops et al., 2008; 2016).

Commodity Purchase Task (Appendix B). Commodity purchase tasks will be used to assess economic demand for chocolate, cigarettes, alcohol, and the cocaine sampling dose (Amlung et al., 2015; Bruner and Johnson, 2014; Murphy and MacKillop, 2006; Rush et al., ongoing). In these tasks, subjects are asked to indicate the hypothetical number of commodity units (i.e., 12 oz. sodas) they would purchase at a future date at monetary increments ranging from $0.00 (free) to $140/unit. In the cocaine task, participants will be asked to make choices based on the sampling dose they received earlier in the session. All choices are hypothetical and will not be purchased or administered. Subjects will complete the Commodity Purchase Tasks following approximately .25 h after the sampling dose.

Drug Dose and Administration. All drugs will be administered under double-blind conditions and under medical supervision. Doses of cocaine HCl will be prepared by weighing out the appropriate amount of powdered cocaine. The powder will then be mixed with lactose monohydrate powder, N.F. to make a total of 80 mg powder. Placebo will be prepared in an identical fashion, but will contain only lactose monohydrate powder. Doses of cocaine will be prepared individually for each subject. Doses of 0, 40 and 80 mg intranasal cocaine will be placed into individual glass vials labeled for each subject for each sampling session. The unit doses of cocaine proposed for the study have been administered to human subjects under similar controlled medical and laboratory conditions without adverse incident by the study team (Stoops et al., 2008; 2010; 2016).

Data Analysis. All data will be analyzed using SPSS (IBM Corporation, Armonk, NY). To test our primary hypothesis, self-reported craving scores and number of cocaine doses earned will be analyzed using two-factor repeated-measures General Linear Model (GLM) with data from the 30 subjects who complete the protocol. The α level will be set at $p \leq 0.05$. Data from subjects who do not complete will not be included in the analyses. Cocaine Dose (0, 40 and 80 mg) and Craving Manipulation (positive, negative and look) will be the factors of the ANOVA. A significant change in craving or self-administration will be inferred if the Interaction of Cocaine Dose and Craving Manipulation attains statistical significance. If the interaction attains statistical significance, the mean square error term will be used to conduct Tukey's HSD post-hoc test to make appropriate pair-wise comparisons. If baseline measures (e.g., craving) differ across conditions, they will be entered into the analysis as covariates. To test our secondary hypothesis, craving scores will be averaged for each of the nine conditions and compared with self-administration outcomes using Pearson correlations. Subjective-effect and physiological data following the sampling dose will be averaged across craving manipulation conditions because they will be collected prior to the craving manipulation and analyzed using cocaine dose and time as factors in a repeated-measures GLM. Exploratory analyses considering relevant biological variables (i.e., sex, age and race/ethnicity) will also be conducted.

8. RESOURCES

This study will take place at the CSC. Study sessions will only be conducted on weekdays. All drug administration will take place at the UK CSC in a room equipped with all the necessary physiologic and computer equipment for the study. Dr. Hays is an adult psychiatrist who has worked extensively with individuals with substance use disorders in both the clinical and research setting and he is the responsible medical investigator for this study. Dr. Rayapati is a psychiatrist who has worked extensively with individuals with substance use disorders in both the clinical and research setting and he is the backup medical investigator for this study. They will be available to attend to medical problems as well as any psychological or psychiatric issues that may arise. Dr. Stoops will provide scientific oversight for the study and has safely completed numerous human behavioral pharmacology studies. Overall, the study team and resources described above are well equipped to protect subjects and successfully implement, carry out, and complete this study protocol.

9. POTENTIAL RISKS

The subject-rated drug-effect questionnaire and physiological measures employed in these studies are benign. The risks to the study subjects are those related to the ingestion of the drug under study. The drug to be administered in the proposed research is commercially available. The relative safety as well as the contraindications and possible side effects of this compound are well known and documented. However, the administration of any drug involves some risks simply because individuals differ in their reactions to drugs. The main risk is that subjects will experience side effects that may be unpleasant.

Common side effects of cocaine include anxiety, restlessness, diuresis, irritability, suppressed appetite, insomnia, gastrointestinal upset, increased heart rate, increased blood pressure, weight loss, and palpitations. More serious side effects following the chronic, unsupervised administration of much higher doses of cocaine have occurred and include arrhythmias, psychotic episodes, suppressed breathing, seizures, myocardial infarctions, heart failure, and death.

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 sessions proposed in this application will be conducted at the CSC and under medical supervision. Side effects of the drugs are temporary, usually dissipating in less than 24 hours. The principal investigator on this project, Dr. Stoops, has had extensive experience over the last 18 years administering therapeutic and supratherapeutic doses of stimulant drugs to subjects in both inpatient and outpatient settings and has never observed a serious, unexpected adverse effect. Dr. Stoops will train all staff on this project.

To avoid potential drug interactions, subjects 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 subject to discontinue taking their medication during their participation.

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

Subjects are carefully screened (history and physical exam, routine labs such as CBC, complete metabolic panel and urinalysis, ECG, and psychiatric assessment) to exclude those with potential increased risk of adverse effects, such as personal or first degree family histories of heart disease, histories of seizure or head injury associated with more than a brief loss of consciousness, hypertension, psychosis, etc. During sessions subjects remain under careful medical observation and are monitored continuously by on-site medical staff. Vital signs will be collected throughout the dosing period. Staff is familiar with the acceptable physiological parameters for these studies and this information is posted in every experimental session room. In addition, Dr. Stoops has substantial experience administering medications to human subjects under a variety of dosing conditions. Lastly, female subjects are also given pregnancy tests prior to each session to ensure that we do not administer active medications to a pregnant woman.

Legal risks including loss of confidentiality: All intake documentation that contains personal information is handled separately from the actual data collected during the study. All information of a personal nature (intake assessments, medical test results) is kept locked either on password-protected computers or in secure filing cabinets all behind locked doors and accessible only to key personnel involved in the research.

11. BENEFIT vs. RISK

The degree of risk to which individual study subjects 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 knowledge gained about learning mechanisms contributing the effectiveness of treatments for cocaine use disorders. The data from this project will contribute to a better understanding of drug abuse and will ultimately contribute to the development of improved prevention, control and treatment procedures. Individual study subjects 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 subjects 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 samples will be collected at screening prior to a subject's participation in the experimental protocol under another IRB approved protocol (Number 44379). These urine samples will be tested for the presence of a full range of drugs of abuse. Urine drug and pregnancy tests will be conducted prior to the conduct of each experimental session. Other data obtained from the subjects will involve subjective effects based on questionnaires, various computer-based tasks, and non-intrusive staff observations and ratings. The consent form states that subject's confidentiality will be protected.

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 practice or experimental session that they complete and will receive a $40 completion allowance for these sessions if they complete the entire experiment. The amount earned by the subject will be disbursed to them upon completion of the session. A subject can earn approximately $800 for participating in this study.

16. COSTS TO SUBJECTS

There will be no cost to the subject 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 LHBP.

17. DATA AND SAFETY MONITORING

Data Monitoring Plan

Data will be collected using a computerized data collection and management system wherever possible. This system automates the collection of 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 after all the tasks are completed. 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. A computer file linking the unique number with the subject's name will be kept on a stand-alone, password-protected computer. All data requiring hand entry (e.g., cardiovascular measures) will be entered by two separate staff members and comparison macros will be run to ensure accuracy. Data files for experimental tasks and physiological measures from each experimental session will be manipulated and combined into a single electronic spreadsheet for each subject by one of the investigators. Data for all subjects will then be combined into a single electronic spreadsheet and separated by experimental measure for statistical analysis using IBM SPSS Statistics (IBM Corportation, Armonk, NY).

In this protocol the primary outcome measure will be the influence of craving manipulations on the reinforcing effects of cocaine. The alpha level will be set at 5%.

As noted above, wherever possible, 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 initial data manipulation described above will be conducted twice and compared. The quality of manipulated data and data analyses will be monitored by random inspection by the PI and/or Co-Investigators.

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. Any potential subject with a history of clinically significant physical disease, current physical disease (e.g., impaired cardiovascular functioning, histories of seizure, head trauma or CNS tumors), or current or past histories of psychiatric disorder that in the opinion of the study physician would interfere with study participation, other than substance use disorder, will be excluded from research participation. 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 and, regular measurement of cardiovascular function. 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, development of serious side effects).

All AEs occurring during the course of the study will be collected, documented and reported to the PI. The occurrence of AEs will be assessed for the duration of participation. Each week a study investigator will review the AE forms from the previous week for events that were reported as new or continuing. The study investigators will follow all AEs to the point of a satisfactory resolution. Subjects may be withdrawn from the study if the medically responsible investigator determines 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 for the duration of participation. Any SAE, whether or not related to the study drug, will be reported to the IRB, CSC, and the FDA. The initial SAE report will be followed by submission of a completed SAE report to all three institutions.

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. Outcome of SAEs will be periodically reported to IRB, CSC, and the FDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to the IRB, CSC, and FDA.

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. Stoops, Rush, Lile, 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 subjects 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. 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 currently holds an IND for intranasal cocaine (#053,164). Dr. Rush has held INDs for behavioral pharmacology research with a number of drugs for over twenty years and is well aware of the necessary reporting requirements and other responsibilities associate with IND sponsorship. He is current on his training in this area. As required by the FDA, Dr. Rush will submit annual reports on the progress of the IND and will also report serious adverse events in accordance with published guidelines. Dr. Rush has trained all study staff on their responsibilities regarding the IND.

Appendix A

Subject-Rated Drug-Effect Questionnaire Description

Drug Effect-Questionnaire (DEQ)-VAS

Individual questions are presented sequentially, one at a time. Subjects rate their response to each question by marking a 100-unit line anchored with "Not at All" on the left side and "Extremely" on the right side.

(1) Is the drug producing "**ANY EFFECT**" right now? (2) Is the drug producing any "**BAD EFFECTS**" right now? (3) Is the drug producing any "**GOOD EFFECTS**" right now? (4) Is the drug making you feel "**HIGH**" right now? (5) Are you experiencing a "**RUSH**" from the drug right now"? (6) How much do you "**LIKE**" the drug right now? (7) Is the drug making you feel "**STIMULATED"** right now? (8) Is the drug "**IMPAIRING YOUR PERFORMANCE**" right now? (9) Is the drug "**IMPROVING YOUR PERFORMANCE**" right now? (10) Based on how the drug effect feels right now, would you be willing to "**TAKE THIS DRUG AGAIN**"? (11) Based on how the drug effect feels right now, would you be willing to "**PAY FOR THIS DRUG**"? (12) Is the drug making you feel "**ACTIVE, ALERT OR ENERGETIC**" right now? (13) Is the drug making you feel "**EUPHORIC**" right now? (14) Is the drug making you experience an "**IRREGULAR OR RACING HEARTBEAT**" right now? (15) Is the drug making you "**TALKATIVE OR FRIENDLY**" right now? (16) Is the drug making you feel "**NAUSEATED, QUEAZY OR SICK TO YOUR STOMACH**" right now? (17) Is the drug making you feel "**SHAKY OR JITTERY**" right now? (18) Is the drug making you feel **"NERVOUS OR ANXIOUS"** right now? (19) Is the drug making you feel "**RESTLESS**" right now? (20) Is the drug making you feel "**SLUGGISH, FATIGUED OR LAZY**" right now?

APPENDIX B

Example Drug Purchase Task

1. Imagine that you were back at home and were given a 12-hour period of time to consume the same drug you were given today.
2. During that time, you would have the opportunity to use the drug whenever you wanted over the 12 hours. For example, you could use multiple doses all at once, you could take one dose several times throughout the day, or you could use multiple doses several times throughout the day.
3. This 12-hour period would be when you have no responsibilities afterwards or the following day.
4. During this 12-hour period, you could use as many doses as you wanted. However, you would have to purchase all of the doses at the beginning of the 12-hour period, and this would be your only opportunity to buy the drug. You would have to use your own money to purchase the drug in the form of cash (assume that your personal finances on that day are the same as they currently are).
5. Importantly, at the end of the 12-hour period, you would not be able to take any leftover drugs away with you. If you don't consume the drug you purchase, you will have to return it and will not get any of your money back. In other words, you wouldn't be able to save the drug for a later date or get a refund.
6. You would also not be able to sell or share any of the drug that you purchase.
7. Finally, assume that you did not use any other drugs or alcohol before this 12-hour period. You would be completely sober at the beginning of the 12 hours.

Given the previous conditions, in a future 12-hour period with no future obligations or responsibilities, how many doses of the drug you received today would you buy at the following prices?

Price Per Hit	Number of Drug Hits
Free	
$0.01	
$0.05	
$0.13	
$0.25	
$0.50	
$1.00	
$2.00	
$3.00	
$4.00	
$5.00	
$6.00	
$11.00	
$35.00	
$70.00	
$140.00	