

Official Title of the Study: Behavioral Effects of Drugs: Inpatient (31)

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1. BACKGROUND

Cocaine (COC) addiction is an unrelenting public health concern. Behavioral therapies are effective for reducing COC use. However, many patients enrolled in behavioral therapy programs are unable to achieve significant periods of abstinence suggesting other strategies like pharmacotherapy are needed. An effective medication has not been identified for COC dependence despite being a high priority for the National Institute on Drug Abuse for nearly 30 years and extensive efforts by the scientific and treatment communities.

COC binds to monoamine transporters (i.e., dopamine [DA], norepinephrine [NE] and serotonin [5-HT]) and prevents their reuptake into the presynaptic terminal. The results of preclinical studies have shown that monoamine releasers attenuate the reinforcing effects of COC. The results of human laboratory studies also suggest monoamine releasers (i.e., d-amphetamine) attenuate the reinforcing effects of COC although the effects are small in magnitude and dependent on the methods used to assess drug reinforcement. The results of clinical trials that tested monoamine releasers for COC abuse are mixed.

Monoamine releasers vary along a continuum from DA/NE selective to 5-HT selective. Theoreticians have postulated that the 5-HT/DA releasing ratio is a critical determinant of the efficacy of a monoamine releaser to attenuate the reinforcing effects of COC. Compounds with intermediate 5-HT/DA release ratios (i.e., 30-40) have been the most effective and specific for reducing COC taking. For example, methamphetamine (5-HT/DA ratio = 31) completely and specifically eliminated responding for COC in monkeys. Consistent with these findings, methamphetamine dramatically reduced COC use in a clinical trial. d-Amphetamine had similar but less robust effects, possibly due to its higher 5-HT/DA release ratio (i.e., 71). Use of amphetamines for managing COC use disorders has met with reluctance due to high abuse and diversion potential. Compounds with a desirable 5-HT/DA releasing ratio and reduced abuse potential need to be tested for COC dependence.

Phendimetrazine (PHEN), a Schedule III medication under the Controlled Substance Act, is indicated for treating obesity. After oral administration, PHEN is converted to phenmetrazine, which is largely responsible for its behavioral and neuropharmacological effects. Consistent with the notion that compounds with intermediate 5-HT/DA release ratios selectively attenuate the reinforcing effects of COC, phenmetrazine (5-HT/DA ratio = 37) completely eliminated COC-maintained responding in monkeys. Recent research with PHEN has also shown that the parent compound reduces COC self-administration. Moreover, PHEN does not maintain self-administration and produces only limited positive subjective effects compared to d-amphetamine in COC users, which suggests that its abuse potential is low. Although PHEN has yet to be tested as a potential pharmacotherapy for COC dependence in human laboratory experiments or clinical trials to our knowledge, the results of extant preclinical experiments suggest it is a viable option.

In an ongoing study, we have demonstrated that COC can be safely administered to patients maintained on 70, 140 and 210 mg PHEN/day. Whether PHEN attenuates the reinforcing effects of COC, the best predictor for treatment efficacy (Comer et al., 2008; Haney and Spealman, 2008), remains to be determined. **The specific aim of this study is to demonstrate that PHEN maintenance reduces the reinforcing effects of intranasal COC.** To accomplish this aim, we will conduct an experiment in which non-treatment seeking COC-using participants (N=36) will be maintained on doses of PHEN (0 and 210 mg/day [target dose, dose will be titrated up as described below]). The reinforcing and other behavioral effects of intranasal COC (0 [placebo], 20, 40 and 80 mg) will be determined after 7 days of maintenance on the target PHEN dose (i.e., 210 mg/day). In order to monitor the safety of the drug combinations, cardiovascular measures will be taken routinely throughout experimental sessions and subjects will complete a daily side effect scale with nursing staff. We hypothesize that PHEN will attenuate the reinforcing effects of COC, as well as other abuse-related effects of COC (i.e., positive subjective effects). We also hypothesize that COC will be well tolerated during active PHEN maintenance.

2. OBJECTIVES

The primary objective of this study is to determine the reinforcing effects of COC during maintenance on PHEN. We will also include a battery of subjective, performance and cardiovascular measures to more fully characterize the influence of PHEN maintenance on the effects of COC.

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, including placebo.

4. STUDY POPULATION

Up to 100 individuals will be screened to participate in this study. We intend to enroll thirty six (24 male and 12 female) completers into the study. These individuals must be English-speaking, English-reading subjects 18-55 years of age of varying ethnic backgrounds and they will be recruited to participate in this five-week experiment. Enrollment in this study will occur between September 1, 2015 and August 31, 2016. Subjects will be required to provide legal proof of age. Subjects must be healthy and without contraindications to COC and PHEN. Subjects must also report recent use of COC and must meet diagnostic criteria for COC abuse or dependence using the Structured Clinical Interview for DSM-IV (SCID). Subjects must provide a COC positive urine during screening to verify COC 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 (03-0509). 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 abuse or dependence 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, M.D. 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 amphetamine, benzodiazepines, barbiturates, COC, tetrahydrocannabinol (THC) and opiates. In order to participate in an experimental session, subjects must provide a urine negative for amphetamine, barbiturates, benzodiazepines and opiates on each day of their participation. Subjects will be allowed to continue if they test positive for COC, if it is determined that this drug was given in a recent session and it is likely that the result is positive due to experimental administration. Dr. Hays or Dr. Rayapati will be notified of COC-positive urines on experimental session days and sessions will only proceed if subjects pass the sobriety test and have vital signs within acceptable limits (see below). Subjects 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

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 # 03-0509). 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). 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 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. Subjects that meet the inclusion criteria will participate as inpatients at the University of Kentucky CCTS Research Inpatient Unit (CRIU). Subjects will be discharged upon completion of the entire protocol.

This experiment will require each subject to participate for approximately five weeks. Experimental sessions will be conducted as outlined in Table 1 below. We would like to note that COC doses will both be given in random order, whereas order of PHEN dosing will be counterbalanced across subjects. We would also like to note that subjects may be maintained on a given PHEN condition for more than 11 days prior to session to avoid testing COC doses on weekends.

Day	Table 1. Experimental Procedures
1	Admission to the CRIU.
2	Practice Session.
3-17	Placebo maintenance. Placebo administered twice daily (0700 and 1900 hours).
14-17	Experimental Sessions. Reinforcing effects of intranasal COC (0 [placebo], 20, 40 and 80 mg) determined using progressive-ratio procedure.
18-32	PHEN maintenance. Administered in divided doses (0700 and 1900 hours). Subjects receive 35 mg twice daily for two days, then 70 mg twice daily for two days, then 105 mg twice daily for remainder of maintenance period.
29-32	Experimental Sessions. Reinforcing effects of intranasal COC (0 [placebo], 20, 40 and 80 mg) determined using progressive-ratio procedure.
33	Discharge

During their participation in the research protocol, subjects will not be allowed to leave the CRIU, nor will visitors be allowed, with the exception that subjects can leave for walks under clinical supervision and if approved by physicians. Research subjects will be allowed to make local telephone calls. After completing the research protocol, interested subjects will be offered a referral to an appropriate drug abuse treatment program.

All subjects will provide urine and expired air samples before and periodically during study participation. The presence of non-nicotine 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 1 practice session and 8 experimental sessions conducted according to the timeline in Table 1 (see above). After admission, subjects will be allowed to acclimate to the CRIU for two days before beginning the study. During this time, subjects 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.

Each day after the practice session, subjects will be awakened at 0700 hours and will receive maintenance medication. Medications will not be administered if a subject's heart rate is ≥ 100 bpm, systolic pressure is ≥ 150 mmHg or diastolic pressure is ≥ 100 mmHg. In addition, the UKU side effects scale will be completed daily to monitor for the emergence of side effects.

Subjects will then be allowed to eat a standard, fat-free breakfast (cereal with skim milk, 2 pieces of toast with jam or jelly and 8 ounces of fruit juice). Tables 2 and 3 (below) outline the activities of maintenance and experimental sessions. The sampling of each session will begin at 0900 hours and will last approximately 1 hour. Self-administration phases will begin at 1330 hours and will last approximately 2 hours. Experimental measures will be completed as outlined in Tables 2 and 3 below. Medications will not be administered if a subject's heart rate is ≥ 100 bpm, systolic pressure is ≥ 150 mmHg or diastolic pressure is ≥ 100 mmHg or if clinically significant and/or prolonged ECG abnormalities are detected.

Subjects will be excluded from further research participation if at any time during the experimental sessions COC increases heart rate above 130 bpm, systolic pressure above 180 mmHg, diastolic pressure above 120 mmHg or if clinically significant and/or prolonged ECG abnormalities are noted. Subjects will remain seated for the duration of the experimental session. Between the sampling and self-administration phases, subjects will be allowed to eat a standard hospital lunch but will not be allowed to smoke. No experimental activities will be scheduled for the remainder of the day after a self-administration session, but subjects will receive their appropriate maintenance medication at 1900 hours. Subjects 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 subjects will be required to be in bed with the lights out by 2300 hours.

Time	Table 2-Daily Activities for Maintenance Days
0700	Patient awakened. Vital signs recorded. Medication administered if vitals are within range and no indication of sedation or withdrawal. 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.

Time	Table 3-Daily Activities for Experimental Days
0700	Patient awakened. Vital signs recorded. Medication administered if vitals are within range and no indication of sedation or withdrawal. Subject eats breakfast.
0900	Vital signs recorded. Computerized tasks completed. ECG monitoring begins.
0930	Vital signs recorded. 0 [placebo], 20, 40 or 80 mg intranasal COC administered if vitals are within range. Measures completed 0, 15, 30, 45 and 60 minutes after drug administration.
1030	Sampling phase ends.
1200	Lunch is served.
1300	UKU is completed.
1330	Vital signs recorded. Computerized tasks completed (including progressive-ratio task). ECG

	monitoring begins.
1430	Vital signs recorded. Portion of intranasal dose earned is administered if vitals are within range. Measures completed 0, 15, 30, 45 and 60 minutes after drug administration
1530	Session ends. Remainder of daily activities identical to those listed in Table 2.

All drugs will be administered under double-blind conditions and under medical supervision. Test doses of COC will be 0 (placebo), 20, 40 and 80 mg, administered in random order. These doses were chosen based on prior work and similar doses have safely been administered to human subjects (Oliveto et al., 1995; Rush et al., Ongoing Study; Stoops et al., 2008; 2010; 2012a; 2012b; Van Dyke et al., 1978). The maintenance conditions will be placebo and 210 mg PHEN/day (target dose). Subjects will be maintained on these doses for at least seven days before beginning experimental sessions. The dose of PHEN was selected based on results of previous clinical research, as well as a recently completed and ongoing studies in our laboratory showing that this PHEN dose is well tolerated by COC users (Bolin et al., Under Review; Stoops et al., Ongoing). Placebo capsules will contain only cornstarch, whereas placebo powder will contain only lactose. Both will be visually identical to the powder and capsules that contain active drug.

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

Modified Progressive-Ratio Procedures. The reinforcing effects of intranasal COC, alone and during maintenance on PHEN doses will be assessed using a progressive-ratio procedure. The outcome measures for this procedure are the break point (i.e., last ratio completed) and number of drug doses ingested.

Testing of each dose of intranasal COC under the proposed modified progressive-ratio procedure involves two phases: 1) Sampling and 2) Self-Administration.

Sampling Phase. Participants will complete a Sampling Phase for each of the active intranasal COC conditions to acquaint them with the drug effects. During each Sampling Phase, participants will receive a single administration of intranasal COC (0 [placebo], 20, 40 or 80 mg). Before each Sampling Phase, participants will be instructed to attend to the effects of the intranasal drug because later that day they will be able to work to receive additional doses of the inhaled drug. Participants will complete the battery of subjective effects questionnaires and performance task 30 minutes before the sampling dose of intranasal COC, immediately following and at 15-min intervals for 60 minutes. Cardiovascular measures will also be recorded at these times.

Self-Administration Phase. Four hours after sampling the available COC dose, participants will complete the Self-Administration Phase. During the Self-Administration Phase, participants will be given up to 10 opportunities to earn 1/10 of the dose of COC dose insufflated during the Sampling Phase or \$0.25. Before the Self-Administration Phase, participants will be instructed that the total amount of drug/money earned will be administered after completing the entire progressive-ratio procedure. Participants must choose one of the two options at each of the 10 opportunities. Participants will be able to earn drug doses or money by responding on a computer mouse according to a progressive-ratio schedule. The ratio for the first choice will be 400 clicks. The response requirement will increase by 100 for a selected option (i.e., 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300 responses if the subject exclusively chooses drug or money). We have conducted several experiments in recent years designed to refine human drug self-administration procedures to enhance our ability to determine the initial efficacy of potential pharmacotherapies for stimulant dependence (Sevak et al., 2010; Stoops et al., 2011). The results of ongoing experiments that used progressive ratio procedures nearly identical to those proposed in this application suggest that the reinforcing effects of oral and intranasal stimulants are an orderly function of dose (Marks et al., Under Review; Pike et al., 2014; Stoops et al., 2012a). Previous studies have also shown that the reinforcing effects of COC are amenable to pharmacological manipulation under a similar arrangement (Greenwald et al., 2010; Stoops et al., 2012a).

Subjective Questionnaires. A battery of subjective questionnaires will also be used to assess drug effects. These measures have previously been shown to be sensitive to the effects of stimulants (Rush et al., 2009). These experimental measures will be taken on all experimental session days. The measures described below will be recorded as described in the tables above. The subjective effects measures are included in Appendix A.

Vital Signs. Heart rate, blood pressure, oral temperature and heart rhythmicity (*via* ECG) will be recorded using a Dinamap digital monitor (Critikon, Pro 1000, Tampa, FL). These measures will be completed at as described in the tables above. Telemetry-certified nurses will interpret the results of the ECG with instructions to contact Drs. Hays or Rayapati regarding abnormalities.

Performance Task. Psychomotor performance will be assessed at the same time as subjective drug-effects during all sessions with a computerized version of the Digit-Symbol-Substitution Test (DSST) (McLeod et al., 1982). In this procedure, the subject uses a numeric keypad to enter a geometric pattern displayed on a video screen. Subjects will have 90 seconds to enter as many geometric patterns as possible. The dependent measures are the number of geometric patterns the subject attempted to enter and the number of patterns entered correctly. This task will be completed immediately following the subjective questionnaires.

Drug Dose and Administration. All drugs will be administered under double-blind conditions and under medical supervision. COC doses will be given in random order. PHEN doses will be given in counterbalanced order across subjects. Doses of COC HCl will be prepared by weighing out the appropriate amount of powdered COC. The powder will then be mixed with lactose monohydrate powder, N.F. to make a total of 100 mg powder. Placebo will be prepared in an identical fashion, but will contain only lactose monohydrate powder. Doses of COC will be prepared individually for each subject. Doses of 0 [placebo], 20, 40 and 80 mg intranasal COC will be placed into individual glass vials labeled for each subject for each sampling session. Doses of PHEN (0, 35, 70 and 105 mg, administered two times daily) will be prepared by over-encapsulating commercially available tablets in a size 0 capsule. The capsule will then be loose filled with cornstarch. Placebo capsules will be prepared in an identical fashion, but will contain only cornstarch.

Data Analysis. Data will be analyzed as raw scores. Statistical significance refers to $p \leq 0.05$.

Progressive-ratio data (i.e., break point, number of COC doses earned) will be analyzed with two-factor mixed-model ANOVA with COC (within-subject variable; 0 [placebo], 20, 40 and 80 mg), and PHEN (within-subject variable; 0 and 210 mg/day) as the factors. A significant attenuation (i.e., rightward shift in the dose response) of the effects of COC will be inferred if the main effect of PHEN or the interaction of COC and PHEN attains statistical significance in the ANOVA. If the COC-PHEN 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 between means. Peak-effect and AUC data for the cardiovascular, performance and subjective effects measures obtained during the sampling phase will be analyzed in a similar fashion. Cardiovascular, performance and subjective effects data from the self-administration phase will not be analyzed because participants will likely ingest varying amounts of COC making these data difficult to interpret.

The primary outcome measures for this study are the break point and number of COC doses earned on the progressive-ratio procedure in subjects maintained on active PHEN or placebo. Considering the complete within-subject design, number of dose levels of each drug (i.e., two PHEN conditions and four doses of intranasal COC) enrolling 36 subjects will provide adequate power to detect an effect size (d) of at least 0.44 for attenuation of the reinforcing effects of COC as a function of maintenance on PHEN and placebo (power = 0.80, α = 0.05, G*Power). We used the results of a previous study conducted in our laboratory to determine an appropriate sample size for the present experiment (Rush et al., 2010). That study demonstrated that d-amphetamine maintenance decreased the reinforcing effects of COC with an estimated effect size (d) of approximately 0.46.

8. RESOURCES

This study will take place at the CRIU. Study sessions will only be conducted on weekdays. All drug administration will take place at the UK CRIU 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 back up 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 have 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 self-administration measure, subjective drug-effect questionnaires, performance and physiological measures employed in these studies are benign. The risks to the study subjects are those related to the ingestion of the drugs under study. All of the drugs to be administered in the proposed research are commercially available. 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. The main risk is that subjects will experience side effects that may be unpleasant.

Common side effects of COC and PHEN include nervousness, restlessness, faintness, irritability, shaking, nausea, headache, flushing, increased urine production, sweating, performance impairment, rash, blurred vision, irritation in nose and throat (due to intranasal insufflation of COC only), difficulty sleeping, loss of appetite, weight change and changes in heart rate or blood pressure. 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.

These side effects may be more frequent and larger in magnitude when testing the COC-PHEN combinations.

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 CRIU 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 15 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. A Certificate of Confidentiality will be obtained from NIDA.

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 putative medications for COC 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 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 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 day they reside on the CRIU and will receive a \$40 completion allowance for these days if they complete the entire experiment. Subjects can also earn an additional \$2.50 during each experimental session depending on how they distribute choices for drug and money. Any money earned in experimental sessions will be added to their overall payment. The amount earned by the subject will be disbursed to them upon completion of the study. Payments will be disbursed in amounts up to \$500 dollars and will be given once per week following discharge until the subject is paid in full. When subjects return on a weekly basis to receive their payments, we will survey them regarding

their drug use since being discharged from the study. A subject can earn approximately \$2660 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 Laboratory of Human Behavioral Pharmacology.

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 SPSS (IBM, Armonk, NY).

In this protocol the primary outcome measure will be the influence of PHEN maintenance on the reinforcing effects of COC. 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 abuse or dependence, 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 and during the follow-up visits at 2 and 4 weeks following study completion. Any SAE,

whether or not related to the study drug, will be reported to the IRB, CRIU, NIDA 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, CRIU, NIDA and the FDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA, the IRB, CRIU 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 COC (#053,164). This application will be modified to combining intranasal COC with oral PHEN. Dr. Rush has held INDs for behavioral pharmacology research with a number of drugs for over eight years and is well aware of the necessary reporting requirements and other responsibilities associate with IND sponsorship. 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

Subjective Drug-Effect Questionnaires Descriptions

Adjectives Rating Scale (ARS)

Individual questions are presented sequentially, one at a time. Subjects rate their response to each question on a 5-point scale (0 = Not at all, 1 = A little, 2 = Moderately, 3 = Quite a bit, 4 = Extremely).

(1) How **"ACTIVE"** do you feel right now? (2) How **"AGITATED"** do you feel right now? (3) How **"CLUMSY"** do you feel right now? (4) How **"ALERT"** do you feel right now? (5) How **"DIZZY"** do you feel right now? (6) How **"CONFUSED"** do you feel right now? (7) How **"ENERGETIC"** do you feel right now? (8) Are you in a **"GOOD MOOD"** right now? (9) How **"DAZED"** do you feel right now? (10) How **"EXCITED"** do you feel right now? (11) How **"SLEEPY"** do you feel right now? (12) How **"DEPRESSED"** do you feel right now? (13) How **"EUPHORIC"** do you feel right now? (14) Are you experiencing an **"IRREGULAR HEARTBEAT"** right now? (15) Do you feel as if you would have **"DIFFICULTY WALKING"** right now? (16) How **"TALKATIVE"** do you feel right now? (17) Are your **"MUSCLES TWITCHING"** right now? (18) How **"DROWSY"** do you feel right now? (19) How **"NAUSEOUS"** do you feel right now? (20) How **"DRUNK"** do you feel right now? (21) How **"NERVOUS"** do you feel right now? (22) How **"FATIGUED"** do you feel right now? (23) Is your **"HEART RACING"** right now? (24) How **"IRRITABLE"** do you feel right now? (25) How **"RESTLESS"** do you feel right now? (26) How **"LAZY"** do you feel right now? (27) How **"SHAKY"** do you feel right now? (28) How **"RELAXED"** do you feel right now? (29) How **"TIRED"** do you feel right now? (30) How **"SLUGGISH"** do you feel right now? (31) How **"SWEATY"** are you right now? (32) How **"SPACED OUT"** do you feel right now?

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?