COVER

Title: Neurobehavioral Mechanisms of Cocaine Choice

NCT#: 04296006

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Protocol

STUDY DESIGN. A randomized, within-subjects design will be used to assess drug-vs-money choice in cocaine use disordered subjects as a function of alternative reinforcer value.

STUDY POPULATION. Men and women of various race/ethnicities will be enrolled.

Inclusion criteria:

-Individuals must meet criteria for cocaine use disorder, report past month smoked or IV cocaine use, and provide a urine sample positive for recent cocaine use during screening.

-Between the ages of 18-55 years.

-Female subjects must be using an effective form of birth control (e.g., birth control pills, surgical sterilization, IUD, cervical cap with a spermicide, or abstinence). Urine pregnancy tests will be conducted prior to sessions to ensure that female subjects do not participate if pregnant.

-Able to speak and read English.

-Otherwise healthy.

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.

-Electrocardiogram abnormalities, including:

-Atrial premature beats (≥ 2 consecutive)

-Ventricular premature beats (Lown's Grade 3 or higher; ≥ 2 consecutive beats, multiform)

-Heartblock (2^{nd} or 3^{rd} 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 head trauma with prolonged loss of consciousness, seizures or CNS tumors, 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.

-Meet diagnostic criteria for psychoactive substance use disorder for substances other than cocaine or nicotine/caffeine that would require detoxification (i.e., alcohol, benzodiazepines or barbiturates). Negative urine/breath samples for these substances, and the absence of withdrawal, will be required during screening.

-Regular use of other medications, with the exception of hormone-based contraceptives for female subjects, daily multivitamins or short-term antibiotic prescriptions.

-Vision or hearing problems that would preclude completion of experimental tasks.

-Poor venous access.

-Seeking treatment for SUD.

Screening procedures for all subjects will be conducted under a separate protocol and include a medical-history questionnaire, drug-use questionnaire, and a brief psychiatric examination. During screening, potential subjects will be

asked to provide a urine specimen that will be screened for the presence of recent use of abused drugs. Urine samples from females will also be tested for pregnancy; women testing positive for pregnancy will be notified and discontinued from the screening process for this protocol.

SUBJECT RECRUITMENT METHODS AND PRIVACY

Subjects are recruited primarily through formal advertisement (i.e., regular newspaper advertisements), local flyers posted in public areas (e.g., bars, marketplaces), online classifieds and social media (e.g., Craigslist, Facebook) and by word-of-mouth. The Terms of Use for all online advertising sites will be followed. These advertisements are approved under our screening protocols. Subjects will make initial contact by phone with one of our recruiters who have completed the research training and regulatory 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. Study investigators may interact with subjects in this setting and appropriate cautions are in place to ensure privacy during the intake process.

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 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 approved to obtain consent will review the protocol and address any questions the subject may have in order to assess the subject's understanding. After this, the subject will receive a copy of the informed consent document and sign a form indicating that they have received a copy of the form they read and signed.

RESEARCH PROCEDURES

Prior to inpatient admission, subjects will complete 2 screening/behavioral qualification sessions. During the screening/behavioral qualification sessions, subjects will complete a battery of cognitive tasks (see below) and complete a training variant of the PRLC task. Subjects who are unable to meet a predefined criterion will be discharged from the protocol. For these outpatient sessions, check-in and check-out procedures will be the standard for studies we have conducted under previously approved protocols. Upon arrival, subjects will relinquish their keys, watch and mobile phones, which will be stored securely until the end of the session. Next, a field sobriety test will be conducted, and urine and expired breath samples collected. Subjects could be observed by a same-sex staff member when providing urine samples, but they will be told beforehand. Subjects must agree to abstain from illicit drugs and alcohol for the 12 hours prior to each experimental session. Breath samples positive for alcohol or signs of intoxication will preclude the subject from participation in that experimental session, and an additional day will be added to the schedule. Repeated violations will result in dismissal from study participation. Female subjects testing positive for pregnancy will be notified and discontinued from participation. Subjects must also agree to abstain from tobacco/nicotine products, solid food and caffeine for 4 hours before each experimental session, and will be provided with a standard, fat- and caffeine-free snack upon arrival. Subjects who smoke cigarettes will be allowed to smoke a single cigarette. Subjects will not be allowed to smoke again until the experimental session has ended. At the end of the session, subjects will be paid for their participation, their personal belongings will be returned to them and they will be released.

The inpatient protocol will typically consist of 1 cocaine-vs-placebo medical safety session (3 mg/70 kg), 1 PRLC money-vs-money session, and 3 PRLC money-vs-cocaine sessions. During the 6 PRLC money-vs-cocaine sessions subjects will choose between 3 mg/70 kg cocaine and 3 different amounts of money ($0.25, $1.00 and $4.00).

During inpatient participation, volunteers will not be allowed to leave the CRU, nor will visitors be allowed. Volunteers will be maintained on a caffeine-free diet. All volunteers will provide urine and expired air samples daily during study

participation. Subjects could be observed by a same-sex staff member when providing urine samples, but they will be told beforehand. The presence of non-nicotine, non-cannabinoid drugs of abuse or alcohol not administered experimentally in the research protocol and not detected at the time of admission will result in immediate dismissal from the research study. Food will not be permitted for 1 h prior to cocaine administration. Subjects will be prepared with an intravenous midline catheter in the non-dominant arm by the UK Healthcare Vascular Access Team (VAT). In addition, a second, standard peripheral IV will be placed by the VAT or 5N/CCTS nurse staff (if the VAT is unavailable) for the medical safety session, which requires two venous access points, and removed after that session. A peripheral IV catheter might also be necessary if issues are encountered with the midline catheter. IV access will be placed and maintained according to UKHC policies.

Drugs will be administered under double-blind conditions and medical supervision. IV cocaine will be prepared by cocaine HCl powder in 0.9% sodium chloride and administered via an FDA cleared programmable pump. Syringes containing 3 mg/70kg cocaine will be prepared from aseptically prepared stock solutions provided by the National Institute on Drug Abuse Drug Supply Program. Syringes will be prepared within 24 h of an experimental session and individually labeled for each subject. The placebo dose will contain only 0.9% sodium chloride.

The initial cocaine-vs-placebo session will be conducted to demonstrate that this dose of cocaine functions as a reinforcer in each subject and will also serve as a medical safety session. Subjects exhibiting cardiovascular hypersensitivity will be excluded from further participation. Cardiovascular hypersensitivity is defined as heart rate > (220-subject age) x 0.85, systolic pressure > 180 mm Hg or diastolic pressure > 120 mm Hg, or ECG abnormalities, sustained for greater than 5 min. 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. Cardiovascular hypersensitivity also includes prolonged abnormal heart rhythmicity assessed via 3-lead telemetry. Abnormal hearth 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 5 min. A cardiovascular emergency will be managed using UK medical center procedures (i.e., response from a code blue team).

Heart rate will be measured continuously during experimental sessions and will be reviewed prior to each dose to ensure that the dosing criterion is met. Subjects must have a heart rate of < 130 bpm to receive a dose, otherwise dosing will be paused. Due to the time required for the blood pressure reading to occur (i.e. cuff inflation and deflation) and the recommended 1-min interval between assessments, measuring BP before each infusion is incompatible with the infusion delivery schedule. Because of these limits on measuring BP in relation to dosing, BP will be assessed at 2-min intervals. If, following any BP assessment, systolic blood pressure ≥ 165 mm Hg or diastolic blood pressure ≥ 100 mm Hg, dosing will be paused. Subjects will also be connected to 3-lead telemetry so that ECG can be assessed at the beginning and end of the experimental sessions. Subjects must exhibit normal heart rhythmicity for intravenous dosing to be initiated (pre-session ECG assessment) and to participate in further sessions (post-session ECG assessment). If cocaine dosing stopping criteria are met, the task will be paused, and vital signs will be monitored by ACLS-certified nursing staff every minute until dosing criteria are met. If dosing criteria are not met within 10 minutes, a physician and the study PI will be contacted for further instructions. If a subject exhibits cardiovascular sensitivity to cocaine, the procedures described above will be followed, and continuous ECG monitoring will be initiated for a minimum of 5 minutes to determine if abnormal hearth rhythmicity is accompanying the elevated HR/BP. If dosing criteria are not met by the scheduled end of the session, but cardiovascular sensitivity criteria are also not met, a study physician will be consulted about possible discontinuation of the subject from the protocol.

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) during non-session times. Research volunteers will be required to be in bed with the lights out by 2300 hours.

Study Outcomes (Inpatient Experimental Sessions)

Medical Safety Session. An initial cocaine-vs-placebo session will be conducted to demonstrate that this dose of cocaine functions as a reinforcer in each subject and will also serve as a medical safety session. For this task (conducted at the CRU), the two choice options will be placebo and 3 mg/70 kg cocaine, labeled Drug A and Drug B. For each trial of this task, the drug and placebo options will be available for self-administration on a fixed-ratio 1 (FR1) schedule of reinforcement, with an inter-trial-interval of 1 min. Prior to the start of the session, subjects will receive a non-contingent sampling dose of Drug A and Drug B to provide experience with the dose effects prior to choice trials. The total number of cocaine and placebo infusions is limited to 40 each, and the task ends as soon as 40 infusions of either IV solution is chosen. This quantity/time of cocaine is consistent with previous studies that administered multiple infusions of 48-50 mg/70 kg cocaine at 14-15 min intervals to individuals with histories of cocaine use comparable to those to be enrolled in this study (Donny et al., 2003; Evans et al., 2001). Subjects will complete the task using a laptop; no control trials will be included.

Probabilistic Reinforcement-Learning Choice Tasks. In the non-drug (i.e., money-vs-money) version of the task, subjects complete a series of trials (e.g., 200-300). In each trial, subjects choose one of two options, signaled by neutral cues (e.g., blue and green boxes). When reinforcement is scheduled for the chosen option, subjects are notified that they have earned money ($0.25) or are informed that they did not earn money. Two probability ratios for the two options are used (6:1, 1:6). Trials are divided into un-signaled blocks, in which the identity of the higher reward probability option is reversed. Once a reinforcer is scheduled for an option, it remains available until that option is chosen, so that the longer an option remains un-chosen, the greater the probability that a reinforcer will be delivered by choosing it.

In the drug-vs-money version of the PRLC task, the cocaine dose will again be 3 mg/70 kg. Due to the probabilistic nature of the task, the maximum number of infusions of 3 mg/70 kg cocaine will vary but are calculated to be approximately 39 infusions over the course of the task, which is estimated to last approximately 37 min. The abbreviated version of the task with fewer trials (e.g., 200) and only two probabilities (e.g., 6:1 and 1:6) will be used. The amount of money available as an alternative will be $0.25, $1.00 and $4.00.

Physiological measures. Heart rate, blood pressure and heart rhythmicity (*via* ECG) will be recorded using a digital monitor. These measures will be collected before intravenous drug administration and continuously (HR) or at regular intervals (i.e., 2 min, BP; pre- and post-session, ECG) throughout IV dosing. Telemetry-certified nurses will interpret the results with instructions to contact Drs. Hays, Anderson or Hatton regarding abnormalities.

POTENTIAL RISKS

The behavioral, subjective and physiological assessment procedures employed in these studies are benign. Adverse events identified as possible risks in this study include:

1. Subject's protected health information (PHI) may be viewed by others not directly involved in the conduct of the proposed research. 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.

2. Embarrassment in disclosing sensitive personal information.

3. Discomfort due to study procedures.

4. Dissatisfaction with the study procedures.

5. Drug administration. Common side effects of cocaine include anxiety, restlessness, diuresis, irritability, suppressed appetite, insomnia, gastrointestinal upset, increased heart rate, increased blood pressure, heart palpitations and

arrhythmias, faintness, irritability, shaking, headache, flushing, sweating, blurred vision, difficulty sleeping, and loss of appetite. 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, stroke, seizures, myocardial infarctions, heart failure and death. It is unlikely that subjects will experience these more serious side effects.

7. Needle insertion and catheter maintenance. This study will require placement of an indwelling venous midline catheter to be placed for the duration of participation, and a standard peripheral IV stick for the duration of a single session, to permit intravenous saline and cocaine administration. In addition, a peripheral IV catheter might also be necessary for drug solution delivery if issues are encountered with the midline catheter. These procedures are accompanied by the risk of bruising, blood clotting, soreness, infection, bleeding, pain, swelling and irritation from the insertion of a needle. There is also a risk that the indwelling catheter could come out of the vein or penetrate the vein; if this occurs, any fluid infused into the catheter could deposit in the arm tissue, resulting in soreness, pain, swelling and irritation. Lastly, there is a risk of syncope.

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.

<u>Study Stopping Criteria</u>

1. If any subject has an unexpected, serious, life threatening adverse event that is related to the study procedures, the study will be stopped.
2. If, after 6 subjects have been enrolled and have completed at least one cocaine dosing session (33% of the proposed sample), and for all subsequent subjects, dosing was paused in greater than 33% of the cocaine dosing sessions, the study will be stopped.
3. If, after 6 subjects have been enrolled and have completed at least one cocaine dosing session, and for all subsequent subjects, greater than 33% of the study sample has been discontinued due to meeting criteria for cardiovascular hypersensitivity, the study will be stopped.

1. Violation of confidentiality.

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 issued. All data will be 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.

2. Embarrassment in disclosing sensitive personal information.

The risk is minimized through the use of confidentiality safeguards described above and below. Subjects can refuse to answer any questions regarding sensitive personal information, although this might impact their ability to continue in the study.

3. Discomfort due to study procedures.

Subjects are informed that they have the right to withdraw from study protocols at any time. A research staff member will always be available to answer questions, and the study subjects have telephone contact information to reach both

the PI and the study physician. 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.

4. Dissatisfaction with the study procedures.

As noted, 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.

5. As described above, Drs. Hatton, Anderson 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 CRU nursing staff 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, Anderson and Hays will screen all potential research subjects for medical contraindications, and Dr. Gurley will review the ECG, prior to study participation. Drs. Hatton, Anderson 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. 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 (CRU nurses, Dr. Hatton, or his anesthesiology collaborators). Detailed information about the criteria for administration of intravenous cocaine, holding doses, resuming doses and discharging subjects due to cardiovascular hypersensitivity is provided above.

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.

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 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, we will follow the recommendations of the UK Department of Neurology, and Dr. Hatton's therapy preference, which consists of the following: 1) Assess and support respiratory and cardiac status; 2) If seizure is sustained for >5 min, give immediate therapy with IV lorazepam (4 mg); and 3) repeat therapy every 5 min as needed for continued/repeat seizures. A physician in Neurology will be consulted if a second treatment dose is required. 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 lorazepam. 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, the medical personnel on this protocol will review the medications currently being taken by potential subjects to determine if it is safe for them to either participate while continuing to take the medications or discontinue taking their medication during their participation. Birth control will be permitted.

Although it is possible that subjects could experience an allergic reaction to cocaine, this is unlikely because they are required to have a history of stimulant use. However, if a subject experiences an allergic reaction, diphenhydramine will be available for oral or parenteral administration.

7. Needle insertion and catheter maintenance. Risks of bruising, blood clotting, soreness, infection, bleeding, pain, swelling, irritation and the integrity of the catheter being compromised are minimal since standard sterile procedures will be used. The likelihood of syncope is uncertain and will vary across subjects; however, all medical staff is prepared to manage the occurrence of syncope.

RESEARCH MATERIALS, RECORDS AND PRIVACY

Information about subjects' drug histories and physical/mental health will be collected for the purpose of selecting subjects for approved research protocols. Similarly, urine samples will be collected and tested for the presence of a full range of drugs of abuse. Females will also be given a pregnancy test. These screening materials will be collected under our screening protocol. During the experiment proper, urine drug and pregnancy tests will be conducted prior to the conduct of each session. Expired breath samples will be used to test for the presence of alcohol prior to the conduct of each session. Other data obtained from the subjects will include questionnaires to assess recent activities, drug use and physical/mental status, in addition to computerized brain imaging, performance and physiological measures, described above, collected during experimental session, along with non-intrusive staff observations and ratings. Collection of these materials should not impact subject privacy because the environment in which these materials will be obtained is not associated specifically with drug abuse research and all personal health information will be kept confidential.

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. Subjects will also be informed that there is a possibility that the data collected may be shared with other investigators in the future. If that is the case the data will not contain identifying information unless further consent is obtained or unless approved by the UK Institutional Review Board. Study materials, including data, will be stored for 6 years after study closure and then destroyed per ORI policy.

Data Analysis Plan

The number of drug choices will be analyzed using within-subjects 1-factor ANOVA with money value ($0.25, $1.00 and $4.00) as the factor. Post-hoc tests will be conducted using Fisher's LSD test.