Influence of Orexin Antagonism on Motivation for Cocaine
NCT03937986
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BEHAVIORAL EFFECTS OF DRUGS (INPATIENT): 39
UNBLINDED PROTOCOL

1. BACKGROUND

Cocaine use disorder continues to be a significant public health concern. In 2016, nearly 2 million Americans reported past month cocaine use and approximately 1 million Americans met diagnostic criteria for cocaine use disorder. A recent finding that Black men had cocaine overdose rates comparable to opioid overdose rates in non-Black men makes the dangers posed by cocaine use even more evident. Despite great strides in our understanding of the neurobiological underpinnings of cocaine addiction in preclinical models, a limited amount of research has translated those findings into clinical populations. Such translation is crucial to identify neurobiological circuits that contribute to the problems posed by cocaine use disorder and to guide treatment based on those neuroscience findings.

One area of intense interest in preclinical research is the role of the orexin (also known as hypocretin) system in addiction. Orexin neuropeptides are produced in the lateral hypothalamus and control sleep, waking, food intake and other adaptive behaviors. Through extrahypothalamic transmission, the orexin system also plays a key part in motivation for maladaptive rewards like drugs of abuse. Exogenous administration of orexin peptides increases cocaine self-administration, as well as cocaine-induced dopamine signaling. Conversely, antagonism of the orexin system by genetic knockout/knockdown reduces effortful responding maintained by cocaine doses (e.g., on a progressive-ratio schedule), cocaine-seeking behavior and cocaine-induced dopamine signaling, relative to controls. Pharmacological antagonism of orexin receptors also attenuates motivation for cocaine, response to cocaine cues and reinstatement of cocaine seeking behavior relative to vehicle. The first and only clinically available orexin antagonist, suvorexant (Belsomra®), attenuates motivation for cocaine and cocaine conditioned place preference, as well as cocaine-associated impulsive responding, in preclinical models. Orexin antagonism, either through genetic manipulation or pharmacological approaches, does not alter adaptive behaviors like food or water intake, nor does it change cocaine-induced locomotion. Taken together, these preclinical findings suggest that orexin system antagonism selectively reduces motivation for cocaine, as well as other maladaptive cocaine-associated behaviors.

Although a robust preclinical literature supports the premise that orexin antagonism attenuates motivation for cocaine, along with cocaine's other abuse-related effects, this area remains unstudied in humans. *The overarching goal of this project is to translate promising preclinical findings into clinical populations, thereby demonstrating that the orexin system plays a key role in motivation for cocaine in humans.*

The first specific aim of this project is to demonstrate that orexin antagonism reduces motivation to earn cocaine doses on a progressive-ratio schedule of reinforcer availability (a widely accepted measure of motivation) in active cocaine users. To this end, 20 non-treatment seeking human subjects meeting diagnostic criteria for cocaine use disorder will sample doses of intravenous cocaine (0, 10 and 30 mg/70 kg) in experimental sessions after at least 3 days of maintenance (i.e., the time necessary to reach steady state) on oral suvorexant (0, 5, 10 and 20 mg). A placebo-controlled, double-blind, within-subjects design will be used such that all subjects experience all dose conditions in random order. After sampling a cocaine dose, subjects will have 10 opportunities to earn 1/10 of the dose of the cocaine dose received during the Sampling Phase or $0.50 on a concurrent progressive-ratio choice task that was developed and validated in our laboratory. The use of concurrent progressive-ratio schedules of drug and non-drug reinforcer availability will allow inferences to be made about the relative influence of orexin antagonism on motivation to obtain these two types of reinforcers.

The second specific aim is to demonstrate that orexin antagonism attenuates positive subjective effects, as well as cocaine cue response and impulsive responding. A battery of subjective drug-effect measures and cognitive tasks that are analogs of those used in the preclinical studies described above, specifically the Visual Probe and n-Back that measure attentional bias to cocaine cues and cocaine-associated impulsive responding, respectively, will be completed during the same experimental sessions in which cocaine choice is assessed.

The research proposed here will translate findings from preclinical research and provide the initial clinical evidence that orexin antagonism reduces motivation for cocaine, as well as other cocaine-associated maladaptive behaviors in active cocaine users. This study will also provide basic science information about the orexinergic mechanisms underlying the pharmacodynamic effects of cocaine in humans. As such the outcomes will contribute to our understanding of the clinical neurobiology of cocaine use disorder. Overall, the proposed work seeks to expand the scope of current clinical neuroscience research on cocaine addiction by focusing on orexin, which has strong preclinical evidence supporting its critical role in addiction but remains unstudied in humans.

2. OBJECTIVES

The primary objective of this study is to demonstrate that orexin antagonism reduces motivation to earn cocaine doses on a progressive-ratio schedule of reinforcer availability (a widely accepted measure of motivation) in active cocaine users. We will also include a battery of subject-rated and physiological measures to more fully characterize the influence of orexin antagonism on the effects of cocaine.

3. STUDY DESIGN

This study will use a double-blind, placebo-controlled design with all subjects receiving all suvorexant and cocaine doses (i.e., suvorexant and cocaine dose are within subject factors) in a randomized order.

4. STUDY POPULATION

Up to 200 individuals will be screened to participate in this study. We intend to admit/enroll 30 (15 male and 15 female) subjects to ensure we have 20 completers (10 male and 10 female) in 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 as inpatients for approximately one month. Enrollment in this study will occur between July 1, 2019 and April 30, 2021. Subjects will be required to provide legal proof of age.

Inclusion Criteria:

-Recent cocaine use via the smoked or intravenous route, verified by a cocaine-positive urine sample.

-Otherwise healthy, without contraindications to cocaine or suvorexant.

-Meet Cocaine Use Disorder criteria, verified by Structured Clinical Interview for DSM-5 (SCID).

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

Exclusion Criteria:

-Chemistry values or screening outcomes including outside normal ranges that are deemed by the study physician to be clinically significant. Lipid levels, which have not typically been included in our screening tests, are included in this protocol as an additional check for cardiovascular health.

-Persistent 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 (2nd or 3rd degree AV block or bundle branch block)

  -Pre-excitation syndromes (Wolff-Parkinson-White or Lown-Ganong-Levine)

-History of serious physical disease, current physical disease, impaired cardiovascular functioning, chronic obstructive pulmonary disease, history of seizure, or current or past histories of serious

psychiatric disorder that in the opinion of the study physician would interfere with study participation.
-First degree family member with significant premature cardiac comorbidity.
-Current or past histories of substance abuse or dependence that are deemed by the study physician to interfere with study completion.

Screening procedures for all subjects will include a medical history questionnaire, laboratory chemistries (blood chemistry screen, complete blood count, ECG and urinalysis) and a brief psychiatric examination. These procedures will be conducted under our lab's screening protocol (44379). All study participants will be judged by the study physicians, Drs. Lon Hays, Abner Rayapati, Kevin Hatton, or their representative, to be healthy.

During the initial screening process, potential subjects will be asked to provide a urine specimen that will be screened for the presence of amphetamine, benzodiazepines, barbiturates, cocaine, tetrahydrocannabinol (THC) and opioids. In order to participate in an experimental session, subjects must provide a urine negative for barbiturates, benzodiazepines and opioids on each day of their participation. Subjects will be allowed to continue if they test positive for cocaine, 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, Dr. Hatton or Dr. Rayapati will be notified of cocaine-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 # 44379). Subjects make initial contact by phone with one of our recruiters who have completed the research training and HIPAA compliance web-based modules. If the subject self-discloses information that would make him/her potentially eligible for the study, they will be invited to 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 Clinical Services Core (CSC). Subjects will be discharged upon completion of the entire protocol.

Table 1.

Day	Details
1	Admission to the CSC and Practice Session. Subjects will be familiarized with the experimental session tasks.
2	Medical Safety Session. Subjects will receive the cocaine doses to be tested in this study (0, 10 and 30 mg/70 kg) separated by 60 minutes.
3-8	Placebo maintenance. Placebo administered once daily (2230 hours [h]).
6-8	Experimental Sessions 1-3. Subjects complete 1 sample and 10 choice trials to receive 1/10 of the sampling cocaine dose (0, 10 and 30 mg/70 kg) or money ($0.50) by responding on the concurrent progressive-ratio schedule. Assessment battery completed following administration of the sampling dose as described below.
9-10	Blinded washout period. Placebo administered once daily (2230 h).
11-16	Suvorexant (5 mg/day) maintenance. Dose administered once daily (2230 h).
14-16	Experimental Sessions 4-6. Details are the same as for days 6-8.
17-18	Blinded washout period. Placebo administered once daily (2230 h).
19-24	Suvorexant (10 mg/day) maintenance. Dose administered once daily (2230 h).
22-24	Experimental Sessions 7-9. Details are the same as for days 6-8.
25-26	Blinded washout period. Placebo administered once daily (2230 h).
27-32	Suvorexant (20 mg/day) maintenance. Dose administered once daily (2230 h).
30-32	Experimental Sessions 10-12. Details are the same as for days 6-8.
33	Discharge.
Note	Dosing order is illustrative. All doses will be administered in random order.

This experiment will require each subject to participate for approximately one month. Experimental sessions will be conducted as outlined in Table 1 above. We would like to note four important points relating to the table above: 1) To avoid experimental testing on weekends, subjects may be maintained on suvorexant or placebo for longer than outlined above (i.e., maintenance conditions may last for two days longer than in the example above). 2) The order of suvorexant maintenance conditions and cocaine experimental sessions will be randomized. 3) All maintenance conditions will be followed by a two-day washout period in which the participant receives a placebo delivered in a double-blinded fashion. 4) If subjects leave the protocol for a reason unrelated to study procedures (e.g., a family emergency or dental problems), they may be re-admitted with physician approval to complete the remainder of the protocol, picking up in the condition where they left off (i.e., sessions/dose conditions that have already been completed will not be repeated). Thus, they may not complete the protocol over one approximately 33-day admission, but can complete the protocol over two admissions totaling approximately 33 days.

During their participation in the research protocol, subjects will not be allowed to leave the CSC, nor will visitors be allowed. 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 daily 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.

Subjects will be allowed to acclimate to the CSC for two days following admission. Following admission, subjects will complete a “Practice Session”. The practice session will follow the session timeline with the exception that no drug or response-contingent money will be available. On the day after the practice session, subjects will participate in a medical safety session in which they will receive

each of the doses IV cocaine that will be available in subsequent sessions (i.e., 1 infusion of 0, 10 and 30 mg/70kg cocaine) administered in ascending order and separated by 60-min intervals; subjects exceeding the predetermined cardiovascular parameters will be excluded from further participation.

Subjects will be maintained on a caffeine-free diet throughout the duration of their participation but will be allowed to smoke tobacco cigarettes *ad libitum*, except during experimental sessions. In numerous experiments conducted in our laboratory, we required subjects to abstain from using tobacco products during the conduct of the experimental sessions that were 4-7 h long, which has been acceptable to subjects. All subjects will provide urine and expired breath samples daily during study participation. The presence of drugs of abuse not administered in the research protocol or alcohol will result in immediate dismissal from the study.

On experimental session days, subjects will be awakened at 0700 h and eat a standard breakfast. Subjects who report smoking tobacco cigarettes will be allowed to have a cigarette after breakfast, because they will not be allowed to smoke again until after completing their daily experimental session. Experimental sessions will begin at 0830 h and follow the outline in Table 2 below. Subjects will remain seated in a hospital chair for the duration of the experimental session. After completing each daily session, no other experimental activities will be scheduled for the remainder of the day. Subjects will be free to engage in recreational activities during non-session times (e.g., watch television, read, listen to music, arts and crafts, use educational computer programs), but will receive their maintenance dose at 2230 h and be in bed with the lights out by 2300 h.

Table 2.

Time	
0830	Sobriety, breath and urine drug testing. Baseline assessment battery measures completed.
0900	Baseline cardiovascular and ECG reading.
1000	Sample dose administered. Subjective measures completed at 15 minute intervals after the dose until end of sampling phase. Cognitive measures completed 15 minutes after sampling dose as noted in task descriptions below. Cardiovascular measures completed at 2 minute intervals until end of sampling phase.
1100	Sampling phase ends
1200	Lunch is served
1300	Vital signs recorded. Purchase tasks and computerized tasks completed (including progressive-ratio task). ECG monitoring begins.
1430	Vital signs recorded. Portion of intravenous dose earned is administered if vitals are within range. Subjective measures completed at 0, 15, 30, 45, and 60 minutes after drug administration. Cardiovascular measures completed at 2 minute intervals until end of sampling phase.
1530	Sessions ends.

Apparatus. Behavioral testing will be conducted on the CSC unit. Subjects will be tested in individual rooms and monitored continuously by research and nursing staff. Subjects will complete the behavioral tasks on a laptop computer, which records and stores each subject's data. This computer system automates the collection of behavioral data, increasing the efficiency and accuracy of data collection and management.

Self-Administration Task. After sampling the intravenous cocaine dose (0, 10 and 30 mg/70 kg), subjects will be given up to 10 opportunities to earn 1/10 of the dose of cocaine dose received during the Sampling Phase or $0.50. 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). Break points for cocaine and money will be the primary outcome variables.

Assessment Battery*.* A battery of subjective and cognitive tasks will also be used to assess drug effects in order to meet Aim 2. Standard safety and tolerability measures will also be included.

Subjective Outcomes (Appendix A)**.** Two valid and widely used questionnaires that measure various aspects of mood and drug effects will be included: 1) Drug-Effect Questionnaire (Rush et al., 2003) and 2) Adjective Rating Scale (Oliveto et al., 1992). The Cocaine Craving Questionnaire (Dudish-Poulsen and Hatsukami, 1997) will also be included. These measures will be completed prior to each cocaine sampling dose and at 15-minute intervals after administration of the sampling dose.

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 the cognitive block and prior to the self-administration task.

Cognitive Outcomes**.** Cognitive tasks will be completed in random order across subjects, but the order of tasks will remain consistent for each subject. Tasks will be completed 15 minutes after the cocaine sampling dose in each experimental session.

n-Back (Appendix C). The n-Back task will be used to measure working memory and working memory capacity (Jaeggi et al. 2010). In this task, subjects are presented with a sequence of numbers and asked to indicate when the current stimulus matches the one from “n” steps earlier. Two settings will be used in this study, the 1-back and the 2-back (i.e., matching 1 and 2 stimuli back, respectively). The primary outcome of this task is the percentage of correct responses.

Hypothetical Delay Discounting (Appendix D). A 5-trial adjusting delay discounting task will be used to rapidly assess discounting rates for various commodities (Koffarnus and Bickel, 2014). In this task, subjects making a series of 5 choices between an immediately available, smaller reinforcer and a larger reinforcer at various delays. Versions of this task with monetary (e.g., $1000 delayed versus $500 now) and cocaine (e.g., $1000 of cocaine delayed versus $500 of cocaine now) commodities will be used. Subjects will be told that all choices are hypothetical. The primary outcome of this task is the discounting rate (*k*). Previous research has demonstrated that this measure provides rapid and accurate discounting rates across a range of commodities (Cox and Dallery, 2016; Koffarnus and Bickel, 2014; Strickland et al., 2017).

Visual-Probe Task. A visual-probe task (e.g., Lubman et al. 2000; Townshend and Duka, 2001) will be used to measure attentional bias to cocaine images as an indicator of cocaine cue response (i.e., allocation of attention to cocaine cues). This procedure is similar to one we have used previously in studies with alcohol- and cocaine-related images (Bolin et al., 2017; Marks et al., 2014). The visual-probe task consists of a total of 80 trials (40 critical trials and 40 filler trials) presented in randomized order. During critical trials of interest, cocaine-related images (n = 10) are presented adjacent to matched, non-cocaine-related, neutral images (n = 10). Immediately after presentation of the images, a visual probe (an “X”) appears in the same location as one of the images and response time (msec) to the probe will be measured. Attentional bias is inferred from differences in response times to probes that replace cocaine versus neutral images during critical trials. Slower response times to probes that

replace neutral images, relative to when the probe replaces a cocaine-related image, are interpreted as the subject's attention being focused on the cocaine image. An attentional bias score will be calculated from response time (RT) data in the visual-probe task as described previously (i.e., $RT_{Cocaine} - RT_{Neutral}$; Bolin et al., 2017; Marks et al., 2014) such that negative scores would suggest a cocaine-cue attentional bias. The attentional bias score will serve as the primary outcome measure for data analysis.

Safety and Tolerability Outcomes

Cardiovascular Measures and Body Temperature. Heart rate, blood pressure, cardiac rhythmicity (i.e., electrocardiograms [ECG]) and body temperature will be recorded before cocaine administration and at frequent intervals after dose administration. Drug administration will be withheld if heart rate > 90 bpm, if systolic pressure > 140 or diastolic pressure > 90. Volunteers 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. Heart rhythmicity will be assessed via 3-lead telemetry continuously during each experimental session, will be printed out and verified as normal prior to dose administration, and will be monitored continuously for a minimum of 15 minutes following each infusion.

Weight. Weight in kg will be measured daily using a digital scale. This measure will be included to determine whether suvorexant produces changes in motivation for homeostatic food intake, although based on the preclinical findings described above and known side effects of suvorexant, we do not expect weight to change as a function of suvorexant maintenance.

Sleep. The Saint Mary's Hospital Sleep Questionnaire (Ellis et al., 1981), a validated self-report measure of sleep quantity and quality, will be completed immediately prior to the practice session and Sessions 1, 4, 7 and 10 to assess the drug effects on sleep. This questionnaire is included because suvorexant is indicated in the treatment of insomnia (Lee-Iannotti and Parish, 2016) and also because cocaine use is known to disrupt sleep (Pace-Schott et al., 2005). The Pittsburgh Sleep Quality Index (PSQI; Smyth, 2012) will be completed at admission and immediately prior to discharge. This questionnaire asks about the past month and has 7 component scores and a global score.

UKU. The UKU is a standardized, validated rating scale that assesses over 50 potential side effects (e.g., sedation, akathisia, weight change) associated with administration of centrally acting drugs (Lingjaerde et al., 1987). It also includes a global assessment of how these side effects interfere with functioning. This questionnaire will be completed daily. We have routinely used this scale to evaluate the safety and tolerability of maintenance doses and cocaine (Lile et al., 2008; Rush et al., 2009; Stoops et al., 2007; 2008; 2016). A subject will be excluded from further participation if at any time he or she exceeds adverse event safety and tolerability thresholds (i.e., an effect rated as severe lasting more than 24 h) after drug administration.

Drug Dose and Administration. All drugs will be administered under double-blind conditions and medical supervision in randomized order. We currently hold an IND for intravenous cocaine administration and will modify it to test intravenous cocaine during suvorexant maintenance. Suvorexant doses will be prepared using commercially available tablets (Belsomra®) placed into opaque capsules. Lactose monohydrate will be used as filler. Placebo capsules will contain only lactose monohydrate but will be visually identical to capsules that contain suvorexant. The total daily doses will be 0, 5, 10 and 20 mg/day. Suvorexant doses were selected based upon clinical dosing recommendations for insomnia (i.e., maximum dose of 20 mg/day; Lee-Iannotti and Parish, 2016). Once daily dosing approximately 30 minutes before bedtime was also selected based on clinical recommendations (Lee-Iannotti and Parish, 2016). Subjects will be maintained on each suvorexant dose for at least three days before experimental sessions begin because this is the time required to

reach steady state (Lee-Iannotti and Parish, 2016). An additional 2-day washout period will follow each maintenance condition. During this period, subjects will receive placebo under double-blind conditions.

Cocaine doses (0, 10 and 30 mg/70 kg) will be aseptically prepared by dissolving cocaine HCl USP (Mallinckrodt, St. Louis, MO) in 1 mL 0.9% sodium chloride, and filtering the solution through a 0.22 µm filters into a sterile, pyrogen-free vial. The sampling doses for administration (10 and 30 mg/70 kg) will be drawn up into syringes within 24 h of an experimental session and individually labeled for each subject. The 0 mg dose will contain only 0.9% sodium chloride. A total of 10 potential self-administration doses will also be prepared within 24 h of an experimental session (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 mg/70 kg labeled Dose 1 through 10 for the 10 mg/70 kg sampling condition). The research staff will inform the nursing staff which self-administration dose (e.g., Dose 1) the subject has earned. Each dose will be administered via a catheter in the non-dominant arm over 30 sec. This method of cocaine preparation has been conducted previously at the UK Investigational Pharmacy and is the method we have used in our previous studies (Lile et al., 2016; In Preparation).

Data Analysis. All data will be analyzed statistically as outlined below using SPSS. Only data from completing subjects will be included in the analyses. Any subjects who do not complete the study will be replaced until we accrue 20 completers. Statistical significance refers to $p \leq 0.05$.

Aim 1: Demonstrate that orexin antagonism reduces motivation to earn cocaine doses in active cocaine users. Motivation to earn cocaine will be determined by evaluation of break points for cocaine and money from the concurrent progressive-ratio choice task. For cocaine and money break points, each of which have one data point for each dose condition, data will be analyzed using two-factor repeated-measures ANOVA. Cocaine (0, 10 and 30 mg/70 kg) and suvorexant (0, 5, 10 and 20 mg/day) will be factors for these analyses. A significant augmentation (i.e., leftward shift in the dose-response curve) or attenuation (i.e., rightward shift in the dose-response curve) of the effects of cocaine will be inferred if the main effect of the suvorexant or the cocaine-suvorexant interaction attains statistical significance in the ANOVA. If the cocaine-suvorexant interaction attains statistical significance, the Mean Square Error (MSE) term will be used to conduct Tukey's HSD *post-hoc* test to make appropriate pair-wise comparisons between means.

Aim 2: Demonstrate orexin antagonism attenuates positive subjective effects, as well as cocaine cue response and impulsive responding. Abuse-related subjective and cognitive effects outcomes will be derived from the assessment battery (i.e., subjective effect questionnaires, IMT, delay discounting, visual-probe). Three sets of analyses will be conducted on the subjective effect data. First, data will be analyzed as peak effect (i.e., maximum effect observed following administration of cocaine sampling doses) using two-factor repeated-measures ANOVA. Cocaine (0, 10 and 30 mg/70 kg) and suvorexant (0, 5, 10 and 20 mg/day) will be factors for these analyses. A significant augmentation or attenuation of the effects of cocaine will be inferred if the main effect of the suvorexant or the cocaine-suvorexant interaction attains statistical significance in the ANOVA. If the cocaine-suvorexant interaction attains statistical significance, the MSE term will be used to conduct Tukey's HSD *post-hoc* test to make appropriate pair-wise comparisons between means. Second, Area Under the Curve (AUC) will be calculated for each subject using the trapezoidal method and analyzed in the same fashion as peak-effect data. Third, these data will be analyzed by repeated-measure ANOVA with cocaine, suvorexant and time as factors. The MSE term for the cocaine-suvorexant-time interaction will then be used to conduct Tukey's *post-hoc* tests to make appropriate pair-wise comparisons.

For the cognitive outcomes, each of which have only one data point for each dose condition, data will be analyzed using two-factor repeated-measures ANOVA. Cocaine (0, 10 and 30 mg/70 kg) and suvorexant (0, 5, 10 and 20 mg/day) will be factors for these analyses. A significant augmentation or attenuation of the effects of cocaine will be inferred if the main effect of the suvorexant or the cocaine-suvorexant interaction attains statistical significance in the ANOVA. If the cocaine-suvorexant interaction attains statistical significance, the MSE term will be used to conduct Tukey's HSD *post-hoc* test to make appropriate pair-wise comparisons between means.

Although not directly relevant to our specific aims, we will also conduct analyses on our safety and tolerability outcomes (i.e., cardiovascular outcomes and body temperature, sleep and UKU ratings).

Three sets of analyses will be conducted on the cardiovascular outcomes and body temperature data. First, data will be analyzed as peak effect using two-factor repeated-measures ANOVA. Cocaine (0, 10 and 30 mg/70 kg) and suvorexant (0, 5, 10 and 20 mg/day) will be factors for these analyses. A significant augmentation or attenuation of the effects of cocaine will be inferred if the main effect of the suvorexant or the cocaine-suvorexant interaction attains statistical significance in the ANOVA. If the cocaine-suvorexant interaction attains statistical significance, the MSE term will be used to conduct Tukey's HSD *post-hoc* test to make appropriate pair-wise comparisons between means. Second, AUC will be calculated for each subject using the trapezoidal method and analyzed in the same fashion as peak-effect data. Third, these data will be analyzed by repeated-measure ANOVA with cocaine, suvorexant and time as factors. The MSE term for the cocaine-suvorexant-time interaction will then be used to make appropriate pair-wise comparisons.

For weight and items from the Saint Mary's Hospital Sleep Questionnaire and the UKU, which will have one data point per day, data will be analyzed using a two-factor repeated-measures ANOVA. Suvorexant (0, 5, 10 and 20 mg/day) and day will be factors for these analyses. The MSE term for the suvorexant-day interaction will then be used to make appropriate pair-wise comparisons.

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. Hatton is an Associate Professor in the departments of Anesthesiology and Surgery, Chief in the Division of Critical Care Medicine and Medical Director of the UK Healthcare Neurocritical Care Service, and has worked on previous intravenous cocaine protocols conducted in our laboratory. 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. Drs. Stoops, Rush and Lile 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 behavioral and physiological assessment procedures employed in this study are benign. The risks to the study subjects are those related to the administration of the drugs under study. Cocaine has safely been administered to human subjects under controlled-laboratory conditions. The relative safety, as well as the contraindications and possible side effects of cocaine and suvorexant 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. The side effects of suvorexant and cocaine may change as a function of the drug combinations, which is why we will not be dosing more than the recommended daily amount of suvorexant (i.e., 20 mg/day) in this study.

Common side effects of suvorexant include sleepiness, sleep walking, changes to behavior or thoughts, diarrhea, dry mouth, upper respiratory tract infection, headache, drowsiness, dizziness, abnormal dreams and coughing.

Common side effects of cocaine include anxiety, restlessness, diuresis, irritability, suppressed appetite, insomnia, gastrointestinal upset, increased heart rate, increased blood pressure, palpitations and arrhythmias. More serious side effects following the chronic, unsupervised administration of much

higher doses of cocaine have occurred and include psychotic episodes, suppressed breathing, seizures, myocardial infarctions, heart failure and death.

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

There is a theoretical risk that subjects might choose to seek out illicit sources of cocaine because of their exposure to the drug in this study. However, this risk is minimal because all drugs are administered under blind conditions and in a setting that is not conducive to the exacerbation of existing cocaine use disorder. Furthermore, all subjects will already have histories of cocaine use. Importantly, the consent document will list all drugs under study and subjects will be debriefed about the drugs under study following participation.

Cocaine will be administered intravenously through an indwelling catheter placed in each subject's non-dominant arm and maintained per UK HealthCare policy. During catheter placement, there is some risk of bruising, soreness, infection, bleeding, pain and irritation from the insertion of the needle. However, these risks are minimal since standard sterile procedures will be used. There is also a risk of syncope. The likelihood of syncope is uncertain and will vary across subjects; however, all medical staff are prepared to manage the occurrence of syncope.

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

10. SAFETY PRECAUTIONS

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

As described above, Drs. Hatton, Rayapati and Hays will screen all potential subjects for physical and psychiatric contraindications to participation. Urine samples will be monitored throughout each study to ensure that female subjects are not pregnant and that all subjects are adhering to the drug use restrictions. All subjects in these studies will be thoroughly informed of the various drug side-effects which they might experience and will be appropriately cautioned concerning their activities in the hours after drug administration. However, this should not pose a significant problem because research subjects will be under the direct supervision of the nursing staff on the CSC at all times during drug dosing. Participation is voluntary, so individuals can withdraw at any time if they find the behavioral procedures or drug effects undesirable. The drug doses to be administered in the present experiments were chosen to minimize, if not eliminate, the chance of these side effects occurring. As noted above, Drs. Hatton, Rayapati and Hays will screen all potential research subjects for medical contraindications, and Dr. John Gurley of the University of Kentucky Gill Heart & Vascular Institute will review the ECG, prior to study participation. Drs. Hatton, Rayapati and Hays will monitor research subjects throughout their participation. We anticipate that careful subject selection, dose selection and subject monitoring

will greatly reduce, if not eliminate, the occurrence of serious side effects. The assembled team of investigators has been conducting inpatient and outpatient human behavioral pharmacology studies with healthy subjects and subjects with histories of drug abuse for more than 60 years combined and have never observed a serious drug-related unanticipated serious adverse event. To monitor for adverse events/side effects, the Udvalg for Kliniske UndersØgelser (UKU) Side Effects Rating Scale will be completed daily with subjects by CSC nursing staff. Staff observations, subjective-effects drug effects and spontaneous subject report will also be used to monitor for adverse events.

To minimize the risk associated with intravenous cocaine administration, dosing will occur under the supervision of ACLS-certified medical staff (Dr. Hatton and CSC nurses). During the medical safety and experimental sessions, heart rate and blood pressure will be recorded prior to cocaine administration and at frequent intervals (i.e., every 2 minutes) afterwards for the duration of the session. Prior to cocaine administration, subjects must have a heart rate of $\leq$ 90 bpm, systolic blood pressure $\leq$ 140 mmHg and diastolic blood pressure $\leq$ 90 mmHg. Heart rhythmicity will be recorded continuously via 3-lead telemetry during each experimental session, and will be monitored continuously for a minimum of 15 minutes following each infusion. Subjects who exhibit hypersensitivity (i.e., HR and BP outside of parameters or abnormal ECG) to the cardiovascular effects of cocaine at any point during these studies will not receive further doses, will be followed until symptom resolution, and will be excluded from further research participation. Cardiovascular hypersensitivity is defined as heart rate > 130 bpm, systolic pressure > 180 mmHg or diastolic pressure > 110 mmHg elevated consistently across a five-minute period of monitoring (see above). Cardiovascular hypersensitivity also includes prolonged abnormal heart rhythmicity, which is defined as ventricular arrhythmias that occur at a frequency greater than 5 per minute, are multifocal, or occur as couplets (2 consecutive beats) or salvos (3 or more consecutive beats), and persist for greater than 15 min. Ischemia or other abnormalities as described in the exclusion criteria would also be cause for discharge. A cardiovascular emergency will be managed using UK medical center procedures (i.e., response from a code blue team).

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

As noted above, serious side effects of stimulants include seizures. The occurrence of seizures appears to be related to the presence of certain predisposing factors including histories of head trauma, seizures or CNS tumors and the administration of concomitant medications that lower seizure threshold. Subjects that report personal histories of head trauma, seizures or CNS tumors or a first-degree family history of seizures will be excluded from research participation. Most seizures resolve of their own accord and typically, individuals with a history of seizures will be the only ones who require

intervention. In the event that a seizure should occur, the standard response is to allow 15 minutes for it to spontaneously resolve. If the seizure has not stopped within the allotted time, diazepam is to be administered by the attending physician or his designee. Because we exclude individuals with a history or risk of seizures, it is very unlikely that a subject will have a seizure or that we will need to administer diazepam. If a research subject experiences a seizure he/she will be excluded from further research participation.

Potential subjects must meet criteria for cocaine use disorder to be enrolled in the proposed experiments. It is possible that these subjects will experience abstinence symptoms once admitted to the CSC. 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 CSC, he or she will be treated in accordance with the standard practice of the University of Kentucky Hospital and then dismissed from the study.

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

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

Legal risks including loss 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, this project qualifies for a Certificate of Confidentiality from NIDA. All PHI will be protected as described above for safeguarding experimental data and PHI in the Research Materials section.

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 these studies are clinical and scientific ones related to the knowledge gained about putative neurobiological mechanisms underlying and medications for cocaine use disorder. The data from this project will contribute to a better understanding of substance use disorder and will ultimately contribute to the development of improved prevention, control and treatment procedures. Individual study subjects are expected to benefit personally from the financial payments that are provided for their research participation, 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 (#44379). 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 CSC and will receive a $40 completion allowance for these days if they complete the entire experiment. Subjects may also earn additional payment during study sessions in the self-administration procedure (up to $60). 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 $2700 for participating in the 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, a unique four-digit number identifies each subject. 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 double entered by two separate staff members and comparison macros 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 the PI. Data for all subjects will then be combined into a single electronic spreadsheet and separated by experimental measure for statistical analysis.

The primary outcomes will be the break points for drug and money in the cocaine self-administration task, analyzed as a function of suvorexant maintenance conditions. Secondary outcome measures will be abuse-related subjective and cognitive effects of cocaine, analyzed as a function of suvorexant maintenance conditions. Tertiary outcome measures will be the physiological and side-

effects of cocaine, analyzed as a function of suvorexant maintenance conditions. Data will be analyzed using repeated measure ANOVA. 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. Potential subjects must meet DSM-5 criteria for cocaine use disorder and must present with a urine sample positive for cocaine at the time of screening. Any potential subject with a history of clinically significant physical disease, current physical disease (e.g., impaired cardiovascular functioning, histories of seizure, asthma, diabetes, head trauma or CNS tumors) or current or past histories of psychiatric disorder, other than substance abuse or dependence, will be excluded from research participation. Females must be using an effective form of birth control in order to participate and must not be pregnant. Methods for monitoring adverse events (AEs) will include observations by the medical and research staff, spontaneous report by the subjects, regular measurement of physiological indices and use of the UKU Side Effects Rating Scale and subjective measures. Subjects will not receive study drug if they have any signs or symptoms that may contraindicate its administration (e.g., heart rate and blood pressure outside of predetermined range for a prolonged period, development of serious side effects).

All AEs occurring during the course of the study will be collected, documented and reported to the PI. The occurrence of AEs will be assessed for the duration of participation and during the follow-up visits at 2 and 4 weeks following study completion. 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, 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, CSC, 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, 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, Hatton 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, Hatton or Rayapati will also communicate with the nursing or

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

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

20. HIV/AIDS RESEARCH POLICY Not applicable.

21. PI SPONSORED FDA-Regulated Research

Dr. Rush holds an IND for cocaine. This application will be modified to combining cocaine with oral suvorexant Dr. Rush has held INDs for behavioral pharmacology research with a number of drugs for over ten 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

Subject-Rated Drug-Effect Questionnaires

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?

Cocaine Craving Questionnaire

Circle one answer for each question below.

1. I want cocaine.
a. Not at all
b. A little bit
c. Moderately
d. Quite a bit
e. Extremely

2. I need cocaine.
a. Not at all
b. A little bit
c. Moderately
d. Quite a bit
e. Extremely

3. I crave cocaine.
a. Not at all
b. A little bit
c. Moderately
d. Quite a bit
e. Extremely

APPENDIX B

Example Drug Purchase Task

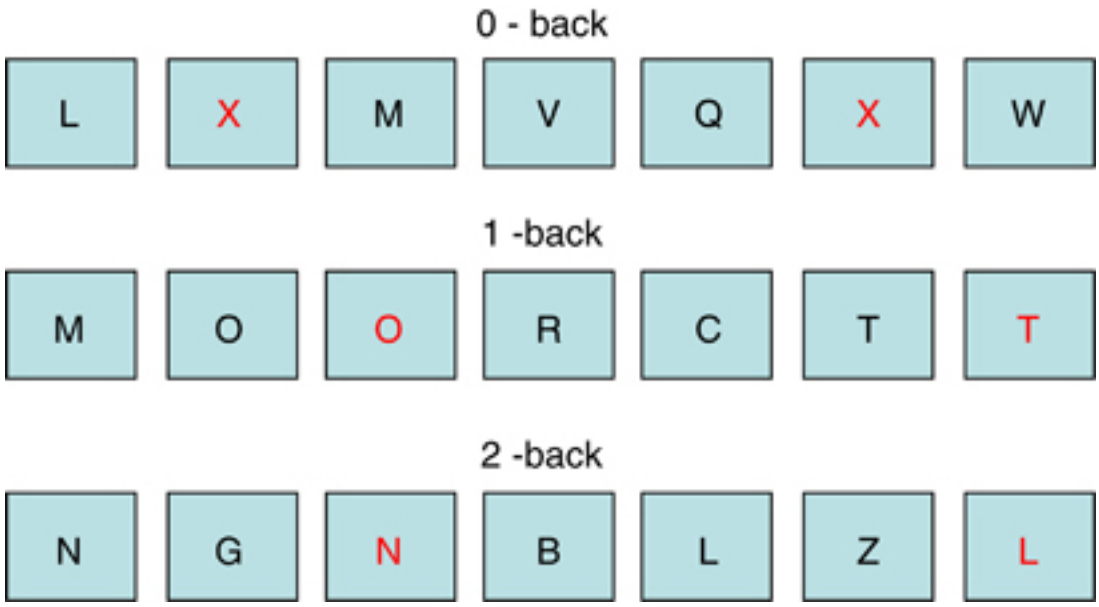
1. Imagine that you were back at home and were given a 12-hour period of time to consume the same drug you were given today.
2. During that time, you would have the opportunity to use the drug whenever you wanted over the 12 hours. For example, you could use multiple doses all at once, you could take 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	

Appendix C

n-Back Trial Diagram (Figure from Borgwardt et al. 2012)



Appendix D

5-Trial Adjusting Delay Discounting Task (Table from Koffarnus and Bickel 2014)

The below table describes the outcomes for the 5-trial task. For each of the 5 choices (i.e., No.), the subject is asked if the would prefer the immediate or delayed reinforcer. The delay to the delayed choice is systematically increased or decreased based on previous trial choice (i.e., Delay Choice; increases if delay is chosen, decreases if immediate is chosen). The primary outcome is k as labeled in the table below.

Table 1
Parameters of the Possible Individual Choice Trials in the 5-Trial Adjusting Delay Task

			ED_{50} (days) if last choice is:		*k* if last choice is:	
Index	Delay choice	No.	Immediate	Delayed	Immediate	Delayed
1	1 hr	5	0.04167	0.05893	24.0	17.0
2	2 hr	4				
3	3 hr	5	0.1021	0.1444	9.79	6.93
4	4 hr	3				
5	6 hr	5	0.2041	0.3062	4.90	3.27
6	9 hr	4				
7	12 hr	5	0.4330	0.7071	2.31	1.41
8	1 day	2				
9	1.5 days	5	1.225	1.732	0.816	0.577
10	2 days	4				
11	3 days	5	2.450	3.464	0.408	0.289
12	4 days	3				
13	1 week	5	5.292	8.573	0.189	0.117
14	1.5 weeks	4				
15	2 weeks	5	12.12	17.15	0.0825	0.0583
16	3 weeks	1				
17	1 month	5	25.28	43.05	0.0396	0.0232
18	2 months	4				
19	3 months	5	74.56	105.4	0.0134	0.00949
20	4 months	3				
21	6 months	5	149.1	210.9	0.00671	0.004741
22	8 months	4				
23	1 year	5	298.2	516.5	0.00335	0.00194
24	2 years	2				
25	3 years	5	894.7	1265.	0.00112	0.000791
26	4 years	4				
27	5 years	5	1633.	2310.	0.000612	0.000433
28	8 years	3				
29	12 years	5	3579.	5368.	0.000279	0.000186
30	18 years	4				
31	25 years	5	7748.	9131.	0.000129	0.000110

Note. ED_{50} = Effective Delay 50%.