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BEHAVIORAL EFFECTS OF DRUGS (INPATIENT): 42
UNBLINDED PROTOCOL

1. BACKGROUND

Cocaine use disorder is a persistent public health concern. In 2019, approximately two million Americans reported current (i.e., past month) cocaine use. Recent findings that cocaine overdose rates are rising, especially in certain underserved populations, make the dangers posed by cocaine use even more evident. Despite strides in our understanding of the neurobiological underpinnings of cocaine addiction in preclinical models, a limited amount of research has translated those findings to 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 findings.

Cocaine potently inhibits the reuptake of serotonin (5-HT). Increased synaptic 5-HT resulting from this reuptake inhibition activates multiple 5-HT receptor subtypes. Some of these receptor subtypes have been implicated in the abuse-related effects of cocaine, including its primary reinforcing effects (i.e., cocaine taking behavior). 5-HT_{1b} receptors, which are autoreceptors on 5-HT nerve endings that regulate 5-HT release and heteroreceptors that also mediate other neurotransmitter release, play a particularly important role in cocaine effects, likely because they are highly expressed in the mesocorticolimbic system. The 5-HT_{1b} system displays profound dysregulation during both active cocaine use and abstinence. Initial preclinical research showed that selective 5-HT_{1b} agonists enhanced the reinforcing and locomotor effects of cocaine during ongoing cocaine administration, but subsequent research showed that these agents robustly attenuated reinstatement of cocaine- and cue-primed cocaine seeking behavior. These findings have been replicated in rigorously conducted studies using multiple schedules of reinforcement and negative sucrose reinforcement controls across laboratories. Notably, though, these preclinical studies used compounds not approved for use in humans, hindering translation. Recently published data show that zolmitriptan, a commercially available selective 5-HT_{1b} agonist migraine medication, also selectively attenuates the reinforcing and other abuse-related effects of cocaine, regardless of stage of use (i.e., ongoing or extinguished cocaine self-administration). Although a robust preclinical literature supports the premise that 5-HT_{1b} activation reduces a number of cocaine-associated behaviors (e.g., self-administration, cocaine seeking), this area remains unstudied in humans. *The overarching goal of this project is to advance these promising preclinical findings, specifically those with zolmitriptan, to a clinical population, thereby demonstrating that the* 5-HT_{1b} *system plays a key role in the effects of cocaine in humans.* Three aims are proposed to translate the preclinical findings:

Aim 1: Demonstrate that 5-HT_{1b} activation reduces the reinforcing effects of cocaine. The primary hypotheses, related to our first specific aim, are that: 1) cocaine will function as a reinforcer on the concurrent progressive-ratio choice task that was developed and validated in our laboratory (Lile et al., 2016; 2020) and 2) zolmitriptan will attenuate the reinforcing effects of cocaine, leading to the reallocation of behavior towards the non-drug alternative (i.e., $6.00) available on the choice task.

Aim 2: Demonstrate that 5-HT_{1b} activation attenuates subjective abuse-related effects of cocaine (e.g., positive subjective effects, craving). The primary hypotheses related to our second specific aim are that: 1) cocaine will produce prototypic effects on subjective outcomes (e.g., increased ratings of drug liking) and 2) zolmitriptan will attenuate these effects (e.g., reduce cocaine related increases on ratings of drug liking).

Aim 3: Demonstrate that 5-HT_{1b} activation attenuates impulsive responding that is a common characteristic of cocaine use disorder and is mediated by the 5-HT system. The primary hypothesis related to our third specific aim is that zolmitriptan will attenuate impulsive responding (e.g., reduce delay discounting of drug and money). This hypothesis is based upon our previous findings and the preclinical outcomes described above.

2. OBJECTIVES

The primary objective of this study is to demonstrate that 5-HT_{1b} agonism 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, cognitive behavioral and physiological measures to have a fuller profile of 5-HT_{1b} agonism on the effects of cocaine.

3. STUDY DESIGN

This study will use a double-blind, placebo-controlled design with all subjects receiving all zolmitriptan and cocaine doses (i.e., zolmitriptan 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 September 1, 2021, and August 31, 2023. Subjects will be required to provide legal proof of age.

Inclusion Criteria:

1. Able to speak/read English,
2. Not seeking treatment for drug use at the time of the study,
3. Female or male between the ages of 18 and 55 years,
4. Report recent illicit use of cocaine (i.e., within the last week) via the smoked or intravenous route,
5. Recent cocaine use verified by benzoylecgonine positive urine, as well as fulfillment of DSM-5 diagnostic criteria for cocaine use disorder,
6. Judged to be medically and psychiatrically healthy other than the diagnosis for cocaine use disorder at the time of the interview by study physicians,
7. ECG, read by a cardiologist, within normal limits,
8. Not taking monoamine reuptake inhibitors (including SSRIs), monoamine oxidase inhibitors (other than cocaine), or cimetidine (contraindications to zolmitriptan),
9. No diagnosis of phenylketonuria (contraindication to zolmitriptan),
10. Females using an effective form of birth control and not pregnant or breast feeding. A pregnancy test will be conducted daily during study participation to ensure female subjects do not contain in the study if pregnant. For this protocol, effective birth control is considered to be: abstinence from heterosexual intercourse, hormonal contraceptives (birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch), intrauterine device (with or without hormones) or double barrier method (e.g., condom and spermicide) during participation and for at least 30 days after the last dose of study medication or surgical sterilization.
11. No other known contraindications or allergies to zolmitriptan.
12. Subjects must have a BMI less than or equal to 30.

Exclusion Criteria:

1. Chemistry values or screening outcomes including outside normal ranges that are deemed by the study physicians to be clinically significant. Lipid levels are included in this protocol as an additional check for cardiovascular health.
2. Persistent hypertension ≥140/80 mmHg or tachycardia (i.e., over 100 bpm) during screening will be excluded during screening (i.e., two or more screening visits).
3. 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)
4. History of serious physical disease, current physical disease, impaired cardiovascular functioning, chronic obstructive pulmonary disease, history of seizure, chest pain, loss of consciousness, seizure, and/or paranoid episode following cocaine use, head trauma, phenylketonuria, or current or past histories

of serious psychiatric disorder and suicidal risk that in the opinion of the study physician would interfere with study participation.
5. Subjects who report a positive first-degree family history of cardiovascular disease or seizure disorders will also be excluded from research participation.
6. Potential subjects that meet moderate-severe diagnostic criteria for any other substance use disorder, other than tobacco use disorder, at the time of screening will not be eligible for study participation. Subjects who are physically dependent on a drug requiring medical detoxification (e.g., alcohol, opioids, benzodiazepines) will also not be eligible for the study, Urine drug screen must be negative for these drugs on admission to the inpatient unit.
7. Subjects with phenylketonuria, who are taking monoamine uptake inhibitors (including SSRIs), monoamine oxidase inhibitors, or cimetidine will not be eligible to participate.

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, methamphetamine, tetrahydrocannabinol (THC), and opioids. 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 forward-and-back, 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 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 who meet the inclusion criteria will reside on the Clinical Research Unit (CRU) at the University of Kentucky Medical Center while they participate. During their participation in the research protocol, subjects will not be allowed to leave the CRU unattended, nor will visitors be allowed. After completing the protocol, all subjects will be debriefed and offered a referral to a drug use treatment program. Subjects will be enrolled for approximately one month. Experimental sessions and dosing will be conducted as shown in Table 1. After three days of maintenance on each zolmitriptan dose (i.e., double the time necessary to achieve steady state concentrations as outlined below; Dixon et al., 1997), the reinforcing and subjective effects of intravenous cocaine (0, 10, and 30 mg/70 kg), as well as a range of impulsive behaviors, will be measured across three experimental sessions. Note, the maximum intravenous cocaine dose will be 40 mg regardless of weight, but we will continue to refer to this dose condition at 30 mg/70 kg throughout the protocol. Following completion of the Practice Session, a nurse from the UKHealthCare Vascular Access Team (VAT) will insert a needle into the subject's arm. The needle will be removed and a long intravenous midline catheter (approximately 3 – 5 inches) will stay in the vein near the subject's armpit. The placement of this midline catheter will allow for longer-term intravenous access (e.g., 30 days) to receive fluids (i.e., saline) and cocaine than a typical venous catheter that would be placed prior to experimental sessions. This eliminates the need to re-insert short-term catheters for IV access (e.g., 2 – 3 days). The removal of the midline catheter will occur upon completion of the last experimental session or when deemed necessary by the study physicians and/or hospital policy. Peripheral intravenous catheter may be inserted in the subject's arm if the midline catheter needs to be removed or if an unforeseen event obstructs administration of cocaine (e.g., leaking).

Table 1.

Day	Details
0	Admission to the CRU. Practice Session wherein subjects will be familiarized with the experimental session tasks.
1	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.
2-7	Placebo maintenance. Placebo administered twice daily (0700 and 1900 hours).
5-7	Experimental Sessions 1-3. Subjects complete 1 sample and 5 choice trials to receive cocaine (0, 10 and 30 mg/70 kg) or money ($6.00) by responding on the concurrent progressive-ratio schedule. Assessment battery completed following administration of the sampling dose as described below.
8-9	Washout. Placebo administered twice daily (0700 and 1900 hours).
10-15	Zolmitriptan (2.5 mg/day) maintenance. Administered in divided doses (0700 and 1900 hours).
13-15	Experimental Sessions 4-6. Details are the same as for days 5-7.
16-17	Washout. Placebo administered twice daily (0700 and 1900 hours).
18-23	Zolmitriptan (5 mg/day) maintenance. Administered in divided doses (0700 and 1900 hours).
21-23	Experimental Sessions 7-9. Details are the same as for days 5-7.
24-25	Washout. Placebo administered twice daily (0700 and 1900 hours).
26-31	Zolmitriptan (10 mg/day) maintenance. Administered in divided doses (0700 and 1900 hours).
29-31	Experimental Sessions 10-12. Details are the same as for days 5-7.
32	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 zolmitriptan 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 zolmitriptan 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 CRU, 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 CRU 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, take their maintenance medication, 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 0800 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 doses at 0700 and 1900 h and be in bed with the lights out by 2300 h.

Table 2.

Time	Details
0800	Sobriety, breath, and urine drug testing. Baseline measures completed.
0930	Session begins. Cardiovascular monitoring initiated.
1000	Sample dose of intravenous cocaine (0, 10 or 30 mg/70 kg) administered. Assessment battery completed after sampling dose as noted in task descriptions below.
1100	Subjects are offered the opportunity to complete the first ratio on the concurrent progressive-ratio task to receive the cocaine dose sampled previously or $6.00. A dose earned or money will be provided immediately after completion of the response requirement. At the end of the session, the money will be collected and held for the subject until he/she is released. Five total choice trials will occur at 60-minute intervals (i.e., 1100, 1200, 1300, 1400 and 1500 h).

Apparatus. Behavioral testing will be conducted on the CRU 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 complete 5 choice trials between that dose and $6.00, separated by 60 minutes. The money amount was selected based on previous research because it functions as a reinforcer but does not completely suppress drug-taking behavior (Lile et al., 2020). The initial response requirement for either choice (i.e., cocaine or money) will be 400 mouse clicks. Response requirements will increase by 200 responses for previously chosen options. For example, if a subject chooses cocaine at the first opportunity, the next response requirement for cocaine would be 600 responses, but the response requirement for money would remain at 400 responses. If a subject were to choose one option exclusively, the response requirements would be 400, 600, 800, 1000 and 1200 responses. These response requirements were based on our previous human laboratory studies that have tested various ratio parameters to maximize drug-maintained responding while minimizing placebo self-administration (Lile et al., 2016; 2020; Sevak et al., 2010; Stoops et al., 2010). Subjects may choose not to complete a ratio for either reinforcer during a choice trial (i.e., an omission), but physiological measures and the assessment battery will still be completed as scheduled and the ratio requirements for each reinforcer will carry forward to the next trial. 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 to meet Aims 2 and 3. 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.

***Cognitive Outcomes*.** Four cognitive-behavioral measures that evaluate impulsive behavior will be included and will be completed 20 minutes after administration of the sampling dose. These tasks were selected because: (i) cocaine users display increased impulsive behavior (Coffey et al., 2003; Fillmore and Rush, 2002; Heil et al., 2006; Liu et al., 2011) which likely contributes to poor treatment response and relapse (Dalley et al., 2011; Poling et al., 2007) and (ii) 5-HT systems are strongly implicated in impulsive behavior (Brunner and Hen, 1997; Cunningham and Anastasio, 2014; Howell and Cunningham, 2015). The selected tasks measure three key, independent aspects of impulsivity: impulsive decision-making (i.e., delay discounting for money and cocaine), impulsive inattention (i.e., n-Back), and impulsive disinhibition (i.e., go/stop task) (Reynolds et al., 2008). Tasks will be completed in random order across subjects, but the order of tasks will remain consistent for each subject.

Hypothetical Delay Discounting (Appendix B). 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).

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.

Stop-Signal Task. Letters (X or O) will be presented on the screen one at a time and participants are instructed to respond on the computer keyboard to identify the letter that was presented. On approximately 30% of trials a stop-signal tone (a 500 ms, 900 Hz tone) will occur, and participants must withhold their response (50 trials). The tone will be random and will occur at one of five delays (10, 70, 150, 230, or 300 ms; stop-signal delay) after the presentation of the letter. The presentation of the stop-signal is divided evenly between letters. Participants are instructed to respond as quickly as possible to letters and not to wait for the tone to occur. The dependent variables from the stop-signal task are the mean proportion of inhibitory failures to the stop-signal and by the estimated mean latency to inhibit a response. The mean RT to the go-signals (i.e., responding to the letters, not in the presence of the stop-signal) will measure response execution to go-signals during a test (i.e. the average time from the onset of letter presentation until a computer key press). Shorter reaction times (i.e. faster responding) indicate greater response execution. The inhibition and execution measures are highly reliable across trials (alpha coefficients >0.90) and stable over sessions (test-retest reliabilities >0.85) in both drug-using and non-drug-using populations (Fillmore and Rush, 2001; Fillmore and Vogel-Sprott, 1999; Mulvihill et al., 1997). The order of letters, stop-signal, and stop-signal delays will be random.

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. Cardiac rhythmicity (i.e., electrocardiograms [ECG]) will be recorded for 30 minutes before intravenous cocaine administration and continuously during each experimental session. No drugs will be administered if a subject's heart rate is ≥ 90 bpm if systolic pressure ≥ 140 or diastolic pressure ≥ 90 mmHg. A subject will be excluded from further participation if at any time he or she exceeds our cardiovascular safety and tolerability thresholds (i.e., heart rate above 130 bpm, diastolic pressure increases above 120 mmHg or systolic pressure above 180 mmHg or clinically significant ECG changes) after administration of zolmitriptan alone, cocaine alone or cocaine-zolmitriptan combinations. 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.

Safety and tolerability outcomes: Udvalg for Kliniske UndersØgelser (*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 at 1630 h. 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 zolmitriptan maintenance. To maintain the blind, only Dr. Stoops and the Investigational Drug Service will have access to dose conditions for subjects.

Zolmitriptan doses, 0, 2.5, 5 and 10 mg/day, will be prepared with commercially available immediate-release doses placed in a size 0 capsule. Although zolmitriptan is available in a spray and slow-release formulation, there are only limited dose preparations available for these formulations. Using only these limited doses of zolmitriptan would undermine a critical contribution of this study by eliminating the evaluation of multiple zolmitriptan doses in combination with cocaine. All capsules will then be filled with cornstarch. Placebo capsules will be identical but will contain only cornstarch. Zolmitriptan will be administered twice daily in divided doses (i.e., 0700 and 1900 hours). Zolmitriptan doses were selected based upon clinical dosing recommendations for managing migraine (i.e., maximum dose of 10 mg/day: Peterlin and Rapoport, 2007). Twice daily dosing of zolmitriptan was selected based on its published plasma levels, with oral immediate release dosing producing sustained plasma levels for 16 hours (Peterlin and Rapoport, 2007). Subjects will be maintained on each zolmitriptan dose for 3 days before experimental sessions. This maintenance period was

selected based on a previous study showing that administration of zolmitriptan doses across approximately 1.5 days was sufficient to reach steady state (Dixon et al., 1997). An additional 1.5 maintenance days are included to allow any transient zolmitriptan side effects to dissipate before experimental sessions. We also include a 2-day washout period after each dosing condition to reduce carryover effects from each previous dose condition.

Cocaine doses (0, 10, and 30 mg/70 kg) will be aseptically prepared by dissolving cocaine HCl USP (NIDA Drug Supply) in 2 mL 0.9% sodium chloride and filtering the solution through a 0.22 µm filters into a sterile, pyrogen-free vial. The 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. Each dose will be administered via a midline catheter or peripheral catheter (if needed in lieu of midline catheter) in the non-dominant arm (if possible) 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; 2020).

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 5-HT$_{1b}$ activation reduces the reinforcing effects of cocaine. The reinforcing effects of 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 zolmitriptan (0, 2.5, 5, and 10 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 zolmitriptan or the cocaine-zolmitriptan interaction attains statistical significance in the ANOVA. If the cocaine-zolmitriptan 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 that 5-HT$_{1b}$ activation attenuates subjective abuse-related effects of cocaine (e.g., positive subjective effects, craving). 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 zolmitriptan (0, 2.5, 5, and 10 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 zolmitriptan or the cocaine-zolmitriptan interaction attains statistical significance in the ANOVA. If the cocaine-zolmitriptan 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, zolmitriptan and time as factors. The MSE term for the cocaine-zolmitriptan-time interaction will then be used to conduct Tukey's *post-hoc* tests to make appropriate pair-wise comparisons.

Aim 3: Demonstrate that 5-HT$_{1b}$ activation attenuates impulsive responding that is a common characteristic of cocaine use disorder and is mediated by the 5-HT system. For the impulsivity 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 zolmitriptan (0, 2.5, 5, and 10 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 zolmitriptan or the cocaine-zolmitriptan interaction attains statistical significance in the ANOVA. If the cocaine-zolmitriptan 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.

Physiological data. 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 zolmitriptan (0, 2.5, 5, and 10 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 zolmitriptan or the cocaine-zolmitriptan interaction attains statistical significance in the ANOVA. If the cocaine-zolmitriptan 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, zolmitriptan and time as factors. The MSE term for the cocaine-zolmitriptan-time interaction will then be used to make appropriate pair-wise comparisons.

Safety and tolerability data. For items from the UKU, which will have one data point per day, data will be analyzed using a two-factor repeated-measures ANOVA. Zolmitriptan (0, 2.5, 5, and 10 mg/day) and day will be factors for these analyses. The MSE term for the zolmitriptan-day interaction will then be used to make appropriate pair-wise comparisons.

Evaluating Relevant Biological Variables. We will conduct exploratory analyses to evaluate potential effects of relevant biological variables. Specifically, we will repeat the analyses described above including factors like sex, age, race, and other drug use to determine whether and how these variables might influence study outcomes. Although exploratory, these outcomes can inform future grant applications in terms of how individual differences influence responses to 5-HT_{1b} activation in people with cocaine use disorder.

Power Analysis. Enrolling 20 completing subjects will provide 80% power (alpha=0.05) to detect effect sizes (f) as small as 0.27. The study is therefore appropriately powered to detect significant effects on our proposed outcomes. For example, we observed an average effect size (f) of approximately 0.54 for bupropion to attenuate the reinforcing effects of cocaine in a progressive-ratio choice task akin to what is proposed for use here (Stoops et al., 2012). In another study, we observed an effect size (f) of approximately 0.53 for n-acetylcysteine to attenuate attentional bias, a cocaine associated impulsive behavior, to cocaine cues (Bolin et al., 2017). In a study from Neisewander and colleagues (Unpublished Data), the effect size (f) for zolmitriptan to reduce cocaine self-administration in rats was quite large (i.e., approximately 2.29).

8. RESOURCES

This study will take place at the CRU. Study sessions will only be conducted on weekdays. All drug administration will take place at the UK CRU in a room equipped with all the necessary physiologic and computer equipment for the study. Dr. 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 zolmitriptan 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 zolmitriptan 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 zolmitriptan (i.e., 10 mg/day) in this study.

Common side effects of zolmitriptan include dry mouth, nausea, pain/pressure in neck or throat, drowsiness, weakness, warmth, redness or mild tingling under the skin, increased heart rate and increased blood pressure. More serious side effects include chest pain, sudden lateral numbness or weakness, sudden headache, confusion, problems with vision, speech or balance, dizziness, severe stomach pain, hematochezia, serotonin syndrome and cyanosis.

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 CRU 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 a midline catheter or peripheral catheter (if needed in lieu of the midline catheter) placed in each subject's non-dominant arm (if possible) and maintained per UK HealthCare policy. During catheter placement, there is some risk of bruising, soreness, infection, bleeding or blood clot, pain, irritation from the insertion of the needle, and malposition of the midline or peripheral catheters. 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 protected health information (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 always available 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 always be under the direct supervision of the nursing staff on the CRU 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 UKU Side Effects Rating Scale will be completed daily with subjects by CRU nursing staff. Staff observations, subjective-effects drug effects and spontaneous subject report will also be used to monitor for adverse events.

To minimize the risk associated with intravenous cocaine administration, dosing will occur under the supervision of ACLS-certified medical staff (Dr. Hatton and CRU nurses). During the medical safety and experimental sessions, heart rate and blood pressure will be recorded 30 minutes prior to cocaine administration and at frequent intervals (i.e., 15 – 30 minutes) afterwards for the duration of the session. Electrocardiograms (ECG) will be recorded continuously during each experimental session. Electrocardiograms (ECG) will be recorded continuously during the medical safety and each experimental session. Cardiovascular hypersensitivity is defined as heart rate > 130 bpm, systolic pressure > 180 mmHg or diastolic pressure > 120 mmHg elevated consistently across a five-minute period of monitoring. 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. Subjects that exhibit hypersensitivity (i.e., heart rate >130 bpm, systolic pressure > 180 mmHg, diastolic pressure > 120 mmHg, or clinically significant ECG changes) to the cardiovascular effects of cocaine and/or zolmitriptan at any point during this study will be excluded immediately from further research participation and will be followed until symptom resolution. In our previous studies with cocaine over the last 20 years, only two subjects have been excluded based on these criteria. Drs. Stoops, Rush, Lile, Hatton, Hays and Rayapati will train all staff on this project. No drugs (i.e., cocaine or zolmitriptan) will be administered if a subject's heart rate is ≥ 90 bpm if systolic pressure ≥ 140 or diastolic pressure ≥ 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. 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 recent 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). 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. If a seizure should occur, we will follow the expert guidance/protocol of the UK Department of Neurology Rapid Response Team for seizure management, 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 (0.1 mg/kg/dose; max 4 mg/dose).
3. Repeat therapy every 5 min as need for continued/repeat seizures.

A physician in Neurology will be consulted if a second treatment dose is required. If the seizure has not stopped within the allotted time, diazepam is to be administered by the attending physician or their 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 CRU. As noted above, we have several safeguards in place to monitor for adverse events. If a subject experiences significant abstinence symptoms following admission to the CRU, he or she will be treated in accordance with the standard practice of the University of Kentucky Hospital and then dismissed from the study.

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

During 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 because 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 $60 for each day they reside on the CRU and will receive a $60 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 $30/session, $360 total). 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 $4,320 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. Grants funded by the National Institutes of Health have no mechanism to pay for research-related injuries.

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 zolmitriptan maintenance conditions. Secondary outcome measures will be abuse-related subjective and cognitive effects of cocaine, analyzed as a function of zolmitriptan maintenance conditions. Tertiary outcome measures will be the physiological and side-effects of cocaine, analyzed as a function of zolmitriptan 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 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 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 visit at 1-month 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 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 visit at 1-month following study completion. If there is an SAE that is continuing, we will schedule special visits with those subjects at 3- and 6-months post-discharge. 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.

If 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, CRU, 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, CRU, 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 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 to discuss any concerns regarding subjects or with respect to the conduct of the study. Subjects may contact the Office of Research Integrity regarding any questions, comments, and/or complaints.

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. Stoops holds an IND for cocaine with oral zolmitriptan (IND# 158,597). Dr. Stoops has extensive experience with INDs and interfacing with the FDA, having previously maintained a separate IND for the concurrent administration of cocaine with putative pharmacotherapies. Dr. Stoops is well aware of the necessary reporting requirements and other responsibilities associate with IND sponsorship. As required by the FDA, Dr. Stoops will submit annual reports on the progress of the IND and will also report serious adverse events in accordance with published guidelines. Dr. Stoops has current GCP training and 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

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%.

Appendix C

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