# Protocol for Targeting Anhedonia in Cocaine Use Disorder

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## 1.0 Project Summary/Abstract

Cocaine Use Disorder (CUD) creates high health burdens and is resistant to treatment [1]. Success rates for CUD treatments are <50%, and there are no FDA-approved medications. One way to improve the success rate of CUD treatments may be to target specific neurobehavioral dysfunctions thought to underlie treatment failure. Anhedonia, i.e. lack of interest or pleasure in non-drug rewards, is one such target. Anhedonia is common in CUD, and individuals who present with anhedonia tend to have worse treatment outcomes. Pre-clinical studies suggest anhedonia may be produced by impairments in any of several reward-related functions, including the ability to experience pleasure, motivation for rewards, or the ability to learn and adapt behavior based on previous rewards. Most of these functions depend critically on dopaminergic brain circuits, and consistent with this, dopaminergic drugs modestly improve CUD outcomes. However, it is unknown which reward-related functions are most important to CUD outcomes, and further, whether improvements in reward functioning are the mechanism by which dopaminergic drugs enhance outcomes. This knowledge gap makes it difficult to target treatments to those who could benefit most, or refine treatments to more effectively engage key mechanisms. The current study tests: 1. How several reward-related functions relate to CUD severity at baseline, 2. Which of these reward-related functions are most important to treatment outcomes, using brief intensive Contingency Management as a model treatment. 3. Whether treatment with a dopaminergic stimulant improves Contingency Management outcomes, and if so, whether restoration of reward-related functioning is key to this effect. To address these questions, 80 individuals with CUD will complete an efficient proof-of-concept clinical trial, consisting of baseline measures of addiction severity followed by four weeks of treatment. Participants will be randomized to one of three treatment groups: One group will receive 4 weeks of intensive Contingency Management with placebo (CM/PL, n=30); one will receive 4 weeks of intensive Contingency Management with 60mg extended-release dextroamphetamine (CM/ER-AMP; n=30), a stimulant that increases dopamine levels, positively affects reward functioning, and has modest stand-alone efficacy for CUD; a third medication-only control group (n=20) will receive 60mg extended-release dextroamphetamine alone for 4 weeks, to answer secondary questions about importance of anhedonia when rewards are not part of treatment, and estimate effects of extended-release dextroamphetamine alone on anhedonia and clinical outcomes. Initial attainment of abstinence is the primary clinical outcome, and multi-modal measures of reward functioning will be taken at baseline and once each treatment week.

## 2.0 Background/Scientific Rationale

Cocaine is the third most abused drug in the U.S. [2], and the drug most often involved in ER visits [3]. Around one-fourth of cocaine users have Cocaine Use Disorder (CUD), and these individuals disproportionately account for cocaine-associated health burdens [3,4]. Yet success rates for CUD treatments are below 50% [5], and unlike nicotine, alcohol and opiate disorders, there are no FDA-approved medications for CUD. Thus, CUD is a critical public health problem that has been relatively intractable to standard treatment development approaches [1].

Limitations of Current Approaches. One major limitation in treatment development for CUD, and all psychiatric disorders, has been a reliance on traditional efficacy testing, in which main effects on clinical outcomes (e.g. abstinence) are the focus. Often clinical trials do not target or even measure putative underlying neurobehavioral mechanisms. This makes trial failures costly and uninformative, as it is unclear whether a mechanism was not engaged, was unrelated to clinical outcomes, or was only active in a sub-set of patients. This has been likened to attempting to treat “stomach pain disorder”, which could be an ulcer, food poisoning, or cancer [6]. Indeed, CUD clinical trials have generally targeted drug use, rather than possible neurobehavioral mechanisms, and only secondarily, if at all, examined which mechanisms are engaged in which patients.

An Alternate Approach: Target Neurobehavioral Dysfunction. An alternative approach, promoted by the NIMH’s Research Domain Criteria (RDoC) project, is to use our knowledge of the brain’s functions to “map” the basic neurobehavioral dysfunctions occurring in psychiatric disorders [7], and include measures of these putative underlying dysfunctions in treatment development from the ground up, as moderators, mediators, and eventually, primary outcomes. This approach could allow us to target pathologies that cut across disorders, with impacts beyond any one diagnosis, and to personalize treatment via more effective subtyping within disorders (as proposed here). The current proposal applies this approach to CUD in a proof-of-concept study: identifying a key neurobehavioral dysfunction, testing whether this dysfunction predicts treatment outcomes, and targeting this dysfunction directly.

Anhedonia: A Key Neurobehavioral Dysfunction in CUD. Several lines of evidence suggest that anhedonia is a key neurobehavioral dysfunction in CUD that contributes to treatment outcomes. Anhedonia, defined here as lack of interest or pleasure in non-drug rewards, is common in CUD [8–10], as are related neural deficits [11], such as low striatal dopamine [12] and deficient responses to non-drug rewards in mesocortical circuits [13–16]. However, not all individuals with CUD have these deficits [14]. Indeed, preliminary data from our previous treatment studies shows that the presence of self-reported anhedonia predicts worse outcomes in Contingency Management [17], an established CUD treatment in which individuals receive monetary rewards for abstinence [18]. Consistent with this, low baseline dopamine also predicts failure to attain abstinence in Contingency Management [19]. Further, medications that enhance dopamine increase Contingency Management success rates [20], and our previous

research suggests such medications enhance responsiveness to reward [21,22]. Putting this evidence together, it appears that variations in anhedonia may explain heterogeneity in Contingency Management outcomes, and that dopaminergic drugs may improve Contingency Management outcomes by improving anhedonia [19]. This study will be the first to test this hypothesis comprehensively, using a sophisticated neuroscience-based approach to anhedonia.

A Neuroscience-Based Approach to Anhedonia. Classically, anhedonia was characterized as inability to feel pleasure, and nucleus accumbens dopamine was thought to underlie pleasure [23]. However, a more nuanced understanding has emerged, identifying three major reward functions: 1. Consummatory reward, i.e. pleasure from rewards, mediated by opioid "hotspots" in the nucleus accumbens and ventral pallidum in a circuit with ventromedial prefrontal cortex and anterior cingulate cortex [24]. 2. Motivational reward, i.e. exertion of effort for reward, controlled by tonic pacemaker-like dopamine activity in the ventral tegmental area that preferentially activates D2 receptors in the nucleus accumbens [25] in a circuit with ventromedial prefrontal cortex, anterior cingulate cortex and amygdala [26]. 3. Reward learning, i.e. adaptation of behavior based on reward history, encoded by fast phasic dopamine bursts in the ventral tegmental area [27] that preferentially activate D1 nucleus accumbens receptors sensitive to higher dopamine concentrations [25], in a circuit with dorsolateral prefrontal cortex [28]. This phasic "prediction error" signal is initially evoked by reward, decreases as reward becomes predictable, and re-appears if reward is unexpected [27]. It is unlikely these functions are totally orthogonal, but they are at least partially independent [11,29], and given its pathology, CUD may impair any or all of them [30]. To target treatment, it is critical to understand the roles these distinct processes play in CUD outcomes. It is unlikely that self-reports alone will cleanly map these distinct functions [31]. Thus, the proposed approach is multi-modal, using subjective, behavioral, psychophysiological and neural measures of reward functioning. Critically, functional Magnetic Resonance Imaging (fMRI) is included to assess underlying neural processes.

## 3.0 Objectives/Aims

The current study will test the primary hypothesis that anhedonia is a key neurobehavioral dysfunction in CUD that underlies variability in Contingency Management outcomes, and that dopaminergic drugs enhance Contingency Management outcomes by reducing anhedonia, through the following specific aims:

**Specific Aim 1. Test the contribution of anhedonia to overall Cocaine Use Disorder (CUD) severity.** Our hypothesis is that higher anhedonia at baseline will relate to greater addiction severity at baseline. This will be tested using linear regression to examine the relationship between a composite score of CUD severity, and anhedonia, defined as scores on the three major reward functions at baseline (see *Section 9.0, Data Analysis* for details on derivation of scores).

**Specific Aim 2. Test the relationship of anhedonia to treatment outcomes in Contingency Management for CUD.** Our hypothesis is that higher anhedonia at

baseline will predict lower probability of achieving abstinence, and further, will be more strongly predictive of outcomes in the Contingency Management groups, where external rewards are part of treatment, than in the dextroamphetamine-only control group. This will be tested using generalized linear modeling of the probability of attainment of initial abstinence, defined as 2 consecutive weeks of cocaine negative urine drug tests, as a function of reward functioning scores at baseline by treatment group. Secondarily, we will use general linear modeling to examine the continuous measure of Treatment Effectiveness Scores, defined as number of cocaine negative urines submitted during the protocol, as a function of reward functioning scores at baseline by treatment group.

**Specific Aim 3. Test the mediating role of anhedonia in medication enhancement of Contingency Management for CUD.** Our hypothesis is that the combination of Contingency Management and extended-release dextroamphetamine will be more effective than either Contingency Management or extended-release dextroamphetamine alone, and that this synergistic improvement in outcomes will be mediated by improvements in anhedonia. This will be tested utilizing Bayesian Structural Equation Modeling to model indirect effects of treatment group (CM/PL, CM/ER-AMP, ER-AMP only) on abstinence, defined using the same primary and secondary measures as Aim 2, with change in reward functioning scores over treatment as the mediator. Of note, change measures are sometimes ill-conditioned (e.g. large error terms, little reliable variability), and if this is the case here, we will use reward functioning scores at a specified midpoint instead.

Design Overview: These aims will be accomplished within a single efficient randomized, controlled, double-blind trial (see *Figure 1. Schematic of Study Design*, below).

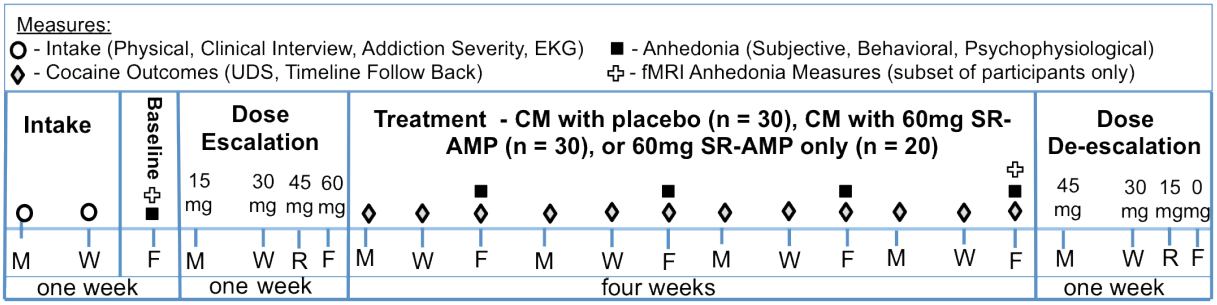


*Figure 1* – Schematic of Study Design for both *Treatment Study* and *fMRI Sub-Study*
Notes: UDS = Urine Drug Screen; EKG = Electrocardiogram; fMRI = Functional Magnetic Resonance Imaging

In the *Treatment Study*, 80 individuals with CUD will complete baseline measures of addiction severity, a 1-week dose escalation, four weeks of treatment, and a 1-week dose de-escalation (see *Figure 1*). Participants will be randomized to one of three groups: one receiving 4 weeks of treatment with intensive Contingency Management with placebo (CM/PL, n=30), one receiving 4 weeks of treatment with intensive Contingency Management with 60mg extended-release dextroamphetamine (CM/ER-AMP; n=30), or an additional control group (n=20) receiving 4 weeks of treatment with

60mg extended-release dextroamphetamine *without* CM, to answer secondary questions about importance of anhedonia when abstinence-contingent rewards are not part of treatment, and estimate effects of dextroamphetamine alone on outcomes and anhedonia. All subjects will complete subjective, behavioral and psychophysiological measures of reward functioning at baseline and once each treatment week.

## 4.0 Eligibility

Participant Overview: Participants in the *Treatment Study* will be 80 treatment-seeking male and female adults aged 18-60 years who meet DSM-V criteria for current CUD of at least moderate severity. Participants will be recruited without regard to race, religion or ethnicity.

### 4.1 Inclusion Criteria

Inclusion Criteria for Main Treatment Study:

Inclusion Criteria:

1. be between 18 and 60 years of age
2. meet DSM-5 criteria for current cocaine use disorder of at least moderate severity (≥ 4 symptoms)
3. have at least 1 cocaine positive urine sample during the baseline screening period
4. be in acceptable health on the basis of interview, medical history and physical exam, per the judgment of our study physician
5. be able to understand the consent form and provide written informed consent
6. be able to provide the names of at least 2 persons who can generally locate their whereabouts.
7. if female, agree to use an acceptable method of birth control during study (surgical sterilization, approved hormonal contraceptives, barrier methods with spermicide, or intrauterine device).

### 4.2 Exclusion Criteria

Exclusion criteria for Main Treatment Study:

1. current DSM-5 diagnosis for substance use disorder of least moderate severity (≥ 4 symptoms), other than cocaine, nicotine, marijuana, or alcohol
2. Physical dependence on alcohol requiring medically supervised detoxification, in the judgment of the study physician
3. current amphetamine use (by self-report in past 30 days or positive urine drug screen), more than 50 lifetime uses of amphetamine, or history of DSM-5 Amphetamine Use Disorder
4. a current DSM-5 axis I psychiatric disorder or neurological disease or disorder requiring ongoing treatment and/or making study participation unsafe, or any history of mania or a psychotic disorder
5. significant current suicidal or homicidal ideation

6. medical conditions contraindicating dextroamphetamine (e.g., significant cardiovascular disease, liver or kidney disease, seizure disorder, hypotension or hypertension)
7. taking medications known to have effects on the central nervous system or that could cause significant drug interactions with dextroamphetamine (e.g., clonidine, prazosin)
8. having conditions of probation or parole requiring reports of drug use to officers of the court
9. impending incarceration
10. pregnant or nursing for female patients
11. inability to read, write, or speak English

### 4.3 Excluded or Vulnerable Populations

Vulnerable Populations and Protections. Children will not be included in this research. The incidence of CUD in individuals under the age of 18 is small, so a study not specifically targeting children for recruitment is unlikely to produce usable information about this sub-group. Further, validated treatment approaches for children with substance use disorders are different than those used with adults (and proposed here). Together this makes the risk/benefit ratio for children unacceptable for this study. Pregnant women will not be included as dextroamphetamine is a Class C drug for pregnancy. Prisoners will not be included, as this is an outpatient study. Based on the demographics of individuals with CUD in the community and our experience to date, the study is likely to include individuals that are socially and economically disadvantaged or homeless. To reduce potentially coercive aspects of the study for these individuals, base compensation is not excessive. Although rewards in Contingency Management can be high, research suggests that Contingency Management is equivalently effective across individuals of different socioeconomic status, suggesting these rewards are not inequitably coercive of behavior for disadvantaged individuals [32]. The nature of the study can place individuals at risk of economic, social or legal consequences, as quantifying drug use is key to the study and the subject are expected to be illicit substance users. To address these risks we have strict confidentiality controls (see *Section 13.2, Subject Confidentiality*), and we carefully inform subjects about any remaining risks that cannot be mitigated. We also exclude individuals having conditions of probation or parole, as dextroamphetamine may produce positive drug tests that could be considered a violation of probation or parole, increasing the risk of legal consequences for these individuals.

Justification of Excluded Populations. The primary exclusion criteria for this study are medical or psychiatric contraindications to dextroamphetamine or other study procedures (e.g. fMRI). These are required to maintain safety. Aside from these, as noted above we additionally exclude children and individuals on probation or parole, as these individuals have less favorable risk/benefit ratios. We also exclude individuals who cannot read, write or speak English as our forms and measures have not been translated and validated in other languages.

## 5.0 Subject Enrollment

Recruitment Strategy: Participants will be non-hospitalized, self-referred persons who call in response to various advertising strategies, including print media (e.g. Chicago Reader, RedEye, Chicago Defender, Chicago Free Press), online media, advertisements on public transit, flyers, posters and brochures placed in the community, and clinic referrals in the Chicago area. Men and women of all ethnic backgrounds will be recruited to participate. It is anticipated that the subject demographic profile will closely mirror the larger population of individuals with CUD from which they are recruited. However, efforts will be made to increase the percentage of women and minorities in the study. These efforts will include (1) having study staff present educational material and referral information at women's clinics in Chicago and the surrounding communities; (2) targeted advertising in newspapers which serve African-American and Latino communities (e.g. Chicago Defender, La Raza, Hoy); (3) distributing flyers and notices in neighborhoods known to have a high minority population; and (4) having the staff contact church and community leaders in minority communities to provide educational material about CUD and its consequences and also provide contact information to aid in referrals to our clinic.

Screening and Intake: Individuals responding to these recruitment strategies will be screened under the ART Lab General Screening Protocol, which has been separately submitted for approval. Briefly, subjects will first complete a short questionnaire on the telephone or online via REDCap, to determine general fit with inclusionary/exclusionary criteria. This screening will include a study-specific description and questions for individuals calling regarding the current study (see attached *Study Description and Study Specific Questions*). Potentially eligible subjects will be scheduled for screening, which consists of interviews, questionnaires, medical screening and feedback. This protocol generally takes 5-6 hours and may be completed over 3-4 sessions, depending on subject availability. At the initial interview session, in a socially-distanced session at the ART Lab in BSB, subjects will complete structured diagnostic interviews, including two measures that will be used to establish addiction severity for Aim 1: *The Structured Clinical Interview for DSM-V (SCID)* [33], a well-established diagnostic interview; *The Addiction Severity Index (ASI)* [34], a semi-structured interview quantifying functional impacts of drug use across life domains; Please note, the SCID and ASI instruments are separately approved as part of the ART Lab Screening Protocol, and will not be used again during the current study, and therefore are not attached here. Participants will then complete a questionnaire session, also via a socially distanced in-person session. Participants who appear likely to qualify based these investigations will be scheduled for medical screening at the Center for Clinical Research, which includes a physical conducted by a nurse practitioner, electrocardiogram, urine samples for drug tests, and blood and urine samples for basic laboratory measures (see ART Lab Screening Protocol for details). Results will be reviewed by the PI, who is a licensed clinical psychologist, the study physician, Dr. Holden, who is an addiction medicine specialist, and our clinical consultant. Dr. Ahluwalia, who is dual board-certified in internal medicine and psychiatry and will provide consultation on ECG interpretation and any questionable medical conditions. This review will establish the inclusion and

exclusion criteria. At the conclusion of the screening process, subjects will receive feedback, including being informed of any pertinent clinical findings from the screening. Participants will be either provided with appropriate referrals (if ineligible) or scheduled for the consent process for the current study (if eligible). Data collected during the screening for subjects that enroll in the study becomes part of the study record, and is stored per study guidelines. Data for subjects that are ineligible or do not complete the consent is stored per the ART Lab Screening Protocol (approved separately).

Consent Session: Participants will provide consent for the standard ART Lab screening separately (see separate protocol). At the conclusion of the screening protocol, eligible subjects will complete the informed consent for the current study. See Section 13.1, Informed Consent for details on consent process for the current study. At the same session, immediately after consent, subjects will complete the 30-day *Timeline Follow Back (TLFB)* [35] interview (see attached), which obtains estimates of recent drug use using standard aids (calendars, marking memorable events), which is given to assess cocaine use for 30 days prior to study enrollment (see *Drug Use Measures*, below). This will be conducted using the study *Timeline Follow Back and Contingency Management Manual*, attached.

## 6.0 Study Design and Procedures

Performance sites. The majority of study procedures (initial intake, consent, treatment visits, behavioral sessions, therapy sessions) will be performed in the Behavioral Sciences Building in the ART Lab and adjoining Office of Applied Psychological Services, the UIC Psychology Department's outpatient psychology clinic. Medical screening (as approved separately under the ART Lab Screening Protocol) will be performed in the UIC Clinical Research Center.

Major Changes for COVID-19. Because the primary outcome for the study is 3x weekly urine samples, we are unable to move to telehealth visits. Instead, we have adapted our in-person procedures as follows.

1. Before each participant visit, cleaning will take place per our approved BioRaft registration.
2. Participants will be required to pass a standard COVID-19 screening questionnaire upon arrival, to wear a mask at the session (masks will be provided for people who do not have one), and to pass a temperature screening upon arrival. If these criteria are not met, the session will be rescheduled, and the participant may be withdrawn from the study, run-down from the medication, and provided with referrals for treatment of COVID-19 symptoms, as appropriate (e.g. for confirmed cases).
3. Research assistants will wear ASTM-certified medical grade masks during any face-to-face interaction with participants.
4. Any procedures that can be conducted via webcam from another room (e.g. therapy sessions) will be completed via webcam using HIPAA-approved UIC web conferencing software (WebEx). Webex rooms will be "locked" at all times when

participants are being given instructions or therapy sessions are happening. Recording of sessions will now also be done using Webex, to secure, on-campus, UIC controlled computers, per UIC approved protocols, rather than using a separate audio recorder. See attached “Distanced Communication Procedures” for details

5. Any procedures that must be completed via face-to-face interaction, but can be completed while maintaining a 6ft. distance (e.g. providing urine samples) will be completed using 6ft. distancing.

6. For the minority of procedures that cannot be completed while maintaining 6ft. distance (e.g. blood pressure measurements) additional PPE will be required for the research assistant, consisting of a face shield and gloves. Face shields will be cleaned in-between participants.

Overview of Study Design. 80 individuals with CUD who participate in the *Treatment Study* will complete a 1-week screening and study intake (described briefly above under *Screening* and submitted separately for approval as the ART Lab General Screening), a 1-week dose escalation, four weeks of treatment, and a 1-week dose de-escalation. All subjects will complete subjective, behavioral and psychophysiological measures of reward functioning at baseline and once each treatment week. Details on each procedure are provided below.

| Procedure | Participant Time | Screening (1-3 visits) | Week 1 - Baseline | Week 2 – Run-up | | | | Week 3 - Treatment 1 | | | Week 4 – Treatment 2 | | | Week 5- Treatment 3 | | | Week 6 - Treatment 4 | | | Week 7 – Run-Down | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | M | W | R* | F | M | W | F | M | W | F | M | W | F | M | W | F | M | W | R* | F |
| Addiction Severity Measures | 60min (part of 3-4hr screening) | X | | | | | | | | | | | | | | | | | | | | | |
| Reward Functioning Assessments | 120min | | X | | | | | | | X | | | X | | | X | | | X | | | | |
| Medication Treatment (mg/day in ER-AMP groups) | 5min * take home dose | | | X 15 mg | X 30 mg | * 45 mg | X 60 mg | X 60 mg | X 60 mg | X 60 mg | X 60 mg | X 60 mg | X 60 mg | X 60 mg | X 60 mg | X 60 mg | X 60 mg | X 60 mg | X 60 mg | X 45 mg | X 30 mg | * 15 mg | X 0 mg |
| Contingency Management | 5min | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| Motivational Interviewing | 60min | | | | | | | X | | | | | | X | | | | | | | | | |
| Drug Use Measures (UDS, TLFB) | 10min | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Safety Measures (vitals, AE/SAE concomitant medication, C-SSRS) | 15min | | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Pregnancy Test (for women) | No additional subject time | X | | | | | | X | | | | | | X | | | | | | X | | | |
| Adherence Measures (MEMS, riboflavin) | No additional subject time | | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Wrap up and referrals (with therapist) | 15-30min | | | | | | | | | | | | | | | | | | | X | | | |

Figure 2. Overview of Study Procedures by Visit

Notes: ER-AMP = extended-release dextroamphetamine; UDS = Urine Drug Screen; TLFB = Timeline Follow Back; AE/SAE = Adverse Events/Serious Adverse Events Questionnaire; C-SSRS = Columbia Suicide Severity Rating Scale; MEMS = Medication Event Monitoring System

Reward Functioning Assessment Sessions. Each Reward Functioning Assessment Session will take 2 hours over 1 visit to the ART Lab. These may be combined with treatment visits, depending on subject availability. Participants will complete 5 Reward Functioning Assessment Sessions in total (one at baseline, one in each week of treatment), so altogether these are expected to take approximately 10 hours of subject time. Eligibility to complete a Reward Functioning Assessment Session will be the absence of acute cocaine intoxication on the day of testing (based on examination of DSM-V symptoms). Participants not meeting this requirement will be re-scheduled. Current withdrawal symptoms will also be examined at each session using the *Cocaine Selective Severity Assessment of Withdrawal* [36], see attached. The anhedonia measures administered have been selected to tap consummatory, motivational and reward learning functions across subjective, behavioral and psychophysiological domains. See *Table 1. Reward Functioning Measures* for a summary. At each Reward Functioning Assessment Session, the following *Reward Functioning Measures* will be administered:

*1. Subjective Reward Functioning Measures.*

*The Snaith-Hamilton Pleasure Scale (SHAPS)* [37] is a measure of consummatory reward consisting of 14 hedonic capacity statements (e.g. "I would enjoy my favorite TV program"). See attached.

*The Temporal Experience of Pleasure Scale (TEPS)*[38] contains 18 statements measuring motivational (e.g. "I look forward to a lot of things in my life") and consummatory (e.g. "I enjoy taking a deep breath of air") reward. See attached.

*2. Behavioral Reward Functioning Measures.*

*The Emotional Picture Rating Task (EPRT)*[21] is a measure of consummatory reward consisting of self-reported positive, negative and aroused feelings while viewing standardized emotional pictures. Positivity and arousal ratings of positive pictures are the primary outcomes.

*The Emotional Picture Keypress Task (EPKT)* [39] is a measure of motivational reward in which subjects expend effort via keypressing to extend or reduce viewing times for emotional pictures. Keypressing to extend positive pictures is the primary outcome.

*The Effort Expenditure for Rewards Task (EEfRT)* [40] is a measure of motivational reward translated from laboratory animal tasks. On each trial subjects choose between a "hard task" requiring many keypresses but worth more money and an "easy task" requiring few keypresses but worth less money. Percent of hard task choices is the primary outcome.

*The Probabilistic Reward Task (PRT)* [41] is a measure of reward learning consisting of trials in which subjects must identify whether a cartoon face has a short or long mouth over a brief presentation. Correct identification of one category (short or long) is rewarded more often with a small monetary reward. Response bias for the rewarded category is the outcome.

*3. Psychophysiological Reward Functioning Measures.* During the EPRT (see above) we will record activity in the corrugator (CR; frown) muscle using electromyography (EMG), skin conductance (SC) and heart rate (HR). Positive pictures suppress corrugator activity (Larsen et al. 2003) giving a measure of

valenced facial responses to pictures. Skin conductance is enhanced to all arousing pictures, positive and negative, giving a measure of sympathetic activity to pictures. Heart rate acceleration in the later seconds of picture viewing is also sensitive to the motivation properties of pictures, with greater acceleration to more positive pictures. Together, these will give a comprehensive assessment of consummatory responses to positive pictures. EMG will be recorded using two 4mm sensors, filled with conductive gel (Biopac System Inc.), and attached to the subject's face over the corrugator using adhesive collars. Signals will be amplified and digitized using an EMG100C/MP150 system (Biopac Sysems, Goleta, CA), and sampled at 1000 Hz throughout the tasks with Acqknowledge software. Magnitude of corrugator responses during positive pictures are the primary outcome. SC will be recorded using two 8mm sensors filled with isotonic gel (Biopac System Inc.) and attached to the subject's palm with an adhesive collar. Signals will be amplified and digitized using an EDA100C/MP150 system (Biopac Sysems, Goleta, CA), and sampled at 1000 Hz throughout the tasks with Acqknowledge software. HR will be measured using electrocardiogram data collected with disposable Ag/AgCl electrodes placed in a standard bilateral configuration on the chest. The data will be processed through a 1-100Hz bandpass filter designed to maximize R-wave frequency.

| | **Reward Function** | | |
|---|---|---|---|
| **Type of Measure** | Consummatory Reward | Motivational Reward | Reward Learning |
| Subjective | SHAPS; TEPS - Consummatory | TEPS - Motivational | |
| Behavioral | EPRT | EPKT; EEfRT | PRT |
| Psychophysiological | CR EMG; SC; HR | | |
| fMRI – *note, only administered in fMRI Sub-Study* | MID – Feedback; EPfT | MID – Anticipation | PCfT |

**Table 1**. Reward Functioning Measures by type and specific reward function

Treatment Visits. During the 1-week medication run-up, 4-week treatment period, and 1-week medication run-down, subjects will make thrice-weekly visits to the ART Lab (ideally Monday/Wednesday/Friday). Each treatment visit will take between 30 min and 1.5 hours depending on activities scheduled for that visit (as detailed below). All together, treatment visits are expected to take 13 hours over 18 visits. Treatment visits may be combined with Reward Functioning Assessment Sessions, fMRI Sessions, or both, depending on subject availability. Treatment visits will consist of the following activities (see *Figure 2, Overview of measures and procedures by Study Session)*:

*Treatment Activities*

1. *Medication.* At every treatment visit (run-up, run-down and treatment weeks) subjects will be administered medication and given take-home doses for intervening days. Participants in CM/ER-AMP and ER-AMP only groups will receive extended-release dextroamphetamine daily, while CM/PL subjects receive placebo. Drugs will be administered double blind in identical capsules with 50mg riboflavin total. Medication dispensing is expected to take 5min at each treatment visit. All

medication will be initiated on a gradual 1-week run-up until target dose is reached (60mg for ER-AMP). Individuals will then remain on the drug for 4 weeks, followed by a 1-week run-down, and either discharge or referral to other treatment as needed. Dextroamphetamine ER (Dexedrine Spansules) will be started at 15mg (day 1–2; 15mg am, 0mg pm), increased to 30mg (day 3; 15mg, BID), 45 mg (day 4; 30mg am, 15mg pm), and 60 mg (day 5; 30mg BID). Participants will remain at this level for 4 weeks, then be titrated down with 45 mg (day 1-2; 30mg am, 15mg pm), 30 mg (day 3; 15mg, BID), 15mg (day 4; 15mg am, 0mg pm), and finally no dose on the final day of the study (see *Figure 2*). Participants in the placebo group will follow the same dosing schedule. This same titration schedule has been used previously to safely titrate individuals with CUD to the targeted dose, maintain them for up to 12 weeks, and safely withdraw them from the drug [47]. In the event that a participant misses 3 or more days of medication (e.g. does not present for study visits despite all contact attempts), a brief re-run up will be conducted (Day 1 15mg, Day 2 30mg, Day 3 45mg, Day 4 60mg) to return them to the study dose.

*2. Contingency Management*. Participants in CM/PL and CM/ER-AMP arms will receive Contingency Management at visits thrice-weekly during the 4 treatment weeks, for a total of 12 Contingency Management sessions, per Schmitz et al. [48]. At each session, results of urine drug screens will be communicated to subjects by a trained research assistant. Research assistants will be trained using the laboratory *Timeline Followback and Contingency Management Manual* (attached), observed during initial Contingency Management administrations by the PI and subject to spot checks for adherence by the PI or other trained staff. Cocaine-negative urine drug screens will result in rewards (vouchers), starting at $15 and increasing by $10 for each consecutive negative urine drug screens, with bonus vouchers worth $10 for 3 consecutive negative urine drug screens [48]. Positive urine drug screens will result in voucher omission, and reset voucher value to $15. Participants can redeem vouchers for cash (≤$25) and gift cards. Participants in the ER-AMP only group will also receive feedback on urine drug screens results at each visit during the treatment period, with no contingencies attached, to control for research assistant contact and social factors. Urine drug screen feedback and Contingency Management at each visit during treatment is expected to take approximately 5 minutes.

*3. Motivational Interviewing*. All subjects will receive two 1-h, manual-based individual Motivational Interviewing sessions in the 1st and 3rd treatment weeks to increase treatment attendance and adherence, per previous uses of the Contingency Management procedure [48]. Session 1 will focus on change motivation, change commitment, and making an abstinence plan. Session 2 will focus on personalized feedback, reassessing change commitment, and reevaluating the change plan. There will also be a 15-30min wrap-up and referral session with the therapist during the run-down week. Referrals will be tailored to the subject's needs. If the subject leaves the study sooner, every effort will be made to contact the subject and provide referrals. The PI or a graduate-level therapist will conduct the Motivational Interviewing and referral sessions. Graduate-level therapists will be trained by the PI using exercises and role-plays, and using the study *Motivational Interviewing Manual* (see attached). All therapy sessions will be recorded locally to

secure, on-campus, UIC-controlled computers using HIPAA compliant WebEx software, with session recordings uploaded to the Psychology Department's secure server and deleted after recording. Graduate level therapists will attend weekly supervision with the PI, where cases and recordings will be reviewed for compliance.

*Treatment Measures.* Efficacy and safety will also be monitored during treatment visits using the following measures:

*1. Drug Use Measures*. At every treatment visit (run-up, run-down and treatment weeks) subjects will complete urine drug screens with a Readitest 6 Cassette urine drug screen (Redwood Toxicology Laboratory), and a *Timeline Follow Back* of drug use since their last visit (see attached *Weekly Timeline Follow Back* form). Drug Use measures are expected to take 10 minutes at each treatment visit.
*2. Safety Measures.* At each check-in visit, a trained research assistant will take subject vital signs, review the *Adverse Events Form* (see attached) and *Concomitant Medication Form* (see attached) with the subjects, and administer the screening version of the *Columbia-Suicide Severity Rating Scale (C-SSRS)*, a validated instrument for monitoring for suicidal ideation in clinical trials [49], see attached. Female subjects will also receive a pregnancy test every two weeks.
*3. Adherence Measures.* Each urine sample taken as part of *Drug Use Measures* will also be tested by trained research staff for riboflavin florescence. All urine samples will be collected in containers coded with subject number and visit, and disposed of immediately after testing. Medication Event Monitoring System caps that record bottle openings will be used to dispense take-home doses, with data downloaded at each treatment visit when the next dose is dispensed. Additionally, self-reported adherence will be briefly assessed by the research assistant at each visit as part of the *Timeline Follow Back*. Adherence measures will not require any additional subject time at treatment visits.

Total Participant Time Commitment and Compensation. Participants are compensated $50 for the initial 3-4 hour Screening Session, which is paid separately through the separately approved screening protocol. Total subject time in study-specific procedures (i.e. excluding the initial screening) is expected to be approximately 26 hours in 20 visits to the clinic over 7 weeks for subjects in the *Treatment Study*. For each of the five 2 hour Reward Functioning Assessment Sessions, subjects will receive $20, plus their winnings from the tasks, which can range from approximately $5.00 - $12 and are estimated at an average of $8.00 per session. For the consent visit and each of the 18 treatment visits (through run-up, run-down and treatment) subjects will receive a base payment of $5. Thus, base subject payment for the *Treatment Study* (assuming subjects attend all visits) will be $195, plus any winnings from the tasks. Participants in the two Contingency Management groups will also have the opportunity to earn money for submission of cocaine negative urines during the 4 treatment weeks. Possible earnings range from $0 to approximately $880, and based on our previous trial using this same procedure, we estimate average earnings will be around $180. All subjects will also receive either parking validation or round trip public transportation passes at

each visit to the clinic, and also can opt to have an Uber called for them for one session per week, to make it easier to attend visits.

## 7.0 Expected Risks/Benefits

Although the medication treatments, behavioral treatments and assessments to be administered in this study have been extremely well studied, including in individuals with CUD, and a favorable risk/benefit profile is expected, there are still possible risks. Risks, protections against risks, and benefits are described below.

Potential Risks and Protections Against Risks:

*1. Emotional discomfort from questionnaires or tasks*: Some of the questions asked may be considered sensitive information, including drug use history and psychiatric symptoms. Answering these questions may be psychologically discomforting to some subjects. To reduce this risk, we make clear that we ask for sensitive information as part of the consent process. Similarly, some of the pictures used in the behavioral tests contain emotionally negative material (e.g. war scenes, attacks) that may be mildly upsetting to some subjects. Participants will be informed during the consent process that they may view such pictures, will be asked to report to the research assistant if they have any particular phobias or triggers, and told to inform the research assistant if they continue to be bothered by any pictures afterwards. Any subjects expressing continued distress after viewing the pictures will be counseled by a trained staff member or the PI.
*Experience to date in this study*: We have not had any reports of emotional discomfort from questionnaires or pictures.

*2. Confidentiality:* Given the sensitive information collected as part of the study, there are may also be social, legal or economic risks associated with loss of confidentiality. Please see *Section 13.2, Subject Confidentiality*, for details on steps we take to minimize these risks.
*Experience to date in this study:* We have not had any breaches of confidentiality.

*3. Psychophysiological monitoring:* We will monitor psychophysiological responses using conductive electrodes attached to the skin of subjects with an adhesive. Approximately 50% of subjects report mild discomfort or irritation as a result of cleaning the sites to apply the sensors, but this should be transient, lasting 15min up to an hour. A few individuals experience red marks at the site of application that can last up to one day after the application. A very small number of subjects (approximately 1 in 100) with particularly sensitive skin may experience marks that last longer (up to a week). This risk will be minimized by asking subjects about sensitive skin or previous allergic reactions to skin products and by rigorous training in correct skin cleaning procedures for research assistants. There are also risks of electrical hazard, when subjects are attached to conductive equipment. To reduce this risk, all equipment will be appropriately grounded and shielded, and stimulus equipment will be optically isolated from the subject making any electrical hazard to the subject extremely unlikely. There are infection risks when subjects' skin is in contact with equipment. To reduce this risk, all surfaces placed in contact

with the subjects' skin are disposable, and all equipment will be thoroughly cleaned between sessions.
*Experience to date in this study*: We have not had any reports of serious skin irritation, electrical hazard or infection.

3. *Study Medication*. Dextroamphetamine is extremely well understood in terms of benefits/effects and risks and has been studied extensively over the past 60 years in many populations. It has been investigated in individuals with CUD and other stimulant use disorders in many previous protocols [47,50–53] Previous studies have generally used fixed doses of the extended release preparation proposed here. When administered in a controlled trial, dextroamphetamine carries modest risks overall. We have a current *Investigational New Drug Protocol* for this study (IND #131221).
*Risks During Regular Use*: **Serious but rare risks** of dextroamphetamine include: 1. Heart related problems, including stroke, heart attack and increased blood pressure and heart rate. We protect against this specific risk by requiring a full ECG and physical examination prior to enrollment in the study, with our study physician excluding individuals with contraindicating cardiovascular conditions, and by reviewing subject vitals at each visit. There have been no reported serious adverse cardiovascular events in closely monitored cocaine dependent populations [47,50,51,53–56]. Any individuals reporting symptoms of cardiovascular complications during the study will be immediately evaluated by the study physician to determine treatment needs. 2. Psychiatric problems, including mania, psychosis and aggression. We protect against this risk by excluding individuals with active psychiatric disorders aside from CUD. We additionally monitor for suicidal ideation at every study visit using a validated screening. Psychiatric adverse effects are rare, even in studies of individuals with amphetamine and cocaine use disorders [47,50,51,53–56]. Any individual showing symptoms of mania, psychosis, suicidality or aggression during the study will be immediately evaluated by the PI, a licensed clinical psychologist, to determine treatment needs. 3. Peripheral vasculopathy, including Raynaud's syndrome. Vasculopathy symptoms are generally intermittent and mild, and reverse with discontinuation of the drug. We protect against this risk by excluding individuals with other medical complications that might put them at risk for vasculopathy, and reviewing reported AEs for potential vasculopathy at each visit. There have been no reports of serious vasculopathy in studies of individuals with CUD taking this drug [47,50,51,53–56]. Any individuals reporting symptoms of vasculopathy during the study will be immediately evaluated by the study physician to determine treatment needs.
**More common but less serious risks** include: allergic reactions, blurred vision, fast or irregular heart beat, decreased appetite, restlessness, anxiety, tremors, headache, trouble sleeping, dizziness, stomach upset, weight loss, dry mouth, diarrhea or constipation, impotence, changes in sex drive, frequent or prolonged erections (see attached *Package Insert*). In addition to protections against specific risks of dextroamphetamine outlined above, our general risk protections include: 1. A gradual 1-week run-up under close supervision by study staff. 2. Regular evaluation of adverse events, side effects, vitals and suicidality at each treatment

visit. Our *Adverse Events Form* includes both open-ended questions and a checklist of common side-effects completed by the subject. *On the open-ended section*: If any key symptoms for heart problems, mania/psychosis or Reynaud's syndrome are spontaneously endorsed, the research assistant will contact the PI (for psychiatric symptoms) or the study physician (for medical symptoms) regardless of reported severity. For any other adverse events/side effects spontaneously endorsed on the open-ended questions, the research assistant will ask additional questions to determine date of onset, pattern, duration and any precipitating events, and degree of interference with life activities. Endorsement of any serious adverse events per FDA criteria, or events that do not meet FDA for an SAE criteria but are endorsed at a "severe" level (upon questioning are interfering with the subject's daily activities) will result in immediate consultation with the PI and study physician. *On the checklist section*: The research assistant will overlay the checklist with a transparency indicating symptoms of particular concern (arrived at in consultation with our study physician) and when to contact the study physician or PI (see *Adverse Events Overlay*, attached). Of note, any symptom endorsed at a severe level will result in contacting the physician and PI. For vitals, if blood pressure is $\geq$ 140/90 (either systolic or diastolic is exceeded), or resting heart rate is above 100bpm, the RA will hold medication and immediately consult with the PI and study physician. The PI and study physician will make the determination whether to continue, temporarily hold or discontinue medication, and make referrals for any needed medical or psychiatric follow up. In either of these cases, the study physician may also consult our clinical consultant, who is dual-board certified in internal medicine and psychiatry, in the event a second opinion is required. Participants requiring additional medical evaluation to make a determination will be transported to the study physician's office via cab or ride service. Any patient showing signs of an emergent SAE (e.g. fainting, hypertensive crisis) will be transported immediately to the emergency room via ambulance. For suicidality, subjects will also respond to the *Columbia Suicide Severity Rating Scale* (CSSR-S) at each visit. CSSR-S evaluations will be conducted by staff who have completed training created by the developers of the scale and been certified. Any endorsement of suicidality will result in medication being held and the PI being immediately contacted to evaluate the subject. Labeling for pill bottles will include the PI's telephone number and institutional information, although there has never been an event requiring emergency breaking of blind at the previous study site.

*Risks During Withdrawal:* There are no known major medical risks to abrupt discontinuation of dextroamphetamine [57]. The withdrawal syndrome consists of dysphoria, irritability, changes in sleep, appetite and craving. We have included a drug taper to avoid the possibility that these withdrawal symptoms might trigger relapse in individuals abstinent at study completion. All reasonable efforts will be made to offer dose tapering to subjects who withdraw early. If someone withdraws due to a positive COVID test, it would be unsafe for us to see them to provide them with a taper. Thus, for the duration of the pandemic, we will issue a sufficient amount of medication for our normal tapering schedule (135mg) to each individual at the start of the treatment month. This will be marked as "for emergency use

under the direction of the physician only". This is similar to our current practice of issuing one day of emergency medication (60mg) in case of missed sessions, which we have been doing without major problems throughout the study. Then, in the even that a participant cannot be safely seen for a run-down, study staff can supervise the participant tapering at home via telehealth, using either phone or UIC-approved tools of WebEx or PHI Zoom. We are aware of the conditions for using these tools (*https://hipaa.uillinois.edu/telehealth-uic/*) and will follow best-practices in the event this is needed. The ART Lab has procedures in place to contact subjects who miss scheduled study visits. These procedures include obtaining initial consent to follow up by telephone, text, e-mail or, if necessary, certified mail to reach the subject or an identified "locator" who can assist in obtaining current contact information. We update this information weekly during the study using our *Weekly Locator Form* (see attached)

*Risks During Pregnancy:* Dextroamphetamine is Category C for use during pregnancy. There are no adequate and well-controlled trials to describe the full spectrum of potential toxic effects of dextroamphetamine on the fetus. No pregnant women will be permitted in study and women and men will be advised to use contraceptive measures that we provide at the clinic. Pregnancy tests will be performed at intake and every two weeks during the study. A positive pregnancy test will result in holding study medication, consultation with the study physician, and referral of the patient for medical follow up. Confirmed pregnancy will result in discontinuation of the study medication and referral for other treatment.

*Risks in Combination with Other Recreational Drugs.* Amphetamine can be safely co-administered with cocaine, the most likely drug combination in our subjects [55]. Previous dextroamphetamine trials [47,50,51,53] in over 200 patients with CUD have not observed hazardous interactions with recreational use of other illicit drugs, or major adverse events, despite the fact that many individuals in these studies were using cocaine and other illicit substances concurrently. Indeed, the dose of dextroamphetamine proposed (60mg) has been used for comorbid cocaine and heroin dependence in combination with methadone over 24-week period with no serious adverse events [51]. However, individuals with current use of amphetamine, >50 lifetime uses of amphetamine, or previous Amphetamine Use Disorder will be excluded, and use of other recreational drugs will be monitored at every check-in visit using breath, urine and self-report measures for potentially hazardous combinations.

*Experience to date in this study*: We have had one SAE to date, which was determined to be not medication related. A subject with a previous history of throat abscesses underwent an overnight hospital stay for removal of an abscess. Medication was temporarily held so as not to complicate treatment. He returned to the study and completed the study on medication. We have had 13 AEs evaluated by the study physician. Common AE's included headache and sleep disturbance which are expected side effects of the medication. The majority were determined to require no change in medication, as they resolved spontaneously. Only two required medication hold or discontinuation. An increase in blood pressure resulted in a medication hold. With reminders about importance of compliance with previously prescribed medications for hypertension, this subject was able to

complete the study on medication. New onset of possible hypomania (unusually increased talkativeness and sociability, markedly increased energy level and decreased need for sleep, inappropriate communications with staff indicating grandiosity) was detected in a subject with no reported history of mania. This resulted in medication discontinuation. This event was detected during the run-up week of the study, medication was immediately discontinued, and the subject completed the remainder of the study off medication. Mania is also a possible, although rare, side-effect of dextroamphetamine, and is listed explicitly on the consent form. Thus this did not represent an unexpected adverse event. In fact, no negative impacts or sequelae of this event were reported by the subject. These events have been reviewed by our DSMB at the most recent yearly meeting, with no changes required to our study protocol.

*4. Behavioral Treatment***.** Participants in the Contingency Management groups will receive rewards for abstinence. Rewards will be given in the form of small cash or e-payments (≤ $25) or gift cards, which could potentially be used or sold to buy drugs. We attempt to minimize this possibility by restricting the amount of awards given in cash to <$25. Previous studies using similar reward procedures have generally demonstrated a beneficial, rather than detrimental, effect of such procedures on drug use [47,58], but it is not possible to completely eliminate this risk.
*Experience to date in this study*: We have not had reports of subjects using rewards to purchase drugs.

5. *Alternative Treatments.* There is also the risk that participating in this study could preclude someone from obtaining alternate, more effective treatment. We believe that our therapeutic interventions provide treatment that is considerably superior to most, if not all treatment opportunities in the community. Nevertheless, we will refer patients to other facilities upon request or when required by other circumstances. We will also conduct regular literature searches on alternative treatments, and in the event that an alternative treatment emerges with clearly superior efficacy, we would suspend the current study and provide all subjects with referrals for this alternative treatment.
*Experience to date in this study*: We have made referrals to other treatment as needed (e.g. if subjects desired to withdraw from the study due to time conflicts). No alternative treatments with better efficacy have emerged.

Potential Benefits: Cocaine use leads to devastating consequences on a personal and societal level. Research participation may assist subjects in abstaining from cocaine during treatment and beyond. This project aims to evaluate a new medication/behavioral treatment combination that is expected to be more effective than other approaches. Both the selected medication and behavioral treatment have shown preliminary evidence of benefit in helping patients reduce cocaine use. Further, this study will pilot new approaches to evaluating treatments that may lead to more personalized and effective treatments for CUD. Thus, by taking part in this research subjects will also benefit others with similar problems because this study is designed

identify what types of treatment work best and for whom.

## 8.0 Data Collection and Management Procedures

Data sources include urine samples, paper forms containing interview and questionnaire responses, electronic records of responses to questionnaires and tasks from screening and Reward Functioning Assessment sessions, video and voice recordings of therapy sessions.

All urine samples will be collected in containers coded with subject number and visit, and disposed of immediately after testing. Paper forms will be kept in locked cabinets in a locked room in the ART Lab. Only the PI and laboratory staff will have access to these paper forms. Wherever possible, subjects will enter information directly into electronic Access databases, or data will be collected automatically by computer programs (e.g. during reward functioning assessment and fMRI sessions). If this is not possible (e.g. for safety forms that require on-the-spot inspection by study staff), trained research assistants will enter data into an existing, relational database. Allowable input values will be restricted to standardized Access entry forms so as to maintain data integrity. All observations will be double-entered to verify accuracy, with any problems detected discussed with the PI. If necessary, re-training of research assistants will be conducted. After the conclusion of the study, therapy session recordings will be transcribed by a HIPAA-compliant service under contract with UIC, and original recordings will be securely deleted. Transcripts will be maintained in the same manner as other electronic study data for future analysis, as language used in therapy can be analyzed to provide insight into processes active during therapy [59]. fMRI session data will also be stored in the same manner on the same secure server. Paper and electronic records of questionnaire and task data will identify study subjects only by a study code, with a separate electronic file (part of our separately established screening protocol and data repository, see separately submitted protocol) linking study codes to identifiable subject information.

Per our separately submitted screening and data repository protocol, we do not plan to delete this separate linking file when data collection is complete. Please see *Section 13.2, Confidentiality*, and our separate screening protocol for additional details and justification. Thus, coded data will NOT be treated as de-identified. Data will be stored for a minimum of 6 years, in accordance with NIH policy, and may be stored indefinitely.

## 9.0 Data Analysis

Primary data analysis will be conducted by the PI. As this study is funded by a Career Development Award from NIDA, the PI will also consult with her designated statistics mentor, Dr. Charles Green, an expert in Bayesian statistics for clinical trials at the University of Texas Health Science Center at Houston. In the event that Dr. Green needs direct access to the data set in this capacity, the PI will follow the guidelines in *Section 13.2, Subject Confidentiality*, including complete de-identification, or if this is not possible, implementation of a Data Use and Transfer Agreement.

Randomization: Participants will be assigned to conditions via urn randomization for even distribution of past 30 days cocaine use (<=15 days vs. >15 days) and baseline SHAPS score (above vs. below an established clinical cut point for anhedonia).

Overall Data Analytic Strategy: The analytic strategy will use parallel Frequentist and Bayesian analyses. Together, these two complementary approaches provide a more accurate evaluation of hypotheses when the sample size is small [60]. In particular, although conventional Frequentist approaches to statistical testing testing permit rejection of the null hypothesis given the observed data or data more extreme, Bayesian analysis permits conclusions regarding the alternative hypothesis: the probability that a subgroup effect of a specified magnitude exists [61,62]. Thus the Bayesian evaluation is considered our primary statistical approach for this initial proof-of-concept study.

Generalized linear modeling and mixed effects models (R v.3.2, WinBUGS v.1.4) will comprise the primary analytic methods. Primary Bayesian analyses will use vague, neutral priors: ~Normal($\mu = 0$, $\sigma^2 = 1 \times 10^6$) for coefficients in the log-form and ~Gamma (Shape = 0.001, Inverse Scale = 0.001) for the dispersion term; sensitivity analyses with pessimistic priors will also be conducted to assess robustness of findings. Clinical outcomes will be analyzed on an intent-to-treat basis, with sensitivity analyses of robustness to assumptions about missing data. For each aim, parallel analyses will be conducted in the full study group (N = 80) and the sub-set (N = 24) with fMRI measures. Significance for Frequentist outcomes will be set at $p = 0.05$, and a Bayesian probability of 80% or greater that an effect exists will be considered to merit further consideration.

Severity Measures: A composite score of CUD severity will be derived from the summed z-scores of severity from the SCID, TLFB and ASI.

Anhedonia Measures: Principal components analysis will be used to determine whether anhedonia measures can be reduced into composites representing consummatory, motivational and reward learning functions, as expected. If this is inappropriate, we will use individual measures with pessimistic priors to address multiplicity.

Potential Confounds: Per published guidelines on confounding in clinical trials [63,64], we will assess all major demographic and baseline variables, and those that either differ between treatment groups or correlate with anhedonia, *and* also relate to outcomes (i.e. severity, abstinence) will prompt two sets of analyses, one with the variable as a covariate and one without, to assess confounding.

Hypothesis Testing:

*Specific Aim 1.* Our *working hypothesis* that higher anhedonia at baseline will relate to greater addiction severity will be tested using linear regression to examine the relationship between the composite of CUD severity, and anhedonia composite scores at baseline.

*Specific Aim 2.* Our *working hypothesis* that higher anhedonia at baseline will predict less chance of poorer outcomes in Contingency Management will be tested using generalized linear modeling. Initial abstinence, defined as two consecutive

weeks of cocaine-negative urines, will be the primary clinical outcome. Treatment Effectiveness Scores, defined as total number of cocaine negative urines submitted across the four treatment weeks, will be a secondary outcome.

*Specific Aim 3***.** Our *working hypothesis* that anhedonia will mediate the effects of ER-AMP on outcomes will be tested utilizing Bayesian Structural Equation Modeling (SEM; MPlus v.7.2) to model indirect effects of treatment group (CM/PL, CM/ER-AMP, ER-AMP only) on outcomes, with change in anhedonia over treatment as the mediator. Of note, change measures are sometimes ill-conditioned (e.g. large error terms, little reliable variability), and if this is the case here, we will use anhedonia at a specified midpoint instead. Initial abstinence, defined as two consecutive weeks of cocaine-negative urines, will be the primary clinical outcome. Treatment Effectiveness Scores, defined as total number of cocaine negative urines submitted across the four treatment weeks, will be a secondary outcome.

Power Analysis: In a Bayesian framework, the goal of a proof-of concept study is to produce the best possible estimate of an effect's likelihood and size, to aid decision-making. Thus, the sample was selected to be the maximum feasible within the financial means available. Traditional power analysis bears on the probability of a false negative, not the probability the alternative hypothesis is true (the focus of our analysis). However, for thoroughness, we conducted Frequentist power analyses for the full sample (N = 80), moderate attrition (N = 64), and fMRI sub-sample (N = 24). For Aim 1, which focuses on the correlation between anhedonia and addiction severity, at $\alpha$ =0.05 and 80% power, the full sample could detect a small $r$ =.31, with attrition a small-to-moderate $r$ =.34 and in the fMRI sub-sample a moderate $r$ =.6. For Aim 2, *Preliminary Data* and [19] suggest a range of $d$ = 0.68-1.60 for the effect of anhedonia on Contingency Management outcomes, depending on measure (self-report vs. imaging). At $\alpha$ =0.05 and 80% power, the full sample could detect a moderate $d$=.64, with attrition a moderate $d$=.72, and the fMRI sub-sample a large $d$=1.04. For Aim 3 Monte-Carlo simulation indicated a prohibitively large sample for this award (N = 200) would be needed to reach a definitive Frequentist conclusion about a moderately-sized mediational effect. A major advantage of our Bayesian approach is that we will be able provide information about the likely magnitude of this effect, even in this smaller study.

Trial Termination Criteria: Because this study is relatively small (group sizes from 20 – 30), and is designed to test a potential moderator of outcomes in the context of an already established behavioral treatment and off-label use of an FDA-approved drug already suggested to be efficacious for CUD, no interim efficacy analysis is planned and no trial termination criteria are set.

## 10.0 Quality Control and Quality Assurance

Primary responsibility for quality control and assurance will rest with the PI and her team, and data quality will be monitored in weekly lab meetings. Most questionnaire data is entered directly into the computer by the subject, reducing data entry error. All behavioral and psychophysiological data is collected automatically by the computer using professional programs designed for this purpose. All hand-entered data

(miscellaneous study forms) will be double-entered into an existing, relational database, with any inconsistencies examined and resolved. Allowable input values will be restricted to standardized Access entry forms so as to maintain data integrity. All psychophysiological data will be scored in two passes by independent raters, with the PI or a trained study coordinator resolving any inconsistencies.

## 11.0 Data and Safety Monitoring

This protocol will continue to be monitored on a yearly basis by the Data Safety Monitoring Board for the Center for Neurobehavioral Research on Addiction (CNRA) at UTHealth, an umbrella board that monitors all studies conducted in the CNRA, where the study is currently located. The board has agreed to maintain this duty after the study moves to UIC. The board is already familiar with the protocol, having conducted the initial review and one interim review so far, so this will assist with continuity in maintaining safety in this protocol. Remote monitoring by DSMBs is both common and highly feasible. The PI will attend via telephone or video conferencing all open meetings of the DSMB, and any other sessions as requested by DSMB members. Please see attached sponsor-approved *Data and Safety Monitoring Plan* for further details on the DSMP.

## 12.0 Statistical Considerations

Not applicable – see Data Analysis Plan above.

## 13.0 Regulatory Requirements

### 13.1 Informed Consent

Consent for the current study will be obtained by the PI or trained study staff at the conclusion of the screening process. Participants will be provided with a verbal description of the study purpose and procedures, and then allowed ample time to read over the consent and then discuss with the PI or staff. If at any time the individual states s/he is unsure about signing the consent or needs more time to consider, the individual is given the option to leave and call back with a decision when ready. After 24 hours, we contact the individual and ask for a decision, and schedule a time to return to sign the consent if the decision is yes. All subjects will be required to provide a brief accurate description of the study procedures in their own words before signing, to ensure comprehension. All subjects will be provided with a copy of the informed consent.

It is expected that the PI will consent the majority of subjects. However, study staff will also be trained to perform informed consent in the unlikely event that the PI is unavailable. In addition to basic human subjects training, staff members conducting informed consent will be required to have completed study specific training, consisting of a discussion with the PI on the key elements of the informed consent, a role-play of informed consent observed by the PI, with feedback given to the trainee, and an accurate informed consent session with an actual subject observed by the PI. In the event that informed consent is not obtained by the PI, subjects will be scheduled for a brief meeting with the PI to

discuss the study prior to first medication dose, so that the PI can ensure subject comprehension and to allow the subject to be familiar and comfortable with the PI in the event that they need to report any issues to the PI.

Original informed consent documents will be stored in a separate binder, in order, for ease of review by regulators. A copy of the informed consent will also be stored in the subject's paper file, to ensure redundancy in recordkeeping for this key regulatory document. Both original and copied informed consents will be stored in a locked cabinet in a locked room of ART Lab.

### 13.2 Subject Confidentiality

During study performance, personally identifiable information is necessary to facilitate appointments, reminders, and subject tracking. We may contact subjects via phone, text, or e-mail with appointment reminders. To minimize risks to subject confidentiality we will ascertain their contact preferences and obtain contact information directly from them. Appointment reminders will not indicate the type of study, and will only reference an "appointment at UIC". We may also contact designated subject locators, in the event that a subject does not arrive for a scheduled visit and is not reachable by other methods. We will obtain names and contact information for these individuals from subjects, and clearly explain when and how these locators may be contacted. Contacts with locators similarly will not indicate the purpose of the study and will only reference an "appointment at UIC".

To reduce risks after data is collected, we have rigorous procedures in place to ensure confidentiality, including locked cabinets for confidential files, subject coding, secure computer systems, and rigorous training of personnel (please see *Section 8.0, Data Collection and Management Procedures*, for additional details). Computer systems are secure and strictly monitored by University IT staff. Laboratory staffers are trained in confidentiality of subject information. No information is allowed to leave the lab or to be accessed by a computer outside of the university's secure computer system, and all data are further protected by permissions and passwords given only to necessary research personnel. As described in *Section 8.0, Data Collection and Management Procedures,* paper and electronic records of questionnaire and task data will identify study subjects only by a study code, with a separate electronic file linking study codes to identifiable subject information. We have already obtained a *Certificate of Confidentiality* for this study to provide additional protection for sensitive information (see attached).

We do not plan to destroy the file that links codes to identifiers at the conclusion of this individual study. Our experiences have indicated that maintaining persistent records of previous subjects is important for safety and research reasons. Substance Use Disorders are relapsing health conditions, and subjects often call in repeatedly to complete subsequent treatment studies in the same laboratory (see also our separately submitted screening and data repository

protocol for further discussion of how we address this). Maintaining persistent records of which studies subjects have completed and when allows us to reduce subject exposure to risks by minimizing repeat medical or psychiatric screenings, and by using key information gathered in one treatment study to exclude the subject from subsequent studies (e.g. if the subject had an adverse response to the drug administered). In addition to these safety reasons, there are also strong scientific reasons for maintaining persistent records of subject identity across studies. Subsequent secondary analyses (e.g. of which characteristics predict subject success in therapy) often combine outcomes across trials to increase the accuracy of prediction. This requires knowing which subjects are unique, and which have completed more than one trial. Given these reasons, we plan to maintain these separate code files in a separate Access database stored on the Psychology Department's secure, encrypted and password protected server. Thus even coded data will NOT be treated as de-identified. Data will be stored for a minimum of 6 years, in accordance with NIH policy, and may be stored indefinitely.

Participants will not be identified in any publications resulting from this study. We will share final data in accordance with NIH policy. Final data will be made available upon direct requests to the PI. Identifiers will be removed from the data before sharing. So as to fully protect the subjects, we will evaluate each data request to ensure that special circumstances do not exist that would permit anyone to deduce the identities of individuals from the shared data. If such case exists, we will share the data on the basis of an agreement that will provide that the data be used solely for research and that no individuals will be identified in any manner, that data will be secured by equivalent electronic safeguards, and that once data analysis is complete, the data will be returned or destroyed.

### 13.3 Unanticipated Problems

Unanticipated problems will be reported to the sponsor, DSMB and FDA per the guidelines laid out in the attached DSMP. Unanticipated problems will be reported to the IRB per UIC policy, as follows (only unanticipated problems applicable to this single-site protocol are listed):

1. Events Requiring Reporting to the IRB within 5 Business Days of the Investigator Becoming Aware
    1. Local, serious adverse events which are unanticipated
    2. Serious unanticipated problems
    3. Major protocol violations that are unplanned and unintentional
    4. Apparent serious noncompliance
    5. Apparent continuing noncompliance
    6. Changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects
    7. Incarceration of a subject
2. Events Requiring Reporting to the IRB within 15 Business Days of the Investigator Becoming Aware

1. Local adverse events or problems that are unanticipated and, while not meeting the criteria of serious, indicate research is associated with a greater risk of harm to subjects or others than previously known.
2. New information indicating an unexpected change to the risks or benefits of the research (i.e., an unanticipated problem).
3. Administrative hold by investigator, sponsor, regulatory authorities or other entities.
4. Other events requiring prompt reporting by sponsor.

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