Developing adaptive interventions for cocaine cessation and relapse prevention; Using event-related potentials to predict treatment outcomes in cocaine use disorder ("Adaptive trial")

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Protocol Title:	Developing adaptive interventions for cocaine cessation and relapse prevention; Using event-related potentials to predict treatment outcomes in cocaine use disorder ("Adaptive trial")
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Study Coordinator:	Jessica Vincent
Population:	N = 160 adults (18-60 years old) with cocaine use disorder recruited from the Houston metropolitan area
Number of Sites:	Single site
Study Duration:	Four years
Study Duration per subject:	14 weeks, with 3 visits per week for a total of 42 study visits

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Project Summary

Drug addiction is a chronic, devastating, but *treatable* disorder, for which there exists a growing armamentarium of evidence-based interventions, including pharmacotherapies and psychotherapies. A core principle of drug addiction treatment, however, states that *no single treatment is appropriate for everyone*; rather, treatments need to be adjusted based on patient characteristics and response in order to be maximally effective. Ideally, clinicians would identify a sequence of interventions that works best across different stages of addiction treatment, from abstinence initiation to relapse prevention. Adaptive treatment interventions have been used successfully to inform this sequential clinical decision-making process. For cocaine use disorders (CUD), the most potent intervention currently available for initiating abstinence is behavior therapy using contingency management (CM) procedures. Intensive CM has been shown to produce initial cocaine abstinence rates of 40%, unmatched by all other forms of behavioral or pharmacological treatment, making it a prototypical first-line therapy for CUD. Importantly, achievement of initial abstinence predicts future abstinence. For the clinician, these research findings translate into a straightforward question: *Can we drive CM response rates even higher with targeted adjunctive interventions?*

The proposed sequential, multiple assignment, randomized trial (SMART) will provide the data needed to answer this question. First, we will determine whether Acceptance and Commitment Therapy (ACT) in combination with CM increases initial treatment response rates. We hypothesize that four weeks of treatment with ACT+CM will produce higher abstinence rates than initial treatment combining standard Drug Counseling with CM (DC+CM). The hypothesized synergism of ACT+CM on primary treatment mechanisms of experiential avoidance and reward sensitivity, respectively, will be examined. Second, for patients who do not respond to initial treatment, we will examine whether dopamine-targeted pharmacotherapy is an effective augmentation strategy. Specifically, we hypothesize that continued ACT+CM treatment with modafinil augmentation will be most effective in promoting abstinence relative to treatment combinations involving continued DC and/or placebo. Third, for patients who respond to initial treatment, we will assess the relative benefit of continued treatment with ACT+CM, as compared to DC+CM, to prevent relapse. ACT emphasizes goal-directed actions based

on values that are intrinsically motivating, and is thereby expected to be a more effective intervention for extending the duration of abstinence following initial treatment with intensive CM.

In summary, results from this Stage II (PA-13-078) project should support a Go/No Go decision about further Phase III, confirmatory studies. The primary aims of this project address an important NIDA research priority and have the potential to significantly impact how we tailor treatment of CUD to maximize outcomes.

Background Information

Cocaine use disorders comprise a public health problem in need of new treatment approaches. Cocaine affects multiple brain circuits, with prolonged exposure compromising cognitive and behavioral processes associated with reward, motivation, learning, and inhibitory control.[1-3] The complexity of the disorder has presented treatment challenges. Controlled studies have demonstrated effectiveness for several types of behavioral therapies, including cognitive-behavioral therapy (CBT), motivational interviewing (MI), and CM,[4,5] along with promising pharmacotherapies.[6,7] Despite the growing armamentarium of CUD interventions available, the treatment field continues to rely on fixed-intervention models (all patients offered the same type or dosage of intervention) which has fallen short of substantially improving clinical care and outcomes.[8] Adaptive intervention methodology responds to the call *for new behavioral and integrative treatment development research to improve effectiveness* by allowing for greater individualization or "tailoring" of treatment to the needs of the individual (PA-13-077; NIDA Principles of Drug Addiction Treatment, 2012).[9]

An adaptive treatment intervention (ATI) for CUD aims to answer the ultimate clinical question -- *what sequence of interventions work best for each individual across the stages of addiction treatment, from abstinence initiation to relapse prevention?* The sequential multiple assignment trial (SMART) is an experimental design used for constructing empirically-supported ATIs. The first decision stage of the SMART provides data for identifying the best initial treatment. The second decision stage of the SMART compares second treatment options for initial treatment responders/non-responders. We propose a SMART design to find the sequence of integrated therapies that will achieve the best possible outcomes for both responders and non-responders over the course of CUD treatment. The following sections summarize the conceptual framework along with **supporting data** for the hypothesized ATIs, shown below.

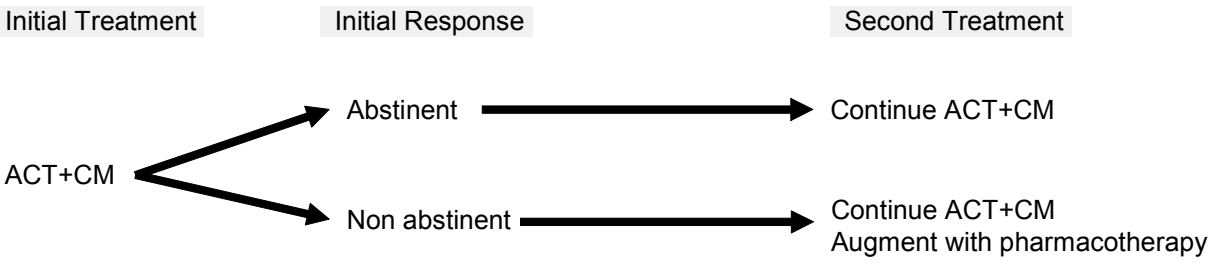


Figure B.1.2. Hypothesized adaptive treatment interventions using integrated therapies.

CM is an efficacious intervention for initiating abstinence from cocaine. Based on operant learning principles, CM interventions seek to increase availability of reinforcement derived from non-drug alternatives, increase constraints on reinforcement derived from substance use, and deliver these environmental contingencies to accommodate the temporal discounting behavior that is characteristic of substance use disorders.[10] An extensive literature of controlled-studies documents the success of these interventions.[11] We [12] and others [13-15] have implemented high-magnitude CM interventions during initial weeks of CUD treatment to produce abstinence rates as high as 40%. To our knowledge, CM is currently the most reliably effective method for facilitating initial abstinence. Given the robustness of initial abstinence in predicting long-term abstinence, e.g.[16,17] it behooves practitioners and treatment researchers to find new approaches to increase the number of CM "responders".

Adding acceptance and mindfulness-based treatment strategies with CM may lead to improved abstinence outcomes. While highly effective, CM response is variable with significant rates of non-response, even to high-magnitude rewards. Little is known about individual-level characteristics associated with CM response, with the exception of intake urine status considered a marker of disorder severity.[15,18,19] To our knowledge, we reported the first study examining ***modifiable*** cognitive-affective characteristics associated with CM response.[20] Ninety-nine treatment-seeking patients with CUD received 4 weeks of high-magnitude CM-based treatment targeting abstinence initiation.[12] A post-hoc comparison of responders, i.e., those achieving two consecutive weeks of cocaine-negative urine screens, and non-responders was performed on pretreatment measures of negative affect, experiential avoidance, cocaine craving/withdrawal symptoms, and impulsivity**.** Notably, while the groups reported similar levels of negative affect, impulsivity, and craving/withdrawal, the non-responder subgroup had higher levels of experiential avoidance (EA). In other words, non-responders differed from responders in their approach to handling negative internal experiences (e.g., craving, negative emotions). EA, or the tendency to avoid or respond inflexibly with drug use behaviors when experiencing aversive states, is thought to provide negative reinforcement for continued use despite the availability of competing non-drug rewards. These findings suggest that targeting problems in EA and behavioral flexibility may prove to be effective in enhancing response to CM.

Acceptance and Commitment Therapy (ACT) is a third generation CBT intervention, emphasizing the role of EA and inflexibility as key mechanisms underlying and positively correlated with psychopathology including drug use.[21,22] ACT uses experiential exercises and metaphors to change the function of distressing thoughts and feelings, essentially helping clients make decisions and choices based on personal goals and values rather than on avoidance or control through substance use.[23] By reducing EA and improving distress tolerance, *ACT may help facilitate sensitivity to, and contact with, non-drug sources of reward made available via CM*. As shown in **Figure B.1.3**, these purported dual mechanisms of action provide a highly plausible rationale for combining ACT with CM as a way to strengthen treatment response, especially for CUD adults who exhibit high levels of EA and relatively low sensitivity to reward contingencies.

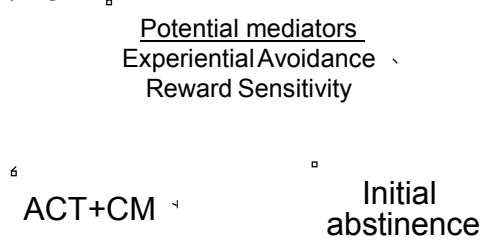


Figure B.1.3. Hypothetical model of experiential avoidance and reward sensitivity as mediators of the effect of ACT+CM on achievement of initial abstinence.

Patients who do not respond to initial treatment may arguably be most in need of adjunctive pharmacotherapy as a secondary treatment. Studies investigating the neurochemistry of CUD have shown that low dopamine transmission is associated with poor response to CM treatment,[24] suggesting that fundamental biological differences in the functioning of the brain reward system explain the inability of some patients to respond to alternative reinforcers.[25] The recommendation follows that

pharmacological interventions that target striatal dopamine signaling might serve as a therapeutic adjunct for enhancing CM responding in this subset of patients. Modafinil has both dopaminergic and glutamatergic activity that may be useful for cocaine dependence. In three independent human laboratory studies, modafinil has been shown to reduce cocaine induced euphoria.[26-28] Modafinil was found to reduce cocaine self-administration in the Hart et al study.[27] In an initial outpatient clinical trial of 62 cocaine-dependent patients modafinil was superior to placebo in achieving abstinence and reducing cocaine-positive urines [29], however subsequent trials have found this benefit limited to subsets of patients, including male participants [30] and those without a history of alcohol dependence [31]. Kampman recently presented data showing that modafinil-treated subjects were significantly more likely than placebo-treated subjects to be abstinent throughout the entire trial, and continuously abstinent from cocaine by self-report (supported by at least two negative and no positive or missing urine drug screens each week) during the last 3-weeks of the trial [32]. Thus, of the numerous candidate pharmacotherapeutics evaluated to promote cessation of cocaine use, modafinil appears to be the most promising.

Patients who respond to initial ACT+CM treatment may benefit from continued ACT to prevent relapse. Achieving early cocaine abstinence is a robust predictor of longer term cocaine abstinence.[33] In our previous feasibility study, patients who achieved two consecutive weeks of abstinence under high-magnitude CM used less cocaine during subsequent treatment, regardless of medication received, compared with subjects who failed to achieve initial abstinence.[12] However 15 of the 33 initial responders (46%) "relapsed" during second treatment, as indicated by the first cocaine-positive urine after achieving initial abstinence. Using 46% as a benchmark for measuring improvement, the goal of the proposed study is to construct an optimal adaptive treatment intervention that reduces relapse (<46%) within this subgroup of initial responders with an otherwise good prognosis.

As mentioned, CM interventions that provide high-magnitude alternative sources of reinforcement have been quite effective in promoting initial, *externally*-motivated, changes in behavior. The long-term efficacy of incentive-based treatments in reducing relapse is less clear. For CM, like most interventions, the magnitude of the treatment effect declines over time.[11] Indeed, one of the most oft-cited concerns with CM has to do with maintenance of behavior change after reinforcement is discontinued or faded. The notion of extending CM according to an "incentives maintenance model", has been suggested, [34] however studies of longer CM interventions have shown lower effect sizes on average than shorter CM interventions.[11] Rather, the common clinical practice is to combine CM with other interventions that focus on sustaining initial treatment gains and minimize relapse risk. Relapse is commonly triggered by aversive internal experiences such as negative affect, stress, craving, and other withdrawal symptoms that can occur during and well beyond the acute phase of cessation.[35] To the extent that avoidant responding to these aversive states is a mechanism underlying cocaine relapse, acceptance-based therapy goals, as described above, are well-suited for relapse prevention. Another major goal of ACT is to help the patient **develop** sustainable, **value driven, goal-directed** approach behaviors as an alternative to avoidance.[36] Learning and practicing to choose behaviors based on important personal values and goals rather than choosing to focus on the immediate reduction of craving, negative affect, or stress, will decrease relapse risk. ACT-based strategies may play an essential role in the maintenance of drug abstinence by shifting patients' motivation from external (e.g., CM) to internal incentives or sources of motivation.

In summary, the proposed SMART design represents a significant departure from standard randomized clinical trial paradigms that fail to address the heterogeneity of treatment response seen among individuals with chronic CUD. Continued progress in treatment development research must overcome this barrier with novel trial designs that formalize clinical decision making, thus having a real-world impact on the treatment of cocaine addiction and other chronic substance use disorders.

Aims and Hypotheses

1. To determine if ACT enhances response to a high-magnitude CM procedure targeting cocaine-negative urines. It is hypothesized that initial treatment (4 weeks) with ACT and CM (ACT+CM) will produce higher response (abstinence) rates than initial treatment that combines standard Drug Counseling with CM (DC+CM).

1.a. To determine if pretreatment EA level moderates the effects of ACT+CM on initial response. It is hypothesized that the benefit of ACT+CM over DC+CM on initial response (abstinence) rates will be greater in the subgroup of individuals with higher pretreatment EA scores.

1.b. To determine if the effects of ACT+CM are mediated by changes in EA and reward sensitivity. It is hypothesized that ACT+CM effects on initial treatment response will be mediated by the primary hypothesized treatment mechanisms, EA and reward sensitivity.

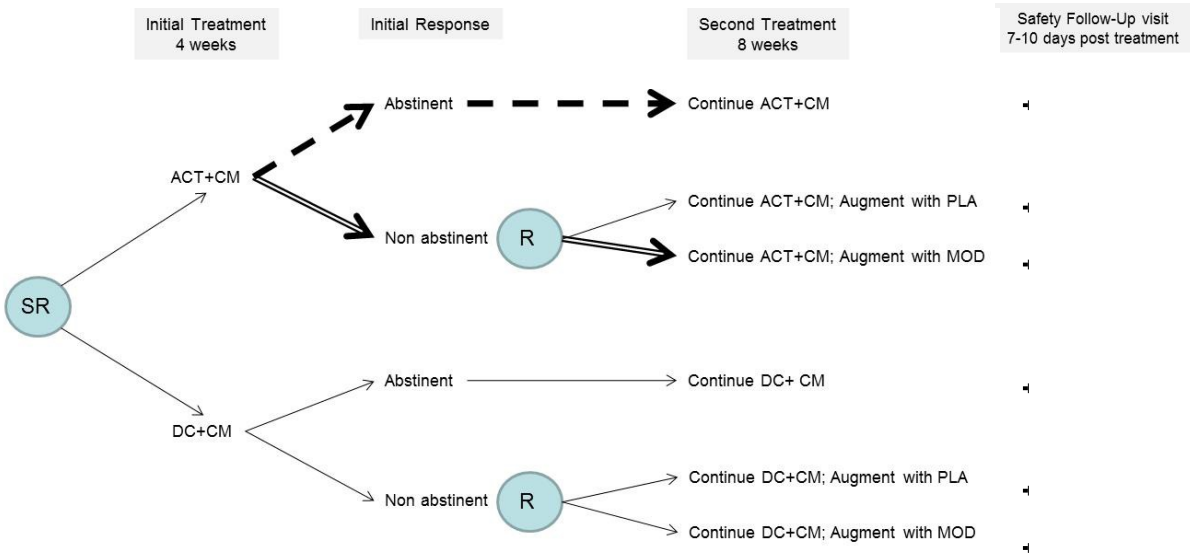
Secondary Aims/Hypotheses:

2. To determine the best sequencing of treatment for initial non-responders. For initial non-responders, it is hypothesized that continued ACT+CM treatment with pharmacotherapy (modafinil) augmentation will be most effective in promoting abstinence relative to treatment combinations involving DC and/or placebo.

3. To determine the best sequencing of treatment for initial responders. For initial responders, it is hypothesized that continued ACT+CM will be more effective (higher abstinence rates; < 46% relapse rate) than continued DC+CM.

Study Design

Overall Research Strategy. We propose an adaptive, two-stage SMART design to test the primary research hypothesis that ACT, when used in combination with CM, will increase initial treatment response rates. Secondary hypotheses will determine the probability of benefit associated with two sequences of treatments, specifically, continued ACT+CM for initial treatment responders (dashed lines in **Figure B.3.2.i**) and continued ACT+CM with modafinil augmentation for initial treatment non-responders (double lines in **Figure B.3.2.i**).



Overview of Study Design. Note: SR=stratified randomization; R=randomization; ACT=Acceptance and Commitment Therapy; DC=Drug Counseling; CM=Contingency Management; PLA=placebo; MOD=modafinil. Abstinent=6 consecutive (2 wks) cocaine-negative (BE<150 ng/ml) urines samples.

Participants. The study will enroll treatment-seeking individuals, 18 to 60 years old, who meet current DSM-5 criteria for CUD of at least moderate severity (≥4 symptoms). Eligible subjects must submit at least one positive urine toxicology screen for the cocaine metabolite (BE ≥ 150 ng/mL) during intake; a standard requirement in most cocaine trials to ensure enrollment of patients actively using cocaine. Subjects meeting moderate or severe criteria for substances other than cocaine, marijuana, alcohol, or nicotine will be excluded. Subjects whose alcohol use meets for physiological dependence requiring detoxification or use that makes participation medically unsafe as determined by the medical director will be excluded. Other exclusion criteria will include the presence of significant and unstable psychiatric disorders, including active psychosis, dementia, or other axis I psychiatric or neurological conditions requiring ongoing treatment and/or making study participation unsafe. Individuals with a past psychiatric history but without symptoms reported within the past 12 months prior to assessment, and who meet other inclusion criteria, may be eligible to participate. Individuals having medical conditions (e.g., severe cardiovascular disease, severe liver impairment) or taking medications (e.g., propranolol, phenytoin, warfarin, or diazepam) known to be contraindicated for modafinil pharmacotherapy will be excluded. To be eligible, females of childbearing potential must agree to use an acceptable method of birth control during study participation and for one month after discontinuation of the study medication. Non-hormonal methods of contraception are recommended, including barrier contraceptives (e.g., diaphragm, cervical cap, male condom) or intrauterine device (IUD). Steroid contraceptives if used with non-hormonal methods are acceptable. No pregnant women will be permitted in study. There will be separate inclusion/exclusion criteria for the Electroencephalogram (EEG) sub-study. Individuals with hairstyles that are incompatible with an EEG net (e.g., tight braids, ponytails, wigs, weaves, dreadlocks, or head scarves, etc.) and are unwilling to change the hairstyle will be excluded only from the EEG portion of the study. Individuals will also be excluded if they have a history of epilepsy or seizure disorder or head injury with loss of consciousness in the past 5 years.

Eligibility criteria (described above) will be evaluated as part of the General Evaluation protocol for all treatment research studies at our clinic. All potential subjects are invited to first participate in this

separate CPHS-approved protocol (**HSC-MS-05-0322** - **"General Evaluation of Eligibility for Substance Abuse/Dependence Research).** Intake evaluation procedures will include a complete psychiatric diagnosis using the Structured Clinical Interview for DSM-5 (SCID-5) administered by trained licensed professional counselors under the supervision of a licensed clinical psychologist. Medical screening will include a history and physical examination, a blood draw for serum chemistry and blood count, urine sample for urinalysis and an electrocardiogram (EKG), and urine testing for drugs of abuse and pregnancy. Lab tests will include a Comprehensive Metabolic Panel (CMP) with tests of liver enzymes: alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), Prothrombin time (PT), partial thromboplastin time (PTT), and bilirubin. We will apply the Child-Pugh criteria to exclude subjects with stage B or C scores, indicating severe liver disease. Upon completion of this intake evaluation, eligible participants will be invited to participate in the current study.

Study Site, Recruitment, Projected Enrollment. The study site is the Treatment Research Clinic of the Center for Neurobehavioral Research on Addictions (CNRA), a university-supported center of excellence within the UT-Houston Department of Psychiatry and Behavioral Sciences and a NIDA-funded Medications Development Center (P50 DA 009262). Since 1995, the CNRA has been the site for more than 20 randomized clinical trials, enrolling over 1,000 patients with substance use disorders, most of these with CUD. Established and effective recruitment strategies have been identified [37] and will be used, including newspaper/newsletter articles, public service announcements on TV and radio, notices mailed to local professionals, and billboards located throughout the local community. We will reach our projected enrollment of N=160 subjects within 40 months, based on our established record of enrolling 4 new subjects per month on average; a rate we have maintained for the past 5 years.

Phase 1 treatments. Consenting subjects will be assigned to one of the two 4-week Phase 1 treatments, ACT+CM or DC+CM, using urn randomization to ensure balance between groups on baseline EA level, coded as "high" if AIS score > 45, or "low"≤ 45. Subjects in both treatments will be scheduled to attend three clinic visits per week (MWF) during the 4-week period. **Two** of these weekly visits will include 1-hour therapy sessions (ACT or DC).

Acceptance and Commitment Therapy-Cocaine Use (ACT). The overarching goal of ACT is to decrease experiential avoidance while increasing acceptance and willingness to experience unpleasant thoughts, feelings, and physical symptoms. More specifically, ACT will assist cocaine patients to notice their internal cravings and triggers, abandon their attempts to manage these triggers via active avoidance, suppression or other control-based strategies, and to make commitments to engage in behaviors consistent with their chosen values or goals. ACT encourages clients to experience thoughts and feelings from an observer perspective, and helps them not to believe distressing thoughts and feelings as if they are literally true and in need of action. ACT treatment will be based on the therapy manual developed and tested previously.[38, 39] The manual covers 10 core topics listed in **Table B.3.2.vi**. Our experienced ACT therapists will be taught to use the manual as a map with flexibility to "go with the client" so long as issues of acceptance, diffusion, values, and committed action are thoroughly covered. Mindfulness exercises, metaphors, and homework sheets will be used to pursue therapeutic goals, more so than didactic instruction. Masters-level therapists with ACT experience from our previous trial [38] will be trained and supervised by Dr. Angela Stotts (Co-I) and Dr. Kelly Wilson (Consultant).

Drug Counseling (DC). We will use the manual-guided individual DC modeled after the NIDA Collaborative Cocaine Treatment Study [40] and used as the active control therapy in our previous studies.[38, 41, 42] DC approximates clinical practice as it is considered the most common type of evidence-

based treatment in the community for patients actively using cocaine. DC educates patients about important concepts in addiction recovery based on the underlying philosophy that physical, emotional, spiritual, and interpersonal needs must all be addressed to support recovery. Accordingly, the DC manual covers the core topics listed in **Table B.3.2.vi**. Masters-level therapists with DC experience from our previous trials [41, 42] will be trained and supervised by Dr. Anka Vujanovic (Co-I).

Contingency Management (CM). We will use the same high-magnitude CM schedule shown previously to be feasible and effective in facilitating initial cocaine abstinence.[12] Subjects will earn vouchers for cocaine-negative urine samples collected at scheduled clinic visits (MWF) each week. Under an escalating reinforcement schedule, voucher values will begin at $15 and increase by $10 for each consecutive negative urine. Provision of a cocaine-positive urine or failure to provide a scheduled sample will result in no vouchers earned and will reset the schedule to the initial value ($15). Bonus vouchers ($10) will be given for completing all study-related tasks in a given week. Subjects will redeem their earned vouchers for cash loaded to the ClinCard, a reloadable debit card.

Initial response and re-randomization. Following Phase 1 treatment, the primary outcome of response/non-response will be determined. Subjects who submit 6 consecutive (2 weeks) cocaine negative urine samples by week 4 will be classified as responders. Those who fail to meet response criteria will be classified as non-responders.

During second (Phase 2) treatment:

- Responders will continue to receive their assigned initial treatment, as described below.
- Non-responders in each initial treatment arm will be re-randomized to a second treatment consisting of pharmacotherapy augmentation with either modafinil or placebo.

All subjects will attend three clinic visits per week (MWF) during the 8 week second treatment period.

Second (Phase 2) treatments

Continued ACT or DC. Twice weekly 1-hour ACT and DC sessions will continue during the 8 weeks of second treatment, covering the core topics shown in **Table B.3.2.vi**.

Table B.3.2.vi. 10 Core Topics for ACT and DC

ACT	DC
Preparing to begin	Planning my recovery
Values	Stages of recovery
Making contact with the cost of using	People, places, things
Creative hopelessness	Self-help groups & support systems
Control v Willingness	Establishing a support system
Defusion & Deliteralization	Spirituality
Distinguishing the person from the programming	Personal Inventory
Barriers to valued action	Character Defects
Making a commitment	Lifestyle evaluation
Maintaining a commitment	Employment and managing money

Contingency Management. CM during Phase 2 treatment will continue to offer subjects the opportunity to earn rewards for engaging in targeted behaviors for either cocaine abstinence or session attendance based on initial treatment response.

Initial treatment non-responders will receive abstinence-based CM using the standard prize bowl method described by Petry who switched to this lower-cost procedure after one month of high-magnitude CM for patients who initiated treatment with cocaine-positive urines.[15] Patients will earn draws every time they submit a cocaine-negative urine at clinic visits (MWF). Draws will escalate by one for each consecutive negative urine sample, up to a maximum of 7 draws per day. Missed visits without a valid excuse will reset draws to one the next time attended. Reset value will return to the highest previously achieved value if patients attend fully for 3 consecutive visits. The standard prize bowl will contain 500 slips with 50% associated with small prizes. Of these, 209 will be small ($5) prizes, 40 will be large ($20) prizes, and one will be a jumbo ($100) prize. Patients will receive earned prizes immediately in the form of cash loaded to the ClinCard, a reloadable debit card provided by UTHealth.

Phase 1 treatment responders will receive attendance-based CM using the same prize bowl method described above. The Petry study found that for initially cocaine-negative patients, reinforcing attendance was as efficacious as an abstinence-based CM in promoting longer durations of abstinence.[15]

Pharmacotherapy augmentation. We chose modafinil as the pharmacotherapy augmentation strategy for non-responders based on growing and encouraging evidence from numerous clinical trials in cocaine dependent treatment-seeking patients.[29, 31, 32, 43] Its dopaminergic and glutamatergic activity make sense theoretically for non-responders who likely represent a subgroup with greater biological/neurochemical impairment and for whom behavioral interventions alone may not sufficiently change dopamine transmission.[24] Modafinil will start at 200 mg (day 1) and increase to the fixed dose of 300 mg (day 2). Placebo capsules will be identical in size, color, coating and shape. Participants in both conditions will take the same number of capsules at the same scheduled times (morning/evening) per day throughout treatment. Capsules will be packaged in blister cards with emergency replacement cards provided in the event that a subject forgets to bring their weekly card to the clinic or to replace lost cards. On clinic visits (MWF) the morning dose on the blister card will be taken by the subject at the dispensing window under observation by study staff. Additional standard methods for monitoring medication compliance will be followed, including pill counts and analysis of urine samples for riboflavin. Compliance will be defined using a cutoff level ≥ 20 fluorescence units, consistent with Mooney et al. [44] and our previous medication trials.[12, 45, 46]

Counselor training and evaluation of treatment integrity. Masters-level licensed professional counselors with > 5 years of experience in treatment of CUD at our clinic will be trained as needed on each of the therapy manuals (ACT, DC). Two counselors with prior training will provide ACT; a second set of two counselors with relevant prior training will provide DC. The two sets of counselors will be matched for number of years of experience. While this design choice does not control for differential counselor effects across conditions, it does prevent cross-contamination of treatment elements. Co-Investigators, Drs. Stotts, and Vujanovic, will provide a review training and ongoing supervision of the ACT and DC manuals, respectively. Dr. Kelly Wilson, co-developer and international trainer of ACT, along with Dr. Stotts will provide an initial ACT training consisting of 2 days of didactics and experiential exercises and audiotaped and rated practice sessions. ACT competency per Dr's. Wilson (Consultant) and Stotts must be demonstrated by relevant study therapists prior to beginning the trial. Several methods used in our previous trials[38, 47] will be used to ensure fidelity of treatment delivery. To monitor deviation or drift from the study protocol, all sessions will be audiotaped and reviewed; remediation will follow, if necessary. Furthermore, randomly selected videos erased of specific identifying information will be reviewed by Dr. Vujanovic (DC) and Dr. Stotts (ACT). In addition, Dr. Wilson will provide group supervision, as needed, and travel to our research site once per year to conduct booster sessions with therapists, and problem-solve particularly difficult cases. A checklist will be adapted from past studies for therapists to use at each session. The checklist will serve as a cue for the therapist to provide each component as designed, and it will be used to measure the "dose" of the intervention delivered to each client. Treatment adherence will be checked by independent raters (who themselves are skilled in the performance of the treatment) who will rate randomly selected audiotaped samples according to adherence rating scales. These scales will list core elements prescribed in the manual. The rater will indicate on a scale from 1 (none) to 5 (very much) the extent to which the treatment element was present in the recorded session.

Safety Follow-Up Visit. A safety follow-up visit will occur 7-10 days post treatment to ensure there are no new or worsening side effects or psychiatric symptoms. For completing the follow-up visit assessments, subjects will be compensated $25.

Assessment Schedule

Treatment mechanisms. A multi-modal measurement strategy will be used, where possible, to minimize method bias in evaluating putative mechanisms as predictors of treatment outcome (Aim 1a) and mediators of treatment effects (Aims 1b).

Experiential Avoidance: The *Avoidance and Inflexibility Scale (AIS)* is a 13-item self-report measure, on which respondents indicate, using a 5-point Likert-style scale, their level of avoidance and inflexibility with regard to internal experiences. The AIS has been adapted for several substance-using and other populations,[38, 48] and in our previous study was modified for cocaine users. Higher scores indicate more avoidant and inflexible responses to internal states associated with cocaine use. The internal consistency of the AIS in our past studies was .89. The AIS will be used as the stratification variable for initial randomization. High avoidance will be defined as AIS scores > 45, based on our preliminary data, showing that this cutoff score distinguished CM responders from non-responders with good sensitivity and specificity indices. The *Acceptance and Action Questionnaire for Substance Abuse (AAQ-SA)* is an 18-item self-report measure on which respondents rate their urges on a 7-point Likert-type scale (1 = "never true" to 7 = "always true"). The AAQ is the standard measure of psychological flexibility. The AAQ-SA is the substance abuse focused version of this measure and has demonstrated good internal consistency, factor structure, and construct validity. [102] The *Valuing Questionnaire (VQ)* is a 10-item self-report measure that assesses the effectiveness of ACT interventions using a 6-point Likert-type scale (1 = "Not at all true" to 6 = "Completely true"). The VQ should provide ACT researchers a convenient, reliable, valid measure for evaluating ACT interventions.[103] The *Five Facet Mindfulness Questionnaire (FFMQ)* is a 39-item self-report consisting of five subscales (observing, describing, acting with awareness, non-judging of inner experience, and non-reactivity to inner experience) that assess a participant's mindfulness based on a 5-point Likert-type scale (1 = "Never or very rarely true" to 5 = "Very often or always true"). Mindfulness facets have been found to be significantly related to meditation experience, psychological symptoms and well-being.[104] The *PTSD checklist (PCL-5)* is a 20-item self-report checklist of traumatic events, PTSD symptoms and severity rated on a 5-point Likert-type scale (0 = "Not at all" to 4 = "Extremely") and will be used to assess new or worsening trauma symptoms. The *Distress Tolerance Scale (DTS)* is a 15-item self-report measure on which respondents indicate, on a 5-point Likert-type scale (1 = "strongly agree" to 5 = "strongly disagree"), the extent to which they believe they can experience and withstand distressing emotional states (e.g., "I can't handle feeling distressed or upset"). The internal consistency of the DTS is ≥ .82.[49] A *Cold Pressor Task (CPT)* will be implemented as an index of physical distress tolerance, otherwise conceptualized as EA of physical distress.[50] This task involves continual application of a cold stimulus, intended to be safe but aversive, to the hand up to the wrist. Consistent with prior work, we will use ice water (1°C; 33°F) and instruct participants to keep hands still while submerged. [51] Pain threshold is defined as the length of time (in sec) until a self-report of pain is made by the participant. Tolerance is defined as the length of time (in sec) until participant reports that the pain or discomfort is no longer tolerable and/or spontaneous termination of the procedure. Endurance is defined as tolerance minus threshold. [52] It should be noted that, in the absence of gold standard self-report or behavioral measures of experiential avoidance or emotional tolerance, the measures selected have shown the most relevance to the mechanisms of interest in the present study based on past work.

Reward Sensitivity: Reward sensitivity will be assessed using two behavior economic measures, *Delay Discounting (DD)* and demand curve analyses via the *Cocaine-Purchasing Task (CPT)*. DD describes how a reward loses value as a function of increasing delay to its receipt. [53-56] Steeper discounting has been

positively associated with vulnerability to substance use disorders, including CUDs. [57-61] The computerized DD task presents the participants with repeated choices between hypothetical monetary outcomes. The two choices will be $1,000 after a fixed delay or a smaller, immediate option ranging from $5 to $955. The value of the immediate option will be titrated to a point of subjective equality using a heuristic based on the participant's responding. The delay values will range from 1 day to 25 years, allowing for a complete characterization of the DD function. Dr. Yoon (**Co-I**) has successfully utilized the DD task in a number of previous studies involving substance use disorders including cocaine.[53, 55, 56, 59, 62] Purchasing tasks such as the CPT simulate changes in price and consumption of drug in order to assess demand curves associated with drug consumption. [63-67] Using demand curves, one can assess the elasticity of demand associated with changes in drug cost. The CPT asks participants how much cocaine they would purchase at the beginning of a hypothetical day as the cost of cocaine increases from $0 to $10,000 assuming that: their income and savings are as they usually are; the quality/type of cocaine is the kind they normally purchase; no other sources of cocaine are available and if they do not buy any cocaine they will not have any to use; any cocaine they purchase must be used that day and cannot be saved or sold to others; and their craving and desire for cocaine is similar to how they feel that day. Purchasing tasks have been shown to have good test-retest reliability [68, 69] and track changes in drug reward sensitivity resulting from treatment. [70]

Cue reactivity: Attention bias (AB) task is a saccade-based eye-tracking measurement, developed by Dr. Lane to assess attentional bias to drug cues. Eye movements (saccades) have advantages over other variables because they are directly observable, ecologically valid, and typically stable across repeated measures. AB measures utilizing eye movements have produced moderate to robust effects for a broad class abused substances, including cocaine. Using our drug specific anti-saccade task, the between-group effect size for anti-saccade error rates in the presence of cocaine cues was large: CUD vs. control Cohen's d_{av} = 0.6 (see Lane protocol HSC-MS-16-0120). A baseline eye tracking session will occur before treatment begins and a follow-up session will occur in week 12, at the end of treatment.

Hedonic Capacity. Recent research has developed a neurobiological measure of hedonic (e.g., rewarding) capacity through brain responses to pleasant, unpleasant, and drug-cue images that is predicative of treatment outcomes in smokers[105, 106]. Specifically, using cluster analysis, it is possible to identify subjects groups with higher and lower likelihood of successful treatment outcomes: smokers with a higher Late Positive Potential (LPP) to pleasant images compared to drug-cue images achieve more long-term smoking abstinence than smokers with a higher LPP to drug-cue images. There is also evidence that a similar effect exists in cocaine use disorder populations, but there are limited studies, none of which has applied cluster analysis technique[107-110]. Picture Viewing Task: Participants will view emotional images while we record their EEG. Four categories of images will be displayed including: pleasant, unpleasant, neutral and cocaine-related images. The pleasant, unpleasant, and neutral images will be selected from the International Affective Picture System (IAPS)[111] and cocaine-related images will be taken from images previously used for cocaine-cue craving research. The images will be displayed for a few seconds followed by a random inter-trial interval that will consist of a black screen with a white fixation cross. The trials will be divided into equivalent blocks, separated by a short pauses in which participants will have the possibility to relax. The picture viewing task will take approximately 30 minutes. Self-Assessment Manikin (SAM): Following the picture viewing task, the participants will be asked to rate hedonic valence and arousal of the images that they viewed [112]. The SAM will take approximately 15 minutes to complete. This portion of the study will be taken at baseline and will include a separate consent form due to additional exclusion criteria and minor risks for participating in an EEG study. Oddball Task: Participants will view a series of letters (English and Chinese) and will be asked to respond when the letter "O" appears. This task will task about 10 minutes. Doors Task: During

this task, the participants will play a guessing game. They are asked to guess which door has a prize behind it. Every time they guess correctly, the participant wins $0.50 and when they guess incorrectly, they lose $0.25. The participants can will a total of $7.50 on this task. The task will last about 10 minutes.

Cocaine Craving. Cocaine craving plays an important role in addiction recovery and relapse. A newer brief measure will be used to assess change in craving as a function of treatment at each clinic visit. The Brief Substance Craving Scale (BSCS) divides cocaine craving into three domains: intensity, duration and frequency. Each domain is measured on a 0–4 likert scale. By adding the three scores a craving composite measure can be derived[116]. An additional cocaine craving measure will be used at baseline after consent on the EEG sub-study. The Cocaine Craving Questionnaire-Brief is a shortened version of the Cocaine Craving Questionnaire-Now originally created to test the 5 factors of craving (i.e., desire, intent, positive expectations, relief, and lack of control)[113, 114]. The brief form includes items that loaded onto "general craving"[114]. The brief form has established good reliability and validity and predicts time to relapse across several demographic populations[114, 115].

Salivary biomarkers. Saliva (buccal cell) samples will be collected at repeated time points (baseline and treatment weeks 4, 8, and 12) according to a standard commercial kit protocol. Recent studies have shown that saliva constituents, i.e., molecular and microbial analytes, may be effective markers of disease detection, monitoring, and prognosis. Compared to blood, collection of saliva has advantages in terms of being easy to administer, noninvasive, safer to handle, economical, and easy to store. Correlations between cocaine use levels during treatment and changes in biomarkers measured in saliva will be conducted.

Cocaine use outcomes. The primary outcome measure of cocaine use/nonuse will be based on qualitative urine drug screen levels of cocaine metabolite BE, coded as "positive" for cocaine use if BE ≥ 150 ng/mL. While this objective measure is considered by some to be the gold standard, we realize that there is no established, "optimal" outcome measure and that urine-based definitions of cocaine use/nonuse have limitations in terms of data loss and carryover effect. Recent procedures for combining self-report and urine BE have been recommended.[71-73] As a secondary measure of cocaine use/nonuse, we will apply the SRPHK1 (SelfReportPHarmacoKinetic1) coding method that classifies daily cocaine use/nonuse based on evaluation of self-report using a Timeline Follow-Back (TLFB) [74] method, quantitative urine BE levels, and the participant's concordance rate (agreement between self-report and urine result). The SRPHK1 is expected to produce fewer missing data and lower use estimates than urine-based only outcomes. [72] We will take advantage of available software programs for applying the SRPHK1 conversion.

Safety monitoring. Vital signs assessed at each study visit will include oral temperature, sitting blood pressure, pulse, respiratory rate, and weight. If blood pressure is > 140/90, or resting heart rate is above 100bpm, hold medication and consult with study physician, who will make the determination about length of hold, and any additional monitoring or referrals needed prior to continuation. Patients with blood pressure readings with either the systolic or diastolic outside the range of 140/90 or resting heart rate above 100bpm over 3 consecutive visits will be discontinued from the study medication and referred for medical follow-up. There is no protocol for dose reduction with retention in the study, only discontinuation. If other AEs are reported, the study nurse will hold medication and consult with the study physician, who will make the determination about length of hold, and any additional monitoring or referrals needed prior to continuation. Any SAE will result in discontinuation of the study medication and referral for medical or psychiatric follow up. AEs that do not meet these criteria (e.g. severe

headache) but interfere with the participant's daily activities and are persistent across 3 consecutive visits will also result in discontinuation of study medication and referral for medical or psychiatric follow up. The Systematic Assessment for Treatment and Emergent Events (SAFTEE) will be administered by trained research staff at each study visit to document patient-reported adverse events, serious adverse events, and/or treatment-emergent symptoms. The Concomitant Medications Tracking Log will be used to record any medications taken during the study. The study nurse completing the form will enter the name of the medication, dose/unit, route of administration, date started/stopped, and indication. Reported use of prohibited concomitant medications will be reviewed by the study physician (Dr. Weaver, Co-I) who will make a reasonable judgement about continued participation in the study. Additional measures will be used to monitor treatment-emergent psychiatric symptoms, including the Clinical Global Impression (CGI) scale, a well-established research rating tool for tracking clinical progress over study period and evaluating any change in the severity of psychopathology; and the Beck Depression Inventory-II, a 21-item, self-report rating inventory that measures symptoms of depression. The study physician (Dr. Weaver, Co-I) will be alerted of any psychiatric adverse events or reactions of treatment such as suicidality or worsening of mood symptoms. If clinically indicated in cases of significant worsening or deterioration of patient's functioning, appropriate actions will be taken, including study termination with proper referral. The *Patient-Reported Outcomes Measurement Information System short form (PROMIS-10)* is a global health assessment tool made publically available that allows measurements of general domains of health functioning including overall health, mental health, social health, pain, fatigue, and overall perceived quality of life using a 10-item Likert-type scale (5 = "Excellent/Completely/Never/None" to 1 = "Poor/Not At All/Always/Very Severe").
Suicide ideation and behavior assessment. The Columbia-Suicide Severity Rating Scale (C-SSRS: http://www.cssrs.columbia.edu) will be used to assess suicidal ideation and behavior occurrence. The CSSRS involves a series of probing questions asked in the patient interview, integrated with information from other sources, to classify suicidal ideation and behavior into 11 preferred categories. The full assessment will be conducted at the initial intake evaluation for screening and eligibility determination. The initial screening questions will be completed at every study visit for every patient by the trained study nurse. The study site has physicians (Co-I: Michael Weaver, MD), psychiatrists, and licensed clinical psychologist (Investigators: Joy Schmitz, PhD, Angela Stotts, PhD, Angela Heads, PhD, Anka Vujanovic, PhD) on site with extensive experience in managing suicidal ideation and behavior according to established protocols in our outpatient treatment research clinic.

Analysis Plan

Bayesian framework. The Bayesian approach addresses the following study questions: 1) What is the probability that ACT+CM confers benefit relative to DC+CM on abstinence at end of first treatment; what is the best estimate of this effect and what is its precision? 2) Among non-responders at end of first treatment, what are the relative probabilities that pharmacotherapy augmentation confers benefit at end of second treatment for those initially receiving ACT+CM versus DC+CM; what are the best estimates of these effects and what is their precision? 3) Among responders at end of first treatment, what is the probability that continued ACT+CM confers benefit relative to continued DC+CM at end of second treatment; what are the best estimates of these effects and what is their precision? By estimating the probability that such effects exists, we are assessing the probability that the alternative hypothesis is true, a probability that is, by definition, not accessible to Frequentist methods. The FDA has discussed the use of Bayesian statistical methods to make decisions regarding the efficacy of new treatments as an alternative to Frequentist methods in developing clinical applications.[75-80] The current proposal will provide the best, unbiased estimates for the benefit conferred across treatment sequences, conditional upon initial response, while also estimating the probability that such effects

exist. Posterior distributions can then be used as informative priors for continued monitoring in expansions of treatments and treatment strategies exhibiting initial promise.

Analytic strategy. Broadly, the analytic strategy will use generalized linear modeling. Continuous, dichotomous and time-to-event data will utilize linear, logistic, and proportional hazards regression respectively. Longitudinal analyses will employ generalized linear mixed models. All of these SAS (ver 9.3) procedures permit Bayesian analyses. Primary analyses will use intention-to-treat principles, with missing observations imputed as positive. Secondary analyses will implement joint modeling of observed outcomes and the missing data which is robust to ignorable missingness.[81, 82] Sensitivity analyses will evaluate robustness of analytic conclusions to missing data. Non-ignorable missing data patterns will be addressed through pattern-mixture modeling methods.[81] Prior distributions for comparison of proportions will use ~Beta(a = 1, b = 1) priors. Linear, logistic and Cox Proportional Hazards regression coefficient priors will take the form ~N (mean = 0, var = 1 x 10^6) in the linear, log (odds) and log scales respectively. Level one error variances will be specified as ~Inverse Gamma (shape = 0.001, scale = 0.001); level two variances will use ~Uniform(0,1000) distributions. Sensitivity analyses using optimistic and pessimistic, skeptical priors will evaluate prior assumptions.[83, 84] Inverse probability weight will permit unbiased effect size estimates in the context of re-randomization. Finally, coding procedures will permit identification of each salient effect. Specifically, at the initial randomization ACT+CM and DC+CM will be coded as 1 and -1 respectively. For the re-randomization: 1) non-responders receiving continuation therapy will be coded 1 while all other participants will be coded 0; 2) non-responders receiving augmentation will be coded 1 versus 0 for all other participants.

Hypothesis testing.
Hyp. 1. Initial treatment with ACT+CM will produce higher response (abstinence) rates than initial treatment with DC+CM. Logistic regression will evaluate cocaine-abstinence rates at week 4 as a function of treatment assignment.
Hyp. 1.a. The benefit of ACT+CM over DC+CM on initial response (abstinence) rates will be greater in the subgroup of individuals with higher pretreatment EA scores. Adding the interaction term (EA-by treatment) to the logistic regression model will evaluate the moderating effect of EA.
Hyp. 1.b. ACT+CM effects on initial treatment response will be mediated by the primary hypothesized treatment mechanisms, EA and reward sensitivity. In the context of the direct effect of treatment on response, mediational modeling will evaluate the *indirect* effect of treatment on response via EA and reward sensitivity variables, using the product moment method with bootstrapped 95% CI and Bayesian posterior distributions.
Hyp. 2. For initial non-responders, continued ACT+CM treatment with pharmacotherapy (modafinil) augmentation will be most effective in promoting abstinence relative to treatment combinations involving DC and/or placebo. Logistic regression will evaluate cocaine abstinence at the end of second treatment in a set of contrasts: (1) modafinil versus placebo within each initial treatment; (2) the sequence of ACT+CM with modafinil augmentation versus DC+CM with modafinil augmentation.
Hyp. 3. For initial responders, continued ACT+CM will be more effective (higher abstinence rates; < 46% relapse rate) than continued DC+CM. Logistic regression will evaluate cocaine abstinence/relapse at end of second treatment as a function of initial treatment (ACT+CM vs DC+CM).

*Power***.** Power estimates for Hypotheses 1, 2 and 3 will use as the primary outcome (i.e., "response"), two consecutive weeks of cocaine abstinence (BE ≤ 150 ng/mL). Initial treatment response (abstinence) rates are expected to be ~40%, based on our previous study [12] and pooled data across cocaine clinical trials[85]; however we predict a difference in response rates, favoring ACT+CM over DC+CM by about 20%, constituting a clinically meaningful treatment effect. Among initial non responders, we expect at least a

small treatment effect favoring augmentation with modafinil, based on our previous trials. [29, 31, 32, 43] Among initial responders, we previously observed that approximately 54% remain abstinent (46% "relapse") over an extended period of treatment, up to 12 weeks. Using this estimate for the control group (DC+CM), we predict a difference in response rates, favoring continued ACT+CM by about 15%, translating into a relapse rate of about 30%. Importantly, these effect size estimates are derived from data in which missing data is counted as non-abstinence, which mirrors the way we will be treating missing data for our primary analyses.

Finally, given the uncertainty inherent in pre-existing empirical evidence and even greater uncertainty for conditional probabilities of response, prudence dictated that robust trial planning rely upon probability distributions of plausible effects that take into account the uncertainty of our predictions of effect, rather than simple point-estimates. Adoption of distributional specification of effect sizes and their associated uncertainty required implementation of a Bayesian statistical approach.

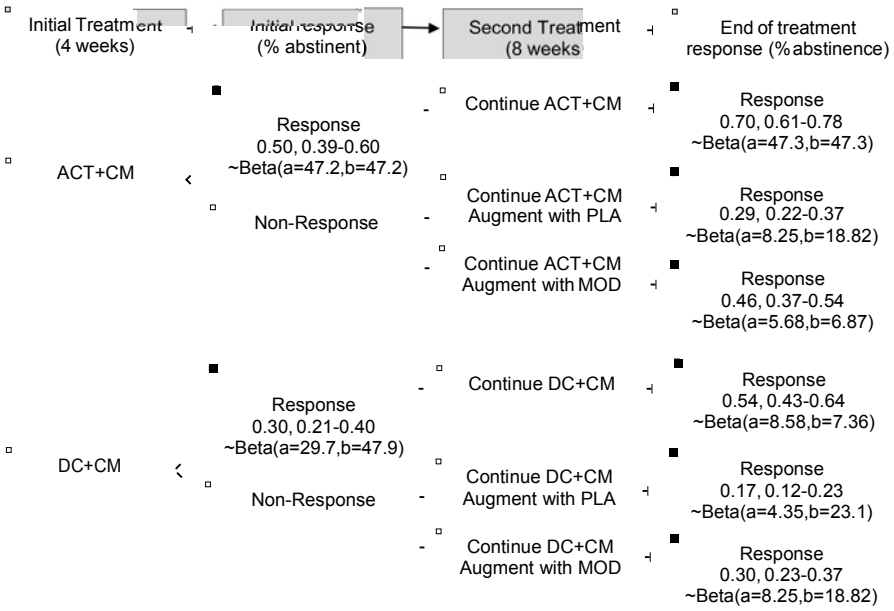


Table B.3.2.x.

Effect	Posterior Probability Pr(θ>0)	Power to Detect Pr(θ>0)	Average Point Estimate	Average Interval (95% C.I.) Estimate
Effect of Initial Treatment **Hypothesis Test Aim 1**:				
Contrast 1 vs 2*	0.90	0.83	0.20	0.05-0.34
Effect of Second Treatment (Initial non-responders) **Hypothesis Test Aim 2**				
Contrast 5 vs 6*	0.80	0.81	0.17	0.06-0.27
Contrast 7 vs 8*	0.80	0.81	0.13	0.05-0.21
Contrast 6 vs 8*	0.85	0.80	0.16	0.07-0.25
Effect of Second Treatment (Initial responders) **Hypothesis Test Aim 3**:				
Contrast 3 vs 4*	0.85	0.80	0.16	0.07-0.25

*Contrast numbers correspond to numbers in black boxes on Figure B.3.2.x.

Data Simulation Model. Using the above outcome estimates, we conducted a Monte Carlo simulation study to determine predicted power for the planned analyses, taking into account uncertainty in parameter estimates. **Figure B.3.2.x** depicts the trial design with probability point-estimates and 95% Credible Limits for each treatment cell, derived from logistic regression models with vague neutral priors, averaged across K = 500 simulations. *Simulated results for anticipated cell sizes are shown in italics.* **Table B.3.2.x** displays estimates of power to detect any benefit (H_A: θ > 0) conferred by the treatment hypothesized as being superior. All primary hypotheses demonstrate a > 80% chance of detecting 0.90 probability of benefit for a sample of N = 160. Also shown in **Table B.3.2.x** are the point-estimates and 95% Credible Intervals of specified effects averaging over the K = 500 simulations.

Summary. Using data-driven effect sizes that take into account uncertainty, simulation results indicate that with a sample size N=160, we have roughly 80% power for all primary hypotheses. Further, we stipulate *a priori* that a > 80% chance of treatment conferring benefit (i.e. Pr (Pr θ > 0|data) > 0.80)

constitutes sufficient evidence for results from this Stage II project to support a "Go" decision to advance to Phase III confirmatory studies.

Protection of Human Subjects

Selection Criteria

Eligible participants will:

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 positive urine BE specimen (≥ 150 ng/mL) during intake
4. be in acceptable health on the basis of interview, medical history and physical exam
5. a agree to use an acceptable method of birth control during study participation and for one month after discontinuation of the study medication. Non-hormonal methods of contraception are recommended, including barrier contraceptives (e.g., diaphragm, cervical cap, male condom) or intrauterine device (IUD). Steroid contraceptives if used with non-hormonal methods are acceptable.
6. be able to understand the consent form and provide written informed consent
7. be able to provide the names of at least 2 persons who can generally locate their whereabouts.

Exclusion criteria include:

8. current DSM-5 diagnosis for substance use disorder (of at least moderate severity) other than cocaine, marijuana, alcohol, or nicotine
9. current alcohol use that meets for physiological dependence requiring detoxification or makes participation medically unsafe as determined by the medical director.
10. have a DSM-5 axis I psychiatric disorder or neurological disease or disorder requiring ongoing treatment and/or making study participation unsafe (e.g., psychosis, dementia).
11. significant current suicidal or homicidal ideation
12. medical conditions contraindicating modafinil pharmacotherapy (e.g., major cardiovascular disease, severe liver disease based on Child-Pugh score of B or C, serious kidney problems)
13. taking medications that could adversely interact with modafinil (e.g., propranolol, phenytoin, warfarin, diazepam)
14. having conditions of probation or parole requiring reports of drug use to officers of the court
15. impending incarceration
16. pregnant or nursing for female patients
17. inability to read, write, or speak English
18. hair style that is incompatible with EEG nets (for EEG sub-study only)
19. history of epilepsy or seizure disorder (for EEG sub-study only)
20. head injury with loss of consciousness in the last 5 years (for EEG sub-study only)

All patients who are excluded will be given referral information on other local treatment programs.

Potential Risks

Medication. Modafinil will be initiated at 300 mg as a single morning dose, as administered in previous trials e.g., [30, 32]. Standard methods for monitoring medication compliance will be followed, including pill counts, analysis of urine samples for riboflavin, observed pill taking at thrice-weekly clinic visits, and blister-package pill counts by the study nurse at weekly clinic visits.

Available safety data suggest a highly favorable risk/benefit profile for this agent. Modafinil is an FDA approved medication for treatment of excessive daytime sleepiness or narcolepsy and has been administered safely to humans in doses of up to 800 mg [86, 87]. In sleep-deprived subjects, modafinil has been shown to improve mood, fatigue, sleepiness, reaction time, logical reasoning, and short-term memory [88]. In addition to its wakefulness-promoting effects, modafinil produces psychoactive and euphoric effects typical of other CNS stimulants in humans. Modafinil is partially discriminated as stimulant-like [86] and is self-administered by non-human primates [89], but has low abuse potential [86, 87], and a neurochemical profile distinct from that of cocaine and amphetamine [90-93]. Its safety when coadministered with other drugs, including dextroamphetamine [94, 95], methylphenidate [96], and cocaine [26, 28] has been established. The dose of modafinil to be used in the proposed study is 300 mg/d. This dose is in the range recommended for the treatment of narcolepsy. Similar dosages have been evaluated in studies of modafinil for the treatment of CUD [32] with favorable safety and efficacy results. Modafinil is generally well tolerated, with reported adverse experiences in the mild-to-moderate range. Common side effects reported (> 5%) more frequently than placebo include headache, infection, nausea, nervousness, anxiety, and insomnia.

Use of modafinil is contraindicated in individuals with advanced arteriosclerosis, symptomatic CVD, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, and glaucoma. The above conditions will be assessed and treated as exclusionary. Modafinil is extensively metabolized by the liver and should be used cautiously in patients with impaired hepatic function. Eligibility screening for this study will include a Comprehensive Metabolic Panel (CMP) with tests of liver enzymes: alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), Prothrombin time (PT), partial thromboplastin time (PTT), and bilirubin. We will apply the Child-Pugh criteria to exclude subjects with stage B or C scores, indicating severe liver disease.

Modafinil 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 modafinil on the fetus. No pregnant women will be permitted in study. Modafinil interacts with steroid contraceptives such as ethinyl estradiol, thus reducing the effectiveness of such methods when used with modafinil and for one month after discontinuation of treatment. Inclusion criteria will require that females of child-bearing potential use one of the following forms of contraception while participating in the study and for one month after discontinuation of medication treatment: non-hormonal methods of contraception, including barrier contraceptives (e.g., diaphragm, cervical cap, male condom) or intrauterine device (IUD). Steroid contraceptives if used with non-hormonal methods are acceptable. Pregnancy tests will be performed at intake and be repeated monthly thereafter.

Because of the risk of treatment-emergent psychiatric reactions, including mania, delusions, hallucinations, suicidal ideation, and aggression, modafinil should be used cautiously in patients with history of psychosis, depression, or mania. Eligibility screening for this study will include a complete psychiatric diagnosis using the Structured Clinical Interview for DSM-5 (SCID-5) administered by trained licensed professional counselors under the supervision of a licensed clinical psychologist. Psychiatric exclusion criteria include active psychosis, dementia, or other axis I psychiatric disorders or neurological

disease or disorders requiring ongoing treatment and/or making study participation unsafe. In the absence of current (past 12 months) symptoms, the study will not exclude individuals reporting a history of psychiatric disorders. Such patients, along with all participants, will be monitored weekly during the study for treatment-emergent psychiatric symptoms. At each study visit monitoring procedures will include (1) The Systematic Assessment for Treatment and Emergent Events (SAFTEE), administered by trained research staff at each study visit to document patient-reported adverse events and/or treatment-emergent symptoms; (2) the Clinical Global Impression (CGI) scale, a well-established research rating tool for tracking clinical progress over study period and evaluating any change in the severity of psychopathology; (3) the Beck Depression Inventory-II, a 21-item, self-report rating inventory that measures symptoms of depression. Weekly individual therapy sessions conducted by trained licensed professional counselors under the supervision of a licensed clinical psychologist will provide additional monitoring of treatment-emergent psychiatric symptoms. The study physician (Dr. Weaver, Co-I) will be alerted of any psychiatric adverse events or reactions of treatment such as suicidality or worsening of mood symptoms. If clinically indicated in cases of significant worsening or deterioration of patient's functioning, appropriate actions will be taken, including study termination with proper referral.

Behavioral Treatment. All participants will receive evidence-based and manual-guided behavioral therapies according to their assigned condition. These therapies include Drug Counseling (DC), Acceptance and Commitment Therapy (ACT), and Contingency Management (CM) procedures. CM will be used to reinforce abstinence and attendance using the well-established prize-bowl method with escalating number of draws for continuous performance of the target behavior. Earned vouchers will be redeemed with cash loaded to the ClinCard, a reloadable debit card provided by UTHealth to be used in lieu of gift cards. Every ClinCard will be assigned to an individual participant with no identifying information made available to outside entities. Subjects will be responsible for replacement card fees which reduces the risk of trading cards on the street in exchange for drugs. However, there is always a risk of subjects exchanging goods bought with money earned in research studies for drugs or alcohol. All efforts will be made to encourage subjects to not participate in this kind of activity.

Psychological. Items on certain questionnaires and interviews might be perceived as psychologically discomforting to some subjects. While subjects may be uncomfortable reporting these issues, the risks of serious sequelae are extremely low.

EEG Computer Session. Participants in the EEG session may experience skin irritation from the placement of the sensors, which is usually treatable and goes away after a few hours. The presentation of emotional images may cause an affective response, which typically subsides rapidly after image presentation. Participants can chose not to participate in the EEG sub-study and can ask to stop the slideshow at any time.

Alternative Treatments. 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.

Adequacy of Protection against Risks

Recruitment and Informed Consent

Participants will be self-referred in response to various study advertisements via newspaper and radio. Individuals who call for information will be given a brief description of the study. Those interested will then be asked to answer questions about their current substance use. A trained research

assistant will conduct this telephone-screening interview. Eligible subjects will be scheduled for an in-person intake visit at the Treatment Research Clinic (TRC), the outpatient research and treatment facility of the UT Department of Psychiatry and Behavioral Sciences, Center for Neurobehavioral Research on Addiction (CNRA). The first intake appointment will begin with the presentation of the informed consent form. The consent form will detail the requirements of study participation (e.g., # of visits, type of data collected, time commitment, etc.).

Subjects will be told that the purpose of the study is to evaluate a strategy for adapting treatments for improving cocaine cessation and relapse prevention outcomes. Information about the treatment components being studied will be explained. This discussion will include details of the different behavior therapies and how CM rewards will be made available during treatment. Subjects will be informed that they will attend thrice weekly clinic sessions. Other information on the consent form will include a full description of study requirements, reimbursement, risks, benefits, alternatives, and the role of the local IRB. All questions will be answered before written consent is requested.

Once written consent is given, eligible participants will also be asked if they are interested in participating in an optional EEG sub-study. These eligible participants will be informed that participation in the sub-study will not affect their treatment or participation in the main study. Interested participants will then be given an additional informed consent form that describes the purpose, reimbursement, risks, benefits, and alternatives specific to the sub-study to review and sign.

All research conducted at the Substance Abuse Research Center requires approval by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center - Houston. The trial will be registered and updated on clinicaltrials.gov.

Protection Against Risk

The following procedures will be taken to safeguard against adverse medication events: (1) careful initial intake evaluation to determine eligibility based on inclusion/exclusion criteria; (2) thorough physical evaluation prior to treatment, consisting of physical examination, standard laboratory tests, electrocardiogram, urine toxicology screen, pregnancy test and vital signs; (3) weekly review of treatment response, adverse events, concomitant medication use, and medication compliance; (4) regular evaluation by the study physician and Medical Director of the CNRA, Dr. Michael Weaver (**Co-I**).

Modafinil interacts with CYP3A4/5 and CYP2C19 substrates. At the initial intake evaluation, the study coordinator and/or nurse will screen potential subjects against the list of prohibited concomitant medications ("conmeds") including those metabolized by CYP3A4/5 (e.g., steroidal contraceptives, cyclosporine, midazolam, triazolam, quetiapine) and CYP2C19 (e.g., phenytoin, diazepam, propranolol, omeprazole, clomipramine). Enrolled subjects will meet with the study nurse weekly during treatment to assess for any new medications. The Concomitant Medications Tracking Log will be used to record any medications taken during the study. The study nurse completing the form will enter the name of the medication, dose/unit, route of administration, date started/stopped, and indication. Reported use of prohibited conmeds will be reviewed by the study physician (Dr. Weaver, Co-I) who will make a reasonable judgement about continued participation in the study.

All participants will be monitored weekly during the study for treatment-emergent psychiatric symptoms. At each study visit monitoring procedures will include (1) The Systematic Assessment for Treatment and Emergent Events (SAFTEE), administered by trained research staff at each study visit to document patient-reported adverse events and/or treatment-emergent symptoms; (2) the Clinical Global Impression (CGI) scale, a well-established research rating tool for tracking clinical progress over study period and evaluating any change in the severity of psychopathology; (3) the Beck Depression Inventory-II, a 21-item, self-report rating inventory that measures symptoms of depression. Weekly individual therapy sessions conducted by trained licensed professional counselors under the supervision of a licensed clinical psychologist will provide additional monitoring of treatment-emergent psychiatric

symptoms. The study physician (Dr. Weaver, Co-I) will be alerted of any psychiatric adverse events or reactions of treatment such as suicidality or worsening of mood symptoms. If clinically indicated in cases of significant worsening or deterioration of patient's functioning, appropriate actions will be taken, including study termination with proper referral.

Modafinil is a schedule IV controlled substance. Our research pharmacy holds a current DEA Certificate of Registration (DEA Form 223) and complies with DEA Security Requirements regarding the storage of controlled substances in securely locked and substantially constructed cabinets. Inventory and recordkeeping requirements adhere to the DEA practitioner's manual. To prevent diversion, the pharmacists dispense one weeks' worth of study medications directly to the Research Nurse, who administers the medications directly to each study participant. Unused pills are returned by the patient to the study nurse at weekly scheduled clinic visits.

Confidentiality will be protected in several ways. All information collected solely for research purpose will be kept in locked, restricted access files. Subject records will be coded and filed by a number code. Subject identities will not be revealed in any publication of the data. Individual subject information will be transferred to outside sources only with the express written request of the subject. Subjects will receive a copy of their signed consent form.

Potential Benefits of the Proposed Research to the Subject and Others

All assessment and treatment services provided in this study will be at no cost to the subject. The treatments should help in stopping cocaine use and preventing relapse. Subjects will be told if unusual information is discovered during the study that will make a difference in treatment for this or other problems. By taking part in this research subjects will help others with similar problems because this study is likely to identify what types of treatment work best and for whom.

Importance of the Knowledge to be Gained

Research participation may assist subjects in abstaining from cocaine during treatment and beyond. Cocaine dependence is highly prevalent and leads to devastating consequences on a personal and societal level. Current treatment approaches are delivered using a fixed-intervention approach. This project aims to develop newer adaptive treatment approaches that "tailor" interventions according to individual patient response. We predict this adaptive approach will optimize outcome and more closely mirror actual clinical practice.

The above stated risks are relatively mild in degree and procedures have been designed to minimize their probability. *We believe this protocol has an extremely favorable risk/benefit ratio.* Our research center has an excellent track record in conducting controlled trials with the utmost attention to safety.

Data and Safety Monitoring Plan

This plan describes the general data and safety monitoring procedures for the proposed study. A detailed DSM plan will be submitted for approval prior to starting the study.

1. The Principal Investigator (Schmitz) will be responsible for knowing the policies of the local IRB (the UT – Houston Committee for the Protection of Human Subjects, CPHS). The PI will adhere to CPHS policies and maintain accurate documentation of CPHS correspondence and reports (e.g., annual report). The PI will be responsible for documentation and handling of all possible study-related adverse events. The Treatment Research Clinic (TRC) within our Center for Neurobehavioral Research on Addictions (CNRA) has longstanding data collection and safety monitoring systems in place that will be available for the proposed study. These include staff training, manual driven processes, weekly audit of data collection/entry, medical screening with results reviewed by on-site nurse and physician, use of standardized assessments, continued medical monitoring during treatment, use of a certified (CLIA)

analytical laboratory to perform urine toxicology testing, procedures to monitor medication compliance (e.g., riboflavin), collaboration with Dr. Green (Co-I) who oversees data analysis and system management. Dr. Schmitz will assure that the above systems are in place and functioning properly for the duration of the study.

2. A DSM Board will be formed to provide additional, independent oversight of data related to patient safety. Membership will include Drs. Marianne Marcus (UT-School of Nursing), Edward Fann (Baylor College of Medicine-Psychiatry, Anne Dougherty (UT-Department of Internal Medicine, Cardiology) and Tom Newton (Baylor College of Medicine). These individuals have served previously on the DSMB for our P50 grant and thus have the relevant expertise and experience in monitoring clinical trials. This committee will perform the following activities: (a) review the research protocol and plans for data and safety monitoring; (b) evaluate study progress, including data quality, participant recruitment rates, retention rates, outcome and adverse experience data, and risk versus benefit profile; (c) make recommendations to terminate the trial because of safety concerns; and (d) protect the confidentiality of the trial data and the results of monitoring.

3. Adverse events (AE) will be reported to the UT-CPHS on an annual basis. Serious adverse events will be reported immediately (verbally within 24 hours) to the UT-CPHS, the DSMB, and to the NIDA. A written report will follow as soon as possible but in no more than three days. The written report will be in the format required by the CPHS and will contain information regarding the date of the AE, description of the AE, severity rating (Grade 1 to 4), assessment of cause, whether the AE indicates an increased risk for current or future subjects, and whether changes to the informed consent form are necessary.

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