Published in final edited form as:

Contemp Clin Trials. 2020 November ; 98: 106187. doi:10.1016/j.cct.2020.106187.

An Adaptive Clinical Trial Design for Cocaine Use Disorder: Extended-Release Amphetamine Salts for Early Behavioral Intervention Non-Responders

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Abstract

Background/Aims: Cocaine use disorder (CUD) persists as a major public health problem in the United States. Response to evidence-based behavioral treatment has been shown to be predicted by dopaminergic dysfunction. Amphetamine formulations modulate dopaminergic systems and are one of the few agents with positive clinical findings but are associated with unique risks. We aimed to find a model for determining the most appropriate patients for treatment with mixed amphetamine salts-extended-release (MAS-ER) for CUD using an adaptive trial design.

Methods: We are enrolling treatment-seeking adults ages 18–60 years. All eligible participants receive biweekly individual counseling augmented with a computer-based intervention based on the community reinforcement approach with contingency management (CRA+CM) for 4 weeks. Participants who fail to achieve abstinence are additionally randomly assigned to 10 weeks of either MAS-ER, titrated up to 80mg daily, or placebo. All participants complete a follow-up assessment after 12 weeks.

Results: Frequency and amount of cocaine use, cravings, retention, and quality of life will be compared between groups. The primary outcome will be having at least 3 weeks of urine toxicology-confirmed self-reported abstinence. Analyses will also be conducted to identify variables that may help identify who is more or less likely respond to the behavioral intervention during the first 4-weeks of treatment.

Conclusions: This trial more closely mimics a personalized medicine approach that is often used in clinical practice. It will help us understand who may be appropriate for psychostimulant therapy as an enhancement to evidence-based behavioral interventions, while limiting exposure to those who would respond to a psychosocial intervention alone.

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The Authors declare that there is no conflict of interest.

ClinicalTrials.gov Identifier: [NCT01986075](https://clinicaltrials.gov/ct2/show/study/NCT01986075)

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Keywords

adaptive intervention; cocaine use disorder; community reinforcement approach; contingency management; mixed amphetamine salts

Introduction

Decades of clinical trials have yet to result in any FDA-approved medication for the treatment of cocaine use disorder (CUD). In recent years, deaths from cocaine use have increased dramatically with nearly 1 in 5 overdose deaths involving cocaine in 2017 [1]. As scientific and policy efforts have shifted toward managing the opioid epidemic, we remain without highly effective treatments for stimulant use disorders despite evidence that we are potentially on the cusp of a cocaine and methamphetamine crisis.

An adaptive clinical trial offers numerous benefits in the substance use disorder population, including finding treatments that are effective for those who do not respond to less intensive treatments, addressing relapses after a period of reduced use or abstinence, limiting the cost, time, or side effect burden when patients are in remission, and discovering evidence-based treatment pathways for rapid and appropriate escalation of care for early treatment non-responders. A sequential, multiple assignment, randomized trial (SMART) is a type of adaptive trial that involves participant randomization at multiple times during the course of the study [2]. Schmitz et al. describe a SMART that first randomizes participants with CUD to either acceptance and commitment therapy (ACT) with contingency management (CM) or drug counseling (DC) with CM and participants who are not abstinent after four weeks will continue in ACT+CM or DC+CM and be randomized to receive augmentation with modafinil versus placebo [3]. This type of innovative trial design permits an assessment of effectiveness at each stage and the development of decision rules based upon variables at each progression to a different stage of treatment.

We have designed a trial with each of the four critical components that define an adaptive intervention, including (1) a sequence of decisions to guide patient care, (2) treatment options at each decision point, (3) variables that trigger a change in treatment, and (4) a sequence of decision rules that links components 1, 2, and 3 [4]. This design offers a number of benefits in the CUD population. First, it allows for the evaluation of more than one intervention at different phases, as well as a comparison of all interventions upon trial completion. Second, it permits only those who would most benefit to be randomized to medication treatment and thus avoids exposing behavioral responders to unnecessary adverse effects of the pharmacologic agent. Third, participants with a significant reduction in cocaine use as it relates to the highly structured clinical environment are not randomized to the medication treatment, and thus it improves the likelihood of detecting a difference between active medication and placebo. The design also will permit a comparison of various neurocognitive elements between behavioral therapy responders versus non-responders to improve these behavioral interventions both with and without the influence of the pharmacologic agent. While SMARTs in this population provide valuable data, we believe that our approach mimics what is often used and preferred in clinical settings where less

intensive approaches are tried first and an escalation to more intensive treatment is only considered if the initial intervention fails. In contrast, some psychopharmacotherapy trials have used a single-blind placebo lead-in phase in an effort to limit the impact of placebo responses on primary outcome measures, but this strategy has failed to improve the ability to detect signals of medication efficacy in depression treatment [5], and limits our understanding of the factors that can predict and or promote an early treatment response as placebo responders are often exited from the trial. An adaptive trial that mimics stepwise clinical practices has the potential to increase the likelihood of detecting a medication effect while permitting further explanation of the contextual and individual level factors associated with an early treatment response. We will, therefore, describe an adaptive trial design that begins with an evidence-based psychosocial intervention for CUD and randomizes only behavioral therapy non-responders to additionally receive amphetamine salts or placebo.

Materials and methods

Study design

This randomized clinical trial will evaluate the efficacy of augmenting a community reinforcement approach and contingency management (CRA+CM) with mixed amphetamine salts-extended release (MAS-ER) for participants who fail to respond to a computerized CRA+CM intervention. A sample size of 155 was chosen to maximize the resolution of the analyses that include demographic covariates and afford greater power to detect medium effects on other indicators of treatment effect, including weekly cocaine use and craving, treatment retention, and quality of life measurements. Eligible participants receive four weeks of twice-weekly computerized CRA+CM in the research clinic. Every other week, participants meet with counselors to review their progress, discuss the application of relapse prevention skills, and tailor the specific computer delivered treatment modules as needed. Those who fail to achieve abstinence by the end of the first four weeks are randomized to receive either MAS-ER or placebo in a double-blind manner, in addition to continuation of the psychosocial intervention as described. Based upon our previous CUD clinical trial experience, we estimated a 35% response rate to behavioral treatment, allowing for 100 participants to be randomized to MAS-ER or placebo. Approximately 15% of participants who enroll at our research clinic fail to be randomized, which would result in 42 and 43 participants in each arm of the secondary treatment phase, exceeding the target of 34 participants in each arm to detect a medium-sized medication effect using an intent-to-treat data analysis. Those randomly assigned to the MAS-ER group will have their dose titrated to 80mg per day over the course of two weeks and maintained on this dose for 10 weeks. At the end of 10 weeks, the dose is tapered for one week and discontinued. A matching dose titration and tapering schedule is also followed for the placebo group. Twelve weeks after study completion, each participant is contacted by phone to determine enduring or emerging effects on cocaine use after study discontinuation. (Figure 1)

Participants

The trial includes men and women ages 18–60 years old who are seeking treatment for a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [6] diagnosis of cocaine dependence. Since the implementation of DSM-5 [7], all participants are additionally

assessed for DSM-5 cocaine use disorder (CUD) criteria, and this nomenclature will be used henceforth for consistency. Only individuals who have used at least four days in the past month are eligible. All participants must be able to give informed consent and comply with study procedures. Participants who meet criteria for bipolar disorder, schizophrenia, or any psychotic disorder other than transient drug-related psychosis, or those with severe major depression, increased suicide risk, or any other unstable psychiatric disorder that might be disrupted by the study medication or require psychotropic treatment or psychotherapy during the study are ineligible. Any current psychotropic medication treatment is also exclusionary. Those with certain medical conditions are excluded, including a history of seizures, unexplained loss of consciousness, traumatic brain injury, allergy to amphetamines, pregnancy or breastfeeding, uncontrolled hypertension, acute hepatitis, uncontrolled diabetes, elevated transaminases (greater than three times the normal limit), coronary vascular disease, or an underweight body mass index. Those with physiological dependence on nicotine or cannabis are permitted to participate, but those with other physiological substance dependence that would require medically supervised detoxification are ineligible, as is anyone legally mandated to participate in substance abuse treatment.

Psychosocial intervention

All eligible and consented participants begin computer-assisted CRA+CM during the first week of the study and continue through the final week of the treatment phase. Self-directed computerized CRA+CM is administered for 30–40 minutes during two of three weekly clinic visits. Additionally, every two weeks, participants meet with a research therapist in the clinic for approximately 50 minutes to review their progress in treatment, discuss the application of relapse prevention skills, and tailor the content of the of computerized modules accordingly. The CRA modules are delivered by the Therapeutic Education System (TES) using 32 core interactive modules, beginning with basic cognitive behavioral relapse prevention skills, like drug refusal skills, and moving on to improving psychosocial functioning, including employment and interpersonal relationships, and HIV risk reduction [8]. All TES sessions occur in a private office with headphones and research staff nearby to ensure compliance, as well as clinical and technical support as needed.

TES is self-directed and sequential, includes a training module, and all text is accompanied by audio for those with reading challenges. It uses personalized content for the user and a variety of interactive exercises to better enhance learning. It is designed to address substance use in general and is inherently flexible, addressing the individual's specific substance-related problems. TES includes a Computer-Assisted Instruction (CAI) that is fluency-based in order to assess the individual's understanding of the material, and consequently adjusts the pacing and level of repetition of skills to promote skill mastery. An electronic reporting system permits counselors to view progress summaries that will be discussed with the participant every two weeks and allows for manual manipulation of the sequence of modules based on progress.

The CM component follows the prize-based incentive procedures used by other community-based drug treatment studies [9]. Participants earn a draw or draws from a prize bowl for every clinic visit in which their urine is negative for the major cocaine metabolite

benzoylecgonine (below the threshold of 300 ng/ml). An escalating voucher schedule is used, in which participants earn an additional prize bowl drawing for each consecutive week of abstinence confirmed by on-site urine testing. The escalating schedule increases to a maximum of 15 draws per visit. A single large prize is awarded when a participant first achieves two weeks of abstinence to offset the low rate of reinforcement during the beginning of the CRA+CM phase. Participants are given immediate feedback on the urine toxicology results and regularly updated on the number of draws earned.

Pharmacotherapy augmentation

Participants who are considered non-responders after four weeks of CRA+CM are randomized to receive either MAS-ER or placebo. A non-responder is defined as an individual who does not achieve three weeks of abstinence during the initial four weeks of CRA+CM, as measured by participant self-report of cocaine use or positive urine toxicology for benzoylecgonine. This criterion was based on secondary analyses of individuals enrolled in a CRA+CM intervention that indicated significantly better outcomes among participants demonstrating three weeks of abstinence during the first month of the behavioral intervention [10]. MAS-ER and matching placebo are prepared by a non-blinded research pharmacist in matching gelatin capsules with lactose filler plus 25mg of riboflavin for medication compliance monitoring. All other study staff are blinded, but a sealed envelope is kept in a locked office if the investigator needs to break the blind in an emergency. MAS-ER or placebo is taken by participants once daily in the morning or early afternoon. The starting dose of MAS-ER is 20mg daily for three days and then increased by 10mg every two days over the course of two weeks to a maximum dose of 80mg daily. A research psychiatrist meets with the study participant at least weekly and may adjust the titration schedule according to medication tolerability. The maximum achieved dose is maintained for eight weeks and tapered to discontinuation during the last week of the medication phase of the study. The psychiatrist may also decide to reduce the medication dose during the maintenance phase based on intolerable side effects. After completion of the 10-week phase, participants are told their treatment assignment by a non-research team physician, if requested. Medications are maintained and distributed per the principal investigator's DEA registration and stored in wall-mounted, double-door, double-locked storage cabinets in the research clinic. The research psychiatrist distributes study medications to the participants on a weekly basis to enhance compliance and reduce the risk of diversion.

Recruitment, screening, and informed consent

Volunteers are recruited from the New York City area by flyers and advertisements in newspapers, Internet, radio, and public service announcements. Potential participants undergo a structured telephone interview upon initial contact and then are scheduled for an on-site screening visit that is completed within 1–2 weeks. At the clinic, a master's or doctoral level psychologist first determines a diagnosis of cocaine use disorder and evaluates for exclusionary psychiatric disorders using the Mini-International Neuropsychiatric Interview [11]. Those who remain provisionally eligible then undergo a structured psychiatric and medical assessment by qualified medical providers, including history, mental status examination, physical examination, vital signs, electrocardiogram, blood and urine tests.

Informed consent for study participation is obtained by a research psychiatrist who is familiar with the study protocol and specifically discusses and documents discussion of the potential side effects and morbidity associated with MAS-ER.

Cocaine use outcomes

Several measures are used to evaluate cocaine use, cravings, and use-related outcomes. At baseline, self-reported cocaine use is measured by the timeline followback (TLFB) method [12]. Participants are asked to assign a dollar amount to the quantity of cocaine used. This method is then used throughout the study after randomization and corroborated with urine toxicology results for benzoylecgonine. The Cocaine Selective Severity Assessment (CSSA), a clinician-rated questionnaire that has been reported to predict abstinence in medication trials [13], is completed at baseline and periodically throughout the study, including at the final follow-up visit, to evaluate the occurrence and severity of cocaine use disorder symptoms. The Brief Substance Craving Scale (BSCS) [14], a self-assessment that assesses the frequency, intensity, and amount of time spent craving cocaine and other substances, is measured at baseline and weekly to evaluate cocaine cravings. The Acceptance and Action Questionnaire-Substance Abuse (AAQ-SA) [15], a self-report assessing psychological flexibility in the context of treatment for CUD, is administered at key decision points, including the beginning of the intervention, during week 4 before the decision to maintain the behavioral intervention alone or randomize participants to a medication arm, and at the end of study week 15. The research psychiatrist will also evaluate global symptom severity and improvement of cocaine-related problems on a weekly basis using the Clinical Global Impression-Observer (CGI-O) scale [16].

Other substance, psychiatric, health, and quality of life outcomes

To evaluate other substance-related behaviors and outcomes, the TLFB and urine toxicology for other substance use, including cannabis, alcohol, and nicotine, and the Addiction Severity Index (ASI) [17] are completed at the same key decision points in the design, as mentioned above. Other self-assessments completed at baseline and periodically include the Risk Assessment Battery [18], which evaluates for behaviors related to the risk of contracting HIV, and the Quality of Life, Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) [19] which evaluates a participant's overall quality of life.

Investigating mechanisms of change

An important aspect of the development of a behavioral therapy platform as related to this clinical trial is to identify cognitive, verbal, and behavioral mechanisms that predict treatment response at critical decision points. A range of assessments are included to assess the relationship between constructs within each of these three domains and treatment outcome. This information may provide a basis for continuing the development of more effective cognitive-behavioral treatment platforms and targeted pharmacotherapy strategies.

Cognitive mechanisms of change are evaluated by computerized testing that are completed at baseline and at week five (prior to study medication randomization) and include the drug Stroop task [20], delay discounting task [21], letter-number sequencing task [22], Wisconsin Card Sort Task (WCST) [23], and the Implicit Relational Assessment Procedure (IRAP)

[24], to respectively measure distractor interference, discounting of delayed rewards, working memory, executive functioning and cognitive flexibility, and implicit beliefs or attitudes. The Behavior Rating Inventory of Executive Function (BRIEF-A) [25], a standardized self-report that assesses an individual's perception of their self-regulation is measured to evaluate cognitive mechanisms that may predict response.

Verbal mechanisms of change will be evaluated by coding each participant's Desire, Ability, Reasons, Need, and Commitment (DARN-C) language [26]. At week 1 and week 5 (before study medication randomization), all participants have audiotaped counseling sessions, which will be coded by consultants who will be blinded to patients' outcomes and treatment assignments.

Lastly, behavioral mechanisms of change will be evaluated by the Relapse Prevention Skills: Coping Strategies Scale (CSS) [27], a questionnaire that assesses coping skills like problem solving and dealing with urges to use substances.

Medication-related outcomes and monitoring

Various assessment will determine medication-related outcomes, including medication compliance, safety and adverse effects. The participants are administered a weekly supply of medication by the research psychiatrist and asked to return all used pill bottles. Research assistants corroborate the participants' self-reports of medication compliance with pill counts to clarify any discrepancies. The riboflavin radiotracer packaged in both MAS-ER and placebo capsules is used for definitive verification of medication compliance by measuring urinary fluorescence at every study visit for all participants randomized to MAS-ER versus placebo.

At least weekly, participants meet with the research psychiatrist for study assessments that include an assessment of side effects related to the study medication. Reported side effects and other treatment-emergent events are recorded in a standardized manner using the Systematic Assessment for Treatment Emergent Events (SAFTEE). At every visit, vital signs, including blood pressure and heart rate, are assessed. Inability to tolerate medication side effects results in medication reduction or temporary or indefinite discontinuation of study medications. Systolic blood pressure greater than 140, diastolic blood pressure greater than 90, or heart rate greater than 100 for two consecutive weeks results in discontinuation of study medications to reduce adverse cardiovascular events of MAS-ER. The Side Effect Questionnaire includes both open-ended self-reported side effects and a checklist of symptoms incorporating major organ system and is also used to assess for the need for dose reduction or early discontinuation of study medication, particularly if there are positive responses related to chest pain, fainting, or irregular heart rhythm.

Finally, at study completion, both the research nurse and participant are asked to comment on whether they believed the study medication was active MAS-ER or placebo, to evaluate the double-blind.

Results

The primary outcome measure, for which the trial is powered to detect medium effect sizes ($d=0.57$; Odds Ratio=2.8), will be a binary indicator of at least three weeks of urine toxicology confirmed self-reported abstinence during weeks 5–14, comparing the CRA+CM with MAS-ER group to the CRA+CM with placebo group (i.e. both non-responder groups). The group that responds to CRA+CM in the first four weeks of treatment will not be included in the analysis of the primary outcome measure, as the primary aim is to determine whether MAS-ER can augment CRA+CM by modulating defective dopaminergic transmission [10]. While there is significant debate regarding meaningful outcome measures in cocaine use disorder treatment trials, including continuous versus dichotomous indicators of response, reduction of use versus abstinence, duration of abstinence, and the most meaningful period of abstinence during a trial [28], three or more weeks of abstinence at any point during the course of treatment has a long history of use in randomized clinical trials [29, 30]. In a pooled sample of randomized trials, this outcome measure was consistently significantly related to “good functioning” and improvements in cocaine use during follow-up [28]. Self-report of cocaine use will be accepted as a “use day” and urine samples with benzoylecgonine (the major cocaine metabolite) levels equal to or greater than the standard NIDA 300 ng/ml will be considered positive. A urine sample will be considered negative if it is preceded within two days by a sample with two times or more its benzoylecgonine level. If none of the three days preceding a positive urine sample has been self-reported as a use day, the day immediately preceding the sample will be labeled a use day. The effect of treatment on this primary outcome measure will be examined using logistic regression adjusted for covariates (e.g., baseline days/week of cocaine use). The primary analyses will be on the intent-to-treat sample (i.e. all randomized participants) and dropouts will be accounted for by examining the primary outcome variables using longitudinal mixed effects models. Previous randomized trials of psychostimulants for CUD have reported that approximately one-third of participants drop out before the end of the maintenance treatment phase [31, 32].

We will test secondary hypotheses that the CRA+CM plus MAS-ER group will demonstrate: 1) a lower proportion of weekly urine toxicology samples testing positive for benzoylecgonine (longitudinal continuous variable); 2) lower cocaine withdrawal symptoms as measured by the Cocaine Selective Severity Assessment (CSSA; longitudinal continuous variable); 3) lower cocaine craving as measured by the Cocaine Craving Questionnaire (longitudinal continuous variable); 4) improved Quality of Life; and 5) greater study retention than the CRA+CM plus placebo group. The longitudinal continuous outcomes will be treated with longitudinal mixed effect models, where patients will be treated as a random factor. The group differences in retention is operationalized as time to dropout, which will be analyzed within a Cox proportion hazard framework.

In addition to the cocaine use-related outcomes, for which the study is powered to evaluate, exploratory analyses will also be conducted in an attempt to detect variables that may help identify who is more or less likely to respond to the psychosocial intervention alone within the first month of treatment. Identifying key cognitive-verbal mechanisms that predict early treatment response can help provide important avenues for guiding future therapy

development and treatment planning. This secondary aim will be examined using a logistic regression model within a generalized linear models framework where responder status at the end of week 4 is a binary outcome (responder and non-responder) and the predictors will be a vector of baseline covariates. Given the exploratory nature of these analyses, a conservative approach to testing the relationships between these cognitive and behavioral variables and 4-week responder status will be utilized. Specifically, variables will be entered in blocks. The first block will include baseline cocaine use and severity of CUD, as these variables have correlated with the treatment response in previous investigations. The cognitive and behavioral variables of exploratory interest will be entered in a single second block (e.g. commitment language strength, coping skills use, and executive functioning). A simultaneous entry of these predictor variables will be utilized as there is no theoretically guided specification of placing an *a priori* importance to one domain (e.g. cognitive) over another (e.g. language). The omnibus block entry will be tested for significance by testing the change in the -2 loglikelihood statistic. If the block entry is not significant, the analyses will stop at this point. If the block entry is statistically significant (i.e. indicating that including this block of variables improves the model's prediction of 4-week responder status)), *post hoc* analyses will be conducted to determine the relationship between each specific cognitive and behavioral predictor variable and 4-week responder status. Variables demonstrating significant relationships to the responder status will be retained in the model. These *pos hoc* analyses include multiple comparisons thus increasing the likelihood of an increased Type-I error rate. Thus, Multiple Comparison Procedures (e.g. Holm step-down procedures) will be employed to protect the family-wise error rate (set at 0.05) while testing the individual variables within this second variable block. The final model will be assessed in terms of its overall goodness of fit and correct classification rate. It is important to note the relatively small sample size and exploratory analysis can increase the likelihood of spurious, sample specific findings, and it is worth reiterating that the trial is not powered to identify participant-level covariates that predict response to CRA+CM among participants with CUD, and there is a risk of identifying overly complicated predictive models with limited usefulness. However, the CRA+CM methods used in the trial will permit exploratory analyses of the cognitive-verbal mechanisms involved in behavior change. The target sample size of 155 participants with an estimated 35% of initial CRA+CM responders may result in statistically significant findings that are clinically meaningful.

In other exploratory analyses, we will test for differences in treatment outcome between the CRA+CM only condition (those who responded to the first four weeks of treatment and were not randomized to medication versus placebo) and each of the medication treatment arms (CRA+CM plus MAS-ER and CRA+CM plus placebo) on the primary and secondary outcomes outlined above. These exploratory comparisons may provide useful information on the relative differences between individuals needing an integrative treatment strategy against those benefiting from the behavioral treatment alone in terms of their trajectory and level of change during a treatment episode. Some non-responders may experience a delayed response to CRA+CM that occurs regardless of randomization to MAS-ER versus placebo, while others may experience a placebo response after randomization regardless of the psychosocial intervention. These exploratory analyses may facilitate an understanding of these trajectories. Finally, this three-level analysis will allow for the implementation of a

more meaningful comparison of the three groups by utilizing strategies described by Nahum-Shani *et al.* [33], which involves an estimation procedure that results in an average weighted outcome for each of the interventions, thereby eliminating the over-/under-representation that would otherwise result in a biased estimator since the initial responder group is not randomized.

Discussion and Conclusions

There are a limited number of moderately effective psychosocial treatment options and no FDA-approved medications for the treatment of cocaine use disorder. Given the surge in cocaine-related deaths in recent years, there is an urgency to improve our available evidence-based behavioral treatments and enhance those treatments through other means such as medication therapies.

Evidence supports the use of a number of psychosocial interventions for the treatment of CUD which have remained the basis of treatment in the absence of FDA-approved pharmacotherapies. In particular, behavioral therapies that impart skills and provide tangible incentives for abstinence, the Community Reinforcement Approach (CRA) and contingency management (CM), respectively, have shown the most robust and consistent effects in reducing cocaine use in those with moderate or severe CUD [34, 35]. The combination of these approaches is particularly robust and more effective than either alone [36, 37]. However, a significant number of individuals fail to respond to this combined psychosocial intervention [36]. Using an innovative imaging and treatment design, Martinez *et al.* demonstrated that deficient dopamine transmission measured with a PET ^{11}C -raclopride displacement paradigm predicted poor response to CRA with CM [10]. Thus, a search for pharmacological interventions remains a priority and prior trials have suggested that combining psychosocial interventions like CM with medications that boost monoamine functioning can enhance treatment response [38–41].

Regarding pharmacologic interventions, more than 100 clinical trials have evaluated the effects of medications that target glutamate, GABA, and monoamines [42]. Only 16 of these pharmacotherapies have been evaluated both in human laboratory and clinical trials, and among them, only dextro (d)-amphetamine has shown consistently positive effects in both study paradigms [43]. Grabowski *et al.* showed improvements in cocaine use that were moderated by medication dose, with higher-dose d-amphetamine groups having more cocaine-negative urines and all doses resulting in more improvement compared to placebo [44]. In a multi-site trial, Levin *et al.* found that among participants with co-morbid ADHD and CUD, robust dosing of d-amphetamine resulted in significant improvements in both ADHD and measures of cocaine use [32]. A group in the Netherlands also found that sustained-release d-amphetamine was safe and effective for treatment-resistant cocaine use disorder among co-morbid heroin-dependent patients on combined heroin-assisted and methadone maintenance therapy [45].

Considering the finding that behavioral therapy non-response was predicted by deficiencies in dopamine transmission, medications like amphetamine salts that potently modulate the dopaminergic system may be of particular interest in this population. However,

psychostimulant treatments for cocaine or other stimulant use disorders is complicated by various medical, psychosocial, and pragmatic factors, including risks of misuse or diversion, medical complications like cardiovascular disease, worsening of psychiatric illness like bipolar or anxiety disorders, and insurance coverage of off-label psychostimulants. These considerations warrant investigations into finding the most appropriate patients for combining psychostimulant treatment with psychosocial interventions and an adaptive intervention design improves the likelihood of answering this question.

This innovative adaptive intervention trial combines the most effective psychosocial treatments for CUD with one of the few medications that has shown consistently positive results across all study paradigms (non-human primate laboratory studies, human laboratory studies, and clinical trials). The adaptive design allows only those with more refractory CUD to be randomized to treatment with mixed amphetamine salts as a means of enhancing the likelihood of response to the behavioral treatment, while simultaneously limiting the unnecessary exposure of participants to a pharmacologic agent. The likelihood of detecting a difference between MAS-ER and placebo is also enhanced with this trial design, as those who respond to the behavioral intervention delivered in a structured clinical treatment setting are also not randomized to the medication treatment condition. Furthermore, this type of trial more closely models the order of treatment that most often occurs in clinical practice, as clinicians typically attempt the more benign treatments and escalate to more intensive therapies only if there is a lack of sufficient response.

The adaptive element of this trial aligns with the SMART design described by Schmitz *et al.* in regard to reserving medication treatments for those who do not respond to an initial psychosocial intervention [3]. A major difference between our multiple, one-stage-at-a-time, randomized trial we describe here and the SMART described by Schmitz *et al.* is that our trial relies on a single treatment (CRA+CM) for all participants, augmented by a computerized therapeutic system whereas the Schmitz *et al.* trial initially compares two psychosocial interventions (ACT+CM versus DC+CM). A benefit of the latter design is to better understand the role of these psychosocial interventions in CUD, while a disadvantage is losing power to understand the role of augmentation with the pharmacologic agent. Both studies, however, emphasize the importance of psychosocial treatments for CUD, as behavioral therapies are often preferred and/or more readily accessible for the treatment of substance use disorders. Both study designs continue the behavioral treatment and view the role of MAS-ER or modafinil as a method of enhancing the behavioral treatment response, rather than discontinuation of psychosocial therapy and switching to a medication-based treatment, allowing an understanding of how to better tailor these psychosocial interventions for non-responders. However, there are limitations to this more simplistic adaptive study design that mimics clinical scenarios and is powered to detect differences in certain phases of the intervention compared to a SMART, including the ability to detect delayed effects of the psychosocial intervention, the ability to better detect prescriptive information from the initial psychosocial intervention, and participant adherence in a trial with fewer adaptive strategies [33]. This trial design is primarily intended to evaluate the efficacy of MAS-ER to facilitate CRA+CM in non-responders with CUD, given the known data regarding dysfunctional dopaminergic transmission in CRA+CM non-responders [10].

We believe that this adaptive intervention trial will better our understanding of which individuals might most benefit from psychostimulant treatment for cocaine use disorder in the context of a psychosocial delivery platform that may facilitate its delivery in community-based treatment centers.

Acknowledgments

Funding: This work was supported by the National Institutes of Health [R01 DA034087, 2013].

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Figure 1: Overview of Clinical Trial Design

CRA=community reinforcement approach

CM=contingency management

MAS-ER=mixed amphetamine salts-extended release