



# A sequential multiple assignment randomized trial for cocaine cessation and relapse prevention: Tailoring treatment to the individual

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## ABSTRACT

Drug addiction is a chronic, devastating, but treatable disorder. A core principle of drug addiction treatment states that no single treatment is appropriate for everyone (NIDA, 2012); treatments need to adjust based on patient characteristics and response in order to be maximally effective. For cocaine use disorders (CUD), specifically, the most potent intervention currently available for initiating abstinence is behavior therapy using contingency management (CM) procedures, with early cessation being a robust predictor of future abstinence. This raises two key questions for treatment development research: First, can we significantly improve initial CM response rates with targeted adjunctive interventions? Second, for individuals who fail to achieve initial abstinence with CM, is pharmacotherapy an effective augmentation strategy? This paper describes how a sequential, multiple assignment, randomized trial (SMART) design has advantages over a fixed-intervention approach when it comes to collecting data needed to answer both questions. The first aim will examine whether Acceptance and Commitment Therapy (ACT) in combination with CM increases initial abstinence response rates (i.e., 2 consecutive weeks of cocaine-negative urine screens). The second aim will examine whether ACT + CM in combination with modafinil promotes abstinence achievement in initial non-responders. Results are expected to inform how we tailor treatment of CUD to maximize outcomes.

## 1. Introduction

Cocaine use disorders (CUD) comprise a public health problem in need of new treatment approaches. Cocaine affects multiple brain circuits, with prolonged exposure to cocaine compromising cognitive and behavioral processes associated with reward, motivation, learning, and inhibitory control [1–3]. The complexity of the disorder has presented numerous treatment challenges. Controlled studies have demonstrated effectiveness for several types of behavioral therapies, including cognitive-behavioral therapy (CBT), motivational interviewing (MI), and contingency management (CM) [4,5], along with promising pharmacotherapies [6,7]. Given the growing armamentarium of CUD interventions available, the treatment development research field has called for use of newer design methodologies that will lead to greater individualization or “tailoring” of interventions to the unique needs of the patient (e.g., PA-13-077; NIDA Principles of Drug Addiction Treatment, 2012) [8].

The sequential, multiple assignment, randomized trial (SMART) is an experimental design used for constructing empirically-supported adaptive treatment interventions (ATIs). For treatment of CUD, an ATI would present a sequence of interventions that work best for an individual patient across the stages of addiction treatment, from abstinence initiation to relapse prevention, dependent upon treatment response. The first decision stage of the SMART provides data for identifying the best initial treatment. The second decision stage of the SMART compares additional treatment options for initial treatment responders versus non-responders. Below we present the rationale for a two-staged SMART design that, compared to traditional fixed-design clinical trials, adapts treatment based on patient response, much like actual clinical practice.

### 1.1. Rationale for the study

This two stage SMART design will evaluate the impact of a sequence

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of treatment combinations for CUD, including CM, Acceptance and Commitment Therapy (ACT) and modafinil (a stimulant medication with low abuse potential that has been shown to facilitate cocaine abstinence). Presently, CM is the most reliably effective treatment for producing initial abstinence in patients with CUD [9]. Based on operant learning principles, CM involves the systematic reinforcement of desired or therapeutic behaviors and the withholding of reinforcement of undesired behaviors. An extensive literature of controlled-studies documents the success of these interventions [10]. We [11] and others [12–14] have implemented high-magnitude CM interventions during initial weeks of CUD treatment to produce abstinence rates as high as 40%. Given the robustness of initial abstinence in predicting long-term abstinence (e.g. [15,16]), it behooves practitioners and treatment researchers to identify and develop creative approaches to increase the number of CM “responders”.

Adding acceptance and mindfulness-based treatment strategies, such as ACT, to CM may lead to improved abstinence outcomes. Broadly, ACT has demonstrated larger effects than treatment as usual, drug counseling, and methadone maintenance alone (relative risk [RR] range: 1.58–4.17; odds ratio [OR] = 2.32), with emerging research also favoring ACT over CBT or intensive 12-step facilitation (RR range: 0.64 to 1.76) [17]. Studies of ACT for drug abuse have enrolled patients with opiate use disorder [69,70] or a mix of drug use disorders [71,72], but not cocaine use disorder in particular. One study of ACT for stimulant use disorder focused on methamphetamine specifically [73]. ACT is transdiagnostic, however, meaning that the key therapeutic processes apply broadly and beyond a single disorder or symptom [74].

ACT targets psychological inflexibility, including experiential avoidance, fusion with unhelpful thoughts and emotions, lack of present moment focus, attachments to rigid ideas about oneself, and detachment from values. Experiential avoidance (EA), or the tendency to engage in escape or avoidance responses (e.g., substance use) in the presence of negative affect, is a significant and potentially modifiable predictor of response to CM [18]. Therefore, providing ACT + CM early in CUD treatment may improve abstinence outcomes. For example, in a sample of 99 patients with CUD who received 4 weeks of CM treatment targeting abstinence initiation [18], post-hoc comparisons showed that the non-responder subgroup (i.e., patients who failed to achieve initial abstinence) had higher levels of EA, as measured by the Avoidance Inflexibility Scale [19]. ACT applies mindfulness and experiential exercises to reduce EA, increase tolerance of negative or aversive emotional and physical states (i.e., distress tolerance), and increase responding in adaptive ways according to relevant contingencies despite negative internal experiences, suggesting synergistic mechanisms of action for combining ACT with CM as a way to improve response. Thus, supplementing CM with ACT may be especially effective for CUD patients who exhibit high levels of EA and relatively low sensitivity to reward contingencies.

Patients who do not respond to initial treatment may arguably be most in need of adjunctive pharmacotherapy as a second treatment. Studies investigating the neurochemistry of CUD have shown that low dopamine transmission is associated with poor response to CM treatment [20], suggesting that fundamental biological differences in the functioning of the brain reward system explain the inability of some patients to respond to alternative, non-drug reinforcers [21]. It follows that pharmacological interventions that target striatal dopamine signaling might serve as a therapeutic adjunct for enhancing CM responding (i.e., responsivity to rewards) in this subset of patients. Modafinil has both dopaminergic and glutamatergic activity that may be useful for CUD. In human laboratory studies, modafinil has been shown to reduce cocaine-induced euphoria [22–24] and cocaine self-administration [23]. In an initial outpatient clinical trial of 62 cocaine-dependent patients, modafinil was superior to placebo in facilitating abstinence and reducing cocaine-positive urines [25]; however, subsequent trials have found this benefit limited to subsets of patients, including male participants [26] and those without a history of alcohol

dependence [27]. Kampman recently presented data showing that modafinil-treated subjects were significantly more likely than placebo-treated subjects to be cocaine abstinent throughout the entire clinical trial period, and to be continuously abstinent from cocaine by self-report during the last 3-weeks of the trial [28]. Thus, of the numerous candidate medications evaluated to promote cessation of cocaine use, modafinil appears to be the most promising.

For patients who achieve early cocaine abstinence, ACT-based strategies may play an essential role in the maintenance of behavior change by shifting patients' motivation from external (e.g., CM) to internal incentives or sources of motivation. As described above, ACT teaches skills for managing stress and other aversive emotional and physical experiences that commonly trigger relapse while, at the same time, helping the patient develop sustainable, value driven, goal-directed approach behaviors [29,30]. Thus, we predict that continuing ACT during the second treatment phase when high-magnitude CM is discontinued will be effective in maintaining cocaine abstinence in initial responders.

## 1.2. Study aims and hypotheses

We propose a SMART design to inform the development of an ATI for cocaine cessation and relapse prevention. Specifically, the design will provide data useful for addressing three primary questions. First, which treatment should be provided initially? Second, which second treatment should be provided to initial responders? Third, which second treatment should be provided to initial non-responders?

Specifically, we will test the following hypotheses: [1] 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); [2] for initial responders, continued ACT + CM will be more effective (higher abstinence rates) than continued DC + CM; [3] 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.

In the context of comparing first and second treatments, we will assess additional information concerning potential moderators and mediators of treatment response. Two secondary hypotheses are specified: [1] the benefit of ACT + CM over DC + CM on initial response rates will be greater in the subgroup of individuals with higher pre-treatment EA scores and higher distress tolerance scores; and [2] the effects of ACT + CM will be mediated by changes in EA and reward sensitivity as measured by behavior economic (e.g., delay discounting) tasks.

## 2. Methods

### 2.1. Trial design overview

As described above and shown in Fig. 1, the SMART design starts with a comparison of two initial treatments (ACT + CM versus DC + CM). Responding and non-responding participants will receive parallel second treatments according to the same sequence of decision rules. Only non-responding participants in each adaptive intervention will be re-randomized to a second treatment.

Eligible participants who complete a 1-week intake evaluation and pre-treatment assessment phase will be randomly assigned to one of the two 4-week initial treatments, ACT + CM or DC + CM, using urn randomization to ensure balance between groups on baseline EA level. Study visits will be thrice weekly (MWF) and will include urine drug screening at each visit and therapy (ACT or DC) sessions on two visits per week. Following initial 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

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