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A randomized factorial trial of disulfiram and contingency management to enhance cognitive behavioral therapy for cocaine dependence☆

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ABSTRACT

Background: This study evaluated the extent to which the addition of disulfiram and contingency management for adherence and abstinence (CM), alone and in combination, might enhance the effects of cognitive behavioral therapy (CBT) for cocaine use disorders.
Methods: Factorial randomized double blind (for medication condition) clinical trial where CBT served as the platform and was delivered in weekly individual sessions in a community-based outpatient clinic. 99 outpatients who met DSM-IV criteria for current cocaine dependence were assigned to receive either disulfiram or placebo, and either CM or no CM. Cocaine and other substance use was assessed via a daily calendar with thrice weekly urine sample testing for 12 weeks with a one-year follow-up (80% interviewed at one year).
Results: The primary hypothesis that CM and disulfiram would produce the best cocaine outcomes was not confirmed, nor was there a main effect for disulfiram. For the primary outcome (percent days of abstinence, self report), there was a significant interaction, with the best cocaine outcomes were seen for the combination of CM and placebo, with the two groups assigned to disulfiram associated with intermediate outcomes, and poorest cocaine outcome among those assigned to placebo and no CM. The secondary outcome (urinalysis) indicated a significant effect favoring CM over no CM but the interaction effect was not significant. One year follow-up data indicated sustained treatment effects across conditions.
Conclusions: CM enhances outcomes for CBT treatment of cocaine dependence, but disulfiram provided no added benefit to the combination of CM and CBT.

1. Introduction

Although cognitive behavioral therapy (CBT) has comparatively strong evidence for its efficacy as treatment for cocaine dependence (Dutra et al., 2008) and appears to be a particularly durable approach (Carroll et al., 1994b), outcomes may be enhanced when combined with pharmacotherapy and/or behavioral therapies that target complementary outcomes and mechanisms (Carroll et al., 2004c). One such approach is disulfiram, which has comparatively good empirical support for the treatment of cocaine dependence (Carroll et al., 2004a; Cubells, 2006; Oliveto et al., 2011; Suh et al., 2006). Disulfiram may contribute to reductions in cocaine use by (1) diminishing some of the reinforcing aspects of cocaine when it is used (Baker et al., 2007; Carroll et al., 1998b, 1994a; Cubells, 2006; Schroeder et al., 2011), and (2) helping cocaine users who also abuse alcohol refrain from concurrent cocaine-alcohol use (McCance-Katz et al., 1998) and hence alcohol-precipitated relapses to cocaine use. Disulfiram may complement CBT in several ways: First, by helping patients achieve longer periods of abstinence during treatment, disulfiram may facilitate greater exposure to and more effective learning of CBT skills and techniques. Second, the ability to implement coping skills for urges to use may be improved if patients perceive cocaine as less reinforcing while taking disulfiram. Third, disulfiram improves early retention,

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potentially 'holding' patients in treatment until the effects of CBT have an opportunity to emerge (Carroll et al., 1998b, 2000a). However, disulfiram's efficacy is dependent on patient adherence which can be problematic among substance users (O'Farrell and Litten, 1992).

Another evidence-based approach for cocaine dependence that may improve CBT's potency is CM (Dutra et al., 2008). One advantageous feature of CM is the precision and specificity with which it can be combined with other therapies to target their specific weaknesses (Carroll et al., 2004c; Petry et al., 2001): Reinforcement of submission of drug-free urine specimens reliably produces abstinence (Higgins et al., 2000; Lussier et al., 2006; Petry et al., 2006); in addition, CM can increase adherence and outcome with medications like disulfiram where efficacy is undercut by noncompliance by reinforcing compliance (Sorensen et al., 2007; Rigsby et al., 2000; Carroll et al., 2001). Although the effects of CM and disulfiram tend to weaken when no longer administered (Carroll et al., 2000a; Higgins et al., 2000), CBT's effects are often more durable and strengthen after treatment ends, presumably due to the persistence of skills learned. Thus, combining CBT with potent but more short-lived approaches that may enhance retention in CBT and foster greater exposure to its active ingredients via CM may ultimately enhance its efficacy.

The current trial evaluated the extent to which outcomes from CBT treatment of cocaine dependence could be enhanced by adding CM, disulfiram, and the combination of CM and disulfiram via a 2×2 factorial design. We hypothesized (1) a main effect for disulfiram over placebo, (2) a main effect of CM over no CM, and (3) an interaction of CM and disulfiram showing superiority of the combined treatments being added to CBT.

2. Methods

2.1. Participants

Participants were recruited from individuals seeking outpatient treatment for cocaine dependence at the APT Foundation, a private non-profit community based substance abuse treatment center. Individuals were included as participants if they were 18 years or older and met current DSM-IV criteria for current cocaine dependence, as assessed by the Structured Clinical Interview for DSM-IV (SCID) interviews at baseline. Individuals were excluded if they (1) were currently dependent on another drug (except tobacco) or whose principal drug use was not cocaine, (2) met lifetime DSM-IV criteria for a non-substance-induced psychotic or bipolar disorder, (3) had a current medical condition which would contraindicate disulfiram treatment (e.g. hepatic or cardiac issues, hypertension, pregnancy), as assessed by baseline physical examination (including EKG, urinalysis and blood work), or (4) were not sufficiently stable for outpatient treatment and had not received addiction treatment in the past 90 days.

Ninety-nine of the 139 individuals screened were determined to be eligible for the study, provided informed consent and were randomized. Reasons for ineligibility are described in Fig. 1. A computerized urn randomization program used in several previous trials (Ball et al., 2007; Carroll et al., 2004a, 2009; Stout et al., 1994) was used to produce equivalent group size and balance groups with respect to baseline level of cocaine use (more or less than 11 days per month), presence of alcohol dependence (yes/no), gender and ethnicity (ethnic minority/non-minority).

2.2. Treatments

All participants received weekly individual CBT. Participants also met thrice weekly with research staff blind to medication condition who collected urine and breath samples, dispensed study medication, and monitored other clinical symptoms. Adverse events and blood pressure were monitored weekly.

2.2.1. Cognitive behavioral therapy. CBT was delivered in 50 min individual weekly sessions by 12 clinicians (3 held doctorates and 9 were masters level PhD candidates; mean age 33.5; mean 4.6 years of experience in delivering CBT) who completed a two-day didactic seminar, and demonstrated competence in CBT by meeting pre-specified criteria for competence on the basis of ratings of audiotapes of their training cases using a validated treatment process rating system (Carroll et al., 1998a, 2000b). As described in the manual (Carroll, 1998), the goal of CBT is abstinence from cocaine and other substances via functional analysis of high risk situations, development of effective coping strategies and altering maladaptive cognitions associated with the maintenance of cocaine use.

2.2.2. Disulfiram. Participants assigned to disulfiram treatment were prescribed 250 mg of disulfiram daily, the dose used in previous trials (Carroll et al., 2004a, 1998b; George et al., 2000; Petrakis et al., 2000). Participants assigned to placebo received identical capsules in order to maintain the blind. All study medication capsules contained a riboflavin tracer (Del Boca et al., 1996; Kapur et al., 1992; Young et al., 1984) to monitor compliance. Of 1218 urine samples collected (1121 positive for the tracer), 92% were consistent with participant self-report; only 91 (8%) did not fluoresce in cases where the patient indicated they had taken their study medication since the last visit. A randomly selected subset of 98 samples was sent to a commercial laboratory for analysis of riboflavin level. Of these, 77 (79%) matched the staff determination (73 positive; 4 negative).

All participants were cautioned not to drink alcohol while in the study and to presume they were taking disulfiram. Breath samples were collected prior to thrice weekly dispensing of medication. Of 1298 breath samples collected during the trial, only one indicated recent alcohol use. To evaluate the medication blind, participants and the project nurse were asked to guess medication assignment at the end of the trial. Sixty-four percent of the 73 participants guessed their condition correctly, significantly better than chance ($X^2 = -2.50$, $p = .012$). The project nurse, who dispensed medication and assessed adverse events, guessed no better than chance (49%).

2.2.3. Contingency management (CM). In this condition, in addition to standard CBT and study medication as described above, participants earned chances to draw prizes from a bowl contingent on two independent behaviors (medication adherence and cocaine negative urine specimens). Using procedures described by Petry (Budney and Higgins, 1998; Petry, 2000; Petry et al., 2000, 2006), participants earned at least one draw each time they ingested study medication witnessed by staff and each time they submitted a submitted a cocaine-free urine specimen. The number of draws earned escalated by one each time the participant exhibited each behavior up to 7 draws maximum for medication adherence and cocaine abstinence per visit. Failure to attend the clinic for medication administration or to take the medication resulted in a reset in the number of medication adherence draws to one at the next visit. Similarly, if a participant submitted a cocaine-positive urine specimen or failed to submit a specimen on a scheduled assessment session, the number of draws decreased back down to one for the next negative sample submitted. Participants consistently abstinent from cocaine and fully compliant with medication visits could earn a maximum of 462 draws during the 12-week treatment period (231 for cocaine-free urine samples and 231 possible medication adherence draws).