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A controlled trial of the adjunct use of D-cycloserine to facilitate cognitive behavioral therapy outcomes in a cocaine-dependent population ☆

Ashley P. Kennedy [a], Robin E. Gross [a], Natasha Whitfield [b], Karen P.G. Drexler [a,b], Clinton D. Kilts [a,*]

[a] Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, USA
[b] Atlanta Veteran's Administration Medical Center, Atlanta, GA 30322 USA

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ABSTRACT

Cocaine dependence is a chronically relapsing disorder for which its predominant behavioral therapies are associated with only partial efficacy. The goal of this study was to determine if the N-methyl-D-aspartate (NMDA) glutamate receptor partial agonist and cognitive enhancer, D-cycloserine (DCS), could boost the cocaine abstinence and treatment retention goals of cognitive behavioral therapy (CBT). This study employed a placebo-controlled, randomized double-blind trial design of 44 cocaine-dependent men enrolled in a 4-week outpatient Substance Abuse Treatment Program (SATP) at the Atlanta Veteran's Administration Medical Center. Subjects received 50 mg of DCS or placebo prior to four weekly sessions of a condensed version of a manual-based CBT for cocaine dependence. Cocaine abstinence and treatment retention measures represented primary outcome variables. Relative to a 12-step based treatment-as-usual, an under-dosed CBT was associated with significant improvements in drug abstinence and treatment retention at 4-weeks and for maintenance of drug abstinence after four more weeks of follow-up. The robust response to the under-dosed CBT was not enhanced by the adjunct administration of DCS at either the 4- or 8-week endpoints. This controlled clinical trial failed to demonstrate an ability of DCS to boost the relapse prevention or treatment retention goals of CBT.

1. Introduction

Cocaine addiction is a chronically relapsing disorder associated with high rates of recidivism in treatment-seeking individuals. To date, treatment for cocaine addiction remains solely reliant on behavioral therapies; there are currently no FDA approved pharmacotherapies for cocaine addiction. The major behavioral therapies including cognitive behavioral therapy (CBT), 12-Step, and contingency management approaches have proven to be effective in promoting recovery and relapse prevention for drug-dependent individuals (Garcia-Rodriguez et al., 2009; Maude-Griffin et al., 1998; Weiss et al., 2005). However, the available addiction behavioral treatments have limited or partial efficacy in reducing the susceptibility to relapse. While drug antibody (Haney, Gunderson, Jiang, Collins, & Foltin, 2010; Martell et al., 2009) and targeted enzyme (Brimijoin et al., 2008; Collins et al., 2009) approaches may eventually provide therapeutic advantages, a more proximal approach might be represented by the adjunct use of a cognitive enhancer to boost the therapeutic cognitions and thus efficacy associated with a behavioral therapy based strongly on learning and memory processes.

Recent theories related to the drug addiction process emphasize the roles of learning and memory processes (Kelley, 2004; Robbins, Ersche, & Everitt, 2008). The formation of addiction memories are dynamic processes reflecting associative learning mechanisms by which conditioned drug cues can elicit intense drug seeking and wanting (Robinson & Berridge, 2001). Neural processing networks exhibiting drug use experience-dependent plasticity represent addiction learning and its associated memories (Everitt et al., 2008). Similarly, in modifying cognitions and behaviors associated with drug addiction, CBT relies for its effectiveness on engaging competing learning and memory processes represented by differing networks modified by treatment experience-dependent neuroplasticity. One of the goals of addiction therapy is relapse prevention due to the drug conditioned stimulus (CS) no longer predicting the conditioned response (CR) represented by drug seeking and use behaviors. This goal can be accomplished by either extinction of the CR to a CS or by changing contingencies such that the drug CS now predicts a

Abbreviations: NMDA, N-methyl-D-aspartate; DCS, D-cycloserine; CBT, cognitive behavioral therapy; SATP, Substance Abuse Treatment Program; CS, conditioned stimulus; CR, conditioned response; PTSD, posttraumatic stress disorder; CET, cue exposure therapy; LTP, long-term potentiation; LTD, long-term depression; VAMC, Veteran's Administration Medical Center; UDS, urinalysis drug screen; EMR, electronic medical records; TAU, Treatment As Usual; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition; SCID, Structured Clinical Interview for DSM-IV Axis-I Disorders; (ASI), Addiction Severity Index; CAARS, Connors Adult ADHD Rating Scale.

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* Corresponding author at: Psychiatry Research Institute, University of Arkansas for Medical Sciences, 4301 W. Markham St, Mail Slot 554, Little Rock, AR 72205, USA. Tel.: +1 501 526 8163; fax: +1 501 526 8199.
E-mail address: CDKilts@uams.edu (C.D. Kilts).

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different CR. Both processes involve new learning and memory. Extinction-based psychotherapies such as prolonged imaginal exposure are effective in extinguishing pathological learned associations in anxiety disorders such as posttraumatic stress disorder (PTSD) (Foa et al., 2005). However, the use of analogous cue exposure therapy (CET) approaches to extinguish the learned associative values of drug use cues in drug-addicted individuals have met with largely negative results (Conklin & Tiffany, 2002; Price et al., 2009) and, in at least one instance, in increases in relapse rates (Marissen, Franken, Blanken, van den Brink, & Hendriks, 2007). Cognitive behavioral therapy for cocaine addiction involves the identification of the thoughts, feelings, and events that precede and follow episodes of cocaine use and the learning and deployment of coping skills to counter drug use urges (Carroll, 1998). Unlike CET, controlled clinical trials have demonstrated the efficacy of CBT in producing significant, enduring drug abstinence in cocaine-addicted populations (Carroll et al., 2004). The maximal beneficial effects of CBT appear to be delayed, suggesting that the coping skills take time to be learned and consolidated (Carroll et al., 2000; Epstein, Hawkins, Covi, Umbricht, & Preston, 2003).

The N-methyl-D-aspartate (NMDA) glutamate receptor is critical for the activity-dependent control of synaptic efficacy, exemplified by long-term potentiation (LTP) or depression (LTD) of synaptic signals, a molecular mechanism of experience-dependent neuroplasticity that underlies learning and memory formation (Malenka & Bear, 2004; Rebola, Srikumar, & Mulle, 2010). D-Cycloserine (DCS), a partial agonist at the NMDA glutamate receptor, binds to the glycine binding regulatory site to facilitate glutamatergic neurotransmission (Kaye, Sansom, & Biggin, 2006). DCS also enhances NMDA receptor-dependent synaptic potentials and facilitates the long-term synaptic plasticity of glutamate neurotransmission (Billard & Rouaud, 2007; Nitsche et al., 2004; Rouaud & Billard, 2003). Several preclinical studies have established that DCS can enhance learning and memory processes related to extinction (Walker, Ressler, Lu, & Davis, 2002) and operant behavior (Hood, Compton, & Monahan, 1989; Lelong, Dauphin, & Boulouard, 2001; Monahan, Handelmann, Hood, & Cordi, 1989). Recent controlled clinical trials have explored the use of adjunct DCS to enhance learning and memory processes related to behavioral therapies for patients with anxiety disorders. The major effect of the adjunct use of DCS with extinction-based psychotherapies for anxiety disorders seems to be an acceleration of extinction learning and memory (Hofmann et al., 2006; Kushner et al., 2007; Ressler et al., 2004; Wilhelm et al., 2008). This effect is mirrored in a facilitation of the rate of extinction of learned associations to cocaine cues in animal models (Botreau, Paolone, & Stewart, 2006; Nic Dhonnchadha et al., 2009; Paolone, Botreau, & Stewart, 2009; Thanos, Bermeo, Wang, & Volkow, 2009; Torregrossa, Sanchez, & Taylor, 2010), suggesting that DCS facilitates the extinction of both aversively and appetitively-conditioned associations. A recent report (Otto et al., 2010) indicated that DCS also facilitates the learning and memory processes associated with CBT in individuals with panic disorder. Based on these observations we hypothesized that DCS might facilitate the rate and extent of therapeutic learning and memory processes associated with CBT for cocaine addiction, and thus lead to enhanced relapse prevention and treatment retention outcomes. This hypothesis was tested using a placebo-controlled, double-blind clinical trial design that assessed the interaction between DCS and a condensed version of a manualized CBT for cocaine addiction (Carroll, 1998).

2. Patients and methods

2.1. Study design

A randomized, double-blind, placebo-controlled study design was used to determine the efficacy and safety of the adjunct use of DCS with CBT to facilitate drug abstinence in a treatment-seeking sample of cocaine-dependent men. The clinical trial was conducted over a period of 23 months (April 2007 to March 2009) in the Substance Abuse Treatment Program (SATP) at the Atlanta Veteran's Administration Medical Center (VAMC) and consisted of 8 weeks of possible outpatient treatment consisting primarily of twelve-step recovery techniques in a group setting. The study design was naturalistic in that it incorporated DCS- and CBT-focused research into a treatment-as-usual milieu common to many VA medical center treatment settings for drug addiction. The core 12-Step recovery techniques were administered by licensed addiction therapists highly experienced with 12-Step techniques in the SATP setting. The IRB-approved protocol and informed consent process did not include the intent to collect intervention integrity data so the 12-Step sessions (or CBT sessions) were not taped or observed and coded for content validity. Study participants were recruited from the SATP at the Atlanta VAMC through self-referrals, and responses to flyer distribution at the VAMC. At intake into the SATP, the project clinical research coordinator (RG) discussed with potential participants the rationale, design, and associated risks related to the clinical trial. Based on their number of past treatment enrollments, subjects were assigned to either 3- or 5-day per week treatment plans for four weeks. Following this intensive outpatient therapy, a four-week follow-up period (Aftercare) consisted of a voluntary treatment extension involving once-weekly group therapy sessions of identical 12-Step content and served as a means of estimating whether any effects of CBT or DCS endured after therapy.

Following screening, eligible study volunteers were randomized to one of three parallel treatment arms (*i.e.*, DCS + CBT, Placebo + CBT, or Treatment as Usual (TAU)). The TAU group represented the delivery of standard SATP/Aftercare quality of care and was a control group for the effect of CBT. In addition to assignment to the DCS + CBT, and Placebo + CBT groups, these subjects also received the standard care for treatment for substance dependence (TAU) in the SATP (*i.e.*, DCS + CBT + TAU, Placebo + CBT + TAU). This study used a fixed dose of 50 mg of DCS. DCS (Seromycin, 250 mg; Eli Lilly and Co, Indianapolis, IN) was reformulated by the research pharmacist into 50 mg capsules with identical placebo capsules. Previous studies of the efficacy of DCS to facilitate exposure-based psychotherapies in fear- and anxiety-related disorders demonstrated that 50 mg of DCS was efficacious in reducing associated symptoms and was well tolerated (Hofmann et al., 2006; Otto et al., 2010; Ressler et al., 2004). Subjects received 50 mg of DCS or placebo one hour prior to once-a-week CBT with a licensed clinical psychologist for four weeks during the SATP phase.TAU subjects met with the study research coordinator once a week as a control measure for the study interactions related to CBT sessions (Fig. 1).

2.2. Drug monitoring

Urine samples were collected by SATP caseworkers at random days and times of day twice weekly over the first four study weeks and weekly in the Aftercare component. Sample collection was not observed but samples were temperature-tested to ensure its current status and donor identity. Halfway house staff submitted urine specimens from study participants to the SATP in response to indications of suspected drug use. Drug use was assessed by urinalysis drug screen (UDS) for cocaine and its primary metabolite (i.e. benzoylecgonine), and other drugs of abuse (i.e. amphetamines, opiates, benzodiazepines). A benzylecgonine concentration of ≥300 ng/mL represented the minimum threshold to detect a cocaine-positive urine specimen. All urinalysis results (±UDS) were reported in the electronic medical records (EMR) entries for each subject. Relapse was defined as a positive UDS result confirmed in the EMR entries. Abstinence was defined as maintaining cocaine-negative UDS results throughout the duration of the 4- and 8-week study endpoints. Unlike most controlled therapy trials in drug-dependent samples, loss to follow-up (i.e. subject does not return for treatment for the

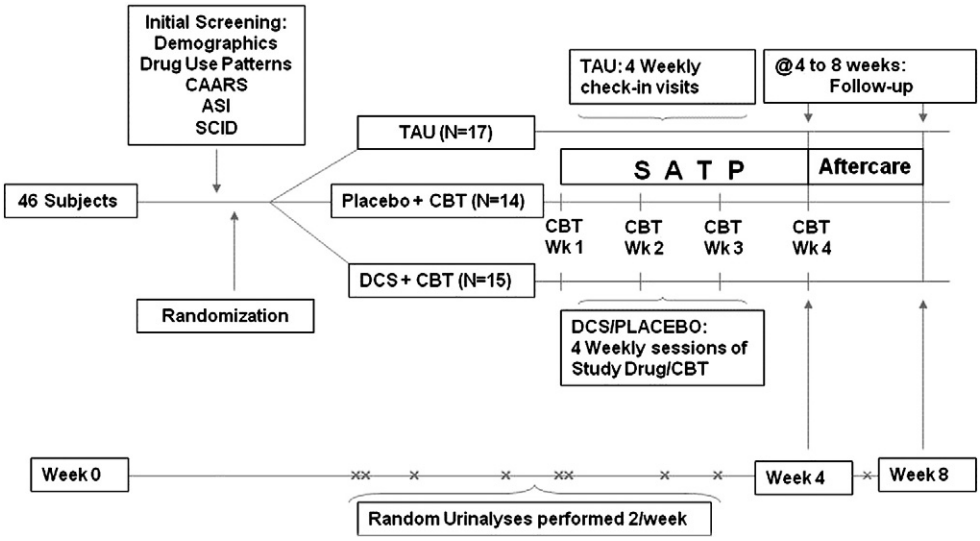

Fig. 1. Study design for a randomized, double-blind, placebo-controlled study of the adjunct use of DCS to boost the therapeutic response to CBT for male cocaine addicts.

remaining duration of the study) was not coded as relapse because the clinical team could not definitively determine whether loss to follow-up was due to reasons other than relapse (e.g., obtainment of employment).

2.3. Randomization

The simple random allocation sequence was achieved by generating a list of random numbers (1, 2, 3) in which a number corresponded to a certain treatment group (i.e. 1 = DCS/placebo, 2 = DCS/placebo, 3 = TAU). The clinical coordinator (RG) used this list to randomly assign participants to either the TAU or TAU/CBT arms. To further randomize subjects to the DCS or placebo groups, the research pharmacist flipped a coin in which heads corresponded to DCS and tails corresponded to placebo. This randomization process allowed a double-blind to be achieved in which research staff (except for the research pharmacist who never interacted with the subjects) and study participants were blinded to the medication (DCS/placebo) group assignments.

2.4. Sample size calculation

A sample size of 15 subjects was proposed for each group and was based on the results of power calculations for effect size and variance estimates from prior controlled clinical trials of the adjunct use of DCS with exposure-based behavioral therapies for persons with anxiety disorders. These studies randomized 13–16 subjects per arm and demonstrated that DCS facilitated the clinical response to behavioral therapies with moderate to large effect sizes (d = 0.73–1.06) (Hofmann et al., 2006; Kushner et al., 2007; Ressler et al., 2004). That DCS resulted in comparable facilitatory effects on extinction learning in animal models of relapse to drug seeking and use behaviors (Botreau et al., 2006; Paolone et al., 2009) and of conditioned fear related to anxiety disorders (Ledgerwood, Richardson, & Cranney, 2003; Walker et al., 2002) provides indirect support for this generalization.

2.5. Inclusion/exclusion criteria

All study subjects provided written informed consent to participate in a research protocol approved by the Emory University Institutional Review Board and the Atlanta VAMC Research and Development Committee. Eligible subjects were cocaine-dependent persons between 18 and 65 years of age enrolled in the SATP at the Atlanta VAMC. All subjects met the Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition (DSM-IV) criteria for diagnosis of cocaine dependence. Potential subjects were excluded for any current Axis-I diagnosis other than cocaine or alcohol dependence or nicotine use, current or prior neurological disease, history of a major medical illness (Axis-III diagnosis), or current use of psychotropic medications. Prior to study participation, medication reconciliation by the study addiction psychiatrist (KPGD) assessed possible adverse drug interactions between DCS and currently prescribed medications.

2.6. Assessments and measures

All study-eligible subjects were evaluated using the following assessment instruments:

I. The Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID) (First, 2002) is a reliable and validated semi-structured 1–2 h interview to diagnosis DSM-IV Axis-I psychiatric disorders.
II. The Addiction Severity Index (ASI) (McLellan et al., 1992) is a validated and reliable instrument that is a semi-structured one hour interview designed to assess the severity of addiction-related functional impairment in drug-dependent populations. The ASI provides an overview of problems related to substance use by addressing the following subscales: drug use, alcohol use, legal status, medical status, employment status, family/social status, and psychiatric status.
III. The Conners Adult ADHD Rating Scale (CAARS) (Conners et al., 1999) is a multi-dimensional self-report instrument used to measure the presence and severity of ADHD symptoms and takes approximately 10–15 min to complete. The CAARS assesses clinically significant domains such as Inattention/Memory Problems, Hyperactivity/Restlessness, Impulsivity/Emotional Liability, Problems with Self-Concept, DSM-IV Inattentive Symptoms, DSM-IV Hyperactive-Impulsive Symptoms, DSM-IV Total ADHD symptoms, and ADHD Index. The Inconsistency Index serves as an internal measure to help identify inconsistencies in responses by study participants.
IV. A study-specific data collection instrument was used to collect demographic information (e.g., age, education, race) and drug use patterns (e.g., past cocaine use in last 7 and 30 days, etc.) from study participants.

All assessments (e.g., SCID, ASI, CAARS, demographic information and drug use history) were completed at the initial screening or baseline (Fig. 1). No additional assessments were collected weekly or at the 4- and 8-week study endpoints. The assessment instruments serve to further characterize study participants and determine if

there were any differences at baseline between the three groups (i.e., DCS + CBT, Placebo + CBT, or Treatment as Usual (TAU)) .

2.7. Cognitive behavioral therapy

Study participants engaged in four condensed sessions of a 12-session manual-based Cognitive Behavioral Therapy for Cocaine Addiction (Carroll, 1998) at one-week intervals for 45 min (http://archives.drugabuse.gov/txmanuals/CBT/CBT1.html). Five of the eight topics in the manual were covered in the four group or individual CBT sessions. The study used a rolling enrollment into the CBT sessions so the sessions involved individual to small groups (≤3). Each session started with a review of the prior session to reinforce topics and skills that had been addressed in the previous session. The therapist for the CBT sessions was a clinically trained, PhD level licensed psychologist (NW) certified in CBT. The CBT sessions were scored on a scale of 1–4 to record the therapist's perception of the level of engagement by individual participants; however, no additional intervention data was collected to assess for consistency of the content of the CBT across subjects and sessions (e.g., inter-related reliability and integrity of CBT sessions). The first CBT session focused on understanding participant's drug craving experiences. Subjects learned the properties of their drug cravings (*e.g.*, the duration of craving episodes), and learned to identify the triggers and cues that precipitated drug cravings. This session also focused on learning strategies to combat or cope with cravings (*e.g.*, recall of negative consequences of cocaine abuse or avoidance of cues). The second CBT session involved increasing motivation and a commitment to stop using illicit drugs. The psychologist (NW) clarified realistic treatment goals for each subject and challenged a subject's ambivalence towards drug abstinence. Subjects also learned a systematic approach to identify and cope with thoughts about cocaine that involved recognizing, avoiding and coping with cue-associated drug cravings. The third CBT session addressed refusal skills in which subjects first learned ways to break contact with individuals who supply or use cocaine. Subjects learned and actively engaged in practicing drug refusal skills in role-playing exercises. The final CBT session encompassed an all-purpose coping plan. Subjects learned to anticipate high-risk situations and to understand seemingly irrelevant stimuli that lead to drug relapse. Subjects also developed a comprehensive coping plan that could be recalled when encountering triggers or cravings. All sessions involved a series of practice exercises in which the skills taught in that particular session were further reinforced by each subject via repetition in an attempt to consolidate the therapeutic memories. All four sessions involved the recall of typical drug use situations and were thus exposure-based and the prevention of responses to the urge to use drugs through a variety of learned and recalled coping strategies.

2.8. Statistical analyses

Data were analyzed using SAS (SAS Institute Inc., Cary, NC, USA). Continuous data (e.g., demographic and clinical characteristics) were analyzed using a series of ANOVAs. Categorical data were analyzed using chi-square or Fisher's exact when sample sizes were relatively small (e.g., n<5). Kaplan–Meier survival analyses were performed on data for 4- and 8-week study time points to determine group effects on cocaine abstinence and treatment retention between the three treatment arms. Loss to follow-up was not coded as relapse in the study and these subjects were censored in the Kaplan–Meier survival analysis. Post hoc analyses were subsequently performed on the survival curves and an adjusted p-value was calculated to determine significance of all pair-wise comparisons of the survival curves. Effect sizes (Cohen's d, following conventions of d = 0.20, 0.50, 0.80 for small, medium, and large effect sizes, respectively) (Cohen, 1988)) were calculated to estimate the effects of CBT and DCS relative to the control (TAU) group for both the 4-week and 8-week study endpoints. These effect size estimations were conducted for the drug abstinence outcome variable only.

3. Results

3.1. Subjects

The flow diagram for study enrollment is illustrated in Fig. 2. Utilizing electronic medical records (EMR), 877 cocaine-dependent males were identified as presenting to the SATP for treatment from April 2007 to May 2009. Of that pool of potential subjects, 584 were excluded by EMR review due to Axis-I or III diagnoses, other drug dependence (*e.g.,* opiate, methamphetamine), refusal of treatment, assignment to another treatment facility, drug-free time > 60 days, and age > 65. Of the 293 remaining persons who qualified for further study evaluation, 238 declined study participation. Of the remaining 55 subjects who consented for the clinical trial, nine were not randomized to treatment due to loss to follow-up, SCID failure, or diagnosis of a new Axis-I or III diagnosis as determined by the psychiatrist on call. Two subjects withdrew after randomization but before their first treatment session. Subjects were considered enrolled in the study upon completion of the first day of treatment. Of the forty-four men actively enrolled in the clinical trial study, 15 were randomized to the DCS + CBT arm, 13 to the placebo + CBT arm and 16 to the TAU arm.

Three of the study subjects were court-mandated to complete the SATP (1 in the TAU group and 2 in the Placebo + CBT arm). Ten subjects were actively being treated for nicotine dependence via nicotine replacement therapy (nicotine patch or gum). Four subjects were prescribed naltrexone for alcohol dependence (1 each in the DCS + CBT and Placebo + CBT arms, and 2 in the TAU group).

3.2. Demographics

The clinical and demographic variables for the randomized subject sample are described in Table 1. Subjects in the randomized sample reported using crack cocaine an average of 9 days (±8) in the past 30 days and had an average of 3.7 (±3.5) prior treatment enrollments. The majority of subjects seeking treatment was homeless and had been assigned halfway house placement (77%) with four primary halfway house settings. 98% of the subjects were African-American. The individuals in each treatment arm did not differ in any of the measured demographic variables including age, education, halfway house assignment, or treatment team assignment (3 or 5 days/week). Groups also did not differ in the levels of addiction-related functional impairment (ASI), ADHD traits (CAARS subscales), and cocaine, nicotine and alcohol use patterns. These comparisons support the success of the randomization procedure, though the three groups did exhibit significant differences in the number of subjects who were alcohol dependent or alcohol abusers.

3.3. Drug abstinence and treatment retention

The survival analysis indicated that subjects who received DCS + CBT or placebo + CBT exhibited numerically greater rates of cocaine abstinence, 86.7% and 92.3% respectively, compared to TAU (59.8%) at 4 weeks, though the effect was marginally statistically significant (p = 0.052, Log rank test) (Fig. 3A). Small effect sizes were noted for the placebo + CBT group (d = 0.34) and DCS + CBT group (d = 0.13) relative to the TAU group at 4 weeks. However, the survival analysis for the 8-week data indicated a significant group difference in rates of cocaine abstinence for groups randomized to the CBT arms versus the TAU group. The DCS + CBT and placebo + CBT groups maintained 86.7% and 92.3% cocaine abstinence, respectively, compared to the TAU group (44.9%) (p = 0.006, Log rank test) (Fig. 3B). The DCS + CBT and placebo + CBT groups did not differ in rates of cocaine

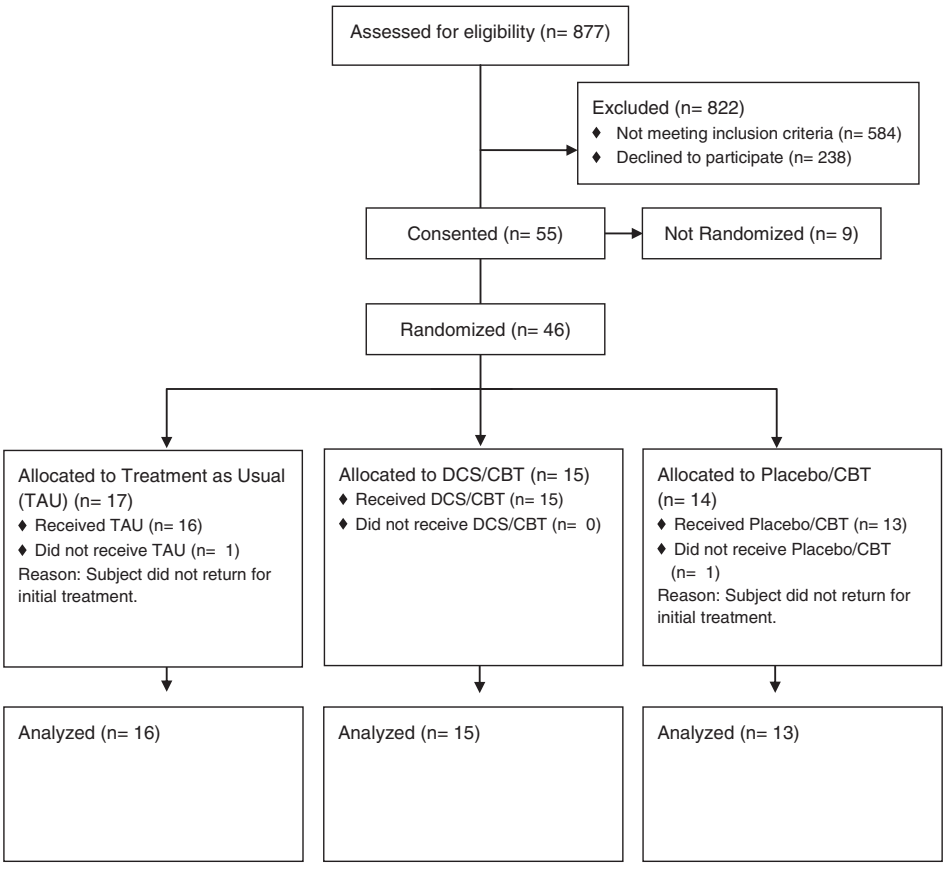

Fig. 2. Flow diagram of study participants. A total of 46 subjects were randomized to the three treatment arms of the study.

abstinence ($p = 0.637$); however, there was a significant difference in the rates of cocaine abstinence at 8-weeks for the TAU and placebo + CBT arms ($p = 0.011$). Small to moderate effect sizes were noted for the placebo + CBT group ($d = 0.55$) and DCS + CBT group ($d = 0.39$) relative to the TAU group at 8 weeks.

The survival curves for treatment retention at 4 weeks indicated a significantly greater treatment retention for those groups receiving CBT versus the TAU subjects; 93.3% and 100% retention for the DCS + CBT or placebo + CBT groups, respectively, compared to 68.8% for the TAU group ($p = 0.037$, Log rank test) (Fig. 3**C**). The DCS + CBT and placebo + CBT groups did not differ in rates of treatment retention ($p = 0.352$). At 8 weeks, there were no significant group differences in the survival curves for percent treatment retention ($p = 0.267$, Log rank test) (Fig. 3D). Subjects in all three treatment arms exhibited a decrease in percent treatment retention at 8 weeks (DCS + CBT, 66.7%; placebo + CBT, 76.9%; TAU, 50%) relative to values at 4 weeks. 86% of all enrolled subjects irrespective of treatment arm completed the entire 4-week intervention (i.e., treatment completion) in the clinical trial. There were no significant group differences in the percent of subjects opting for the Aftercare extension of treatment - 86.7% of subjects in the DCS + CBT group opted for Aftercare as compared to 76.9% and 56.3% for the placebo + CBT and TAU groups, respectively.

Table 1
Demographical and clinical characteristics of the randomized subject sample.

	DCS + CBT	Placebo + CBT	TAU
Variable			
N	15	13	16
Age (years)	48.3 ± 5.4	48.3 ± 5.2	47.6 ± 6.1
Race (AA/CA)	15/0	13/0	15/1
Education (years)	13.7 ± 1.8	12.5 ± 1.4	13.4 ± 1.4
Drug related functional impairment (Addiction Severity Index, ASI)			
Alcohol	0.45 ± 0.33 (14)	0.31 ± 0.27 (11)	0.22 ± 0.28 (12)
Drug	0.27 ± 0.06 (14)	0.18 ± 0.10 (11)	0.21 ± 0.08 (12)
Drug use patterns			
Cocaine use past 7 days	0.53 ± 1.1	0.38 ± 0.8	0.72 ± 1.4
Cocaine use past 30 days	11.0 ± 8.6	6.3 ± 6.5	9.2 ± 8.5
# Alcohol dependent/ abuse*,**	4/8	9/3	10/2
#of prior treatment enrollments	2.9 ± 3.3	3.7 ± 3.8	4.4 ± 3.6
Total days in treatment	131.0 ± 128.8	108.8 ± 78.2	80.1 ± 74.2

Note. Race: AA = African-American; CA = Caucasian; deviations in sample sizes from the total are listed as (n) in the columns for the respective variables. Values represent mean ± SD (*Fisher Exact Test) (**p-value < 0.05).

4. Discussion

The primary goals of this controlled clinical trial were to ascertain the acute treatment efficacy (0–4 weeks) and post-treatment durability of DCS administration as a means of boosting the relapse prevention and treatment retention goals of CBT, an empirically supported therapy with partial efficacy for the treatment of cocaine addiction. A major barrier to drug abstinence in this population is the uncountered drug use motivation triggered by conditioned external and internal drug-related cues that predict drug seeking and use behaviors. These learned associations are associated with strongly consolidated drug use memories that are highly resistant to extinction (Weiss et al., 2001), a property that perhaps underlies the general ineffectiveness of extinction-based CET approaches to prevent relapse (Conklin & Tiffany, 2002). Alternative treatment approaches such as CBT seek to counter addiction by modifying cognitive and behavioral representations of drug use that oppose the prior learned associations such that conditioned drug cues no longer predict drug

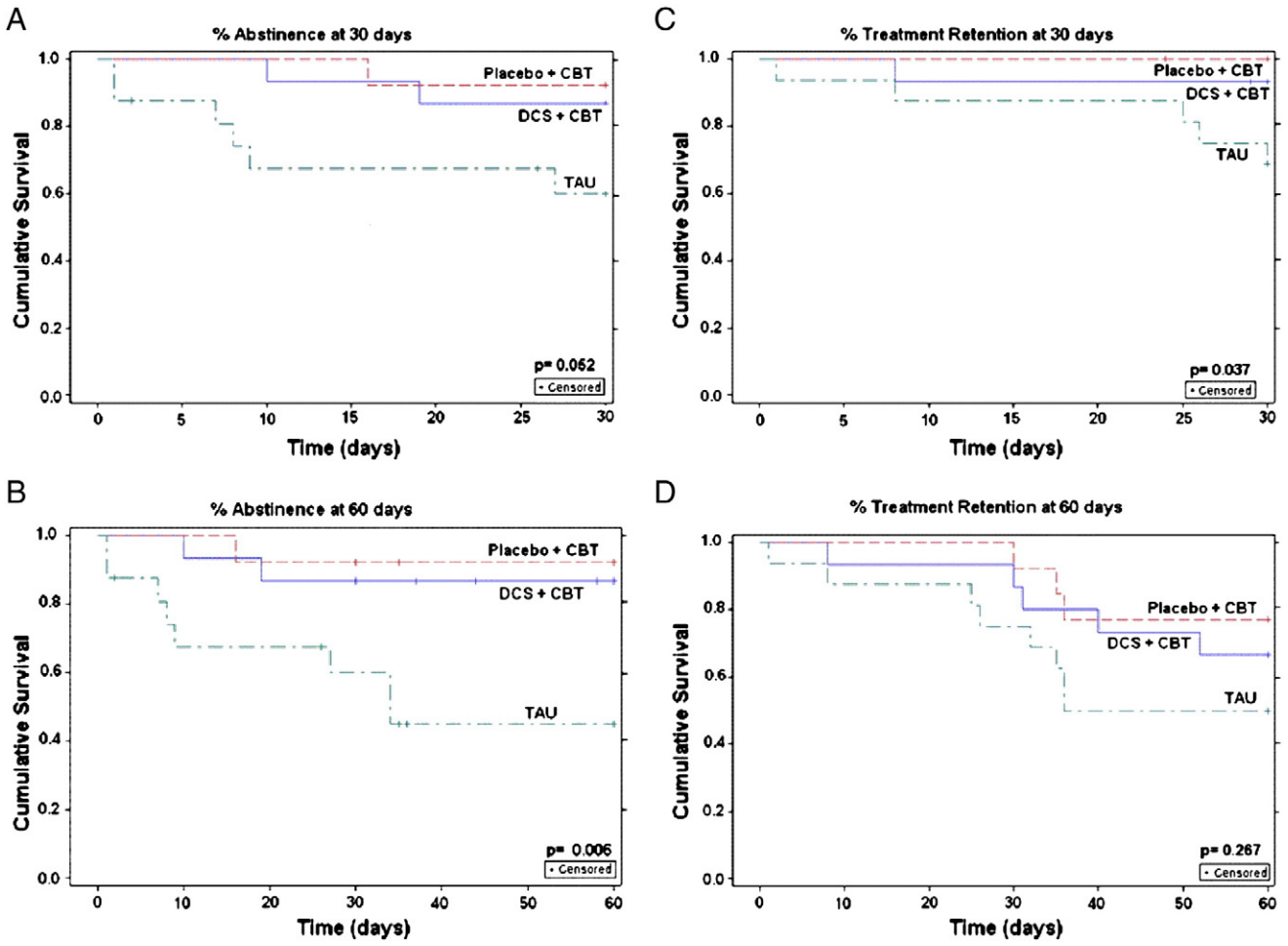

Fig. 3. A, B. Kaplan–Meyer survival curves for drug abstinence for the three treatment groups (DCS + CBT, Placebo + CBT, TAU) at the 4-week ($p = 0.052$, Log rank test) and 8-week endpoints ($p = 0.006$, Log rank test). C, D. Kaplan–Meyer survival curves for treatment retention for the three treatment groups at the 4-week ($p = 0.037$, Log rank test) and 8-week endpoints ($p = 0.267$, Log rank test). (Censored = no "event" or relapse).

abuse. A premise of this study was that CBT, like extinction, involves therapeutic learning and memory processes that are mediated by glutamatergic neurotransmission and are thus amenable to enhancement with DCS administration. This premise was tested by pairing weekly DCS pretreatments with four weekly sessions of CBT representing a condensed version of a 12-session CBT (Carroll, 1998). This abbreviated CBT protocol was used to allow the assessment of possible response-enhancing effects of DCS. A similar strategy was recently used to demonstrate DCS augmentation of exposure-based CBT outcomes for individuals with panic disorder (Otto et al., 2010).

The results of this clinical trial indicate that a condensed and abbreviated version of a manual-based 12-session CBT for cocaine addiction (Carroll, 1998) resulted in significant improvements in relapse prevention and treatment retention, the primary study outcome variables. The gains relative to the TAU group also endured over a one-month follow-up period. The effect sizes for CBT versus TAU, irrespective of receiving placebo or DCS, reflected small to moderate enhancements ($d = 0.13–0.55$) of the relapse prevention outcomes for TAU. This clinical trial also revealed that DCS as an adjunct treatment to CBT offered no advantage relative to placebo in promoting drug abstinence and treatment retention in a cocaine-dependent population; both CBT arms were comparably more effective than a relatively intensive 12-Step-based TAU. Therefore, the intent of the study design to assess the ability of DCS to boost the partial clinical response to an "under-dosed" version of CBT was not realized.

A robust response to brief CBT precluded the opportunity to assess the ability of co-administered DCS to facilitate the clinical response to CBT. Attrition in addiction treatment programs and loss to follow-up for clinical trials in drug-dependent populations are well-recognized problems. The goal of combination therapies to facilitate a more rapid and efficient treatment response (i.e., fewer CBT sessions) would be of significant clinical value. The pairing of DCS with a more standardized, dose-adjusting form of CBT such as computerized CBT (Carroll et al., 2008) would perhaps represent an improved experimental design of heightened translational significance.

A major premise of this study is that DCS would facilitate the retention of therapeutic learning and memory consolidation. Recent fMRI studies have demonstrated that DCS facilitates hippocampal mechanisms of learning and memory consolidation in humans (Kalisch et al., 2009; Onur et al., 2010). Future studies of the value of DCS as a treatment adjunct in cocaine-addicted individuals could be enhanced by a similar use of in vivo functional neuroimaging technology to define its effect on putative neural mechanisms of therapeutic learning and memory processes.

4.1. Strengths and limitations

Strengths of the study include that all of the study participants were involved in active treatment (*i.e.* all subjects received the standard of care at the Atlanta VAMC study site). It should be mentioned, however, that interaction between the 12-Step-based TAU and the study CBT might have limited the ability to assess the efficacy of adjunctive DCS. The comparison of CBT outcomes with and without DCS in the absence of the 12-Step TAU would have been a less

ambiguous design. Adherence to the regimen of DCS study medication was 100% as noted by observation and no spontaneous reports of adverse events occurred throughout the clinical trial. An added strength of the study was that it was an outpatient study, which allowed the assessment of treatment response by subjects exposed to cocaine cues in their everyday environment. An inpatient study could have possibly caused inflated treatment effects while in the controlled setting of the hospital and dramatic decreases in treatment efficacy once the patient was re-exposed to his drug use environment. Spot urinalysis was conducted in halfway house settings when subject's behavior required further surveillance and was indicated in the EMR, and thus complemented the random UDS measures of relapse in the SATP.

Limitations of the study include that the majority of the participants were homeless and with varying shelter environments making this a difficult clinical population for longitudinal study. Another limitation of the study is that the SATP is an abstinence-based treatment program in which a lapse to cocaine use could trigger termination of treatment. Therefore, a common measure of treatment response — the cumulative incidence of drug positive urines as a function of time - could not be ascertained. The fixed study dose of 50 mg of DCS was selected based on the effectiveness of this dose in boosting the response to extinction-based behavioral therapies and CBT in individuals with anxiety disorders, and the dose-dependent properties of DCS as a partial NMDA receptor agonist. However, it is unknown as to whether acknowledged differences in the cognitive mechanisms of drug addiction and anxiety disorders would justify a differing dose-relatedness of the cognitive enhancing effects of DCS to the differing therapies for the two groups of disorders. It is also unknown as to whether clinical response to a longer trial of CBT, or a longer follow-up period of assessment, would represent a more effective trial of the clinical value of adjunctive DCS. Finally, the robust response to the CBT also precluded the ability to estimate the variance of the effect size.

5. Conclusions

The results of this clinical trial study replicated the efficacy of CBT for cocaine dependence and demonstrated that adjunct DCS with a condensed version of CBT was comparable to the placebo + CBT arm in treatment retention and drug abstinence at 4- and 8-week treatment endpoints. The results also suggest that the addition of an under-dosed, manualized CBT is more effective than a standard 12-Step treatment approach alone in promoting relapse prevention and functional recovery in a cocaine-dependent sample.

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Contributors

Author Ashley Kennedy participated in data collection, conducted the statistical analyses, and wrote the first draft of the manuscript. Author Robin Gross screened, assessed and enrolled potential subjects, administered tests, and collected data for the study. Author Natasha Whitfield conducted the cognitive behavioral therapy for the study. Author Karen Drexler served as the study medical director and conducted medication reconciliation with potential subjects. Author Clinton Kilts designed the study, wrote the protocol, and directed the writing of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare no disclosures or conflict of interest.

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