**Efficacy of D-Cycloserine Augmentation of Cognitive Behavioral Therapy for Delusions: A Randomized Clinical Trial**

**Running Title: DCS Augmentation of CBT for Delusions**

Erica D. Diminich, PhD1, 2, Faith Dickerson, PhD, MPH 3, Iruma Bello, PhD4,Corinne Cather, PhD5, David Kingdon, MD6, Pamela J. Rakhshan Rouhakhtar, MS7, Chenxiang Li, MS 8, Andrea B. Troxel, ScD 8, Donald C. Goff, MD9,10

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1. Program in Public Health, Stony Brook University, Stony Brook, NY
2. Department of Family, Population and Preventive Medicine, Stony Brook University, Stony Brook, NY
3. Sheppard Pratt Health System, Baltimore, MD
4. New York State Psychiatric Institute, Columbia University Vagelos College of Physicians and Surgeons, New York, NY
5. Massachusetts General Hospital, Boston, MA
6. Academic Department of Psychiatry, Faculty of Medicine, University of Southhamptom, Southampton, UK
7. Human Services Psychology Department, University of Maryland Baltimore County, Baltimore, MD
8. Department of Population Health, Division of Biostatistics, NYU School of Medicine, New York, NY
9. Department of Psychiatry, NYU Langone Health, New York, NY
10. Nathan Kline Institute for Psychiatric Research, Orangeburg, NY

**Corresponding author:**

Donald C. Goff, MD

One Park Avenue, Office 8-212

New York, NY 10016

Email: Donald.Goff@nyulangone.org

Office: (646) 754-4843

**BACKGROUND:** D-Cycloserine (DCS) promotes consolidation of extinction learning. This study extends earlier work by examining whether DCS can enhance cognitive behavioral therapy (CBT) for delusions.

**METHODS:** Adults reporting moderate or greater delusions were randomly assigned to receive DCS 50 mg or placebo prior to 10 weekly CBT sessions. The primary outcome was change in severity of delusions measured with the Psychotic Symptom Rating Scale delusion subscale (PSYRATS-D). Secondary outcomes included persistence of response at 3 and 6 month follow-up and the effects of DCS on memory consolidation and cognitive flexibility. Fifty-six participants were randomized and 44 completed the trial.

**RESULTS:** The DCS and placebo groups did not differ in change from baseline to end of CBT on PSYRATS-D, nor did DCS improve memory consolidation or cognitive flexibility compared to placebo. However, at the 3 month follow-up visit (week 24), 47% of participants receiving DCS reported a 20% or greater decrease on PSYRATS-D compared to 15% in the placebo group (p= .04). Change in distress across CBT sessions interacted with treatment group to predict change from baseline to week 24 in PSYRATS-D total score (p= .03). Improvement of distress was associated with greater response at week 24 in the DCS group compared to placebo.

**CONCLUSIONS:** DCS augmentation of CBT did not improve delusions compared to placebo during treatment; however, DCS improved response rates at 3-month follow-up. These results suggest that while DCS may not enhance CBT efficacy it may improve the durability of the effects of successful CBT sessions.

**Clinical Trials Registration:** This study was registered on ClinicalTrials.Gov as “D-Cycloserine Augmentation of Cognitive Behavioral Therapy for Delusions” (Identifier: NCT01981759; <https://clinicaltrials.gov/ct2/show/NCT01981759>)

**Introduction:**

Antipsychotic-resistant delusions occur in approximately 30% of individuals with schizophrenia, are often distressing, and increase the risk for incarceration and self-injury. Clozapine is the only pharmacologic treatment with established efficacy for delusions unresponsive to other antipsychotics, but less than half of patients benefit (1). Cognitive behavioral therapy (CBT) is also recommended as an evidence-based treatment for refractory psychosis (2); however, efficacy is quite modest when evaluated by masked raters (3, 4).

A new therapeutic approach that utilizes pharmacotherapy to enhance learning during CBT for delusions follows from evidence suggesting that the persistence of delusions may represent an inability to “unlearn” or “extinguish” false beliefs (5). For example, Holt and colleagues demonstrated that individuals with schizophrenia exhibit a selective failure to consolidate fear extinction memory (14) which was highly correlated with delusions (15).

D-cycloserine (DCS) is an NMDA receptor partial agonist that enhances memory consolidation. When administered prior to extinction training in rats, DCS increases 24-hour extinction memory retention, but tolerance rapidly develops with daily dosing (6, 7) and DCS facilitation of memory consolidation may be restricted to new learning (8). In humans, DCS facilitates consolidation of both fear-related and fear-unrelated extinction learning (8). Based on evidence for enhancement of fear extinction training in animals, DCS was developed as an adjunct to CBT for anxiety disorders (9) and has demonstrated consistent, although modest, efficacy relative to placebo (24, 25). In individuals with autism spectrum disorder, DCS did not enhance initial learning of social skills training but significantly increased durability of learning (10). In addition, D-serine, a full agonist at the glycine site of the NMDA receptor, was found to enhance cognitive flexibility in rats as measured by reversal learning in the Morris Water Test (11) and in patients with schizophrenia as measured by perseverative errors on the Wisconsin Card Sort Task (12). Whether DCS enhancement of cognitive flexibility might facilitate CBT for delusions has not been established.

In two placebo-controlled studies, DCS improved memory consolidation in individuals with schizophrenia. In one, a single dose of DCS 50 mg significantly improved 7-day thematic recall on the Logical Memory Test (LMT) compared to placebo (13). Seven-day thematic recall was selected because memory consolidation is known to solidify the “gist” (relational themes) of new learning. In the second study, once-weekly DCS 50 mg significantly improved learning of an auditory discrimination task but did not enhance performance on cognitive tasks that were not practiced (14). In addition, we previously conducted a random-order, counter-balanced, two session placebo-controlled pilot trial of DCS facilitation of CBT for delusions (32). Twenty-one schizophrenia subjects with medication-resistant delusions received DCS 50 mg or placebo one hour prior to each of two sessions of CBT. While DCS did not improve delusions more than placebo overall, participants who received DCS prior to the first session exhibited a large reduction (effect size 0.8) in PSYRATS measures of delusional severity compared to subjects who received placebo prior to the first session (p<0.05), consistent with the finding that DCS only facilitates consolidation of novel learning (8).

Here we report results from a double blind randomized, parallel-group trial that tested the hypothesis that DCS augmentation of once-weekly CBT sessions would lead to a greater reduction in delusions compared with placebo and would extend the duration of improvement. Secondary hypotheses were that drug effects on delusions would be mediated via improvement of memory consolidation measured by the 7-day thematic recall on the Logical Memory Test and via improvement of cognitive flexibility measured by the number of responses generated during the Alternative Beliefs Exercise.

**Methods and Materials:**

Participants:

Potential participants were recruited from physician referrals, newspaper advertisement and outpatient psychiatry clinics and were studied at New York University Medical Center and Shepard Pratt Hospital in Baltimore. Participants were evaluated for eligibility by a psychiatrist who completed a medical and psychiatric assessment, physical examination and screening laboratory assessment including electrocardiogram and pregnancy test. Inclusion criteria included adults 18- 65 years old who met criteria for schizophrenia, schizoaffective disorder or delusional disorder based on the Structured Clinical Interview for DSM-IV and had a global delusion score of 3 “moderate” or greater on the Scale for the Assessment of Positive Symptoms (SAPS) (15) at screening. Exclusion criteria included treatment with clozapine or with a selective serotonin reuptake inhibitor (SSRI) based on evidence that SSRIs may attenuate the facilitative effect of DCS on CBT (16) and that addition of DCS to clozapine may worsen negative symptoms in schizophrenia (17). Potential participants were also excluded for alcohol or substance abuse within six weeks; seizures or unstable medical illness; pregnancy or nursing; anemia; renal insufficiency; cardiac conduction delay, or a change in antipsychotic treatment within 8 weeks of study entry. Individuals who had not taken antipsychotic medication for at least six months were eligible to participate.

The protocol for the trial is available in the supplement. Institutional review boards at New York University Langone School of Medicine and Sheppard Pratt Hospital in Baltimore, Maryland, approved the study. All participants provided written informed consent and received financial compensation for completion of each study visit. The study is registered on Clinicaltrials.gov (NCT01981759).

Design and Procedure:

A 12-week manualized CBT protocol targeting delusions was developed for this study (see supplement). After a 4-week screening period, all participants received placebo, single-blind, prior to the first two introductory sessions of CBT. Participants who continued to meet the criterion of a score of 3 or greater on the SAPS received randomized treatment with placebo or DCS 50 mg administered double-blind, one hour prior to CBT sessions 3 through 12. Randomization was in a 1:1 ratio, stratified by site; the sequence of treatment assignments was constructed by a statistician using permuted random blocks with variable block sizes. Study drug and placebo were prepared in identical capsules and labelled by a research pharmacist. All other research personnel remained blinded until the end of the study. DCS was stored under conditions of strict temperature and humidity control.

CBT Sessions:

Therapists at both study sites were clinical psychologists with expertise in CBT. All therapists followed the same manualized treatment protocol, consisting of 12-weekly 50-minute individual sessions. CBT sessions 1 and 2 consisted of assessment of the presenting delusion and formulation of the CBT treatment plan. Sessions 3, 4 and 12 included the Alternative Beliefs Exercise (ABE) in which participants were instructed to produce alternative explanations for a series of vignettes of social interactions, leading up to individualized vignettes tailored by the CBT therapist to address the participant’s target delusion identified during the introductory session. The ABE was the intervention associated with improvement in delusions when augmented with DCS in a previous pilot study (18). The remaining sessions included exploration of participants’ delusional beliefs, testing of exploratory models and cognitive restructuring. Therapists participated in weekly supervision led by a senior CBT therapist (CC, IB). Audio recordings of CBT sessions were reviewed by a senior CBT therapist to monitor fidelity.

Outcome Measures:

The primary outcome measure was change in delusion severity from week 3 to 12 using the Psychotic Symptom Rating Scale delusion subscale (PSYRATS-D) (19). The PSYRATS is a 17-item scale that measures the severity of hallucinations and delusions. Six items assess severity of delusions: preoccupation (amount/duration), conviction, distress (amount/intensity), and disruption. PSYRATS-D scores range from 0 to 24, with higher scores indicating greater severity of delusions. Assessments were conducted at week 0, immediately prior to CBT sessions at weeks 2, 3, 4, 6, 8, 10, 12, and at follow-up visits completed at weeks 24 and 36.

Seven-day delayed thematic recall on the Logical Memory Test (LMT) of the Wechsler Memory Scale (WMS-III) (20) was used as a measure of memory consolidation. Participants were administered Story A at week 1, one hour after the first single-blind dose of placebo (2 weeks prior to baseline) and Story B at baseline, one hour after the first randomized dose of DCS or placebo and thematic recall was recorded after 7 days, prior to the next dose of DCS. The mean number of alternative beliefs generated for each vignette during the ABE completed during CBT sessions 3, 4 and 12, was used as a measure of cognitive flexibility. Participants were asked to rate the level of distress associated with delusions at the beginning and conclusion of each CBT session and to rate perceived benefit after each session using a 100-point scale (0=no distress, 100=maximum distress; 0=not helpful, 100=extremely helpful).

Statistical Analysis:

- Primary Analysis:

Intention to treat analysis included all randomized participants who received at least one dose of study medication and had both a baseline and at least one post-baseline outcome measure. Assessments performed at week 3, one hour prior to the first administration of DCS, were defined as the baseline for all outcome measurements. The primary outcome, which was the change from baseline (week 3) to week 12 in delusion severity measured by the PSYRATS-D total score was analyzed using a Linear Mixed Model for Repeated Measures (MMRM). Models were adjusted for the baseline PSYRATS total score (Model 1-2). *P* values for pairwise comparisons were Bonferonni adjusted. Alpha level was set at .05

We used a random intercept to account for heterogeneity of scores across individuals. An autoregressive (AR1) covariance matrix was used to model within-person residual correlation. Study visits (4-12) were coded as indicator variables, treatment group (DCS, Placebo) and an interaction between visit 12 and treatment group were included as fixed effects. Two sensitivity analyses were performed; in one, the sample was restricted to more severely symptomatic participants defined by a total score greater than 5 on the PSYRATS-D and in the second, comparisons were adjusted for baseline SANS scores since we previously found that once-weekly DCS improved negative symptoms (13).

- Secondary Analyses:

Effect of DCS on Durability of CBT Effects on Delusions:

To examine the temporal pattern and persistence of response, defined as a 20% or greater reduction in PSYATS-D total score at the end of CBT (week 12) and through post-treatment follow up visits at weeks 24 and 36, generalized estimating equations (GEEs) for binary outcomes (20% PSYRATS-D reduction: yes, no) were used to determine whether treatment differed between groups. GEE models were fitted with treatment group as the between participant factor, visit as the within group factor and baseline PSYRATS-D as a covariate. An autoregressive (AR1) covariance matrix was used to model within-person residual correlation.

Memory Consolidation:

A 2 x 2 (Group x Visit) univariate analysis of variance (ANOVA) for Logical Memory Test thematic recall score was conducted to examine the group difference (DCS, Placebo) on memory consolidation following the first administration of DCS. Visit was treated as the within subjects factor and differences between the DCS and placebo group were treated as the between subjects factor.

Cognitive Flexibility:

A mixed model for repeated measures (MMRM) with visit, group and treatment group x visit interaction was conducted to examine if the mean number of ABE responses differed between groups at week 12. Independent samples Mann-Whitney *U* tests were used to examine if the number of ABE responses from week 3 to week 12 differed between treatment groups. Finally, we performed a linear regression to assess whether change in the number of ABEs predicted change from baseline to week 12 in PSYRATS-D score x group.

Exploratory Analyses:

 To explore whether change in distress and participants’ perceived benefit of each CBT session predicted a reduction in delusions at weeks 12, 24 and 36, we conducted a series of linear regressions. Change in PSYRATS-D total score from week 3 to visits 12, 24 and 36, was the dependent variable and the average change in distress and perceived benefit of CBT sessions were independent variables, along with PSYRATS-D score at week 3 as a covariate in separate models. Interactions between average change in distress and average perceived benefit of CBT x treatment group were tested.

Cohen’s *d* effect sizes (21) were calculated for the difference between groups in change from baseline based on two independent samples using the estimated marginal means from the MMRM. For linear regression models, we report unstandardized coefficient estimates (β) and standardized estimates with confidence intervals (CI) and percent variance accounted for by the model as a whole. Statistical analyses were conducted using SPSS, version 24 (IBM Corp).

Power Estimate:

A sample size of 60 participants was estimated to provide greater than 85% power to detect an effect size of 0.8 in the two-group mean comparisons of 12-week PSYRATS-D total score and greater than 95% power to detect a difference in the response rate of DCS vs placebo assuming the response rate for placebo was 10% and the response rate for DCS was 50%. Based on our previous two-session pilot trial (18) in which we found a between group effect size of 0.8, we anticipated a substantially larger effect given the expansion to 10 DCS-facilitated CBT sessions in this trial.

**RESULTS:**

One hundred eleven potential participants were screened, 58 were randomized, 57 were evaluable, and 44 completed the 12-week CBT trial (Consort diagram, Figure S1). Demographic and clinical characteristics at baseline for randomized participants are presented in Table 1. Completers were significantly older (M=47.6 years, SD=12.03) relative to non-completers, (M=37.0 years, SD=11.04) (Table S1). There were no other differences between treatment groups or between completers and non-completers (Table 1; Table S1). Of the randomized participants, 16 (N=7, placebo group, N=9 DCS group) were medication-free (Table S2).

Effects of DCS on Delusion Severity:

Table 2 presents the estimated change in PSYRATS-D total scores between groups across weeks 4-36. The MMRM results of the primary analyses are reported in the supplement, (Table S3, model 1). The main effects of visit (*F*=.522, p=.72), treatment group (*F*=.555, p=.46), and visit by group interaction (*F*=.594, p=.67) on change from baseline to week 12, in PSYRATS delusion severity were not significant (Figure 1). When participants with baseline PSYRATS-D total scores less than 5 (N=4) were excluded from analysis, again there was not a significant effect for visit (*F*=.903, p=.47), treatment group (*F*=.572, p=.46), or visit by group interaction, (*F*=.584, p=.68) (Table S3, Model 2); the between-groups effect size remained unchanged (*d=*.19, 95% C.I.= -1.64, 1.77). Similarly, there was not a significant effect of visit, (*F*=.542, p=.71), treatment group, (*F*=5.73, p=.056) or visit x treatment interaction, (*F*=.621, p=.65), when the MMRM was repeated with baseline SANS score included as a covariate (Table S3, Model 3).

Characterizing Duration of DCS:

After controlling for baseline PSYRATS-D, main effects of treatment group, (GEE test Chi-square (1) =.007, p=.94) and visit (GEE test Chi-square (2) =2.208, p=.33) on the rate of response, defined as a 20% reduction in PSYRATS-D, were not significant.However, there was a significant group x visit interaction (GEE test (2) =8.89, p=.012); 47% of participants receiving DCS were responders at week 24 compared to 15% of participants receiving placebo (Fisher’s exact test p=.04). The higher response rate in the DCS group did not persist at week 36 (29% response with DCS vs 30% response to placebo; Fisher’s exact test p= .89). Percent change in PSYRATS-D scores from baseline after the first dose of study drug (week 4), after 12 weeks, and at follow-up at weeks 24 and 36 is shown in Figure 2.

Memory Consolidation:

The 2 x 2 ANOVA to examine 7-day recall of story themes following the first administration of DCS revealed a main effect of visit (*F* (1,47) = 4.04, p=.05, ηp2=.079). Participants in both the DCS and placebo group demonstrated a significant decrease in the total number of story themes recalled at week 4 compared to baseline. However, we did not find an effect for group (p=.24; ηp2=.029) or group x visit interaction (p=.69; ηp2=.004) (Figure S2).

Cognitive Flexibility:

We repeated the MMRM analyses used for our primary outcome to examine if the mean number of ABEs generated at study visits 3, 4 and 12, differed between groups. We did not find a significant difference for group (*F*=.102, p=.75), visit (F=1.01, p=.37), or group x visit interaction (*F*=.082, p=.92; Figure S3). Mann Whitney *U* tests revealed that the change from week 3 to week 12 did not differ between group (*p*=.606; Hedges’ *g*=.156), nor did the mean ABE total predict change from baseline to week 12 in the PSYRATS-D total from week 3 to week 12 for either group. Finally, change in number of ABE responses did not predict change in PSYRATS=D from baseline to week 12 (*F*=(1,41)=.233, *p*=.63).

Exploratory Analyses of Perceived Benefit and Change in Distress Post CBT:

In linear regression analyses, there was a significant interaction between treatment group and change in level of distress (β=.140, p=.031, 95% CI .013-.267, Figure 3) such that the average change in level of distress from baseline to week 12 predicted a greater reduction in delusion severity for participants randomized to the DCS treatment condition relative to placebo participants. Self-reported perceived benefit of CBT was not associated with a greater reduction in PSYRATS delusions at follow up visit week 24. We did not find any other significant main effects or interactions for perceived benefit of CBT or change in distress across other study visits (Table S4, Figures S4 & S5).

Safety and Tolerability:

Dropouts did not differ between groups (DCS 27% vs placebo 28%), nor did the rate of worsening, defined as an increase of 20% or greater on the PSYRATS-D on at least one post-baseline assessment (DCS 43% vs placebo 40%). There were no serious adverse events. The frequency of treatment-emergent side effects did not differ significantly between groups (176 vs 145); no side effect occurred in 20% or more of individuals in the DCS group and at a rate twice or greater than in the placebo group, whereas trouble sleeping (36% vs 17%) drowsy (25% vs 10%) weakness (39% vs 13%) and muscle cramps (43% vs 13%) were reported more frequently in the placebo group than in the DCS group (Table S5).

**Discussion:**

DCS augmentation of CBT was not superior to placebo on the primary outcome of change from baseline to week 12 in delusion severity. However, the response rate was increased at follow-up (week 24) in the DCS group compared to the placebo group, suggesting that DCS may have enhanced durability of CBT effects. In addition, the average reduction in distress following CBT sessions across weeks 4-12 predicted the decrease in PSYRATS-D delusion severity at week 24 for participants randomized to DCS, suggesting that DCS may have consolidated positive effects of successful CBT sessions. Overall, these results are consistent with an emerging model based on results from studies in anxiety disorders that DCS does not enhance efficacy of individual CBT sessions but, by consolidating learning, DCS augmentation may increase the durability of CBT effects, both positive and negative (22, 23). Hence, the benefit of DCS augmentation may be limited by the modest efficacy of CBT for delusions.

We did not replicate prior findings that DCS improved memory consolidation (13, 14) and enhanced efficacy of a single CBT session for delusions (18), which raises a concern about whether “target engagement” was achieved with DCS in this study. This failure to replicate occurred despite precautions to avoid potentially confounding factors, including careful humidity control to obviate the risk of DCS degradation (24), supervised dose-taking to obviate the risk of nonadherence, exclusion of individuals taking SSRIs to avoid the previously-reported interference of antidepressants with DCS effects (16), and the avoidance of tachyphylaxis and the preservation of novel learning by initiating once-weekly DCS concurrently with the first CBT exercise (6, 7). Given the precautions taken to avoid a false-negative result, the failure to replicate most likely reflects the poor reliability of studies conducted in small or moderate-sized convenience samples. We also found no evidence that DCS enhanced cognitive flexibility, although conclusions are limited because the ABE was not performed prior to the first administration of DCS and hence we did not have a drug-free baseline. We found no difference between groups in post-treatment performance on the ABE and no association between post-treatment ABE performance and change in PSYRATS-D scores.

The DCS dose used in this study initially was established by a placebo-controlled dose-finding trial in patients with schizophrenia treated with first generation antipsychotics in which a daily DCS dose of 50 mg for two weeks produced improvement in negative symptoms and working memory (25). Studies of DCS augmentation in anxiety disorders have employed doses ranging from 50 mg to 500 mg, but a meta-analysis did not find evidence for a dose-response relationship (26). Furthermore, once-weekly administration of DCS 50 mg in patients with schizophrenia was found to enhance both memory and negative symptoms in two prior placebo-controlled trials (13, 14).

Memory enhancing effects of DCS have been well-established in animal studies and in healthy humans (27, 28). However, it is not clear whether cognitive effects are attenuated by second generation antipsychotic medication or whether they differ in individuals with schizophrenia compared to healthy controls. Given evidence that second generation antipsychotics may alter NMDA receptor subunit composition, it is possible that adding DCS to second generation agents in the current study may have reduced efficacy as a result of a pharmacodynamic interaction (29-31). For example, in the CONSIST trial, improvement of negative symptoms with add-on glycine or DCS was significantly greater compared to placebo in participants treated with first generation versus second generation antipsychotics (32). In addition, Forsyth and colleagues (33) recently reported that DCS 100 mg improved working memory in schizophrenia patients but only enhanced plasticity measured by visual stimulation of the EEG in healthy subjects and not in participants with schizophrenia, suggesting that cognitive effects of DCS demonstrated in animal models and in healthy controls may not be replicated in medicated patients with schizophrenia.

Analysis of persistence of response, defined as a 20% reduction in ratings of delusion severity, revealed no difference between groups at week 12, but a significantly higher rate of response was found in the DCS group compared to placebo at week 24, three months after completing CBT. The benefit of DCS did not persist at week 36, however. This finding is similar to the report by Wink and colleagues (10), in which individuals with autism spectrum disorder who received once-weekly DCS 50 mg during a 10 week course of social skills training did not display greater improvement at the completion of the social skills training program compared to the placebo group but did retain significantly greater improvement at week 22 follow-up. Findings from other randomized trials suggest that benefits of CBT for psychosis (34) and of cognitive remediation (35, 36), may continue to accrue after the completion of interventions, suggestive of delayed benefits of enhanced brain plasticity rather than merely persistence of effect. A meta-analysis of studies of DCS augmentation of exposure-based CBT in anxiety disorders found improvement with DCS compared to placebo both at end of treatment and at follow-up, but not evidence of increased benefit at follow-up compared to end of treatment (37). In our study, DCS may have extended the effects of CBT on delusions for several months, whereas the benefits of CBT alone were rapidly lost after completion of 12 sessions. “Booster” CBT sessions augmented by DCS may be worthy of study to preserve CBT effects long-term.

Some studies of DCS enhancement of CBT in patients with anxiety disorders have found that consolidation of extinction memory is only of therapeutic benefit if the CBT session produces an improvement in symptoms (23, 38). Improvement of delusions at week 24 was predicted by the degree to which CBT sessions reduced distress in the DCS group compared to placebo. Notably, while DCS may have been consolidating the therapeutic benefit of successful CBT sessions, the mean improvement at week 12 did not differ between treatments and the confidence intervals for change in PSYRATS-D at week 12 were larger in the DCS group compared to the placebo group, suggesting DCS may also have consolidated learning in unsuccessful CBT sessions that reinforced or intensified delusions, thereby producing greater variability and no net effect on mean PSYRAT-D scores. Because consolidation of learning may be achieved by administering DCS within approximately two hours of the training session (39), it may be possible to administer DCS selectively after the conclusion of successful sessions (22). Further work is needed to evaluate this strategy.

Finally, studies in animals and in healthy human subjects have indicated that tolerance develops for the memory-enhancing effects of DCS with repeated dosing (6, 7). Given this concern, participants received the first dose of study drug an hour before the first CBT session that included the alternative beliefs exercise. Despite this precaution, we observed no therapeutic benefit following the first session of CBT. A recent study in healthy subjects found that DCS enhanced extinction of associative learning when extinction occurred in the identical context to acquisition but not in a novel context (40). It is possible that the context of a CBT session is sufficiently different compared to the context under which a delusion was first formed to make extinction with DCS of limited benefit in terms of real-world functioning. Whether other forms of extinction, such as virtual reality exposure, might be more effective for delusions also remains to be studied.

Limitations:

The 95% confidence intervals for the null finding at week 12 are sufficiently wide that we cannot fully exclude the possibility of a clinically-significant positive or negative effect of DCS on mean delusion severity scores based on the results of this single study. In addition, while we originally hypothesized that DCS would increase the durability of CBT effects during the follow-up period, we did not predict benefit at week 24 only, and so this finding must be considered exploratory. Finally, the number of participants who were medication-free (n=6) was too small to allow an analysis of the impact of medication status as a moderator of response to DCS.

Conclusions:

Once-weekly dosing of DCS 50 mg prior to ten CBT sessions did not improve delusion severity compared to placebo. However, exploratory analyses revealed that the response rate in the DCS group was greater than placebo at 3-month follow-up and improvement with DCS was predicted by the degree to which distress was reduced by individual CBT sessions, suggesting that DCS did not enhance CBT efficacy but did improve the durability of the effects of successful CBT sessions. Additional studies are needed to replicate these findings and to test the approach of selectively administering DCS after successful CBT sessions.

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**Disclosures:**

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Table 1: Baseline demographic and clinical characteristics of randomized participants.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | DCS(N=30) | Placebo(N=28) | *p* Valuea |
| **Sex** |  |  | .79 |
| Women, n (%) | 11 (36.7) | 12 (42.9) |  |
| **Race** |  |  | .54 |
| Black | 9 (30.0) | 12 (42.9) |  |
| White | 14 (46.7) | 10 (35.7) |  |
| Hispanic | 2 (6.7) | 3 (10.7) |  |
| Asian | 1 (3.3) | 0 (0.0) |  |
| Other | 1 (3.3) | 0 (0.0) |  |
| **Age, Years** |  |  | .78 |
| Mean (SD) | 44.60 (13.3) | 45.55 (12.0) |  |
| Range | 21-68 | 24-67 |  |
| **Education** |  |  | .86 |
| Mean (SD) | 13.23 (2.8) | 13.11 (2.5) |  |
| **Employment Status, N (%)** |  |  | .40 |
| Full Time | 0 (0.0) | 1 (3.6) |  |
| Part Time | 5 (16.7) | 7 (25.0) |  |
| Unemployed | 25 (83.3) | 20 (71.4) |  |
| **Diagnosis** |  |  | .59 |
| Schizophrenia | 14 (48.3) | 17 (63.0) |  |
| Schizoaffective Disorder | 11 (37.9) | 8 (29.6) |  |
| Delusional Disorder | 3 (10.3) | 2 (7.4) |  |
| **Duration of Untreated Psychosis, Years** | (N=22) 17.8 (13.9) | (N=21) 15.5 (12.6) | .58 |
| Prior Hospitalizations | 5.30 (6.2) | 8.11 (9.3) | .18 |
| PSYRATS-D Total | 11.88 (6.0) | 14.16 (5.2) | .12 |

Note: DCS: D-Cycloserine, DUP: PSYRATS-D: Psychotic Symptom Rating Scale - Delusion Subscale; aValues based on *X*2 tests for dichotomous variables and *t* tests for continuous variables.

Table 2: Estimated mean change scores (visit week minus baseline) for PSYRATS-D total score by treatment group.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | DCS | Placebo |  |  |
| Visit | Mean (SD) | Mean (SD) | *p*-Value | Effect size |
| Week 4 | 0.14 (4.74) | -0.35 (4.38) | 0.70 | 0.11 |
| Week 6 | 0.08 (7.01) | -0.80 (4.04) | 0.59 | 0.15 |
| Week 8 | -1.08 (5.42) | -0.21 (4.54) | 0.55 | 0.17 |
| Week 10 | -0.61 (4.35) | -1.29 (3.94) | 0.59 | 0.16 |
| Week 12 | -0.19 (3.68) | -1.36 (4.66) | 0.37 | 0.28 |
| Week 24 | -1.42 (3.72) | -0.50 (2.70) | 0.38 | 0.28 |
| Week 36 | 0.06 (4.25) | 0.10 (4.77) | 0.98 | 0.10 |
|  |  |  |  |  |

Figure 1: Mean PSYRATS - Delusion Subscale total scores by treatment group during CBT



Note: 0 = Week 3 (baseline); Error bars indicate ± 2 S.E.

Figure 2: Mean percent change from baseline in PSYRATS Delusion Subscale total score by treatment group after the first medication-augmented session (week 4), the last medication-augmented session (week 12) and follow up visits at weeks 24 and 36.



\*

Note: \*Significant group difference at follow up visit, week 24 between DCS and Placebo group, p<.03.

Figure 3: Association between change from baseline to week 24 in PSYRATS-D total
score and change in distress during CBT sessions by treatment group

