



D-cycloserine facilitation of cognitive behavioral therapy for delusions in schizophrenia[☆]

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ABSTRACT

Glutamatergic N-methyl-D-aspartate (NMDA) receptor hypofunction has been proposed as a mechanism underlying psychosis. D-cycloserine, a partial agonist at the glycine site of the NMDA receptor, enhances learning in animal models, although tachyphylaxis develops with repeated dosing. Once-weekly dosing of D-cycloserine produces persistent improvement when combined with cognitive behavioral therapy (CBT) in anxiety disorders. Delusional beliefs can be conceptualized as a learning deficit, characterized by the failure to use contradictory evidence to modify the belief. CBT techniques have been developed with modest success to facilitate such reality-testing (or new learning) in delusional beliefs. The current study evaluated whether D-cycloserine could potentiate beneficial effects of CBT on delusional severity. Twenty-one outpatients with schizophrenia or schizoaffective disorder and moderately severe delusions were randomized in a double-blind cross-over design to receive a single-dose of either D-cycloserine 50 mg or placebo in a counterbalanced order on two consecutive weeks 1 h prior to a CBT intervention involving training in the generation of alternative beliefs. Assessments were completed at baseline, 7 days following the first study drug administration and 7 days following the second study drug administration. Contrary to prediction, there was no significant D-cycloserine treatment effect on delusional distress or severity as measured by the SAPS or PSYRATS. An unexpected finding was an order effect, whereby subjects who received D-cycloserine first had significantly reduced delusional severity, distress, and belief conviction on PSYRATS compared to subjects who received placebo first. However, this finding is consistent with animal models in which D-cycloserine enhances learning only when accompanying the first exposure to training.

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1. Background and introduction

Approximately 30% of individuals with schizophrenia continue to experience psychotic symptoms despite treatment with dopamine antagonists. Whereas the formation of delusional beliefs may involve abnormal affective salience resulting from dysregulated release of dopamine (Kapur, 2003), the persistence of delusional beliefs can be viewed as a cognitive deficit which results in a failure to correct or “unlearn” the delusional belief in the face of contradictory evidence. Cognitive-behavioral techniques have been developed with modest success to facilitate such reality-testing or “unlearning” of delusional

beliefs (Wykes et al., 2008). In addition, pharmacologic approaches targeting cognitive impairment might also play a role in the treatment of antipsychotic-refractory delusions.

Converging evidence has linked hypofunction of glutamatergic N-methyl D-aspartate (NMDA) receptors to both cognitive deficits and psychotic symptoms in schizophrenia (Goff and Coyle, 2001). It is also well-established that enhancement of NMDA receptor activity by single-dose administration of D-cycloserine improves learning in animal models, including extinction of conditioned fear (Davis et al., 2006). At low concentrations, D-cycloserine is a full agonist with twice the potency of glycine at NMDA receptors containing the NR2C subunit, whereas at increasing concentrations partial agonism (approximately 50% activity compared to glycine) at receptors containing NR2A and NR2B becomes prominent (Dravid et al., 2010). NR2C subunits are involved in fear conditioning, consolidation of fear extinction memory and working memory (Hillman et al., 2011). NR2C expression was found to be reduced in prefrontal cortex in patients with schizophrenia (Beneyto and Meador-Woodruff, 2008). In patients with anxiety

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disorders, D-cycloserine significantly improved outcomes when administered as a single dose prior to once-weekly exposure therapy, a key element of cognitive behavioral treatment for anxiety disorders (Norberg et al., 2008). In both animal and human studies, D-cycloserine does not improve performance during training; memory effects are only detected when tested 24 h or more after training, indicating a specific enhancement of memory consolidation, which has been shown to require NMDA receptor activation (Kandel, 2001; Wittenberg and Tsien, 2002).

Consistent with a defect in NMDA receptor function, individuals with schizophrenia exhibit deficits in memory consolidation when tested 24 h after both procedural memory training (Manoach et al., 2004) and conditioned fear extinction training (Holt et al., 2009) compared to healthy controls. A single dose of D-cycloserine selectively improved memory consolidation in schizophrenia participants as evidenced by enhanced recall of a story from the Wechsler Logical Memory Test after a delay of 7 days, whereas immediate recall was not affected (Goff et al., 2008). Repeated daily dosing with D-cycloserine rapidly produces tolerance for memory consolidation in rodents (Quartermain et al., 1994; Parnas et al., 2005) and did not produce cognitive benefit in schizophrenia patients despite improvement in negative symptoms (Goff et al., 1999). In contrast, single or intermittent dosing with D-cycloserine may promote neuroplasticity by producing long-lasting changes in synaptic efficiency (Yaka et al., 2007). For example, in a placebo-controlled trial, once-weekly dosing with D-cycloserine for eight weeks produced improvement of negative symptoms measured seven days after the last dose (Goff et al., 2008). Of additional potential relevance to the treatment of delusions, D-serine, an agonist at the glycine site of the NMDA receptor, enhanced cognitive flexibility or “reversal learning” in mice performing the Morris Swim Test (Duffy et al., 2008).

We conducted a double-blind placebo-controlled, random-order, single-dose crossover trial of D-cycloserine facilitation of a cognitive behavioral therapy (CBT) exercise designed to increase participants' capacity to generate alternative explanations for their delusional beliefs. We hypothesized that D-cycloserine, by enhancing learning and cognitive flexibility, would reduce delusional severity and distress, measured one week after the CBT exercise.

2. Methods

The trial is registered as NCT00742079 at ClinicalTrials.gov. The Partners HealthCare IRB approved the protocol.

2.1. Participants

Participants constituted a convenience sample of adult outpatients, ages 18–65 years, at an urban community mental health clinic who met DSM-IV criteria for schizophrenia or schizoaffective disorder (depressed type), and who had experienced persistent delusions despite treatment for at least six weeks with a stable dose of antipsychotic medication. To be eligible, patients had to be medically stable without history of renal insufficiency, dementia, or seizure disorder and without substance abuse or dependence for at least six months. Patients were excluded if they were taking clozapine or had previously engaged in CBT.

All patients met with a research clinician who obtained written informed consent and confirmed the diagnosis based on interview, chart review and consultation with the patient's clinician. Delusional severity was assessed using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). Participants were required to score a minimum of 3 (“moderate”) on the global measure of delusional severity to qualify at screening. During the screening visit, the three most strongly held delusional beliefs were identified for targeting with the CBT intervention. A medical history and screening laboratory tests were also completed. All participants and study personnel were blind to treatment condition.

2.2. Measures

Baseline measures, including a clinical battery and the Alternative Beliefs Assessment, were repeated prior to study drug administration and the CBT exercise at each of two visits, separated by one week. The SAPS global delusions score was the primary outcome. In addition to SAPS, the clinical battery included the Delusions subscale of the Psychotic Symptom Rating Scales (PSYRATS) (Haddock et al., 1999), a six-item scale designed to assess the frequency, intensity, distress, belief conviction, and functional interference associated with delusions, each question scored on a 0 to 4 point scale. Responses to two PSYRATS Delusions items, amount and intensity of associated distress, were summed to reflect a composite “Distress” item. A computerized version of the Probability Reasoning Task – Bead Task, (Garety et al., 1991; Dudley et al., 1997) a decision-making task which requires participants to determine how many beads they would choose from a jar comprised of red and white beads before guessing the color in advance of drawing a new bead, was administered. Individuals with paranoia have been found to gather less data (e.g., select fewer beads) and to express “overconfidence” in their judgments on this task, which is thought to reflect a tendency to “jump to conclusions,” a process which may be relevant in the etiology and maintenance of delusional beliefs. (Garety et al., 1991; Bentall et al., 2001)

The Alternative Beliefs Assessment (Gottlieb & Cather, unpublished) was performed at baseline to assess cognitive flexibility, or the ability to generate alternative explanations for particular situations. This approximately one-hour assessment used nine vignettes describing social interactions. Three vignettes were neutral in content (e.g., “A man is carrying boxes out of an apartment”), three were negatively-valenced and therefore designed to elicit paranoid interpretations (e.g., “Your phone rings one time late at night”) and three were tailored to each participant's specific delusions (e.g., for a patient with a somatic delusion about infection: “You go to your doctor for a check-up and she tells you that your blood test results show no sign of infection.”). Participants were asked to generate as many explanations as they could for each scenario and the number of explanations produced in response to each item was recorded. Three versions of the Alternative Beliefs Assessment per participant were presented in a randomized, counterbalanced order. This assessment was initially completed at baseline without any training or feedback from the assessor. It was also used as the CBT exercise (including training and feedback from the psychologist) at each of two study visits one hour after administration of study drug.

2.3. Procedure

Following the baseline assessment battery, participants received a single oral dose of D-cycloserine 50 mg or placebo double-blind in identical capsules in random, counter-balanced order. One hour later, patients were trained on techniques for producing alternate explanations using several practice vignettes and employing techniques to challenge patients' paranoid appraisals. Participants then completed the Alternative Beliefs Assessment on their own. At Visit 2, one week later, participants again completed the clinical assessment battery. Following the same procedure as their first visit, they then received D-cycloserine or placebo and, one hour later, completed the alternative explanations training and the Alternative Beliefs Assessment. Participants returned for Visit 3 one week after the second CBT session and repeated the clinical battery (see Fig. 1).

2.4. Statistical analysis

Continuous and categorical baseline characteristics were compared by *t*-test and Fisher's exact test, respectively. Data from each participant's three assessment times (baseline, 7 days following first treatment, and 7 days after cross-over treatment) were analyzed

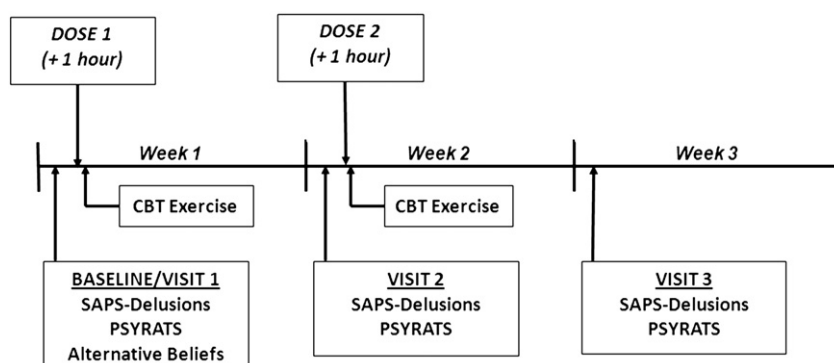


Fig. 1. Study design.

using a linear mixed model with fixed effects for the six combinations of randomized drug order and assessment times and years of education and with random participant-specific intercepts and slopes. Linear contrasts of the cell-mean estimates were used to test for four specific effects: (1) learning effects over each observation interval (change scores over time averaged across randomization order), (2) a first-visit treatment effect (treatment-dependent differences in the change from baseline to the first follow-up assessment, which are thus unconfounded by any carry-over or treatment \times time interaction), (3) an average treatment effect (treatment-dependent differences in change scores averaged over the two 7-day observation intervals, which assumes no carry-over or treatment \times time interaction), and (4) a delayed treatment effect (differences in change

from baseline to the final assessment associated with the first treatment received), which is equivalent to an order effect on the final scores. The primary outcome measure was the SAPS global delusions score. The secondary outcome measure was the total score on the Delusions subscale of the PSYRATS. Exploratory analyses additionally were planned using the Conviction and Distress items of the PSYRATS Delusion subscale if the secondary outcome achieved significance. Effect sizes (ES) are the ratio of the a given linear contrast estimate divided by the square-root of the sum of residual and participant-specific variance from a linear mixed model for each outcome measure with fixed effects for each order \times visit combination and participant-specific random intercepts. Note that ES and p-values for a given outcome are not one-to-one since only within-participant

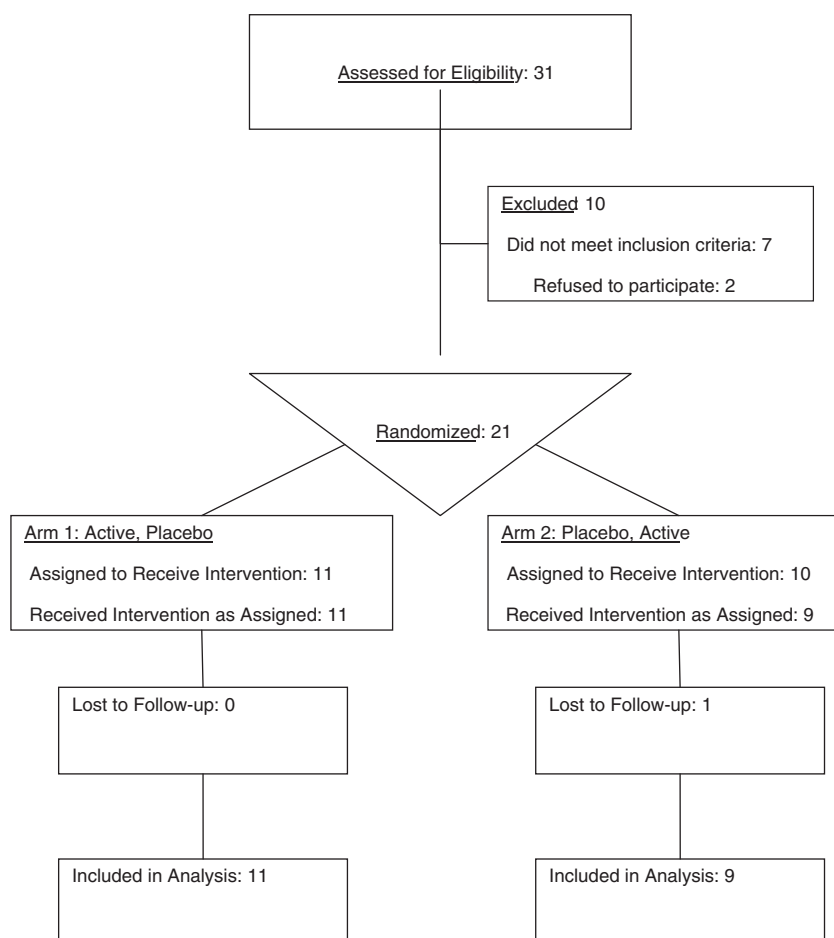


Fig. 2. D-cycloserine facilitation of a cognitive behavioral therapy exercise for delusions in schizophrenia.

Table 1
Baseline characteristics of sample.

Demographics	Overall (N = 20)	Treatment group		P-value
		Placebo first (N = 9)	D-Cycloserine first (N = 11)	
Gender				0.37
Female	7 (35%)	2 (22%)	5 (45%)	
Male	13 (65%)	7 (78%)	6 (55%)	
Age	50.2 (10.7)	51.4 (13.0)	49.2 (9.0)	0.65
Age of illness onset	25.6 (6.4)	29.5 (7.3)	23.5 (5.0)	0.06
Duration of illness	23.7 (9.8)	19.5 (10.1)	26.5 (9.4)	0.29
Number of hospitalizations	8.1 (8.0)	5.3 (4.0)	10.0 (9.7)	0.22
Years of education	13.7 (2.7)	14.6 (3.3)	13 (2.0)	0.20
Ethnicity				1.00
African American	4 (20%)	2 (22%)	2 (18%)	
Caucasian	13 (65%)	6 (67%)	7 (64%)	
East/Southeast Asia	3 (15%)	1 (11%)	2 (18%)	
Antipsychotic				1.00
First generation	2 (10%)	1 (11%)	1 (9%)	
Second generation	17 (85%)	8 (89%)	9 (82%)	
Unmedicated	1 (5%)	0 (0%)	1 (9%)	
Diagnosis				0.57
Schizophrenia	17 (85%)	7 (78%)	10 (91%)	
Schizoaffective disorder	3 (15%)	2 (22%)	1 (9%)	

variance contributes to uncertainty in drug effects given the cross-over design. Sample sizes required for a future trial of equivalent design were estimated by scaling up the current sample size by the square of the ratio of ($z_{\alpha/2} + z_{\beta}$) over the observed Wald statistics for selected estimates, where z_p is the p -th quantile of the standard normal distribution. Reported p -values are from two-tailed tests without correction for multiple comparisons.

3. Results

Participants were enrolled from Sep 2006 through May 2010. Of 31 enrolled patients, 21 were randomized and 20 received study drug (Fig. 2). All 20 participants completed both sessions of CBT and all assessments. The mean age of participants was 50.2 ± 10.7 years with a range of 28–66 years. Most were Caucasian (65%), male (65%) and unemployed (95%). Seventeen were diagnosed with schizophrenia and three with schizoaffective disorder, depressed type (Table 1). No adverse effects were reported following ingestion of study drug. At baseline, there was no significant demographic or clinical difference between the groups that received D-cycloserine first versus placebo first.

The number of alternative explanations generated on the Alternative Beliefs Assessment significantly increased after the first ($p < 0.001$; ES 1.2) and second ($p = 0.03$; ES 0.49) CBT exercises with no difference between D-cycloserine and placebo conditions ($p > 0.4$) (Fig. 3). D-cycloserine did not affect reasoning skills compared to

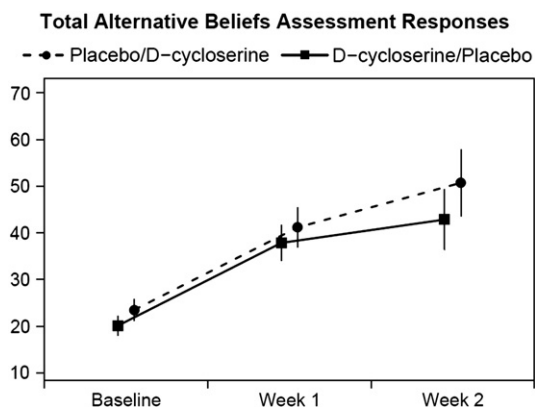


Fig. 3. Total Alternative Beliefs Assessment Responses. (Vertical lines indicate ± 1 SE.).

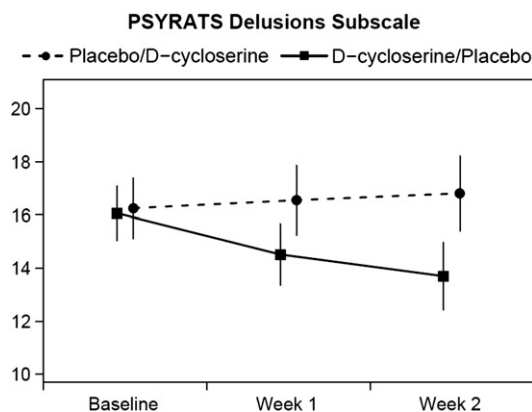


Fig. 4. PSYRATS Delusions Subscale. (Vertical lines indicate ± 1 SE.).

placebo as measured by the Probability Reasoning Task–Bead Task ($p > 0.6$). Change in SAPS global delusions score did not differ between treatment groups (first-visit ES = 0.38, $p = 0.31$; average ES = 0.04, $p = 0.88$). Similarly, PSYRATS total delusions score did not differ between treatment groups (first-visit ES = 0.49, $p = 0.16$; average ES = 0.10, $p = 0.73$). However, a significant order effect was found, such that subjects who received D-cycloserine first had significantly reduced ratings of delusional severity at the end of study compared to subjects who received placebo first (ES 0.77; $p = 0.03$; Fig. 4). PSYRATS ratings of delusional distress also exhibited a significant order effect with improvement at end of study in subjects who received D-cycloserine first (ES 0.74; $p = 0.04$, Fig. 5) together with improvement on PSYRATS ratings of delusional conviction (ES 1.03; $p = 0.05$).

4. Discussion

Our primary hypothesis, that D-cycloserine would decrease delusional severity and distress when combined with a single session of a CBT exercise designed to increase cognitive flexibility, was not supported by our a priori analytic approach, nor did D-cycloserine enhance cognitive flexibility, as measured by the Alternative Beliefs Assessment or reasoning performance on the Bead Task. Performance on the Alternative Beliefs Assessment improved with the CBT exercise regardless of whether subjects were pretreated with D-cycloserine or placebo and did not correlate with change in delusional severity. The striking finding of this study was the significant order effect; subjects who received D-cycloserine prior to the first CBT exercise session experienced significantly greater reductions in delusional severity, distress, and belief conviction at the end of the study than did subjects who received placebo first.

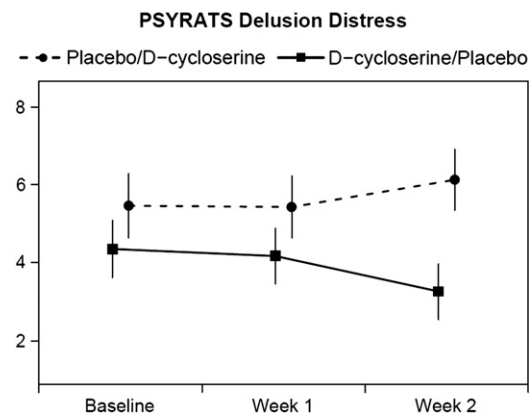


Fig. 5. PSYRATS Distress about Delusions Subscale. (Vertical lines indicate ± 1 SE.).

Several factors may have contributed to our pattern of findings. First, the cross-over design, with a one-week washout between intervals, may have been inadequate and led to carry-over effects which would diminish our estimate of treatment effects. Furthermore, the sample size may have been too small to reliably detect D-cycloserine effects compared to placebo on delusional severity, despite effect sizes of 0.4 and 0.5 for SAPS and PSYRATS scores, respectively, after the first CBT exercise. A sample size of $n = 74$, nearly four-fold larger, would have been required for 80% power to detect the observed PSYRATS effect size.

While the significant order effects for response of delusional severity, distress, and conviction were not anticipated, animal experiments examining the roles of NMDA receptors and D-cycloserine in learning provide a possible explanation for this finding. It is well established that D-cycloserine enhances learning in animal models (Davis et al., 2006) and that repeated training sessions further enhance learning, consistent with the reduction in delusional severity in subjects who received D-cycloserine first, followed by a second “booster” CBT exercise. However, NMDA activation appears to facilitate learning during the first exposure to new learning only. For example, blockade of hippocampal NMDA receptors has been shown to prevent learning during the first training exposure in several tasks, including fear conditioning (Sanders and Fanselow, 2003) and conditioned avoidance (Roesler et al., 1998), but does not affect subsequent learning if the rat had been pre-exposed to the training or training environment. Similarly, Langton and Richardson (2008) found that D-cycloserine facilitated extinction of conditioned fear when administered during the first period of training but had no effect when administered during a second “re-training” session.

Our results are consistent with this model—subjects who received D-cycloserine with their first CBT exercise demonstrated moderate improvement ($ES = 0.41$ for PSYRATS delusions) in delusional severity after the first session and a further reduction following the second session ($ES = 0.22$). In contrast, in subjects who received placebo first, the first CBT exercise had no effect on delusions ($ES = -0.08$) and D-cycloserine subsequently did not enhance response to re-exposure to CBT in the second session ($ES = -0.07$). While speculative, this possible explanation for our findings would suggest that D-cycloserine should be administered within one hour prior to an initial CBT session for the treatment of delusions to exploit the facilitation of “new learning,” whereas subsequent sessions may reinforce learning and further reduce delusional severity, distress, and conviction, even if unaccompanied by D-cycloserine.

If our findings are replicated, the clinical implications could be substantial since antipsychotic-refractory delusions are generally challenging to treat with standard CBT. A recent meta-analysis by Wykes et al. (2008) of 34 trials of CBT in schizophrenia found an effect size for positive symptoms of 0.31 when assessors were masked to treatment allocation. Whereas these trials typically consisted of 20 or more sessions, subjects in our study who received D-cycloserine with the first of two CBT sessions achieved a comparable effect size. Treatment trials of longer duration combining D-cycloserine with CBT are needed to examine the full therapeutic potential of this approach. An important follow-up study design would be provision of a single dose of D-cycloserine prior to an initial CBT session, followed by weekly CBT sessions to further enhance the learning primed by the D-cycloserine. Our findings suggest that within this proposed follow-up design, participants may need fewer CBT sessions than the standard CBT for Psychosis model (Wykes et al., 2008), given the potentially substantial priming effects of the initial dose of D-cycloserine prior to the start of the CBT.

The mechanism by which D-cycloserine facilitated CBT also remains to be further elucidated. Cognitive flexibility as measured by the number of alternative explanations generated did not improve with D-cycloserine and did not predict response of delusions, suggesting that D-cycloserine effects on general cognitive flexibility are unlikely to explain the effect. The reductions in delusional severity

and distress after two CBT sessions may reflect a direct enhancement of learning similar to D-cycloserine's facilitation of delayed extinction recall in rodent models. We previously found that individuals with schizophrenia who received a single dose of D-cycloserine prior to listening to a story displayed no improvement in immediate recall but did recall significantly more of the “gist” of the story when tested 7 days later (Goff et al., 2008). If the mechanism of D-cycloserine enhancement of CBT similarly involves memory consolidation, therapeutic effects would not be expected to be apparent until 24 h or more after CBT sessions and would be expected to persist.

In conclusion, the cross-over design of this pilot study produced results that are difficult to interpret due to a significant order effect. However, we did find improvements in delusional severity, distress, and belief conviction after two sessions of a CBT exercise in subjects who received D-cycloserine with the first session. While this was not our a priori hypothesis, this result is consistent with animal studies that have found that D-cycloserine enhances learning only when accompanying the first exposure to training. Larger parallel-group trials of longer duration, which also take into account other important variables, such as negative symptoms and abstraction deficits, are needed to assess whether this approach may benefit patients with medication-resistant delusions.

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Contributors

Dr. Jennifer Gottlieb was partially responsible for the design of the study, writing the protocol, managing and overseeing all of the treatment and data collection; delivering portions of the psychotherapeutic intervention, contributing to the data analyses, and writing the second (and consecutive) drafts of the paper. Dr. Corinne Cather contributed to the design of the study, the data collection and the delivery of the psychotherapeutic intervention, and contributed to data analysis and drafts of the manuscript. Ms. Meghan Shanahan and Mr. Timothy Creedon made significant contributions to the overseeing of various aspects of the study as well as participant recruitment and progression through the protocol. Dr. Eric Macklin was responsible for statistical design and analysis. Dr. Donald Goff was partially responsible for the design of the study, contributed to the writing of the protocol and the supervision of the pharmacological intervention, and writing the first draft of the manuscript. All authors contributed to and approved the final manuscript.

Conflict of interest

During the last calendar year, Dr. Don Goff has served as a consultant or advisor to: Indevus Pharmaceuticals, H. Lundbeck, Schering-Plough, Eli Lilly, Takeda, Biovail, Solvay, Hoffman-La Roche, Cypress, Dainippon Sumitomo, Bristol-Meyers Squibb, Abbott Laboratories and Endo Pharmaceuticals. He served on a DSMB for Otsuka. He received research funding from Pfizer, Novartis, Janssen, and GlaxoSmithKline.

Dr. Corinne Cather has served as a consultant to United Biosource and as a speaker to Reed Medical.

Dr. Jennifer Gottlieb, Dr. Eric Macklin, Ms. Meghan Shanahan, and Mr. Timothy Creedon report no financial relationships with commercial interests.

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