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Once-Weekly D-Cycloserine Effects on Negative Symptoms and Cognition in Schizophrenia: An Exploratory Study

Donald C. Goff, MD^{1,2}, Corinne Cather, PhD^{1,2}, Jennifer D. Gottlieb, PhD^{1,2}, A. Eden Evins, MD, MPH^{1,2}, Jared Walsh, BA¹, Lisa Raeke, MA¹, Michael W. Otto, PhD⁴, David Schoenfeld, PhD^{2,3}, and Michael F. Green, PhD⁵

¹ Massachusetts General Hospital, Psychiatry Department, Freedom Trail Clinic, 25 Staniford St., 2nd Floor, Boston, MA 02114, USA

² Harvard Medical School, 25 Shattuck St. Boston, MA 02115, USA

³ MGH Biostatistics Center, 50 Staniford St. Boston, MA 02114, USA

⁴ Boston University Center for Anxiety and Related Disorders, 648 Beacon St, 6th Fl. Boston, MA 02215, USA

⁵ UCLA Semel Institute of Neuroscience and Human Behavior and the VA Greater Los Angeles Healthcare System, BOX 956968, 300 Medical Plaza, Ste 2263, Los Angeles, CA 90095-6968 USA

Abstract

Background—Daily dosing with D-cycloserine has inconsistently improved negative symptoms in schizophrenia patients, whereas intermittent dosing significantly facilitated exposure-based therapy in two studies of patients with phobic anxiety. In animal models, single dose administration enhances memory consolidation, but tachyphylaxis develops with repeated dosing. The objective of this exploratory study was to assess whether once-weekly dosing with D-cycloserine will produce persistent improvements in negative symptoms and cognition.

Methods—Fifty stable adult schizophrenia outpatients treated with any antipsychotic except clozapine were enrolled and 38 were randomized, double-blind, in a parallel-group, 8-week add-on trial of D-cycloserine 50 mg or placebo administered once-weekly. Symptom rating scales and a cognitive battery were administered at baseline and week 8 before the dose of study drug. As an exploratory analysis of memory consolidation, the Logical Memory Test, modified to measure recall after 7 days, was administered at baseline and after the first weekly dose of D-cycloserine. The primary outcome measures were change from baseline to week 8 on the SANS total score and on a composite cognitive score.

Corresponding author: Donald Goff, MD, Freedom Trail Clinic, 25 Staniford St. Boston, MA 02114, Ph: 617 912 7899, Fax: 617 723 3919, goff@psych.mgh.harvard.edu.

Author email addresses: Corinne Cather, PhD, ccather@partners.org

Jennifer D. Gottlieb, PhD, jgottlieb2@partners.org

A. Eden Evins, MD, MPH, a_edan_evins@hms.harvard.edu

Jared P. Walsh, BA, jpwalsh@partners.org

Lisa H. Raeke, MA, lraeke@partners.org

Michael W. Otto, PhD mwotto@bu.edu

David Schoenfeld, PhD, dschoenfeld@partners.org

Michael F. Green, PhD, mgrgreen@ucla.edu

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Results—Thirty-three subjects (87%) completed the trial. D-cycloserine significantly improved SANS total scores compared to placebo at week 8. Cognitive performance did not improve with D-cycloserine at 8 weeks. Delayed thematic recall on the Logical Memory Test was significantly improved with the first dose of D-cycloserine compared to placebo. Performance on immediate thematic recall and item recall on the Logical Memory Test did not differ between treatments.

Conclusions—Once-weekly dosing with D-cycloserine for 8 weeks produced persistent improvement of negative symptoms compared to placebo, although statistical significance was, in part, the result of worsening of negative symptoms with placebo. Consistent with animal models, a single dose of D-cycloserine facilitated memory consolidation tested after 7 days on a test of thematic recall. These results must be considered preliminary since a number of outcomes were examined without correction for multiple tests. These findings suggest that once-weekly dosing with D-cycloserine for the treatment of negative symptoms merits further study, as do D-cycloserine effects on memory consolidation.

Introduction

Converging lines of evidence have implicated dysregulation of N-methyl D-aspartate (NMDA) receptors as a factor contributing to clinical and cognitive features of schizophrenia (Goff and Coyle, 2001). The observation that NMDA channel blockers produce positive, negative, and cognitive symptoms characteristic of schizophrenia in healthy subjects (Krystal, et al., 1994) led to clinical trials of agents that activate this receptor complex. A meta-analysis of clinical trials in schizophrenia found that glycine, a full agonist at the glycine modulatory site of the NMDA receptor, significantly improved negative symptoms (Tuominen, et al., 2005). The glycine-site partial agonist, D-cycloserine, was effective for negative symptoms in one placebo-controlled trial in 47 schizophrenia patients (Goff, et al., 1999b), whereas several studies were negative (Duncan, et al., 2004, Goff, et al., 2005, van Berckel, et al., 1999) and D-cycloserine did not achieve significant efficacy in the meta-analysis (Tuominen, et al., 2005). More recently, the Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST) failed to find efficacy with either glycine or D-cycloserine compared to placebo for negative symptoms or cognitive deficits in 171 schizophrenia patients, although significant differences in outcomes between sites complicate interpretation of this negative finding (Buchanan, et al., 2007).

In contrast to the inconsistent findings in clinical trials with D-cycloserine, facilitation of learning and memory has been well-established in rodents and nonhuman primates with single dose administration of D-cycloserine. Cognitive impairments produced by anticholinergic agents (Andersen, et al., 2002), hippocampal lesions (Andersen, et al., 2002), early social deprivation (Stromme and Myhrer, 2002), and 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) (Schneider, et al., 2000) have been reversed by D-cycloserine in single dose experiments. In healthy animals, D-cycloserine significantly enhanced avoidance learning (Flood, et al., 1992), extinction of conditioned fear (Parnas, et al., 2005), performance on maze tasks (Quartermain, et al., 1994), and visual recognition memory (Matsuoka and Aigner, 1996). Memory effects of D-cycloserine do not become evident until 24 hours after learning, a delay that is believed to reflect NMDA receptor modification of memory consolidation (Santini, et al., 2001). Whereas single-dose administration of D-cycloserine consistently produced positive effects on memory and learning, several studies have demonstrated tachyphylaxis with repeated administration. For example, pre-treatment with D-cycloserine for 15 days attenuated facilitation in mice of a maze learning task (Quartermain, et al., 1994). Increasing the D-cycloserine dose from 3 mg/kg to 20 mg/kg did not counter the tolerance produced by 15 days of pre-treatment. Similarly, five daily doses of D-cycloserine administered over a 10-day period completely attenuated the facilitation of extinction of conditioned fear in rats (Parnas, et al., 2005). Recent evidence suggests that elevated concentrations of glycine or

D-serine at the glycine recognition site “prime” the NMDA receptor for removal from the cell surface to the intracellular compartment (Nong, et al., 2003). This process of “internalization” is believed to represent a mechanism for desensitization of NMDA receptors.

In anxiety disorders, intermittent treatment with D-cycloserine combined with cognitive behavioral therapy has produced persistent therapeutic effects (Davis, et al., 2006). Ressler and colleagues (Ressler, et al., 2004) treated 28 acrophobia patients with D-cycloserine 50 mg, 500 mg, or placebo prior to two sessions of desensitization using virtual reality exposure. Treatments were separated by 1–2 weeks. Outcomes for the two D-cycloserine treatment groups did not differ significantly and were combined. D-cycloserine pre-treatment was associated with significantly greater improvements in acrophobia symptoms, physiological measures of anxiety, and behavioral ratings one week and three months after treatment. Similarly, Hoffman and colleagues (Hofmann, et al., 2006) treated 27 patients with social anxiety disorder with D-cycloserine 50 mg or placebo one hour before each of 4 weekly cognitive behavioral exposure sessions for public speaking anxiety and found that D-cycloserine significantly improved all outcome measures following completion of treatment and at 4-week follow-up.

D-cycloserine is a relatively selective partial agonist at the glycine site with approximately 35%–68% activity compared to glycine for NMDA receptors containing NR2A or NR2B subunits and 192% activity for receptors containing the NR2C subunit (Sheinin, et al., 2001). D-cycloserine readily crosses the blood-brain barrier and is cleared by the kidneys unmetabolized with a serum half-life estimated between 7–15 hours (Hanngren, et al., 1961). In an oral single-dose challenge study in 16 healthy subjects, D-cycloserine 15, 50 and 150 mg achieved maximal plasma levels beginning 30–60 minutes after administration; plasma levels remained stable over the four-hour period of monitoring (van Berckel, et al., 1997). D-cycloserine was originally developed as an antibiotic; it is administered at doses up to 2 g for treatment-refractory tuberculosis.

Given the compelling evidence of enhanced learning with single-dose D-cycloserine administration in animal models and impressive therapeutic effects in recent clinical trials in anxiety disorders, we questioned whether tachyphylaxis with daily dosing may have attenuated D-cycloserine effects in previous schizophrenia trials. We adopted the approach of a one-week interval between doses of D-cycloserine 50 mg from successful trials in anxiety disorders to see if efficacy for cognitive deficits and negative symptoms of schizophrenia could be enhanced in an eight-week add-on trial. In addition, as an exploratory analysis, we examined whether the first dose of D-cycloserine affected memory consolidation by measuring delayed recall.

Methods

Subjects were stable adult outpatients at an urban community mental health center, ages 18–65 years, with a diagnosis of schizophrenia, treated with any antipsychotic except clozapine. Subjects had been taking a stable dose of antipsychotic medication for at least four weeks, did not have an unstable medical condition, seizure disorder, renal insufficiency or dementia, did not have a lifetime history of ketamine or phencyclidine abuse, and denied using alcohol or illicit substances within three months of study entry. Patients meeting entry criteria were identified by their clinicians and, if interested in participating, were referred for study. After the study was explained and written informed consent obtained, a research psychiatrist confirmed the diagnosis of schizophrenia by interview, review of records and consultation with clinicians, using DSM-IV criteria and performed a complete medical history and physical exam.

At baseline the following scales were administered: Positive and Negative Syndrome Scale (PANSS) (Kay, et al., 1987), Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1983), Clinical Global Impressions Scale (CGI), and the Systematic Assessment for Treatment-Emergent Side Effects (SAFTEE) (Levine and Schooler, 1986). A cognitive battery was also administered at baseline. Patients unable to complete the cognitive battery at baseline were dropped from study.

Cognitive assessment was approached in two different ways. First, a cognitive battery was administered at baseline and at eight weeks to provide a broad measure of cognitive functioning consistent with standard trial design for cognition enhancers in schizophrenia (Buchanan, et al., 2005). Second, we added a test of delayed recall of episodic memory after the first D-cycloserine dose to assess D-cycloserine effects on longer-term memory consolidation.

The cognitive battery assessed six cognitive domains: 1) *visual learning* as measured by the Faces I and II (delayed) subtests of the Wechsler Memory Scale III (WMS-III), 2) *verbal learning* as measured by the Hopkins Verbal Learning Test (HVLT) (Benedict, et al., 1998) using two different versions in counterbalanced order, 3) *problem solving* as measured by perseverative errors on the Wisconsin Card Sorting Test (WCST) (Heaton, 1990) and Trails B minus Trails A on the Trail Making Test (Spreen and Strauss, 1991), 4) *verbal fluency* as measured by Phonemic Fluency (F,A, S) and Category Fluency (animals) (Benton and Hamsher, 1978), 5) *working memory* as measured by Letter-Number Sequencing (with and without reordering; WAIS-III, The Psychological Corporation) and 6) *psychomotor speed and dexterity* as measured by the total time for dominant and non-dominant hands on the Grooved Pegboard (Lafayette Instrument). Tests were reverse scored if needed so that higher scores always indicated better performance. Test scores were standardized (mean = 0 and SD = 1). For domains with more than one test, test scores were averaged following standardization to yield a single summary score for each domain. A composite cognitive score was calculated as the mean of all 6 standardized domain scores. The North American Adult Reading Test (NAART) was administered at baseline, to characterize the sample in terms of estimated premorbid cognitive functioning.

The test of episodic verbal memory was the Logical Memory Test (LMT) from the Revised Wechsler Memory Scale (WMS-R) (Wechsler, 1997) which assesses memory for brief passages, similar to newspaper stories. Subjects were assessed on immediate recall, according to standard practice. Instead of the usual 30 minute interval for delayed recall we used a 7-day delayed recall to capture the overnight consolidation that is of interest with D-cycloserine. Subjects were not instructed in advance that they would be re-tested on the story after a delay of 7 days. We administered the LMT story A at baseline and story B at week 1. . The first administration of drug occurred at week 1 after the LMT delayed recall from baseline was tested. Whereas delayed recall was tested one week after subjects last heard the story, we identify results of delayed recall according to the time of story and study drug administration rather than the time of recall; for example, delayed recall of story A was tested at week 1 but is labeled as the baseline (week 0) LMT delayed recall score. The total number of thematic units recalled after a 7-day delay was the primary measure for memory consolidation at week 1. We expected that story themes would be more reliably recalled than story items after such a prolonged delay and would better represent memory performance involved in psychotherapy or rehabilitation interventions.

Subjects were randomly assigned in blocks of four using a computerized randomization schedule to placebo or D-cycloserine prepared in identical capsules by the research pharmacy. All research personnel were kept blind to treatment assignment. Subjects returned to the clinic weekly for 8 weeks; at each visit side effects were recorded using the SAFTEE and subjects were administered a single capsule of placebo or D-cycloserine 50 mg. At week 8, subjects

were assessed with the SANS, PANSS, CGI and completed the cognitive battery prior to study drug administration. Subjects who missed a study visit by more than 7 days were dropped from study.

Statistical Analysis

All demographic and clinical variables were compared between treatment groups at baseline using t-tests and chi-square tests. The primary endpoints were the change from baseline to week 8 in negative symptoms as defined by the modified SANS total score (SANS minus the Attention subscale), and in the composite cognitive score. Both analyses were performed using ANCOVA controlling for baseline. The treatment effect on negative symptoms was secondarily analyzed by comparing response rates, with response defined as a 20% or greater improvement from baseline at week 8 in modified SANS total score.

Secondary analyses included comparisons of treatment effects on the Positive Syndrome Subscale of the PANSS and CGI global improvement score at week 8, using ANCOVA and t-test, respectively. We also examined the change from baseline at the first repeat administration of the LMT at week 1 in all subjects that completed both assessments using ANCOVA. All results are given as means $\pm$ standard deviation (SD) except where otherwise noted. Two-sided tests of significance were used with an alpha of 0.05. Because the study was exploratory in nature, no corrections were made for multiple comparisons.

Results

Fifty subjects were enrolled; 38 completed screening and were randomized (Figure 1). Baseline and week 1 assessments were completed by 37 subjects (97%); 33 subjects (87%) completed week 8. Placebo and D-cycloserine groups did not differ significantly on any demographic or clinical variable at baseline (Table 1), nor did they differ in dropout rates (Figure 1). Dropouts did not differ from completers on any demographic or clinical variable at baseline.

The modified SANS total score significantly improved at week 8 in the D-cycloserine group compared to the placebo group ($p=0.048$; Table 2). However, the 31.3% response rate in subjects treated with D-cycloserine did not differ significantly from the 11.8% response rate in the placebo group ($p>0.1$). In the D-cycloserine group, change from baseline on the modified SANS total score did not correlate significantly with age, gender, antipsychotic type (typical or atypical), or baseline SANS or PANSS total score. The change from baseline to week 8 on the PANSS positive symptom subscale and the CGI at week 8 did not differ between treatment groups (Table 1).

There was no effect of drug on the cognitive composite at week 8 (Table 2). Compared to placebo, the D-cycloserine group significantly improved on delayed thematic recall of the LMT administered at week 1 which reflected the first dose of study drug ($F(1, 34) = 6.77$, $p = .01$, effect size 0.9), but did not differ from the placebo group in immediate thematic recall on the LMT or in immediate or delayed item recall from week 1 (Figure 2). Response on the delayed thematic recall of the LMT in the D-cycloserine group did not correlate with age, gender, antipsychotic type or baseline score.

Side effects

D-cycloserine was generally well-tolerated (Table 3). No dropouts were directly attributed to D-cycloserine side effects, although one subject in the D-cycloserine group dropped out with worsening of psychosis after discontinuing her antipsychotic medication.

Discussion

Our results suggest that once-weekly dosing with D-cycloserine for eight weeks may be sufficient to produce improvement compared to placebo in negative symptoms. Furthermore, because the SANS rating at week 8 was performed prior to the weekly D-cycloserine dose, this finding indicates that intermittent dosing with D-cycloserine may produce persistent alterations in excitatory synapses involved in expression of negative symptoms. Whether the magnitude of the effect is of clinical significance is uncertain, since the CGI did not differ between treatments and the significant difference between groups in SANS scores at week 8 was in part the result of worsening in the placebo group. Because the treatment groups were comparable in all demographic characteristics and on all clinical measures at baseline, as well as in change scores on other symptom ratings, it is most likely that the significant difference in SANS scores at week 8 represents a true drug effect and is not the result of clinical worsening unique to the placebo group. The 16.6% net reduction in SANS total score with D-cycloserine compared to placebo (0.7 effect size) was the result of an 8% improvement in the D-cycloserine group and an 8% worsening in the placebo group and was close to the threshold for statistical significance ($p=0.048$). While of uncertain significance, the net difference in SANS score change in a previous positive 8-week study of daily dosing with D-cycloserine was also 16% (0.8 effect size) although, unlike the current study, negative symptom scores improved in the placebo group (Goff, et al., 1999b). In addition, preliminary evidence has suggested that the magnitude of D-cycloserine's effect on negative symptoms might be greater when D-cycloserine is added to first generation antipsychotics, as in the daily dosing trial, than to atypicals (Evins, et al., 2002, Goff, et al., 1999a, Goff, et al., 1995).

In contrast to the beneficial effect on negative symptoms, we did not find enhancement of cognitive function as measured by a standard cognitive battery at week 8. Previous trials employing daily dosing in schizophrenia also failed to produce cognitive benefit at eight weeks (Goff, et al., 1999b, Goff, et al., 2005) although one trial found improvement on Sternberg's Item Recognition Task after two weeks of daily dosing with D-cycloserine 50mg (Goff, et al., 1995). However, we observed enhancement of delayed recall on the LMT following the first D-cycloserine dose. It is unclear whether this effect would have persisted with repeated once-weekly dosing. Parnas and colleagues (Parnas, et al., 2005) found that a single pre-exposure dose of D-cycloserine resulted in partial tolerance to D-cycloserine's facilitative effect on fear extinction and that 5 pre-exposure doses separated by 48 hours fully attenuated the effect. In contrast, a 28 day interval was sufficient to restore the facilitative effect of D-cycloserine on conditioned fear extinction (Parnas, et al., 2005). The effect of medication-free intervals shorter than 28 days was not studied. While it is not known whether repeated dosing with full agonists at the glycine site will similarly produce tachyphylaxis, Boje and colleagues (Boje, et al., 1993) demonstrated that desensitization of NMDA receptors on cultured granule neurons occurred with partial agonists and with the full agonist, glycine. Because effects of D-cycloserine on memory consolidation may underlie the augmentation of cognitive behavioral therapy previously demonstrated in anxiety disorders, the identification of a dosing schedule that avoids tachyphylaxis will be of considerable importance if D-cycloserine is also to be used to enhance psychosocial interventions in schizophrenia.

The significant improvement in delayed but not immediate thematic recall on the LMT following the first administration of D-cycloserine is consistent with animal models in which learning effects of D-cycloserine are first detectable after a 24 hour interval, possibly reflecting the role of NMDA receptors in memory consolidation (Santini, et al., 2001). Similarly, in patients with acrophobia, anxiety symptoms recorded during desensitization procedures performed 2–4 hours following study drug administration did not differ between the D-cycloserine and placebo groups; therapeutic benefit was observed when anxiety symptoms were assessed 1 week later (Ressler, et al., 2004). Enhancement of memory consolidation may

be of particular relevance to schizophrenia. In a study of procedural memory assessed during training and again after 24 hours, schizophrenia patients exhibited a specific deficit in memory consolidation compared to healthy subjects (Manoach, et al., 2004). Cognitive tests designed to assess learning after an interval of 24 hours or longer will be important for future studies to test the hypothesis that memory consolidation is impaired in schizophrenia and facilitated by glycine site agonists.

Several factors complicate interpretation of cognitive findings in this trial. The use of a 7-day recall condition with the LMT was added as an exploratory measure to capture memory consolidation effects, but has not previously been studied or validated as an outcome measure. Because the story at week 1 (story B) was different from that at baseline (story A) proactive interference from story A may have influenced recall of story B. The worsening of performance in the placebo group may reflect this effect. Recently, the glycine site full agonist, D-serine, was found to preferentially enhance reversal learning in mice, possibly mediated by long term depression (LTD) of glutamatergic neurotransmission (Duffy, et al., 2007). Such an effect would be consistent with D-cycloserine's enhancement of conditioned fear extinction and might have contributed to enhanced learning of story B one week after learning story A. The enhancement of reversal learning by glycine site agonists is expected to reduce perseveration and increase cognitive flexibility (Duffy, et al., 2007). Moreover, NMDA channel blockade with ketamine increases perseverative errors on the WCST in healthy subjects (Krystal, et al., 1994). However, we found no difference in perseverative errors on the WCST between treatment groups at week 8 ($F(1, 29) = 1.80, p = .19$). Similarly, Tsai and colleagues did not find an effect on perseverative errors on the WCST in schizophrenia subjects after six-weeks of daily dosing with D-serine, whereas the number of categories completed increased compared to placebo (Tsai, et al., 1998). Finally, the absence of cognitive effect at week 8 is based on a standard cognitive battery that did not specifically target memory consolidation effects.

The enhanced delayed recall of verbal memory after week 1 administration suggests that D-cycloserine effects on cognition may not be restricted to facilitation of conditioned fear extinction. In animals, spatial memory and visual recognition tests have also shown enhancement following a single dose of D-cycloserine (Matsuoka and Aigner, 1996, Quartermain, et al., 1994) suggesting that a range of cognitive functions may respond in a similar pattern to D-cycloserine. It is not clear, however, that our findings will apply to other clinical populations. The hypothesized dysregulation of NMDA receptors in schizophrenia may result in a pattern of cognitive response to D-cycloserine unique to this illness (Goff and Coyle, 2001). In addition, antipsychotics have been shown to alter NMDA sensitivity by a variety of mechanisms, including alterations in NMDA receptor density and subunit composition, changes in pharmacologic sensitivity of the glycine site, and in regulation of glutamate release (Goff, et al., 2002, Millan, 2005). Similar trials in healthy, unmedicated subjects utilizing tests sensitive to memory consolidation effects will be needed to better characterize D-cycloserine effects on cognition.

The improvement in negative symptoms and absence of improvement in cognition at eight weeks suggest that glutamatergic pharmacologic mechanisms may differ between these two psychopathological domains. It is possible that only negative symptoms and not cognitive deficits are potentially responsive to glycine site agonists, a puzzling finding, given that the full range of negative, positive and cognitive symptoms of schizophrenia are elicited by NMDA antagonists (Krystal, et al., 1994). Previous trials in which glycine site agonists demonstrated efficacy for negative symptoms clearly displayed a gradual improvement in symptom ratings over time with a plateau after approximately six weeks (Goff, et al., 1999b, Heresco-Levy, et al., 1999, Tsai, et al., 1998). In contrast, we found an effect on memory consolidation after a single dose; memory effects have been shown to attenuate with repeated dosing in animal studies. It appears that the mechanisms underlying potential therapeutic effects on negative

and cognitive symptoms may be distinctly different. While negative symptom effects increase over time with repeated dosing, enhancement of memory appears to diminish. It is possible that cognitive effects reflect enhancement of NMDA receptor activation, whereas effects on negative symptoms reflect a compensatory process of reduced activation that corresponds to attenuation of memory facilitation. Alternatively, the effects of glycine site agonists on negative symptoms may be mediated by a different subpopulation of NMDA receptors than those that mediate learning and memory.

Conclusion

D-cycloserine 50 mg administered once-weekly for eight weeks significantly improved negative symptoms compared to placebo in schizophrenia patients treated with a variety of antipsychotic agents. Once-weekly D-cycloserine did not improve cognitive functioning after 8 weeks. However, an exploratory test of verbal memory following a delay in recall of 7 days significantly improved after the first dose of D-cycloserine. This finding is consistent with animal studies in which D-cycloserine facilitates memory consolidation, an effect that may only become evident after a delay of 24 hours. As the first study of once-weekly dosing in schizophrenia, this study was exploratory and so results must be considered preliminary, particularly since negative symptoms worsened in the placebo group and several outcome measures were examined without correction for multiple comparisons. Additional studies are needed to replicate these findings and further characterize the possibly distinct pharmacology of D-cycloserine effects on negative and cognitive symptoms of schizophrenia.

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Figure 1.
Enrollment and Randomization

Figure 2. LMT Immediate and Delayed Thematic Recall by Treatment (n = 37)

*p=.01

Note: Error bars indicate standard error of the mean.

Table 1
Baseline Characteristics of Subjects by Treatment

Demographic	Treatment Group	
	D-Cycloserine (N = 19)	Placebo (N = 19)
Age (years)	50.1 ± 9.15	48.0 ± 6.66
Sex		
Female, N (%)	9 (47.4)	6 (31.6)
Male, N (%)	10 (52.6)	13 (68.4)
Ethnicity, N (%)		
White, non-Hispanic	14 (73.7)	14 (73.7)
White, Hispanic	2 (10.5)	4 (21.1)
African-American	2 (10.5)	0 (0)
Native-American	1 (5.3)	0 (0)
Other	0 (0)	1 (5.3)
Duration of Illness (years)	23.9 ± 12.5	21.6 ± 8.7
Education	12.7 ± 2.3	12.4 ± 2.5
Symptoms Ratings		
SANS – Total	26.5 ± 9.88	24.0 ± 10.38
PANSS – Positive Subscale	17.7 ± 5.09	19.6 ± 5.35
CGI	4.11 ± 0.99	4.17 ± 0.99
Cognitive		
NAART: Errors	34.84 ± 14.29	38.68 ± 14.7
HVLIT: Total Immediate Recall	18.0 ± 4.73	17.0 ± 4.71
WCST: Perseverative Errors	14.28 ± 8.32	15.32 ± 12.65
Trails B: Total Time*	91.39 ± 45.11	74.47 ± 55.24
FAS: Total	35.26 ± 11.54	27.58 ± 12.59
Animals: Total	16.21 ± 5.45	15.47 ± 6.20
Pegboard: Total	218.68 ± 113.37	271.42 ± 127.77
Faces I: Immediate Recall	33.90 ± 5.34	34.0 ± 5.21
Faces II: Delayed Recall	34.42 ± 4.97	33.16 ± 4.83
Letter Span: W/O Reordering	12.26 ± 2.60	11.47 ± 3.12
Letter-Number: W/Reordering	7.95 ± 2.80	7.32 ± 2.47
Cognitive Composite	-.11 ± .72	.12 ± .60
Logical Memory – Thematic		
Immediate Recall (Story A)	4.42 ± 1.74	4.00 ± 1.89
7-Day Delayed Thematic Recall (Story A)	2.05 ± 1.39	2.42 ± 1.57
Logical Memory – Unit		
Immediate Recall (Story A)	8.95 ± 3.84	9.53 ± 3.98
7-Day Delayed Unit Recall (Story A)	2.95 ± 2.25	3.67 ± 3.18

All comparisons between treatment groups are non-significant ($p > 0.1$);

Values are means ± SD or N(%);

* Trails B = Trails B–Trails A

Table 2
Antipsychotic by Treatment

Demographic	Treatment Group	
	D-Cycloserine (N = 19)	Placebo (N = 19)
Antipsychotic Type, N (%)		
First Generation	3 (15.8)	2 (10.5)
Second Generation	16 (84.2)	17 (89.5)
Antipsychotic, N (%)		
Aripiprazole	3 (15.7)	3 (15.7)
Risperidone	4 (21.1)	5 (26.3)
Ziprasidone	2 (10.5)	1 (5.3)
Olanzapine	6 (31.6)	6 (31.6)
Quetiapine	1 (5.3)	2 (10.5)
Fluphenazine	2 (10.5)	1 (5.3)
Haloperidol	0 (0)	1 (5.3)
Loxitane	1 (5.3)	0 (0)

Table 3
Change Scores on Cognitive and Symptom Measures at Week 8

	D-Cycloserine (N = 16)	Placebo (N = 17)	F	P-value
Measure				
Cognitive				
Cognitive Composite *	.05 ± .23	-.06 ± .32	1.27	.27
Symptoms				
PANSS Positive *	0.19 ± 2.10	-0.19 ± 4.65	.15	.70
SANS Total	2.06 ± 5.03	-2.11 ± 7.05	4.21	.048
Affective Flattening	0.94 ± 3.32	-1.41 ± 3.66	2.92	.10
Anhedonia	0.81 ± 1.64	-0.41 ± 2.67	3.16	.09
Alogia	0.19 ± 3.08	0.29 ± 1.86	.08	.78
Avolition	0.13 ± 2.16	-0.59 ± 1.80	1.04	.32

Values are means ± SD

For all scores, higher values equal greater improvement.

* placebo (N = 16) D-cycloserine (N=16).

F= Change from baseline ANCOVA for treatment × time effect (Baseline to Week 8)

Table 4

Incidence of Treatment-Emergent Side Effects

Side Effect	D-Cycloserine (N = 19)	Placebo (N = 19)
Anxiety	-	1
Bronchitis	1	-
Chest Pain	-	1
Depression	1	2
Diarrhea	-	2
Fatigue	1	-
Fracture (Foot)	-	1
Headache	2	-
Heartburn	-	2
Nausea	-	1
URI	2	2
Vertigo	-	1
Vomiting	1	-