A Pilot Study of d-Cycloserine in Subjects With Autistic Disorder

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Objective: The authors assessed the effects of d-cycloserine on the core symptom of social impairment in subjects with autism.

Method: Following a 2-week, single-blind placebo lead-in phase, drug-free subjects with autistic disorder were administered three different doses of d-cycloserine during each of three 2-week periods. Measures used for subject ratings included the Clinical Global Impression ( CGI ) scale and Aberrant Behavior Checklist.

Results: Significant improvement was found on the CGI and social withdrawal subscale of the Aberrant Behavior Checklist. d-Cycloserine was well tolerated at most of the doses used in this study.

Conclusions: In this pilot study, d-cycloserine treatment resulted in significant improvement in social withdrawal. Further controlled studies of d-cycloserine in autism appear warranted.

No drugs have been shown to consistently improve the social and communication impairments central to autism. Open-label studies of serotonin reuptake inhibitors and atypical antipsychotics have suggested improvement in certain aspects of social relatedness, but this has yet to be proven in placebo-controlled trials. In a previous randomized, placebo-controlled study of 101 children with autism and severe irritability (1), risperidone led to significant improvement in irritability, hyperactivity, and stereotypic behavior, but not in social withdrawal or inappropriate speech. Thus, treatments for the core social and communication impairments that characterize autism are needed.

Several authors have drawn parallels between the negative symptoms of schizophrenia and the social and communication impairment observed in autism. Low-dose d-cycloserine, a partial agonist at the N-methyl-D-aspartate ( NMDA ) glutamate receptor subtype, has been shown to reduce negative symptoms in adults with schizophrenia (2). Drugs affecting the glutamate system have begun to be explored as therapeutic agents in several neuropsychiatric disorders (3) but have received limited attention as a possible therapeutic option in autism. Carlson has hypothesized that autism is a hypoglutamatergic disorder on the basis of NMDA antagonist effects in humans and mice (4). With these points in mind, we undertook a pilot study of d-cycloserine to determine whether it had any short-term clinical benefits or adverse effects in subjects with autism.

Results

Two subjects withdrew from the study after completing only the 2-week placebo lead-in phase. One of these subjects dropped out because of worsening stereotypic behavior, and the other subject dropped out because of non-compliance. The remaining 10 subjects (eight male and two female subjects; mean age = 10.0 years, SD = 7.7, range = 5.1–27.6) completed all 8 weeks of the study and were included in the final data analysis. The mean daily doses of d-cycloserine were administered three different doses of d-cycloserine during each of three 2-week periods. Measures used for subject ratings included the Clinical Global Impression ( CGI ) scale and Aberrant Behavior Checklist.

Results: Significant improvement was found on the CGI and social withdrawal subscale of the Aberrant Behavior Checklist. d-Cycloserine was well tolerated at most of the doses used in this study.

Conclusions: In this pilot study, d-cycloserine treatment resulted in significant improvement in social withdrawal. Further controlled studies of d-cycloserine in autism appear warranted.
D-cycloserine at each of the three dose levels (low, medium, high) are shown in Figure 1.

D-Cycloserine was associated with a statistically significant improvement in the CGI severity rating ($F=4.58$, $df=3, 44$, $p=0.02$). A post hoc comparison indicated that ratings following treatment with both the medium ($p=0.02$) and high doses ($p=0.008$) of D-cycloserine were significantly different from baseline. For CGI improvement ratings, response rates for the placebo, low-dose, medium-dose, and high-dose phases were 0%, 30%, 40%, and 40%, respectively.

A statistically significant improvement was also seen on the Aberrant Behavior Checklist social withdrawal subscale (Figure 1). A post hoc comparison indicated that scores following treatment with the highest dose of D-cycloserine were significantly different from those at baseline ($p=0.02$). At this dose, there was a 60% decrease in symptom severity. There were no significant differences on the other Aberrant Behavior Checklist subscales (irritability, stereotypic behavior, hyperactivity, inappropriate speech), Social Responsiveness Scale, or Children’s Yale-Brown Obsessive Compulsive Scale.

Two subjects experienced adverse effects (a transient motor tic and increased echolalia) at the highest dose they received (2.8 and 3.0 mg/kg/day, respectively). End-of-study physical examination results and laboratory values were not significantly different from pretreatment.

**Discussion**

In this preliminary study, D-cycloserine treatment was associated with reduced social withdrawal and increased social responsiveness in a group of subjects with autism. In 40% of these subjects, the improvement was clinically meaningful, and both the parent and clinician rated them as “much improved.”

Relative strengths of this study include the use of well-characterized drug-free subjects and the prospective, placebo-controlled, single-blind design. Limitations include the wide age range, lack of clinician blinding, and the absence of a parallel control group. Given the small number of subjects in this exploratory study, it is likely that a type II error exists. Indeed, the means of several of the outcome measures improved during D-cycloserine treatment but failed to reach the level of statistical significance. This raises the possibility that some of the improvement seen during the study was due to the effects of D-cycloserine on related symptoms of mood disturbance or behavior.

In addition, because the order of treatments was not randomized, we cannot rule out that the effects seen at the higher doses of D-cycloserine were secondary to a delayed placebo effect or to longer duration of treatment with lower doses of D-cycloserine. This is also important because it is possible that the adverse effects seen during the highest dose of D-cycloserine were due to longer duration of treatment. Furthermore, because a full range of D-cycloserine doses was not tested in this study, it is possible that the optimal dose of D-cycloserine may lie in between those specifically examined. Finally, it is possible that some of the clinical effects seen in this study are due to NMDA receptor antagonism rather than agonism, since D-cycloserine is a partial agonist with different affinities for NMDA receptor subtypes (5).

Overall, these preliminary results suggest that D-cycloserine might have efficacy for certain aspects of social impairment in autism. A randomized controlled trial of D-cycloserine in autism appears warranted.


We have recently studied auditory cortical processing in adults with autism using complex speech-like sounds (1) and found less activation of the left temporal word processing network in autistic adults than in healthy comparison subjects. The results obtained in autistic adults suggest a dysfunction of specific temporal regions specializing in the perception and integration of complex sounds (2). Such stimuli are never recognized as speech; therefore, an abnormal pattern of activation found in autistic adults could reflect basic anomalies of prelinguistic auditory processing rather than a consequence of abnormal language development (3). Since autism is a developmental disorder, we believed it important to investigate the cortical response to sounds in children with autism. All reported activation studies in autism have been performed in adults, but no data are available for children, to our knowledge. Therefore, we performed a positron emission tomography (PET) auditory activation study in autistic children using the same speech-like stimuli previously described in the autistic adult study. Autism is associated with abnormal auditory behavior, including aversive reactions to everyday life sounds. In addition, autistic children are often initially misdiagnosed as deaf (4). An abnormal perception of speech-like sounds in childhood may account for inadequate behavioral response to sounds and thus for language impairments typical of autism.

**Method**

Eleven autistic children (10 boys) ages 4 to 10 years (mean=6.6, SD=1.6) with primary autism were selected. Autism was diagnosed according to DSM-IV criteria. The Autism Diagnostic Interview—Revised (5) confirmed the diagnosis: mean social interaction score=27.3 (SD=6.6); mean nonverbal communication score=11.9 (SD=3.5); mean stereotypy score=7.9 (SD=4.7); mean age-onset criteria=4.3 (SD=0.8). Four children had verbal communication; their mean score was 17 (SD=7). Their IQ or development quotient was