

Research Letter**Donepezil Effects on Language in Children With Down Syndrome: Results of the First 22-Week Pilot Clinical Trial[†]****To the Editor:**

In earlier pilot studies, we reported improvements in global function [Kishnani et al., 1999] and expressive language function [Heller et al., 2003] in adults with Down syndrome (DS) following cholinergic therapy (donepezil hydrochloride). In this study, we report results of a small open-label clinical trial of donepezil in children with DS. To our knowledge, this is the first study evaluating the effects of donepezil on language in children with DS.

After obtaining IRB approval and written informed consent, we enrolled seven children (2M:5F) between the ages of 8 and 13 years (mean age = 10.5 years) with DS (trisomy 21 by blood chromosome analysis) and their primary caregivers in a prospective open trial of donepezil. All subjects were verbal, able to hear speech at a conversational level, and able to ingest oral medication. None of the subjects had active thyroid disease, vitamin B12 deficiency, clinically-confirmed pregnancy, or clinically-significant systemic disorders, (e.g., bradycardia (HR < 50), insulin-dependent diabetes mellitus, active peptic ulcer, celiac disease, significant reactive airways, or seizure disorder) at the time of entry into the trial. They had not previously ingested cholinesterase inhibitors or any other investigational or alternative therapies used to treat the symptoms of DS in the 30 days prior to or during the trial. IQs of six subjects (obtained from school reports) ranged from 46 to 66 (mean IQ = 50). The IQ of one subject could not be determined from records.

This 22-week trial (16 week open treatment study followed by a 6-week washout) was completed at the General Clinical Outpatient Research Unit at Duke University Medical Center. Subjects attended four sessions, week 0 (baseline), week 8 (low dose), week 16 (high dose), and week 22 (washout). At the completion of the baseline visit, donepezil was dosed orally at 2.5 mg once daily for 8 weeks. Based on tolerability, the dose was increased to 5 mg daily for the remaining 8 weeks. Subjects were monitored closely for safety by regular phone calls in

between scheduled visits. Two language measures were used, the Test of Problem Solving [TOPS, Zachman et al., 1984] and the Clinical Evaluation of Language Fundamentals-3 [CELF-3, Semel et al., 1995]. The CELF-3 was administered at baseline, week 16, and week 22. The TOPS was completed at all four visits. Because the CELF-3 and TOPS have not been standardized for individuals with DS and the subjects' language performance was significantly below standard age norms, performance-based comparisons were made with raw scores and age equivalencies.

The effect of the medication on language performance was measured by change from baseline performance at the week 8 and week 16 assessments. One subject was excluded from all analyses because of a protocol deviation in administered dosage. No patient experienced serious adverse effects or withdrew from the study. Performance comparisons (completed by repeated measure *t*-tests) were based on a total *n* of 6 (five subjects for the baseline vs. week 8 TOPS comparison). Due to the preliminary and exploratory nature of the study, we did not correct for multiple comparisons. *P* values at or below 0.05 (two-tailed) were viewed as significant.

Overall, language performance levels were low. The average TOPS age score was below the 3 years 5 months test basal for all sessions, and the average CELF-3 age score was 4 years 3 months at baseline, and 4 years 7 months at week 16. Essentially no change in language performance with treatment was noted on the TOPS at week 8 (the difference between mean baseline and week 8 scores was <1) and at week 16 (Table I). However, a significant improvement (*t* = 3.11; *P* = 0.0265) in overall CELF-3 performance from baseline to week 16 was found (Table I).

Additional analyses of the expressive and receptive components of the CELF-3 Total Language Score showed a statistically significant gain of 5 points in expressive language performance (*t* = 3.14; *P* = 0.0256) and a similar gain of 4.5 points (approaching statistical significance) in receptive language performance (*t* = 2.55; *P* = 0.0513). A review of subject performance on individual expressive and receptive language subtests of the CELF-3 revealed that the largest improvements were made on the word structure and sentence structure subtests.

As we noted in our adult study [Heller et al., 2003], these findings should be viewed as preliminary and interpreted with caution because of methodological limitations such as an extremely small sample size, lack of power for formal statistical control, repeated comparisons across a relatively short time span (16 weeks), and the lack of an untreated control group. Our primary finding, which is consistent with the results of our two adult studies, was an improvement in selective aspects of language performance (particularly aspects of expressive language) in children with DS following donepezil therapy. This result is noteworthy in the context of similar findings of language improvement in autistic children treated with two different cholinesterase inhibitors, donepezil hydrochloride [Chez et al., 2000, 2001] and rivastigmine [Chez et al., 2004].

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*Correspondence to: James H. Heller, Down syndrome Clinic, Box 3528, Department of Pediatrics, Duke University Medical Center, Durham, NC 27710. E-mail: helle001@mc.duke.edu

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TABLE I. Changes in Raw Score Language Performance From Baseline to 16 Weeks as Measured by the Test of Problem Solving (TOPS) and the Clinical Evaluation of Language Fundamentals (CELF)-3

Measure	Baseline (n = 6)	16 weeks (n = 6)	P value
	Mean (SD)	Mean (SD)	
TOPS	13.5 (11.3)	14.8 (11.5)	0.3276
CELF-3 Total Language Score	38.7 (28.9)	48.2 (31.8)	0.0265
CELF-3 Expressive Language Score	21.2 (18.3)	26.2 (20.5)	0.0256
CELF-3 Receptive Language Score	17.5 (11.1)	22.0 (12.1)	0.0513
CELF-3 expressive subtests			
Word structure	8.7 (7.5)	12.5 (8.7)	0.0028
Formulating sentences	6.5 (7.0)	7.5 (8.8)	0.3481
Recalling sentences	6.0 (5.0)	6.2 (3.8)	0.8863
CELF-3 receptive subtests			
Sentence structure	9.2 (3.3)	12.7 (5.0)	0.0362
Concepts and directions	4.3 (4.2)	3.7 (2.8)	0.3632
Word classes	4.0 (4.3)	5.7 (5.7)	0.2332

The CELF-3 is analyzed in three forms Total Language Score, Expressive and Receptive Language Scores, and by individual subtest score.

Taken together the results of our work with individuals with DS and Chez's studies of individuals with autism suggest a relationship between language performance and the cholinergic system that extends across syndromes and that cholinergic therapy is a potential treatment for language impairment in children and adults with significant developmental delays.

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James H. Heller*

Departments of Pediatrics and Surgery
Duke University Medical Center
Durham, North Carolina

Gail A. Spiridigliozzi

Departments of Pediatrics and Psychiatry
Duke University Medical Center
Durham, North Carolina

P. Murali Doraiswamy

Department of Psychiatry, Duke
University Medical Center, Durham,
North Carolina

Jennifer A. Sullivan

Bythe G. Crissman
Priya S. Kishnani
Department of Pediatrics
Duke University Medical Center
Durham, North Carolina