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Safety and Efficacy of Donepezil in Children and Adolescents with Autism: Neuropsychological Measures

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Abstract

Objective: There has been recent interest in the use of cognitive enhancing drugs, such as cholinesterase inhibitors, as a possible treatment for executive functioning (EF) deficits in autism spectrum disorder (ASD). The goal of this study was to assess the tolerability, safety, and efficacy of donepezil on EF in a sample of children and adolescents with ASD.
Method: Thirty-four children and adolescents with ASD (age range 8–17 years; IQ >75) were enrolled in a 10-week, double-blind, placebo-controlled trial of donepezil (doses of 5 and 10 mg), followed by a 10-week open label trial for placebo nonresponders.
Results: The effect of donepezil treatment on EF was examined. Despite improvement on a number of EF measures, no statistically significant between-group differences were found (with gains observed for both the placebo and donepezil groups).
Conclusions: The results suggest that short-term treatment with donepezil may have limited impact on cognitive functioning in ASD. Future controlled trials may need to consider a longer treatment period to detect significant gains on EF measures.

Introduction

The past decade has witnessed a steady increase in the incidence of autism spectrum disorder (ASD), with recent study findings of 60–66 per 10,000 affected individuals (Fombonne 2005; Centers for Disease Control and Prevention 2007). Symptoms typically include deficits in the area of communication, social reciprocity, and stereotypic interests and behaviors (American Psychiatric Association 2000). While a range of psychopharmacological interventions has been shown to be efficacious in addressing secondary symptoms of the disorder (e.g., hyperactivity, irritability, and self-injury), no pharmacological treatment has yet been identified to address the core features of ASD (Handen and Lubetsky 2005).

One area that has received increasing attention in the ASD treatment literature is deficits in executive functioning (EF). This refers to a set of higher order cognitive processes that provide the foundation for complex problem solving and organized, meaningful behavior. EF includes functions such as set-shifting and cognitive flexibility, verbal and nonverbal working memory, planning and strategy formation, generativity, inhibitory control, and self-reflection/self-monitoring (Welsh and Pennington 1988). In fact, a number of investigators in the field have suggested that EF deficits are a primary characteristic of ASD and might underlie the expression of the core features (Ozonoff and McEnvoy 1994; Russell 1997; Rajendran and Mitchell 2007). For example, a series of investigations support a multiple primary cognitive deficit model for the cognitive basis of behavior in ASD (Just et al. 2007; Minshew et al. 1994, 1995, 2000). Neuropsychologic functioning in their samples was characterized by intact attention, sensory perception, elementary motor, simple associative memory processes, formal language, and rule-learning aspect of abstraction and by deficits in complex motor (motor apraxia), memory for complex information, higher order interpretative aspects of language, and concept formation abilities. In the reasoning domain, the pattern of performance was characterized by deficits on concept formation tests and intact rule learning abilities. Visual spatial abilities appeared to be spared. Hence, this model of ASD as a selective disorder of complex information processing has significant potential in explaining atypical, idiosyncratic, and problematic behaviors based on this profile of cognitive abilities and deficits.

The desire to address EF deficits in ASD stems from the hypothesis that improvement in this area will enhance learning and academic achievement, as well as promote more successful behavioral and social functioning. Consequently, there has been increased interest in the use of cognitive enhancing drugs, such as cholinesterase inhibitors, as a possible treatment for ASD. The

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cholinergic system plays a significant regulatory role in neuronal differentiation and synapse formation during early development. Laboratory experiments in rats have demonstrated the importance of cholinergic innervations. For example, delayed cortical neuronal development along with permanent changes in cortical architecture and cognitive functioning was found in rats whose cholinergic innervations were disrupted during early postnatal development (Hohmann and Berger-Sweeney 1998). Among individuals with ASD, neurochemical abnormalities have also been documented in the cholinergic system. For example, Bauman and Kemper (1994) noted an increase in the number and size of basal forebrain (septal) cholinergic neurons in children with ASD, but a smaller number and size in adults. Autopsy tissue from individuals with ASD evidenced significantly greater cerebellar nicotinic alpha-4 receptor loss in comparison to tissue from normal controls and non-ASD individuals with intellectual disability (Lee et al. 2002). Finally, Perry et al. (2001) found a decrease in the number of cortical M_1 receptors in the parietal cortex, a decrease in $alpha_4$ and $beta_2$ nicotinic receptor subunits in the parietal cortex, and a decrease in nicotinic receptors in the parietal and frontal cortices following autopsy of seven adults with ASD.

A few recent studies have suggested that cholinesterase inhibitors may enhance behavioral functioning, language, social behavior, and core features of ASD. However, there has been limited focus on the effects of such agents on EF measures. In a retrospective study of eight children with ASD who had been prescribed donepezil (mean dose 9.37 ± 1.76 mg/day), significant decreases were found on the Irritability and Hyperactivity subscales of the Aberrant Behavior Checklist (Hardan and Handen 2002). Chez et al. (2003) also documented gains on measures of expressive and receptive language as well as core ASD features (using the Childhood Autism Rating Scale) in a double-blind study of 43 children who were placed on a 2.5 mg/day dose of donepezil. However, the results were equivocal, as between-group statistical analyses were not conducted and the placebo group evidenced greater improvement on some measures than those on active medication (Yoo et al. 2007). Niederhofer et al. (2002) reported the results of a double-blind, placebo-controlled crossover trial of galantamine with 20 children with ASD. Focusing primarily on behavioral measures, slightly lower (but statistically significant) ratings were reported on parent and teacher measures of irritability, hyperactivity, inappropriate speech, and poor eye contact with the use of galantamine versus placebo. A 12-week, open label trial of galantamine (dose range 12–24 mg/day) was conducted among 13 children with ASD (age range 4–17 years) (Nicholson et al. 2006). Based upon gains on the Inattention subscale of the Conners Parent Rating Scale, the Irritability and Social Withdrawal subscales of a parent-completed Aberrant Behavior Checklist, and ''Anger'' (from a physician-completed Children's Psychiatric Rating Scale), eight subjects were deemed responders. Chez et al. (2004) documented significant improvement on behavioral measures, expressive vocabulary, and core features of autism in a 12-week, open label trial of rivastigmine involving 32 children with ASD. Finally, Hertzman (2003) conducted a case study of galantamine with three adults with ASD (dose range 4–16 mg/day) in which some gains were reported on verbalizations and socially appropriate behavior.

We add to this line of inquiry by reporting the results of a double-blind, placebo-controlled trial to assess the tolerability, safety, and efficacy of donepezil on cognitive functioning in a sample of children and adolescents with ASD. Subjects in the placebo arm of the double-blind trial were offered a 10-week open label trial at the conclusion of their participation. Donepezil was hypothesized to be superior to placebo in improving performance on a range of EF tasks.

Method

Inclusion criteria included being between 8 and 17 years of age with an intelligence quotient (IQ) >75. Subjects also had to meet research diagnostic criteria for ASD (autistic disorder, pervasive developmental disorder–not otherwise specified (POD–NOS), Asperger's disorder), based upon both the Autism Diagnostic Interview–Revised (ADI-R) (Rutter et al. 2003) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 1999). For subjects prescribed concomitant psychotropic medications before starting the trial, dose levels needed to be stable during the time of study participation. Allowed medications were limited to those that did not interact with donepezil. Finally, subjects were required to score at least one standard deviation below mean (for gender and age) on either the Verbal Fluency (VF), 20 Questions Test, or the Card Sorting Test of the Delis-Kaplan Battery of Executive Function System (D-KEF) (Delis et al. 2001).

After obtaining signed consents from families/guardians and assent from subject, study eligibility criteria were established using the following assessment tools (administered by three of the authors—B.L.H., C.R.J., and A.Y.H.):

The Autism Diagnostic Interview–Revised

ADI-R (Rutter et al. 2003) is a valid and reliable, semistructured parent interview that is used together with the clinical psychiatric interview and ADOS to establish an ASD diagnosis. It has been shown to have excellent reliability and validity.

Autism Diagnostic Observation Schedule

The ADOS (Lord et al. 1999) is a semistructured clinical interview. Used in combination with the ADI-R, the ADOS assesses the child's behavior in a more naturalistic setting. A *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV)–based algorithm is used to make a diagnosis of autism, nonautistic PDD, or non-PDD.

Wechsler Abbreviated Scale of Intelligence

The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999) is a standardized measure of intelligence (normed for individuals 6-0 to 80-0 years of age) that provides Verbal, Performance, Full Scale IQ scores. It has excellent reliability and validity and is linked to other, more comprehensive intelligence tests.

The Diagnostic Interview for Children and Adolescents–Revised

The Diagnostic Interview for Children and Adolescents–Revised (Reich et al. 1997) is a computerized, parent-completed tool that was used to assess for psychiatric comorbidity. Developed for individuals aged 6–17, the Diagnostic Interview for Children and Adolescents–Revised is a DSM-based diagnostic interview that has repeatedly been revised to reflect changes in the DSM classification system.

Medical History

Medical history was obtained by subjects' parents. Subjects were also given a brief physical (including Tanner staging). Baseline measures included electrocardiogram, hematology

(complete blood count and differential; platelet count), urinalysis (urine routine and microscopy), and chemistry (albumin, astra 7, bilirubin-total, calcium, cholesterol, protein profile, serum glutamic oxaloacetic transaminase, thyroid stimulating hormone, and thyroxine). These same measures were repeated at weeks 5 and 10. Fragile X syndrome karyotyping was obtained in cases where assessment had not previously been performed.

A 10-week, double-blind, placebo-controlled, parallel groups design was used. Subjects were randomly assigned to either donepezil or placebo. Randomization was conducted by the study pharmacist and the sample was stratified based upon tanner stage (stages 1–2 and 4–5) and gender. Dosing began at 2.5 mg/day dose and was increased to 5.0 mg/day after a 1 week period. Subjects were re-evaluated after 4 weeks at the 5 mg/day dose. Doses were subsequently increased to 7.5 mg/day for a 1-week period and then titrated to 10.0 mg/day for the final 4 weeks of the double-blind trial. A second re-evaluation was conducted following 4 weeks on the 10 mg/day dose. In addition to the re-evaluation visits, subjects were seen at weeks 1 and 6 to assess safety and to determine if the individual was able to have his/her medication titrated to the next dose level (these assessments were conducted by the author, A.Y.H., as well as by other psychiatrists associated with the study). If side effects were reported that were determined to be interfering with a subject's functioning or well-being, the medication dose was reduced to previous the highest tolerated dose and maintained at that level for the remainder of the study. If problems persisted, a final re-evaluation was completed at that time and the medication discontinued.

Families were asked to complete daily logs, track when medication was given, and to note if there were any problems to assess compliance with the medication regimen. Concomitant medications (e.g., aspirin, cold medicine) were also tracked on the daily log. Families were required to return the medication bottles at each visit to conduct a pill count. The hospital research pharmacy packed all medication. Both donepezil and placebo were placed in opaque capsules. At the conclusion of the 10-week re-evaluation, all subjects who had been placed on placebo were offered a 10-week open-label trial (involving the same titration schedule as used in the double-blind study). Subjects participating in the open-label study were re-evaluated at week 5 (5 mg/day dose) and week 10 (10 mg/day dose).

The following dependent measures were obtained at baseline, week 5, and week 10 for both the double-blind and open-label trials:

Delis-Kaplan Battery of Executive Function System

The Delis-Raplan Battery of Executive Function System (D-KEF) (Delis et al. 2001) is a comprehensive, normed battery incorporates many traditional EF measure formats, including attention, language, and perception to generate higher level abstract reasoning skills and creative thought process. It is appropriate for use from ages eight through adulthood. Three subtests (Card Sorting, VF, 20 Questions) have two versions for repeated administration. For Card Sorting and VF, the first subtest was given at baseline and the second at the week 10 assessment (10 mg/day). There was no week 5 (5 mg/day) assessment. The first version of Twenty Questions was given at baseline and the second version was split into two forms (one given at the week 5 and the second at week 10). The Word Context subtest was split into three sections: one given at baseline and the other two given at weeks 5 and 10. The remaining subtests (Trail Making Test [TMT], Design Fluency Test, Tower Test, and Color-Word Interference [CWI] Test) served as secondary measures and were administered at all three assessments. Finally, subtests given during the open label trial included TMT, VF, Card Sorting, Design Fluency, and CWI. The D-KEF was selected for use because it assesses a wide range of executive functions, including those that have been identified previously as possible areas of deficit in ASD.

Trail Making Test

The TMT measures multitasking and the ability to process written information. The child is given a series of timed paper and pencil tasks involving drawing lines between numbers and letters in a quick manner. These tasks include having to visually scan numbers and to cross out all examples of a specified target number, to draw lines connecting numbers in numerical order, drawing lines connecting letters in alphabetical order, switching back and forth between connecting numbers and letters in sequence, and tracing over a dotted line connecting circles in a rapid manner. The primary dependent measure was total time.

Verbal Fluency

This test measures verbal multitasking skills. The child is required to generate words verbally that begin with a particular letter or belong to a particular category. The child also is then required to generate words verbally that belong to two different categories and alternate between the two categories. The primary dependent measure is total number of switches between categories.

Design Fluency Test

This test measures skills involving visual attention to written tasks and efficient processing of written information. Sets of filled dots and empty dots are presented and the child is asked to make designs using four lines connecting the filled dots alone, the empty dots alone, and then to alternate between filled and empty dots. The number of completed alternating designs within a set time limit served as the dependent measure.

Color-word-interference Test

This test measures flexibility in thinking with verbal information. The child is required to name colors as quickly as possible, read color words as quickly as possible, name colors of words printed in different color inks (e.g., the word ''red'' printed in blue ink), and alternate between naming ink colors and reading color words. Time to complete the alternating task served as the primary outcome measure.

Sorting Test (STCC and STFS)

This test measures verbal and nonverbal problem-solving skills, concept-formation skills, abstract reasoning, and flexibility of thinking. The child is required to sort cards into groups based on verbal and perceptual features and verbally describe the concepts used to generate the sorts. Dependent measures included Confirmed Correct Sorts (the number of correct sorts generated by the subject: ''STCC'') and Total Free Sort (the number of correct verbal descriptions generated by the subject: ''STFS'').

Twenty Questions Test

This test measures verbal categorization and abstract reasoning skills. The child is required to ask the examiner the fewest number of yes/no questions to identify which one of 30 pictures selected by

the examiner. Total number of questions asked served as the outcome measure.

Tower test

This test measures spatial reasoning skills, spatial planning skills, and problem solving skills. The child is required to move discs of varying size across three pegs to build designated towers with the fewest number of moves possible. The dependent measure was total number of moves.

Word context Test

This test measures verbal deductive reasoning skills, integration of information, and flexibility of thinking. The child is given three made-up words, each used in five ''clue sentences.'' Each clue sentence provides additional detailed information about the word. The child is required to guess the meaning of each of the made-up words. Zero to five points are awarded for guessing each word, with more points awarded for guessing the word with fewer clues. The dependent measure was total number of points earned.

Executive Functions Rating Scale

This 17-item instrument was developed to provide a broad range of frontal lobe behaviors and is comprised of three areas: (1) Selection and Execution of Cognitive Plans; (2) Time Management; and (3) Self-Regulation. Items within the three areas are rated by an informant on a scale of 1 (most severely impaired) to 5 (normal, typical functioning) (Sohlberg and Mateer 1989). This measure provided a global index of overall functioning and was given at baseline and week 10 of the open label trial.

Language testing

Expressive One Word Vocabulary Test (Brownell 2000). This is a measure of expressive language in which subjects are asked to name successively presented pictures. The Expressive One Word Vocabulary Test (EOWVT) was given at baseline and weeks 5 and 10. This measure was selected because data from Chez et al. (2003) indicated that significant gains in expressive language (using the EOWVT) were noted with the use of donepezil in 6–9-year-old children with ASD. The result is expressed as a scaled score. The EOWVT was given for both the double-blind study and open label extension.

Memory testing

California Verbal Learning Test-Adult and California Verbal Learning Test–Children's Version. This test provides an assessment of strategies and processes involved in remembering by measuring encoding strategies, learning rates, and error types using both long-term and short-term delay (Delis et al. 1994). Two lists of 16 words are presented to the subject. Free recall of the A list is evaluated over five trials, after which a second, or interference, list is presented. Then, free and category-cued recall of the first list is assessed, followed by a 30-minute delay. After the delay, free recall category recall and recognition memory of the first list are assessed. Percent correct was used as the primary outcome measure. The California Verbal Learning Test-Adult and California Verbal Learning Test–Children's Version was given at baseline, week 5, and 10 during the double-blind study only.

Selective Reminding. The selective reminding assessed short-term auditory memory skills and was used for the open-label trial only (Buschke and Fuld 1974). A list of 14 nouns was read aloud and the subject was asked to recall as many words as possible. Nonrecalled words were repeated by the evaluator, and the subject was again asked to recall the entire list of words. A total of four trials was conducted with the percent of correct answers serving as the primary outcome measure. A set of three parallel versions was used.

Paired-Associate Learning Test. The Paired-Associate Learning Test (Swanson and Kinsbourne 1976) served as a measure of short-time visual memory and was used for the open label trial only. A set of 12 pictures of common objects and numbers was presented, with each picture paired with a unique number. The subject was shown each picture and associated number for 5 seconds. Following a 1 minute break, the subject was randomly presented with a picture and asked to name the correct number. Correct responses were praised and the evaluator provided the correct response whenever the subject was wrong. The set of pictures was reshuffled and presented a total of five times. The percent correct was the primary outcome measure. A set of three parallel versions was used.

Adverse events

Adverse events were assessed by having parents complete a 20-item checklist of the most common side effects for donepezil at each visit. Each adverse event was rated using a 6-point Likert scale: ''0'' (not present); ''1'' and ''2'' (mild); ''3'' and ''4'' (moderate); and ''5'' and ''6'' (severe).

Data analysis

Statistical software, SPSS® (SPSS Inc., Chicago, IL) version 15 with general linear model repeated measures procedures, was used to run a repeated measures analysis of variance (ANOVA). One between-group factor study and one within-subject factor study were used for double-blinded data. Drug condition (drug and placebo) served as the between-group factor and time (baseline, 5 mg dose in week 5, and 10 mg dose in week 10) served as the within subjects factor. Within-subject studies were used for open-label data. A test of sphericity assumption was initially performed and corrections (either Greenhouse-Geisser or Huynh-Feldt) were made to the F test if the assumption was violated. *Post-hoc* tests were conducted where appropriate and the Bonferroni adjustment test was used for pair-wise comparisons.

An intent-to-treatment approach was employed by the last observation being carried forward (LOCF) in cases where subjects did not complete the entire 10-week protocol (typically because of significant adverse side effects). When this occurred, the final observations attained during the either donepezil or placebo phase that was conducted prior to the trial's end were carried forward and included as data for the 5 or 10-week study visit. When no statistically significant different conclusions were found between the repeated measures ANOVA and the LOCF repeated measures ANOVA, the latter was used. A subsequent ANOVA was used to examine the potential effects of age, IQ and autism severity on treatment response.

Finally, a repeated measures ANOVA was used with LOCF for subjects who were unable to complete the open label donepezil trial (for placebo nonresponders). Side effects were examined using descriptive statistics only.

Results

Of 34 subjects randomized for the trial, 31 were able to complete the protocol as designed. Two subjects were found to be unable to

Table 1. Demographic Information

	Placebo (n = *16*)	*Donepezil* (n = *18*)
Age	Mean 11 years 8 months (range 8 years 1 month to 16 years 6 months)	Mean 11 years 6 months (range 8 years 7 months to 16 years 8 months)
ADOS score	Mean 11.2 (range 7–17)	Mean 10.2 (range 7–18)
IQ	Mean 96.7 (range 82–146)	Mean 96.8 (range 73–142)
Gender	14 male; 2 female	17 male; 1 female
Race	14 Caucasian 1 African American 1 other	17 Caucasian 1 other
Concomitant medications	Atomoxetine (1) Adderall (2) Escitalopram (2)	Atomoxetine (1) Adderall (2) Escitalopram (1) Citalopram (1) Sertraline (1)

ADOS = Autism Diagnostic Observation Schedule; IQ = intelligence quotient.

tolerate the 10 mg/day dose and were maintained on a 5 mg/day dose. An additional subject terminated the trial prematurely due to increased aggression and irritability. There were no statistically significant between-group differences found for age, gender, IQ, or ADOS score. Table 1 summarizes the demographic information for the study sample. Mean age for the placebo group was 11 years 8 months and 11 years 6 months for the donepezil group. Full scale IQ means were 96.7 and 96.8, respectively; mean severity of autism symptoms (based upon the Total score on the ADOS) was 11.2 and 10.2, respectively. Of 34 subjects, 11 were prescribed a single concomitant medication during the trial. Two were prescribed atomoxetine, five were treated with an SSRI, and four were prescribed stimulants. All concomitant medication trials had been initiated before subject enrollment and all medication doses were maintained during the donepezil trial.

Table 2 provides a summary of the neuropsychological measures at baseline, 5 mg, and 10 mg/day doses. A second article, focusing on behavioral measures, is currently in press (Hander et al., in press). Significant improvement was noted for a number of variables across time, when comparing both the 5 and 10 mg doses to performance at baseline. However, in most cases improved performance occurred equally for subjects assigned to active medication and subjects assigned to placebo. For example, the percent correct recall on the California Verbal Learning Test-Adult and California Verbal Learning Test–Children's Version improved significantly for both treatment conditions at the 5 mg dose (both $p < 0.05$) and for the active medication group at the 10 mg dose ($p < 0.01$). However, the between-group analysis was not significant. Trail Making Time improved at both the 5 and 10 mg dose for the placebo group ($p < 0.05$ and $p < 0.001$, respectively), but the between-group analysis was not significant. DF switching improved for both treatment groups at the 10 mg dose only, but no between-group differences were found. The potential effects of age, IQ, and autism severity on treatment response also were not found to be statistically significant.

Table 3 provides the neuropsychological test and Executive Functions Rating Scale results for the open label donepezil trial for 14 subjects who had been assigned placebo. With the exception of two measures, no statistically significant improvement on perfor-

Table 2. Neuropsychological Means and Standard Deviations

	Baseline		*5 mg*		*10 mg*		
Dependent measures	*Drug*	*Placebo*	*Drug*	*Placebo*	*Drug*	*Placebo*	*Between-group* p
TMT time[a]	123.6 (56.5)	154.9 (77.8)	125.3 (56.1)	128.7 (50.6)[b]	118.3 (79.1)	104.7 (53.4)[c]	0.72
VF switching	6.83 (3.17)	8.31 (2.73)	—	—	6.17 (5.12)	6.94 (4.97)	0.372
DFT switching	3.44 (2.5)	4.75 (2.79)	4.50 (2.57)	5.37 (2.90)	5.22 (2.69)[b]	4.31 (4.25)[b]	0.57
CWI inhibition/switch[a]	93.3 (38.3)	90.5 (25.4)	92.1 (34.2)	86.6 (20.4)	81.3 (28.9)[b]	79.7 (34.2)[b]	0.74
STCC[d]	6.72 (2.97)	7.19 (1.87)	—	—	5.89 (3.1)	5.69 (4.36)	0.89
STFS[d]	25.2 (11.1)	26.6 (7.6)	—	—	19.4 (11.6)	21.7 (10.9)	0.57
TQT 20 quest total[a]	24.7 (13.7)	18.9 (8.9)	23.2 (11.8)	19.2 (5.2)	22.2 (10.8)	15.1 (8.5)	0.06
TT total[a]	12.1 (4.1)	12.3 (4.9)	14.9 (5.0)[c]	15.4 (3.7)	15.2 (4.7)[b]	14.9 (7.7)[c]	0.94
WCT raw score	4.9 (4.9)	6.1 (3.3)	3.5 (3.4)	3.9 (2.8)[b]	3.0 (3.2)	3.8 (4.9)	0.43
EOWVT standard score	104.6 (22.4)	108.7 (17.0)	107.9 (21.4)[b]	112.7 (17.5)[b]	109.7 (21.0)[c]	114.5 (16.1)[c]	0.50
Memory							
CVLT % correct	40.7 (14.1)	47.1 (10.3)	48.1 (10.8)[e]	52.6 (9.7)[e]	50.2 (11.0)[b]	51.3 (14.7)	0.28

[a]A lower score at the 5 and 10 mg reassessment indicates improvement.
[b]$p < 0.05$.
[c]$p < 0.001$.
[d]These subtests had two versions. The second version (given at 10 mg) appeared to be more difficult, as both groups had poorer performance at the follow-up assessment. WCT was split in a way that it, too, was more difficult at the 5 and 10 mg doses assessments.
[e]$p < 0.01$.

CWI = Color-Word Interference; DFT = Design Fluency Test; EOWVT = Expressive One Word Vocabulary Test; TMT = Trail Making Test; TQT = Twenty Questions Test; TT = Tower Test; VF = Verbal Fluency; WCT = Word Context Test; CVLT = California Verbal Learning Test.

Table 3. Open Label Trial: l Neuropsychological Test Means and Standard Deviations

Dependent measures	*Baseline*	*5 mg*	*10 mg*	p *baseline vs. 5 mg*	p *baseline vs. 10 mg*	p *5 mg vs. 10 mg*
TMT time[a]	108.3 (42.7)	101.5 (48.6)	98.0 (46.2)	0.999	0.809	0.999
VF switching	8.15 (2.73)	—	8.23 (3.79)	—	0.938	—
DFT switching	5.23 (2.59)	5.23 (2.28)	5.69 (2.63)	0.999	0.820	0.999
CWI inhibition/switch[a]	87.4 (23.6)	87.2 (33.1)	84.2 (26.9)	0.999	0.888	0.999
STCC	6.54 (2.11)	—	8.31 (1.70)	—	0.004	—
STFS	23.15 (7.90)	—	30.92 (6.90)	—	0.001	—
EOWVT standard score	110.7 (12.9)	111.6 (14.0)	113.3 (14.4)	0.999	0.156	0.071
Memory						
Selective remind	32.5 (6.1)	36.2 (6.1)	35.8 (7.2)	0.335	0.623	0.999
PAL	36.5 (5.7)	36.1 (8.3)	37.0 (6.1)	0.999	0.999	0.999
Executive Functions Rating Scale						
Cognitive plans	19.46 (5.65)	19.08 (4.80)	19.46 (5.27)	0.999	0.999	0.999
Time management	11.31 (5.01)	11.15 (3.39)	11.62 (5.01)	0.999	0.999	0.999
Self-regulation	17.08 (4.91)	16.15 (4.98)	17.69 (4.59)	0.999	0.999	0.537

[a]A lower score at the 5 mg and 10 mg reassessment indicates improvement.

CWI = Color-Word Interference; DFT = Design Fluency Test; EOWVT = Expressive One Word Vocabulary Test; PAL = Paired-Associate Learning Test; TMT = Trail Making Test; VF = Verbal Fluency.

mance between baseline and either of the two medication doses was found. Conversely, statistically significant gains were found on both the SCTT and STFS between baseline and week 10.

As indicated previously, one subject withdrew from the double-blind study prematurely due to concerns with increased aggression and agitation. He was found to have been assigned to placebo. The majority of subjects reporting side effects at baseline experienced a decrease in those side effects during the study trial itself. These included decreases in reported rates of trouble sleeping, decreased appetite, and depression. The only symptoms that saw a slight increase in rate were diarrhea, headache, and fatigue. Overall, donepezil appeared to be well tolerated; there were no severe adverse events.

Discussion

This article summarizes changes on measures of EF following a double-blind, placebo-controlled trial of donepezil in 34 children and adolescents with ASD. The findings are at odds with the results of other studies of cholinesterase inhibitors and ASD, in which gains in behavioral and/or receptive/expressive language skills were noted (Niederhofer et al. 2002; Chez et al. 2003, 2004; Hertzman 2003; Nicholson et al. 2006). In the current study, subjects tended to improve under both treatment conditions at the 5 and 10 mg doses. While the placebo and active medication groups outperformed each other for some variables, between-group differences were not found to be statistically significant.

There are some possible explanations for the differences between the current study outcomes and that of prior research. For example, Chez et al. (2003) used a much younger age group (2–10 years of age) and the overall medication dose was also lower (2.5 mg). It may be that cognitive enhancers, such as donepezil, have their greatest effects among younger children with ASD who are still in earlier stages of development. Additionally, the possible existence of a therapeutic window might explain the benefits of lower dosages observed by Chez, but not at higher ones as used in the current study. In an attempt to replicate the Chez findings, the EOWVT was included in the current study. Interestingly, we noted significant gains on this test for both the active medication and placebo groups (resulting in no between-group differences). As discussed earlier, the Chez study failed to conduct between-group analyses (only reporting within group statistics). Therefore, it is difficult to accurately interpret the results or to truly compare them with the current study's outcomes.

The other available studies of cognitive enhancers have focused primarily upon changes in behavioral measures or measures of core features of ASD. Consequently, this study represents one of the first efforts to examine changes in neuropsychological functioning. The fact that few subjects displayed global deficits in cognitive functioning at baseline may have made it difficult to obtain significant gains after treatment. Subjects were selected based primarily upon a diagnosis of ASD. Significant deficits across a wide range of EF measures was not an inclusion criteria (only deficits in selected functioning areas). Consequently, there may have been a ceiling effect, or relatively limited room for improvement. It is also possible that improving EF requires a greater period than was allotted in the present study design. It may require an additional 6–12 months before one is able to note the cumulative effect of improved neuropsychological functioning.

As in a number of pharmacological studies in ASD, a robust placebo effect was noted (Handen et al. 2009; King et al. 2009). In the current study, this may be attributable to learning effects following multiple exposures to the assessment tools. The need to repeat the neuropsychological assessments at 5 and 10 weeks presented some methodological obstacles. While some subtests contained two or more parallel versions, these versions did not always prove to be of equal difficulty. For example, the Sorting Test had two parallel versions, which were given only at baseline and week 10. However, the second version appeared to be the more difficult of the two. Other subtests had parallel versions created by dividing up the stimuli. For example, the Word Context Test subtest required subjects to guess a word based upon clues given. We divided the six available words into three versions, so that two different words were used at each assessment. However, it appears that the words selected for the weeks 5 and 10 assessments were more difficult than those selected for baseline. Other subtests, such as the TMT, were given at each assessment using the same stimuli (leading to an expected learning effect).

The open-label study for subjects who had been on placebo during the double-blind trial included some additional short-term memory tests as well as a parent-completed tool assessing EF. No statistically significant gains were found on any of the measures for either the 5 mg or 10 mg dose. Parent questionnaires may not have the needed sensitivity to detect changes in EF over such a short time frame.

The results of the current donepezil trial are inconsistent with prior studies in the area. One reason may be this study's focus on neuropsychological measures. As discussed earlier, there are some possible methodological reasons that could account for the findings. Additional controlled trials of cholinesterase inhibitors should consider focusing on more specific areas of EF deficits and the selection of subjects who display weaknesses in those areas. Also, consideration should be given to having a more extended study period (3–6 month minimum) to insure ample time for treatment to be effective. Yet, it is also possible that cholinesterase inhibitors, when examined carefully via a well-controlled clinical trial, have no real effect on EF within the ASD population. Only through the continued use of well-controlled, double-blind psychopharmacological studies will evidence-based treatments for individuals with ASD be developed.

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