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Relevance of Donepezil in Enhancing Learning and Memory in Special Populations: A Review of the Literature

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Abstract This review discusses the laboratory and clinical research supporting the rationale for the efficacy of donepezil (Aricept® USA) in enhancing cognition in autism, Alzheimer disease, Down syndrome, traumatic brain injury, Attention Deficit Hyperactivity Disorder (ADHD), and schizophrenia. While preliminary animal models have shown effective, human studies exclusive of Alzheimer disease are sparse. Although attention and memory are unlikely a sole operation of the cholinergic system, evidence indicates a promising direction for further examination of this hypothesis in autism. Studies that examine changes in operationally defined behaviors and reliable and valid measure of changes in attention and memory are needed.

Keywords Autism · Donepezil (Aricept) · Acetylcholine

Autism is a pervasive developmental disorder characterized by atypical social and communicative development, and repetitive, stereotyped behaviors (APA, 2000). Mental retardation and associated impairments in attention and visual memory are common in autism (Smith, 1999) (e.g., stimulus over-selectivity, see Reed & Gibson, 2005), and are the premise for treatment with cognitive enhancers (Stahl, 2000; Williams & Saunders, 1997).

Currently, various modes of cognitive enhancement in autism are available. Many treatments are directed at reducing challenging behaviors, thereby indirectly promoting persons with autism to be more amenable to acquisition of language, social skills, and other interventions, which in turn further decrease problem behaviors and enhance cognition (Carr & Durand, 1985; Kahng, Iwata, & Lewin, 2002). Intensive behavior interventions have produced higher mean IQ and increased speech in children with autism than those in the control group (Smith, Eikeseth, Klevstrand, & Lovaas, 1997). Some of these children were reported to be virtually indistinguishable from the typically developing peers (McEachin, Smith, & Lovaas, 1993), substantiating the evidence for cortical reorganization via experience alone (Rosenzweig & Bennett, 1996).

A number of pharmacotherapies have been tried for elevating communicative, social, and behavioral deficits in autism, including the hormone secretin (Owley et al., 1999; 2001) and multivitamins (see Ellis, Singh, & Ruane, 1999 for review). The majority of these proved no better than placebo. Various psychotropics, including stimulants, Serotonin Reuptake Inhibitors, and atypical neuroleptics have also been used to target the core symptoms of autism with mixed results (Lindsay & Aman, 2003). Among these, risperidone in particular has shown effective in treating aberrant behaviors in children autism, including stereotypy and

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hyperactivity. Its effect on social and communication deficits, however, were limited (McCracken et al., 2002).

Attention and memory performance in persons with autism are affected by variables in the environment, yet they are also largely affected by neurochemical factors (Frick, Stearns, Pan, & Berger-Sweeney, 2003). Interactions of several neurotransmitter are known to contribute to these skills, including glutamate, GABA, dopamine, serotonin, norepinephrine, and acetylcholine (Myhrer, 2003; Tsai, 1999). In recent years, acetylcholine (ACh) in particular has been implicated for taking a larger role in attention and memory performance than previously thought (Berger-Sweeney & Hohmann, 1997; Graham, Martin-Ruiz, Teaktong, Ray, & Court, 2002; Lee et al., 2002; Levin, 2000; Mirza & Stolerman, 2000; Paterson & Nordberg, 2000). The purpose of this review is to summarize the research supporting the rationale for the effectiveness of donepezil in enhancing cognition in children with autism.

Learning, Memory, and the Putative Mechanism of ACh

Generally, learning and memory involve neurophysiologic changes resulting from long-term potentiation. These changes occur at the synaptic level in the hippocampal formation (i.e., subicular complex, hippocampus, dentate gyrus) in the limbic cortex located in the temporal lobe (e.g., Kandel, 2001). Long-term potentiation is facilitated by the activation of NMDA and AMPA receptors by glutamate. In order for NMDA receptors to become activated, the receptor must be simultaneously stimulated by glutamate and the neuron must be partially depolarized. Beyond these actions, the mechanism underlying long-term potentiation is not well understood.

ACh is the transmitter at the autonomic ganglia, parasympathetic postganglionic synapses, and the neuromuscular junction, localized in the thalamus and the basal forebrain (Cooper, Bloom, & Roth, 1996; Harris, Courchesne, Townsend, Carper, & Lord, 1999; Stahl, 2000). ACh is produced in the presynaptic neuron and released into the neural cleft, where it is catabolized in 150 microseconds by the enzyme acetylcholinesterase (AChE) to acetate and choline (Cooper et al., 1996). Choline is reabsorbed into the presynaptic neuron, which reconnects it with acetate to form ACh again (Krnjevic & Reinhardt, 1979). A way to increase ACh activity is to decrease the concentrations of AChE via AChE inhibitor such as donepezil, which slows the breakdown of the ACh, thereby increasing the amount of ACh in the neural cleft (Rogers, Yamanishi, & Yamatsu, 1991).

Various reports have indicated disturbances in cerebellar nicotinic ACh (nACh) receptors during early postnatal period resulted in delayed neuronal development and cognitive dysfunction in general (Bauman & Kemper, 1994; Hohmann & Berger-Sweeney, 1998). That is, impaired cholinergic activity during ontogenesis may be related to various forms of developmental disabilities (Court, Martin-Ruiz, Graham, & Perry, 2000). It is hypothesized that changes produced by cognitive enhancers affecting ACh, specifically nACh, affect NMDA receptor function which in turn enhance learning and memory (Narahashi, Moriguchi, Zhao, Marszalec, & Yeh, 2004).

Low levels of ACh have been reported in a small sample of persons with non-autistic MR and Trisomy-21 (Hohman & Berger-Sweeney, 1998; Lee et al., 2002; Prasher, Huxley, & Haque, 2002). Therefore, correcting the low levels of basal forebrain ACh in autism and related disorders may lead to improvements in attention and memory, as cholinergic cerebellar abnormality is strongly implicated in deficits of rapid attention shifts and orientation processes (Lee et al., 2002; Perry et al., 2001; Sarter & Bruno, 1999).

Donepezil (E2020, Aricept^{TM}) is an FDA-approved AChE inhibitor for the treatment of Alzheimer disease (Mori, 2002; Sugimoto, 2001). Prior to donepezil and since 1993, tacrine (Cognex^{TM}) was the only AChE inhibitor approved by the FDA. However, its risk, such as drug-induced hepatotoxicity and elevation of aminotransferase activity, outweighed its benefits, and deterred investigation of ACh in disorders characteristic of cognitive dysfunctions at least partially related to ACh levels, such as autism and other developmental disabilities. Unlike tacrine, however, donepezil has been shown to be safe. Donepezil has high degree of selectivity (≥ 1250-fold) for AChE over butyrylcholinesterase in vitro (this selectivity is absent in tacrine). Such high selectivity leads to improved separation of the desired elevation of ACh in the brain and unwanted peripheral cholinergic effects. Upon oral administration, peak plasma concentration is achieved within 4 h, and the elimination half-life is about 70 h. Therapeutic lag time is estimated at 15 days (FDA, 2000).

Extensive laboratory and clinical trials examining the role of AChE inhibitor for improving attention and memory have been conducted. While preliminary animal models have shown efficacious, animal models do not necessarily generalize to humans, and serious

limitations remain in bridging the gap between species. Thus, the following findings from animal models should be viewed as a building block for human research. However, there are converging lines of evidence to bolster the proposition that donepezil or other indirect or direct cholinergic agonists should be effective in alleviating some core symptoms of autism. We are aware of only a handful of published papers on off-label clinical use of this medication for treatment of autism, so we cannot estimate the frequency of prescription in this population. Internet searches will produce a host of links to discussions and claims of efficacy for treating autism and autism spectrum disorders. There are few published studies to date to support enthusiasm for donepezil treatment for autism.

The summaries of the relevant studies are presented below and in Table 1. Relevant studies were identified by conducting a literature search using the Pubmed database. Specific terms used in our search included: ''donepezil'', ''AChE inhibitor'', ''memory'', ''learning'', in combination with the terms—''rodents'', ''primates'', ''Alzheimer disease'', ''down syndrome'', ''ADHD'', ''traumatic brain injury'', ''schizophrenia'', and ''autism''. Those studies with a stated purpose of determining the effects of donepezil on cognitive performance (e.g., memory, learning, attention, language) in the aforementioned populations were included in this review. Studies using AChE inhibitors other than donepezil were excluded.

Rodents

The largest body of literature on donepezil comes from the rodent literature (McDonald & Overmeier, 1998). Donepezil has shown to improve performance on attention and memory tasks in aged rodents (Barnes et al., 2000; Kosasa, Kuriya, Matsui, & Yamanishi, 1999) and rodents with experimentally induced cholinergic deficits (Tokita, Yamazaki, Yamazaki, Matsuoka, & Mutoh, 2002), especially on the spatial memory task (Luine, Mohan, Tu, & Efange, 2002). These effects are thought to be mediated via nicotinic receptors and possible alterations of dopamine release (Zhang, Zhou, & Dani 2004). Improvements have also been seen in performances on the Morris water maze task (MWM), the hot plate reaction test, the radial eight-arm maze, T-maze continuous alternation task, and the Y-maze, in comparison to placebo (Anderson & Higgins, 1997; Barnes et al., 2000; Nicolodi, Galeotti, Ghelardini, Cartolini, & Sicuteri, 2002; Spowart-Manning & van der Staay, 2004). Performance on a computerized maze showed similar improvements. In particular, accuracy and time to completion were significantly enhanced at a low dose (6 mg/kg), but showed inefficacious at high dose (8 mg/kg), indicating dose-dependent effects (Braida et al., 1998). Additional research has demonstrated that the timing of administration of donepezil may affect performance on memory tasks (Prickaerts, Ş ık, van der Staay, de Vente, & Blokland, 2005). Specifically, the administration of donepezil prior to learning trials, as opposed to after, resulted in improved performances on an object recognition task in a dose dependent fashion.

The effects of donepezil have also been evaluated in rodent models of Alzheimer's disease. In each of the various models of Alzheimer's disease, donepezil was found to improve performance on memory tasks such as spatial discrimination tasks, spatial reversal learning, fear-conditioning, and MWM (Csernansky et al., 2005; Dong et al., 2005; Spowart-Manning & van der Staay, 2005; Van Dam, Abramowski, Staufenbiel, & De Deyn, 2005). Donepezil was also found to show synergistic effects when used in combination with FK960, an experimental AChE inhibitor (Tokita et al., 2002). Moreover, several findings indicate minimal risk for development of tolerance (Levin et al., 1990; Levin & Torry, 1996). Thus far, cumulating work with animals has shown that low ACh levels are strongly related to attention and memory.

Primates

Only three primate studies have been conducted to date. Administration of donepezil in nine young male rhesus monkeys improved the accuracy in spatial and visual recognition tasks (Rupniak, Tye, & Field, 1997). Furthermore, in a 5-week study of donepezil in 12 rhesus monkeys on the delayed match-to-sample task, sex-related differences were found. That is, in males, peak performance required less than half of the dose given to females, possibly implicating gender differences in memory processing and differential physiological response to cholinergic agents (Buccafusco, Jackson, Stone, & Terry, 2003). Finally, the effects of donepezil on AChE levels in the prefrontal cortex of young (5.2 ± 1.1 years) and aged (20.3 ± 2.6 years) macaca mulatta monkeys was evaluated using functional imaging (PET scans), microdialysis, and behavioral cognition tasks (oculomotor delayed response task and visually guided saccade task) (Tsukada et al., 2004). Results revealed that donepezil improved performance on behavioral cognitive tasks for the aged; however, dose-dependent increases of AChE were seen in the prefrontal cortex of the young only. Each of the primate studies reviewed revealed discriminative improvements, and taken together, the studies provide

Table 1 Summary of studies evaluating the effects of donepezil on cognitive performances*

Species Disorder	Author	Design/Procedure/Independent Variable	Dependent variable	Results	Effect size
Rodents	Anderson and Higgins (1997)	Between group assessment; Compared response differences in knockout mice and wild type litter mate controls. Donepezil dose = 2.5–5 mg/kg, scopolamine, & scopolamine methylbromide	Tremor, hypothermia, Morris water maze, Y-maze position bias, choline activity in the brain, coronal sectioning, and plasma cholesterol levels	No behavioral, histochemical, and biochemical differences in two mice types.	N/A
	Braida (1998)	*N* = 8–10 rats; Random assignment to donepezil & tacrine; 7 day tx counterbalanced pre-training to criterion on maze, habituation to injection; 0.25 mg/kg scopolamine to induce deficits, wait 60 min, then 2, 3, 6, 7, & 8 mg/kg donepezil	Errors, duration to complete computerized maze	Parabola-shaped results (error & total time); improvement in memory retention; reduction in errors and time to complete maze with 6 mg/kg	N/A
	Barnes et al. (2000)	Study I: *N* = 27 rats; Determined 60% inhibition of AchE—analogous to therapeutic levels. Pretraining, 85% ad libitum. Study II: *N* = 32 rats; random assignment; Radical 8-arm maze w/30s delay, no delay, session termination after criterion Saline, galantamine, donepezil	Spatial working memory (errors), hippocampal synaptic plasticity & long term potentiation, induction/decay, and nicotine receptor density & affinity	Doses required for 60% inhibition of AChE activity: donepezil = 0.695 mg/day, galantamine = 0.277 mg/day; No significant findings in errors and 30-s delays, significant for pretraining days	N/A
	Luine et al. (2002)	Pre- and post with 5 in each group, including a control group (saline); Chromaproline (n agonist) 270μg/kg/day), chromaperidone (n agonist) 279 μg/kg/day & donepezil 1 mg/kg/day	Visual recognition memory task (object recognition), spatial memory task (object placement), 6-min open field (grid crossing, beh's)	Improvement on both tasks for donepezil only, chromaproline showed improvement in spatial memory after 3 week administration	N/A
	Tokita et al. (2002)	FK960 vs. donepezil and FK 960 + donepezil in rats; Scopolamine 30 mins after habituation trial, NBM lesions, aged rats placed in passive avoidance task FK906, donepezil separate and combined in different knockout rats	Retention latency and percent of rats reaching criterion	FK960 improved all rats; Donepezil improved deficits induced from scopolamine and NBM lesion, but not in old rats; Combination of the two were most optimal	N/A
	Spowart-Manning and van der Staay (2004)	*N* = 60; C57BL/6JIco; Donepezil dose = 0.3, 1, or 3 mg/kg, administered to counter scopolamine 7 groups total (vehicle; various combinations of scopolamine 0.75 or 1mg/kg and donepezil, or 1mg/kg scopolamine and 3mg/kg donepezil)	Performance on T-maze, Continuous Alteration Task	Highest dose of donepezil found to reverse the effects of scopolamine	N/A

Table 1 continued

Species Disorder	Author	Design/Procedure/Independent Variable	Dependent variable	Results	Effect size
	Csernansky et al. (2005)	*N* = 404; C57BL/6Hsd mice pretreated w/ donepezil (0.1, 0.3, 1 mg/kg) then administration of MK-801 (0.05 or 0.1 mg/kg). Also evaluated physostigmine and galantamine	Performance on spatial reversal learning, locomotion, fear conditions, and shock sensitivity	Significant decreases in the number of trials to acquire the spatial learning task and reversal learning, significant increase in freezing behavior, no effect on locomotion or shock sensitivity	N/A
	Dong et al. (2005)	*N* = 32 9-month-old Tg2576 mouse model of AD and control littermates; Donepezil dose = 0.1, 0.3, 1.0 mg/kg, administered over 6 week period. Also evaluated physostigmine and saline	Performance on spatial reversal learning, ambulation, fear conditioning, and foot shock sensitivity	Significant decreases in number of trials to acquire the spatial learning task, reversal learning and increases in fear-conditioning paradigm; no effects on ambulation or shock sensitivity	N/A
	Prickaerts et al. (2005)	*N* = 24, 4-month-old; Donepezil dose = 0.1, 0.3, 1.0 mg/kg, administered before and after first trial. Also evaluated metrifonate and sildenafil	Performance on the object recognition task	No improvements were noted on the task for donepezil treatment that followed the task however, improvements were seen for the highest dose when administered before the task.	N/A
	Van Dam et al. (2005)	*N* = 60, 4-month-old APP23 mice & wildtype; Random assignment to donepezil dose (0.3 or 0.6 mg/kg) Also tested vehicle, memantine, rivastigmine, & galantamine	Performance on the Morris water maze	No differences seen in wildtype mice; Significant effects seen on path length and escape latency for APP23 on both doses of donepezil	N/A
Primates	Rupniak et al. (1997)	*N* = 9 young male rhesus monkeys, 4–5 kg, all familiar with the two tasks; Each animal received all: placebo, 0.003–0.06 mg/kg donepezil, with at least one drug-free day between drugs	Accuracy on spatial and visual recognition tasks	Increase in accuracy from 59% to 71% at 0.03 and 0.05 mg/kg; No observable side effects; Bell-shaped dose-response curve for visual recognition task; Dose-dependent reduction in spatial task, except at 0.06 mg/kg.	N/A
	Buccafuso et al. (2003)	3 females; 3 males 5-week study 4 ascending donepezil doses (0.01–0.1 mg/kg)	Accuracy on color matching-to-sample with zero, short, medium, and long delays	Males: accuracy best at 0.025 mg/kg, and at less than half the dose given to females; Females: increase accuracy after the highest dose	N/A
	Tsukada et al. (2004)	*N* = 5 (5.2 ± 1.1 yrs), *N* = 5 (20.3 ± 2.6 yrs); Male rhesus monkeys; Donepezil or saline (50- or 250μ/kg)	PET scan 45 minutes after donepezil or saline administration; Oculomotor delayed response task and visually guided saccade task were assessed 30 minutes after donepezil or saline	Donepezil produced dose-dependent increases in acetylcholine in frontal cortex of young monkeys and smaller but similar changes in the aged monkeys; dose-dependent improvements in working memory were seen for aged monkeys	N/A

Table 1 continued

Species Disorder	Author	Design/Procedure/Independent Variable	Dependent variable	Results	Effect size
Humans Alzheimer Disease	Rogers and Friedhoff (1996)	*N* = 161, 12-week multi-center, randomized double-blind, parallel-group trial (placebo, 1, 3, or 5 mg donepezil) followed by 2-week single-blind placebo washout	Plasma donepezil concentration, red blood cell acetylcholinesterase activity, ADAS-cog, MMSF	Dose-related improvements in ADAS-cog and MMSF scores	N/A
	Rogers, Farlow, et al. (1998b)	*N* = 473, 24-week multi-center, randomized double-blind, placebo-controlled (placebo, 5, 10 mg donepezil), followed by 6-week washout	ADAS-cog, CIBIC plus, MMSE, CDR-SB, Quality of Life (QoL)	Cognitive and global improvements seen with 5 and 10 mg at 12, 18, and 24 weeks, no difference between groups after 6-week placebo washout	N/A
	Rogers, Doody, et al. (1998a)	*N* = 468, 12 week multi-center, randomized double-blind, placebo controlled parallel group trial (placebo, 5 mg, and 10 mg donepezil) followed by 3-week single-blind washout	ADAS-cog, CIBIC plus, MMSE, donepezil plasma concentration and red blood cell acetylcholinesterase activity	Significant changes in cognitive scores after 3 weeks, global improvements after 9–12 weeks	N/A
	Rogers and Friedhoff (1998)	*N* = 133, multi-center open-label extension study (3–10 mg/day donepezil) following a 14-week double-blind placebo-controlled trial	ADAS-cog, CDR-SB, red blood cell acetylcholinesterase activity	Scores on both measures remained at baseline levels for 26 –38 weeks, then deteriorated thereafter with disease progression	N/A
	Meyer et al. (2002)	*N* = 10, placebo-controlled with comparison group/ 15 months (BL, 3–6 month interval visits); Mean donepezil dose = 9 mg/day	MMSE, CCSE	Cognitive improvements seen post-tx; others without tx continued to decline	MMSE $d = 0.49$; CCSE $d = 0.54$; MMSE annual cognitive changes $d = 0.02$; CCSE annual cognitive changes $d = 0.19$
	Pratt, Perdomo, Surick, and Ieni (2002)	*N* = 1,920, randomized placebo-controlled safety study (placebo, 5 mg, & 10 mg/day donepezil)	Side effects, physical exam and laboratory tests	Adverse events in 11% of donepezil group, 7% in placebo group	N/A
	Pratt et al. (2002)	*N* = 893, selected for vascular dementia, combined analysis of two previous 24-week placebo-controlled study; Donpezil dose = 5 & 10 mg/day	ADAS-cog, CIBIC plus, MMSE	Dose-related improvement on cognition with 10 mg/day, less with 5 mg/day	N/A
	Seltzer et al. (2004)	*N* = 153 (range 50–92 yrs), 24 week multi-center, randomized, double-blind, placebo-controlled; Starting dose = 5mg (6 weeks); Final dose = 10 mg or placebo	Assessments conducted at screening, baseline, and 6 week intervals during treatment on the ADAS cognitive subscale, MMSE, Clinical Dementia Rating Scale-Sum of the Boxes, Computerized Memory Battery Test, and the Apathy Scale	Improvements and or stable responding was noted for donepezil use except on CDR-Sum of the Boxes and Apathy Scale	CMBT: Facial recognition $d = 4$; First & last name total acquisition $d = 2.5$; Name-face association delayed recall $d = 2.0$

Table 1 continued

Species Disorder	Author	Design/Procedure/Independent Variable	Dependent variable	Results	Effect size
	Hashimoto et al. (2005)	*N* = 147 (54 donepezil; 93 control), Prospective cohort study	MRI completed at beginning and end of study; ADAS	Significant effects of donepezil on hippocampal volume (lower atrophy) and on performance on the ADAS	Hippocampal vol. *d* = –0.43; ADAS *d* = –0.64
Down syndrome	Kishnani et al. (1999)	*N* = 4, 6 month open trial; Donepezil dose = 5mg/day for 6 weeks, 10 mg thereafter	Caregiver diary, interviews, global impressions, Vineland Adaptive Behavior Scale (VABS)	Improvements in communication subscale, socialization, and adaptive behavior composite on the VABS	Communication *d* = 2.14; Socialization *d* = 1.09; Adaptive *d* = 2.13
	Lott et al. (2002)	*N* = 15 (9 donepezil; 6 control); 128 day open label controlled trial; Donepezil dose = 5 mg/day for 50 days, 10 mg/day for 78 days	Down Syndrome Dementia Scale	Improvements in dementia scores for donepezil group	N/A
	Prasher et al. (2002)	*N* = 30, 24 week randomized double-blind, placebo-controlled, parallel-group trial; Donepezil dose = 5 mg/day for 4 weeks, 10 mg/day thereafter	Dementia Scale for Mentally Retarded Persons (DMR), Severe Impairment Battery (SIB), Neuropsychiatric Inventory (NPI), and Adaptive Behavior Scale (ABS)	Slight, non-statistically significant improvements in all measures	N/A
	Heller et al. (2003)	*N* = 6, 24 week open trial; Donepezil dose = 5 mg/day for 6 weeks; 10 mg/day thereafter	TOPS, Clinical Evaluation of Language Fundamentals—Revised (CELF)	Improvement in TOPS after 12-weeks; CELF showed no change, but gains were greater in those with higher baseline language skills	N/A
	Prasher et al. (2003)	*N* = 25; Mean ages 51 and 56 yrs; Follow up of Prasher et al. (2002); 80 week open label trial of donepezil; Control and treatment group; Donpezil dose range = 2.5 to 10 mg/day	Outcomes on the Dementia Questionnaire for Mentally Retarded Persons, Severe Impairment Battery, Neuropsychiatric Inventory (NPI), and ABS	For treatment group, decreased rate in decline of dementia and significant decreases on the ABS; improvements on the NPI for both groups	Dementia *d* = –0.42; ABS *d* = 0.66; NPI *d* = –0.19
	Heller et al. (2004)	*N* = 7; Mean age 10.5 (range 8–13 yrs); Open label trial of donepezil; 16-week treatment, 6-week washout; Starting dose 2.5 mg/day; Highest dose 5 mg/day	Pre- post-measures on the Test of Problem Solving Clinical Evaluation of Language Fundamentals-3 (CELF-3)	No differences found on the Test of Problem Solving; Significant increases in expressive and receptive language subscale on the CELF-3; Word structure *d* = 0.44; Formulating sentences *d* = 0.11; Recalling sentences *d* = 0.05	Expressive *d* = 0.24; Receptive *d* = 0.37
	Kondoh et al. (2005)	*N* = 2 (22, 38 yrs); Case study evaluations of donepezil; Assessments completed by caregivers blind to tx dose	Measures on the ABS	Modest improvement in ABS language subscale score for one participant	N/A
Traumatic Brain Injury	Taverni et al. (1998)	*N* = 2; open label study; Donepezil dose = 5 mg/kg	Memory tests, subjective observations	Memory improvement within 3 weeks	N/A
	Whitlock (1999)	*N* = 9 (7 with TBI)	MMSE	3 out of 9 showed 5+ point increase on MMSE	N/A

Table 1 continued

Species Disorder	Author	Design/Procedure/Independent Variable	Dependent variable	Results	Effect size
	Whelan et al. (2000)	*N* = 53 psychiatric patients w/TBI; Retrospective review; Donepezil dose = 5–10 mg/kg	WAIS, Hooper Visual Organiz. Test (*n* = 22)	IQ and ratings showed improvement	WAIS VIQ *d* = 0.40; WAIS PIQ *d* = 0.34; WAIS FSIQ *d* = 0.54; VOT raw *d* = 0.30
	Masanic et al. (2001)	*N* = 4, 16 week open label; Donepezil dose = 5mg/kg/day for 8 weeks, 10 mg/kg for 4 weeks, then 4 week wash-out period	Neuropsyc tests: RAVLT, CFT, RBMT, and NPI	Improved memory, fewer disturbances in behavior	RAVLT: –Learning *d* = 0.34; –Short-term *d* = 0.64; –Long-term *d* = 0.86; CFT: –Short-term *d* = 0.47; –Long-term *d* = 0.44; RBMT *d* = 1.16; RMD *d* = –0.67; RBEMC: –Family *d* = –0.14; –Subject *d* = –0.24
	Bourgeois et al. (2002)	Case report of an adult male hit by a train; donepezil 5mg/day, venlafaxine, 75 mg/kg, risperidone 2mg/qhs	MMSE	MMSE score went from 18 to 28, 29 at follow-up	N/A
	Kaye et al. (2003)	*N* = 10; Mean age=41 (range 26–60 yrs); Open label trial of donepezil; Starting dose = 5 mg (4 weeks), Final dose = 10 mg (4 weeks)	Pre- and post-measures were taken on the Global Memory Scale of the Memory Assessment Scale and CGI	No change in memory	N/A
	Morey et al. (2003)	*N* = 7; ABAC design; B Condition – 5 mg donepezil for 1 month, then up to 10 mg donepezil for 5 months C Condition – 5 mg donepezil for 6 months	Cognitive testing conducted during baseline and after each condition. Brief Visual Memory Test Revised, Hopkins Verbal Learning Test, Digit Span and Letter-Number Sequence subtests of the WAIS-III, Controlled Oral Word Association Test, and Memory Functioning Questionnaire	Significant improvements were obtained for visual memory on the highest dose of donepezil	N/A
	Walker et al. (2004)	*N* = 36; Mean age 32.2 (range 18–58); Young group (18–34 yrs), Middle-age group (38–59 yrs); Retrospective, between/within subjects; Starting dose = 5 mg, increased to 10 mg for some	Data collected during admission and discharge on the Functional Independence Measure Score	No significant differences found	N/A

Table 1 continued

Species Disorder	Author	Design/Procedure/Independent Variable	Dependent variable	Results	Effect size
	Zhang, Plotkin, et al. (2004)	*N* = 18; 24 week randomized, placebo-controlled, double-blind, crossover trial; Starting dose = 5 mg (2 weeks), Final dose = 10 mg (8 weeks); Washout phase (4 weeks), Placebo (10 weeks); Group A (donepezil-placebo) Group B (placebo-donepezil)	Wechsler Memory Scale-Revised and the Paced Auditory Serial Addition Test conducted during baseline and weeks 10 and 24 of the study	Significant increases in scores on both measures obtained for both groups; Differences were maintained for Group A after placebo administration.	N/A
	Khateb et al. (2005)	*N* = 10; Mean age 43 (±8 yrs); 3 month open label trial of donepezil	Measures during baseline and donepezil treatment on fluency tasks, Trail Making Test (A&B), RAVMT, and Test for Attentional Performance	Slight improvements for executive functioning and learning and memory	Executive - Stroop color naming d = –0.41; Learning/mem d = 1.16; Divided atten d = –1.07
ADHD	Hoopes (1999)	2 retrospective case reports of children (ages 11 & 13 yrs) on donepezil for 8+ months, dx with Tourettes & ADHD who did not respond to previous meds; Child 1: donepezil = 2.5 mg/day, Child 2: unknown dose	Parental/teacher and self report	Child 1: Improved tics, less impulsivity, aggression, good grades, making friends; Child 2: calmer, happier, less OCD, better grades and social life; Both report no side effect	N/A
	Wilens et al. (2000)	*N* = 5 (mean age = 13.6; range 8–17 yrs); Retrospective electronic chart review; Children with ADHD who received donepezil for at least 1 week in pediatric psychopharm unit; Donepezil dose (m = 9.5 mg; max = 20 mg)	CGI, dx, meds, donepezil doses, side effects, & responses to donepezil	4 children had comorbid dx, all nonresponders to previous meds, including stimulants; Per parental report, improved organization, mental efficiency, attention; 3/5 participants remained on donepezil at 6 months follow-up	CGI d = –3.2
Schizophrenia	MacEwan et al. (2001)	*N* = 1 (36 yrs); ABAB design; Starting dose = 5 mg (1 week), Final dose = 10 mg (11 weeks); 6 week washout, repeat for additional 12 weeks	North American Adult Reading Test, CPT, RAVLT, Tests A&B; Controlled Oral Word Association Test, WCST, Letter Number Sequencing Test, and Selective Attention Test conducted at baseline and at the end of each phase	Corresponding increases and decreases in performance were obtained for donepezil for word fluency, card sorting performance, & CPT; Scores for other measures remained stable over each phase.	N/A
	Risch et al. (2001)	*N* = 1 (38 yrs); 12 week double-blind, placebo-controlled, cross-over study; Starting dose = 5 mg (6 weeks), Final dose = 10 mg (6 weeks); Washout phase 2 weeks; Olanzapine administered concurrently	Measures taken at baseline, 6 weeks, 12 weeks, 20 weeks, & 26 weeks on the ADAS, cognitive subscale of the WCST, Trail Making A &B, Wechsler Memory Scale-Revised, Grooved Pegboard, and Digit Span of the WAIS-III fMRI and COWAT conducted at baseline and end of placebo	Improvements were found in executive functioning and verbal memory and on the ADAS; During *f*MRI assessment, more words per minute were generated on donepezil with more activity seen in the left dorsolateral prefrontal cortex, temporal lobe, and basal ganglia	N/A

Table 1 continued

Species Disorder	Author	Design/Procedure/Independent Variable	Dependent variable	Results	Effect size
	Buchanan et al. (2002)	*N* = 15; 6 week open label trial of donepezil; Starting dose = 5 mg daily, Highest dose = 10 mg daily; Donepezil adjunctive with olanzapine	Pre- post-measures of P-50 activity, Benton Visual Retention test, RAVLT, Grooved Pegboard, WAIS-III digit symbol, and Gordon Diagnostic System	Moderate improvements observed for verbal recall memory, processing speed, and visual memory; small improvements on P-50 activity	Verbal $d = 0.46$; Processing speed $d = 0.48$; Visual Memory $d = -0.24$; P-50 $d = 0.30$ *Effect sizes as noted by authors
	Friedman et al. (2002)	*N* = 36; 12 week double-blind, parallel-design treatment phase; Starting dose = 5 mg (4 weeks), Final dose = 10 mg (8 weeks); Concurrent use of risperidone allowed, limited use of benzodiazepines	Pre-post measures on the Simple Spatial Working Memory Test, CPT, Trail Making Tests Parts A&B, WCST, RAVLT, and Digit Span Distraction Test	No significant differences between donepezil and placebo found for any of the measures.	N/A
	Howard et al. (2002)	*N* = 1 (54 yrs); Case study; Donepezil dose = 5 & 10 mg/day; Concurrent use of quetiapine, haloperidol, lorazepam, methotrimeprazine, and benztropine	Kaufman Brief Intelligence Test (KBIT), Immediate Face Memory and Logical Memory from the WAIS-III, Trials A, and RAVLT at baseline, 3-, and 6-weeks	Improvements were noted on KBIT, Trials A, Face Memory, and RAVLT	N/A
	Nahas et al. (2003)	*N* = 6 (range 22–53 yrs); 26 week randomized double-blind, cross-over, placebo control; Starting dose = 5mg (6 weeks), Final dose = 10mg (6 weeks); 2 weeks placebo washout; Concurrent use of olanzapine, risperidone, or both	*f*MRI and Controlled Word Association Task during the *f*MRI taken during baseline, and at 12 & 26 weeks	No significant differences in performance on the Controlled Word Association Task for the group although individual differences were found; Increases in left frontal lobe and cingulate activity were found with donepezil	N/A
	Stryjer et al. (2003)	*N* = 6 (range 54–74 yrs); Single-blind design; Donepezil dose = 5 mg (4 weeks); All patients stable on antipsychotic medication	Pre- and post-treatment measures on the MMSE and ADAS cognitive subscale	All but one patient showed improvements on the MMSE; Four patients showed improvements on the ADAS cognitive subscale	MMSE $d = 0.56$; ADAS $d = -0.22$
	Tuğal et al. (2004)	*N* = 12; 12 week double-blind, placebo-controlled, cross-over study; Donepezil dose = 5 mg	Wechsler Memory Scale-Revised, Trail A&B, and WCST at baseline, 6 weeks, and 12 weeks	Treatment not significant for any of the cognitive measures	N/A
	Erickson et al. (2005)	*N* = 24 (range 20–60 yrs); 18 week double-blind, crossover study; 8 weeks on drug 8 weeks on placebo 2 week wash-out; Donepezil dose= 5 mg	Measures taken during baseline, treatment, and post treatment on cognitive functioning using the RAVLT, Trail A&B tests of executive functioning	Improvements reported on the RAVLT for the group who received donepezil first then placebo; No differences found for donepezil on the Trials A&B tests	N/A
	Freudenreich et al. (2005)	*N* = 30; Mean age 48.7 (range 24–64 yrs); 8 week parallel-group, placebo-controlled, double-blind study; Starting dose = 5 mg, (4 weeks) Final dose = 10 mg (4 weeks)	Measures taken at baseline and then 2, 4, 8 weeks on Digit Span subtest of the WAIS-III, Hopkins Verbal Learning Test-Revised, Trail A&B; Benton Oral Word Association Test, and Grooved Pegboard Test	No significant differences found for any of the cognitive measures	N/A

Table 1 continued

Species Disorder	Author	Design/Procedure/Independent Variable	Dependent variable	Results	Effect size
Autism	Hardan (2002)	*N* = 8 (mean age=11; range 7–19 yrs); systematic chart review of patients seen once/month; Review of dx, demographics, vital signs, other meds—only included if they were kept constant, donepezil given only if other interventions and at least 2 other meds failed; Dx: dev disability & donepezil (all but 1 child on 10 mg)	Pre-post ABC, retrospective CGI completed after chart review by experimenters, side effects	4/8 participants were responders, statistically significant improvement on CGI (4.3 v. 3.7) and ABC (varied for each subscale)	CGI d = 0.67; ABC: –Irritability d = –0.83; –Lethargy d = –0.50; –Hyperactivity d = –0.88
	Niederhofer et al. (2002)	*N* = 20; Mean age 7.4 yrs; Randomized, Placebo-controlled, double-blind crossover trial of galantamine	Pre- post-measures on the ABC	Decreased ratings during galantamine treatment on irritability, hyperactivity, inadequate eye contact, and inappropriate speech	Irritability d = –0.47; Hyperactivity d = –0.35; Eye contact d = –0.25; Inappr. speech d = –0.48
	Chez et al. (2003)	*N* = 43; Mean age 6.8 (range 2.1–10.3 yrs); 6-week randomized double-blind, placebo-controlled trial followed by 6-week open trial	CARS, Gardner's Expressive & Receptive One-Word Picture Vocabulary Test-Revised	Improvements seen in scores of expressive and receptive language and in CARS	CARS d = –0.29; Expressive d = 0.13; Receptive d = 0.37
	Hertzman (2003)	*N* = 3 (21, 32, 42 yrs); Case study evaluations of galantamine; Starting dose = 4 mg/day, Highest dose = 16 mg/day	Clinical impressions of verbal fluency	Improvements reported in speech and cognition	N/A
	Chez et al. (2004)	*N* = 32; Mean age 6.9 (range 2.9–12 yrs); 12 week open trial of rivastigmine tartrate; Starting dose = 0.8 mg/day, Highest dose = 1.6 mg/day	Pre- post-measures on Gardner's Expressive and Receptive One-Word Picture Vocabulary test, CARS, and Conners' Parent Rating Scale	Significant improvements were obtained for the CARS, Expressive One-Word Picture Vocabulary test, and the Conners' Parent Rating Scale	CARS d = –0.44; Vocabulary test d = 0.08; Conners' d = –0.62

* Although some studies tested drugs other than donepezil, we are presenting the findings for donepezil only in this table with the exception of the autism studies of AChE inhibitors

** Only variables relevant to cognitive processes are listed in the table

*** CARS (Childhood Autism Rating Scale); ABS (Adaptive Behavior Scale); CPT (Continuous Performance Test); RAVLT (Rey Auditory Verbal Learning Test); WAIS-III (Wechsler Adult Intelligence Scale-Revised); MMSE (Mini-Mental State Examination); ADAS (Alzheimer's Disease Assessment Scale); WCST (Wisconsin Card Sorting Test)

**** Effect sizes reported were determined by dividing the differences between group means by treatment group's standard deviation and were reported when means and standard deviations were provided by authors

support for the use of donepezil for improving accuracy for cognitive tasks.

Humans

Alzheimer Disease (AD)

The degree of memory loss in old age is strongly correlated with decline in ACh levels (Mori, 2002; Perry et al., 1978; White & Ruske, 2002). A comparison of postmortem brains of patients with AD with normal, non-afflicted age-matched individuals revealed significantly lower levels of ACh and AChE (Paterson & Nordberg, 2000). Examination of parts of the brain rich in ACh neurons (i.e., cerebral cortex to basal nucleus) revealed a massive degeneration in these areas, leading to a conclusion that ACh in the basal nucleus is responsible for memory decline in AD (Coyle, Price, & deLong, 1983; Davis & Maloney, 1976). Subsequent studies have also shown low levels of receptor binding (Davis, Doyle, Carroll, Emmerling, & Jaen, 1995; Giacobini, 1993).

Support for this finding is also evident from studies of the ACh antagonists mecamylamine and scopolamine, both of which readily cross the blood-brain barrier. Healthy, typical adults given scopolamine showed deficiencies in the same memory tasks that were most difficult for those with AD (Newhouse, Potter, Corwin, & Lenox, 1992). Administration of drugs that inhibit AChE (e.g., donepezil) reversed this memory deficit (Nordberg, 2001; Rusted, Graupner, O'Connell, & Nicholls, 1994; van Reekum, Black, Conn, & Clarke, 1997). Rapidly cumulating literature indicate therapeutic responses occurred in majority of the participants with AD as measured by several rating scales, such as the Mini-Mental State Exam (MMSE) (e.g., Bullock & Dengiz, 2005; Seltzer et al., 2004; Whitehead et al., 2004). Research findings have also demonstrated that donepezil improves attention in those diagnosed with AD (Foldi, White, & Schaefer, 2005). Furthermore, donepezil has been found to decrease hippocampal atrophy when compared to control patients (Hashimoto et al., 2005). Minimal side effects were reported across studies (Meyer, Chowdhury, Xu, Li, & Wuach, 2002; Pratt, Perdomo, Surick, & Ieni, 2002, Pratt, Perdomo, & The donepezil VaD 307 and 308 study groups, 2002; Rogers et al., 1996, 1998a, 1998b, 1998c).

Down Syndrome (DS)

A substantial number of individuals with DS show symptoms of AD by age 40, and their neuropathological evidence postmortem is virtually indistinguishable from those with AD alone (Mann, 1988; Mann & Esiri, 1989). In comparison to other developmental disabilities, persons with DS are five times more likely to develop dementia (Zigman et al., 1995), and males with DS are three times more likely to develop AD than females (Schupf et al., 1998).

Several studies have shown effectiveness of donepezil in the treatment of cognitive decline related to dementia in DS. In two cases of adults with DS, improvements were noted on scores on the Adaptive Behavior Scale (ABS) with a dose of 3 mg/day of donepezil (Kondoh et al., 2005). In a 24-week open trial of 5 and 10 mg donepezil in 6 adults with DS aged 20 to 41 years, improvements were noted in the expressive language performance as measured by Test of Problem Solving (TOPS). Transient side effects included diarrhea, nausea, decreased appetite, cramps, and hypotension on the 10 mg (Heller et al., 2003). Another open trial in 4 adults with DS showed improvements in communication, expressive language, attention, and mood according to the Clinical Global Impression scores (CGI; NIMH, 1985) and the caregiver reports. Side effects included agitation and diarrhea, but they disappeared with continued treatment (Kishnani et al., 1999). Significant improvements in ''cognitive functioning'' were also observed in 6 participants according to the Down Syndrome Dementia Scale during a 5-month nonrandomized trial of donepezil (Lott, Osann, Doran, & Nelson, 2002).

A 24-week, randomized, double-blind, placebo-controlled trial of donepezil in 27 adults with DS and AD showed less deterioration for the treatment group in comparison to the placebo group, according to the Dementia Scale for Mentally Retarded Persons (DMR), which covers short and long term memory. Severe Impairment Battery and the Adaptive Behavior Scale showed similar results. However, the scores on the Neuropsychiatric Inventory showed no significant improvement with donepezil treatment. Common side effects included diarrhea, insomnia, fatigue, and nausea (Prasher et al., 2002). Following participation in this medication trial, participants were provided with the opportunity to enroll in an open label study of donepezil treatment (Prasher et al., 2003). After a total of 104 weeks, those individuals that continued donepezil treatment showed less of a decline in dementia than those who had never been on donepezil; however, no individual performed as well as they did during baseline.

Finally, research has been conducted to evaluate the effects of donepezil on language in children with DS (Heller et al., 2004). Children between 8 and 13 years of age participated in a 22-week open-clinical trial.

Preliminary results have revealed that the use of donepezil resulted in improvement in selective areas of language, with significant improvements in expressive language, especially on word and sentence structures, and near significant improvements in receptive language. Furthermore, none of the participants were reported to have experienced adverse side effects.

Traumatic Brain Injury (TBI)

Although the exact mechanism of the therapeutic effects observed in TBI with donepezil is unknown, the working hypothesis is that severe insult to the brain leads to disruptions in the various neurotransmitter systems, including the cholinergic system (Hayes, Lyeth, & Jenkins, 1989). Nonetheless, results of the effectiveness of donepezil have been mixed. There have been open-label reports of improved memory in persons with TBI treated with donepezil (e.g., Bourgeois, Bahadur, & Minjares, 2002; Masanic, Bayley, van Reekum, & Simard, 2001; Morey, Cilo, Berry, & Cusik, 2003; Taverni, Seliger, & Lichtman, 1998; Whitlock, 1999). For example, Whelan, Walker, and Schultz (2000) examined 5 and 10 mg/day donepezil in 53 persons with TBI for 2 years. Positive effects were reported as measured by the MMSE and increased IQ scores. Zhang, Plotkin, Wang, Sandel, and Lee (2004) found that donepezil improved short-term memory and attending as assessed by the Auditory Immediate Index (AII) and the Visual Immediate Index (VII) of the Wechsler Memory Scale-III and the Paced Auditory Serial Addition Test (PASAT). However, in a study by Kaye, Townsend, and Ivins (2003), there were no improvements in memory although participants did report improvement in processing speed. In another study, Walker et al. (2004) found no significant improvements in cognition as measured on the Functional Independence Measure Score (FIM) between those on donepezil and controls. In addition to memory and processing-speed improvements, donepezil, as well as other AChE inhibitors, have been found to improve attention and have been associated with an overall increased ability to concentrate, improvements in learning and divided attention (Khateb, Ammann, Annoni, & Diserens, 2005; Tenovuo, 2005; Zhang et al., 2004). Decreases in behavioral disturbances have also been reported, as measured by the Neuropsychiatric Inventory (Masanic et al., 2001).

Attention Deficit Hyperactivity Disorder (ADHD).

Abnormal catecholaminergic neurotransmission has been reported in persons with ADHD (Conners et al., 1996; Levin, 1992; Levin et al., 1996). The basis for the use of cholinergic agents in persons with ADHD also comes from reports of improvement in attention with trials of an ACh agonist, nicotine (Levin, 1992; Levin et al., 1996; Wilens, Biederman, Wong, Spencer, & Prince, 2000). Limited, uncontrolled, retrospective studies of the use of AChE inhibitors in ADHD are available. Wilens et al. (2000) examined 5 children with ADHD receiving an average of 9.5 mg/day donepezil and other concurrent medications. All children were nonresponders to other classes of medication, including stimulants. According to parental report and the CGI scale scores, children showed improvements in organization, mental efficiency, and attention. Learning and memory were not objectively measured. One of the 5 children reported diarrhea as a side effect. No drug interactions were reported. Three of the 5 children remained on donepezil at a 6-month follow-up.

Similar results were found in two children with ADHD and Tourettes (Hoopes, 1999). Per parent, teacher, and self-report, the children were calmer, happier, and making better grades with 2.5 mg/kg donepezil treatment. Decrease in tics, impulsivity, aggression, and obsessive-compulsive behaviors were also noted. Again, no apparent side effects were reported. Hoopes (1999) speculated that ACh may decrease dopamine levels thereby proving efficacious in treating co-occurrence of ADHD and Tourettes.

Schizophrenia

Progressive cognitive dysfunction is a common characteristic associated with schizophrenia. The use of donepezil has been evaluated for the remediation of these cognitive deficits. The basis for the hypothesized potential effectiveness of donepezil in schizophrenia is that cognitive deficits are presumed to be caused by cholinergic reductions at muscarinic and nicotinic receptors (Stryjer et al., 2003). (Nicotinic cholinergic receptors are involved in the process of sensory information processing.) To date, the results of various trials of donepezil have been mixed. The combined use of donepezil and antipsychotic treatment was associated with improvements in cognitive function as reflected by increases in scores on the MMSE, CGI, and other assessments that measure verbal learning (Erickson et al., 2005; Howard, Thornton, Altman, & Honer 2002; Stryjer et al., 2003). Additionally, *f*MRI studies have evaluated the effects of donepezil on brain activity. Risch et al. (2001) found increased activation of the prefrontal cortex and the basal ganglia, and improvements on cognitive assessments typically used to assess AD such as the Alzheimer's Disease Assessment

Scale (ADAS). A second imaging study found increased activity of the left frontal lobe and cingulate and improvements on the Controlled Word Association Task (COWAT) (Nahas et al., 2003). Other studies have found improvements on select behavioral and cognitive assessments. For example, Buchanan, Summerfelt, Tek, and Gold (2002) attained the most significant effects for donepezil on a task that measured dexterity (Grooved Pegboard) and modest effects on cognitive performance such as verbal recall, processing speed, and visual memory. Another study evaluated the effects of donepezil on various assessments of cognition using a reversal design (ABAB) (MacEwan, Ehmann, Khanbhai, & Wrixon, 2001). These results revealed improvements word fluency when on donepezil. However, there are also studies conducted using a double-blind, placebo-control design that have not found any improvements in cognitive performance associated with donepezil use (Friedman et al., 2002, Freudenreich et al., 2005; Tuğal, Yazıcı, Yazıcıoğlu, & Göğüş, 2004).

Autism

The potential mechanism of action of donepezil on autism is to increase ACh at the central sites (i.e., cerebral cortex and basal forebrain) that affect attention and memory. This is especially apropos, given a postmortem study by Perry et al. (2001) indicating a substantially lower (30%) cortical muscarinic 1 receptor binding in the parietal cortex in the autism sample than levels observed in the matched-controls. Furthermore, the brain-derived neurotrophic factor in the basal forebrain was three times higher in the autism sample than in the matched-controls. Low levels of cytosolic choline concentration (i.e., choline/creatine ratio) measured by hydrogen proton magnetic resonance spectroscopy was related to severity on the Children's Autistic Rating Scale scores (r = .66, p = .04) in 10 children with autism (Sokol, Dunn, Edwards-Brown, & Feinberg, 2002).

Hardan and Handen (2002) retrospectively examined donepezil in 8 children with autism, age 7–19 years. Mean optimal dose was 9.37 mg/day. Results showed statistically significant decrease in irritability and hyperactivity according to the Aberrant Behavior Checklist (ABC) and the CGI scores. Effects on attention and memory were not measured. Two of the 8 children experienced transient adverse effects (i.e., vomiting, irritability). Because of the absence of experimental design, inadequate measurement of behavior change, and administration of concomitant medications, isolating the effects of donepezil is problematic.

A single controlled study (Chez et al., 2003) has been published to date. It examined donepezil (2.5 mg/day) in 43 children with autism or pervasive developmental disorder, ages 2–10 years. A 6-week double-blind, randomized parallel group (placebo vs. 2.5 mg/day donepezil) design was used, followed by a 6-week open trial with 2.5 mg donepezil in both groups. The study reported significant improvements in receptive and expressive language scores, and improved ratings of autistic symptoms as assessed via Childhood Autism Rating Scale (CARS) scores in both groups following 6 weeks of active drug. The study concluded that "these improvements were statistically significant when compared to placebo"(p. 83) and donepezil appears to improve language and overall autistic features lending support to cholinergic enhancement treatments. These conclusions must be interpreted with caution, however, because the between groups, placebo vs. drug data were not analyzed. The conclusions were based on analyses of pooled non-blinded baseline vs. blinded and non-blinded assessments, and within-group analyses. The latter analyses showed the largest constant effects on within group comparisons of non-blinded baseline and non-blinded 12 week, active drug phases. No statistical analyses were made between the placebo group and drug group data. A close examination of the data shows that the results of the controlled portion of the study (i.e., the 6 week assessments) showed a greater improvement in autistic symptoms for the placebo group over the active drug group. Because of the lack of comparisons of blinded drug conditions with blinded placebo conditions, this study is susceptible to the same potential confounds as all open label studies, such as placebo effects. The results are suggestive but not conclusive.

The data from the two studies above are suggestive that cholinergic enhancement treatment may reduce symptoms of autism. To date, there are no data from controlled comparisons of donepezil to verify the efficacy of such treatments, and hence donepezil should be considered as experimental and speculative. Additional studies have been conducted to evaluate the effects of two other cholinesterase inhibitors, rivastigmine tartrate and galantamine, on language and cognition in those with autism (Chez et al., 2004; Hertzman, 2003). In a 12-week open-label study of rivastigmine tartate, Chez et al. (2004) found significant improvements in scores of various measurements (Childhood Autism Rating Scale, Gardner's Expressive One-word Picture Vocabulary Test, and the Conners' Parent Rating Scale). Hertzman (2003) reported three cases involving the prescription of galantamine to promote verbalization in adults with autism. Each patient

showed marked improvement in verbalization and in some cases, social behavior. One individual experienced side effects and discontinued treatment with galantamine and attempted a trial of donepezil; however, use of donepezil resulted in regression of skills. Using the Aberrant Behavior Checklist as a dependent measure during a placebo-controlled, double-blind crossover randomized controlled trial of galantamine, Niederhofer et al. (2002) found decreases in irritability, hyperactivity, inadequate eye contact, and inappropriate speech in children with autism.

Discussion

Taken together, the data from the preclinical and clinical studies reviewed above are suggestive that cholinergic enhancement treatment may efficacious in reducing the symptoms of autism. However, the results appear to be mixed within several of the populations studied and the designs used to evaluate the effectiveness of donepezil are varied from study to study. Furthermore, measures of learning and memory were not specifically targeted in these trials. Rather, measures were limited to parental reports and their responses to rating scales. Other studies measured more global changes such as language and mood. Therefore, the specific changes reported in these studies cannot be isolated or directly attributed to learning and memory.

Across the clinical populations, those studies employing a more rigorous methodology appear to demonstrate improvements in symptoms for some disorders (i.e., Alzheimer's disease, Down Syndrome) and mixed results were obtained for other populations (i.e., traumatic brain injury, schizophrenia). In addition, to date, there are no data from controlled comparisons of donepezil to verify the efficacy of such treatments, and thus, donepezil should be considered as experimental and speculative.

A general criticism of AChE inhibitors is their limited effects on additional neurotransmitter systems also involved in memory (e.g., nicotinic acetylcholine and NMDA receptors) (Narahashi et al., 2004). Additional studies have evaluated the effects of various other AChE inhibitors on cognitive functioning and the effects of donepezil in combination with other drugs (e.g., monoamine oxidase-B inhibitor, NMDA antagonists). In rats with scopolamine induced memory impairments, the combined use of selegiline, a monoamine oxidase-B inhibitor, and donepezil significantly improved performance times in the MWM (Takahata, Minami, Kusumoto, Shimazu, & Yoneda, 2005). Future research should perhaps evaluate the effects of AChE inhibitors in combination with other drugs to determine if combined use of drugs yields significant improvements in cognitive functioning than the sole use of AChE inhibitors.

As reviewed above, the impact of cholinergic abnormality is consistent across species, in addition to the evidence supporting the efficacy of AChE inhibitor in reversing such impact with minimal safety risks. Caution should be taken, however, in simply extrapolating animal models to humans. Differences in phylogeny and ontogeny certainly preclude such generalization, in addition to the absence of an animal model for cognitive deficits in autism.

In addition to cautioning about generalization of effects across species, caution should also be taken regarding the general results. Of the 55 studies included in this review, seven studies reported a lack of improvements on any of their dependent measures. Although an overwhelming majority of the studies reviewed provided evidence supporting the use of donepezil and only a few presented a lack of support for the beneficial effects of donepezil on cognition, we cannot overlook the possibility that additional studies with similar findings exist but have either not been submitted for publication or accepted for publication. Remedying this possible "file drawer" effect (Rosenthal, 1991) would empirically strengthen this area of study.

An operating assumption in the literature is that agents effective in treating deficits stemming from low levels of ACh in persons without autism will be similarly effective in treating these conditions in persons with autism. Currently, such support for their use in persons with autism lack the use of convincing experimental design, sensitive, valid, and reliable measures, and sufficient sample size to evaluate efficacy in persons with autism. Although attention and memory are unlikely a sole operation of the cholinergic system, evidence to date indicates a promising direction for further examination of this hypothesis. Studies that examine changes in operationally defined behaviors and reliable and valid measure of changes in attention and memory are needed, as even a minute improvement in concentration and memory can be of functional significance in this population.

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