Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2007;24:28–35
DOI: 10.1159/000102569

Accepted: February 28, 2006
Published online: May 10, 2007

Cognitive Predictors of Donepezil Therapy Response in Alzheimer Disease

Daniel Saumier[a, f] Susan Murtha[c] Howard Bergman[a, f] Natalie Phillips[d, e] Victor Whitehead[a] Howard Chertkow[a, b, e, f]

[a]Bloomfield Centre for Research in Aging and Lady Davis Institute, McGill University, and [b]Centre de Recherche, Institut Universitaire de Gériatrie de Montréal, Montréal, Que., [c]Department of Psychology, York University, Toronto Ont., [d]Department of Psychology, Concordia University, [e]Department of Clinical Neurosciences and the Division of Geriatric Medicine, Sir Mortimer B. Davis-Jewish General Hospital, and [f]Department of Neurology and Neurosurgery, McGill University, Montreal, Que., Canada

Key Words
Alzheimer's Disease · Donepezil · Treatment outcome

Abstract
Objectives: To examine whether the presence of domain-specific cognitive impairments would predict a response to donepezil medication in patients with mild-to-moderate Alzheimer disease (AD). ***Methods:*** The protocol was an open-label study of 30 AD subjects (mean age 74 years; education 11 years; Mini-Mental State Exam (MMSE) 23 of 30) beginning a 6-month course of treatment with donepezil. Global response to treatment was determined using a combination algorithm based on changes over 6 months in the ADAS-cog, MMSE and CIBIC. In addition, a set of neuropsychological and experimental cognitive tests designed to test five domains of cognition were administered before beginning therapy in order to determine which domain of testing would be predictive to response to treatment. The tests examined attention, short-term and working memory, learning and memory, visuo-spatial motor skills, and lexical-semantic knowledge. ***Results:*** Eighteen of the thirty subjects were rated as having responded (stable or improved scores on the combination algorithm) to the therapy. Responders were significantly less impaired prior to treatment on the following tests: the Clock Drawing Test, a Visual-Spatial Motor Tracking Test, and the Boston Picture Naming Test. No significant initial group differences were noted on the other neuropsychological or experimental cognitive measures. ***Conclusion:*** The tests that most reliably predicted response to donepezil in AD subjects were in the domains of visual-spatial motor abilities and lexical-semantic functioning.

Introduction

The only class of prescription medication indicated for mild-to-moderate Alzheimer disease (AD) is treatment with cholinesterase inhibitors [1–7]. The administration of acetylcholinesterase inhibitors (tetrahydroaminoacridine (THA), donepezil, rivastigmine, galantamine) in randomized controlled clinical trials has been found to moderately improve test performance on global measures of dementia, such as the Mini-Men-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1420–8008/07/0241–0028$23.50/0

Accessible online at:
www.karger.com/dem

Howard Chertkow
Bloomfiel Centre for Research in Aging
Sir Mortimer B. Davis-Jewish General Hospital
McGill University, Montreal, Quebec, H3T 1E2 (Canada)
Tel. +1 414 340 8260, Fax +1 514 340 8295, E-Mail howard.chertkow@mcgill.ca

tal State Exam, (MMSE) [8], the Alzheimer Disease Assessment Scale – cognitive sub-scale (ADAS-cog) [9], and the Clinician-based evaluation of change (CIBIC) [5]. While global response and improvement occur, however, the efficacy of these medications is variable and moderate, with improvement rates that vary from 20 to 60% [4, 10, 11].

The variable response rates to cholinesterase inhibitors in AD patients provide a strong rationale for the development of correlate measures that can predict improvement in cognitive outcome. Careful scientific studies of a variety of potential correlate and predictor measures have begun to emerge in recent years (see [12] for review). These have included apoliprotein genotyping [7, 13–17] pretreatment measures of postural blood pressure reduction [18, 19] quantitative electroencephalography (qEEG) [20, 21], behavioral assessments [22], neuroimaging [23], and disease progression rate [24]. While qEEG profiling has shown promising results [12], most of the other correlate measures have been found to be poor predictors of cognitive response. However, pretreatment cognitive measures of AD which reflect the status of an individual's cholinergic system may have value in predicting response to treatment with ChEIs. While some studies have examined cognitive markers of treatment in terms of global measures such as the Mini-Mental State examination, there are virtually no studies that have specifically looked across widespread cognitive domains to evaluate whether there are specific aspects of cognition which predict cholinergic treatment response.

The fundamental goal of the current study is to characterize the response of ChEI therapy in terms of measures of and individual's cognitive function, and to derive cognitive measures that may predict which individuals will respond best to the therapy. Detailed domain-specific standardized neuropsychological and experimental cognitive tests were used to predict response to donepezil (Aricept, Pfizer). The tests utilized assessed five domains of cognition that have been previously found to be impaired in AD individuals. They included attention, short-term and working memory, visual-spatial motor abilities, learning and memory, and lexical-semantic knowledge. The development of cholinesterase inhibitors has been predicated on the notion that cholinergic function is important in learning and memory in the normal human brain [25]. In addition, there is evidence of a cholinergic basis to attention [26–30] and lexical-semantic knowledge [31]. The degree to which acetylcholine is involved in normal function of the other domains is largely unknown.

Measures used in the current trial were initially tested on a group of AD subjects prior to a 6-month open-label therapeutic trial with the acetylcholinesterase inhibitor donepezil. Therapeutic response to the cholinesterase inhibitor treatment was then carefully gauged on the basis of three global measures: the MMSE, the ADAS-cog, and the CIBIC. The key question addressed was whether results on tests run of prior to treatment would predict 6-month response to donepezil treatment, as assessed by the global measures.

Materials and Methods

Assessment and Selection of Subjects

Thirty-four subjects with AD were recruited from the Sir Mortimer D. Davis Jewish General Hospital Memory Clinic, a tertiary medical center referral clinic. Diagnosis of 'probable AD' or 'possible AD' was established according to diagnostic criteria for dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition revised (DSM-III-R) [32], and all subjects were diagnosed as having probable AD according to standard clinical criteria [33]. Standard blood work and neuroimaging (CT or MRI) were also carried out, and the diagnosis was supported by abnormal performance on neuropsychological testing. Global severity of the dementia was ascertained on the basis of the ADAS-cog, MMSE and CIBIC. Subjects were excluded from the study if they were without a reliable caregiver. Also excluded were subjects who had already began donepezil therapy or other cholinesterase inhibitors or cognitive enhancing medications, were receiving medications that were considered to be contraindications to donepezil, or who were taking anti-hypertensive or other cardiac drugs. Finally, subjects were not recruited if they had intrinsic cardiac disease (arrhythmia, intraventricular conduction defects, evidence of cardiac ischemia, cardiomyopathy), or serious systemic disease (e.g. malignancy, uncontrolled hypertension, or neuropathy or seizure disorder). All subjects were judged competent to give consent by their treating physicians. They all signed an informed consent form approved by the McGill University or Jewish General Hospital ethics committees prior to clinical and neuropsychological testing.

Neuropsychological and Experimental Cognitive Testing

Two sets of tests were completed by all subjects prior to the donepezil treatment period. The first set included generally utilized standardized neuropsychological tests of attention, short-term and working memory, learning and memory, visual-spatial motor abilities, and lexical-semantic knowledge. However, since standard paper and pencil neuropsychological tests assessing cognition tend to be less sensitive to cognitive alteration, and are more influenced by variables such as fatigue, stress and depression, cholinergically based cognitive impairments may remain undetected unless adequately assessed with reaction time measures. Thus, in addition to the neuropsychological testing, the current study also included experimental cognitive tasks involving reaction time (RT) measures. The following is a brief description of these tests.

(1) Attention: The neuropsychological tests of attention included the Mental Control sub-scale of the Wechsler Adult Intelligence Scale-revised (WAIS-R) [34].

The RT cognitive measures of attention included the five following tests: a Choice Reaction Time Test, a Stroop Test, a Stroop Picture Naming Test, and a Visual Search Test. The Choice Reaction Time Test is a measure of selective attention. The test requires subjects to attend to two possible stimuli (e.g. numbers 1 or 2) and respond accordingly by pressing one of two response options (e.g. left or right button). General effects of psychomotor speed and response preparation were factored out from the Choice Reaction Time Task by requiring subjects to perform a simple reaction time task and a cued choice reaction time task. In the simple reaction time task, subjects pressed a button upon the presentation of a single stimulus (a dot), while the cued choice reaction time task required pressing a button for a validly cued stimulus (No. 1 or No. 2 stimulus cue presented before target 1 or target 2 was presented, respectively). In order to factor out general effects of psychomotor speed and response preparation between groups, search performance was determined for each subject by calculating the ratio of choice/simple reaction mean reaction times and the ratio of cued/simple mean times, respectively. Overall reaction time performance was then estimated on the basis of an average of these two measures. A similar measure was also obtained for error rates.

The Stroop Test assesses the ability to attend to relevant information while ignoring distracting information. In particular, the test measures the interfering effect of naming the ink color of color names when the ink colors and words are incongruent (e.g. responding 'red' for the word 'blue' printed in red ink). There were 24 colored color words randomly presented in a 4×6 line array. Subjects responded as quickly and as accurately as possible and the time to name all items in the word array was recorded.

The Stroop Picture Naming Test is similar to the Stroop Test in that it requires subjects to attend to relevant information while ignoring distracting information. However, in the Stroop Picture Naming Test, subjects viewed computerized presentations of letter strings presented within animal drawings, where each letter string could represent the name of the pictured animal (congruous condition), the name of a different animal (incongruous condition), or a sequence of x's (neutral condition). Subjects were required to name as quickly and as accurately as possible the pictured object while ignoring the embedded letter string. For each subject, the interference of the distracting information was assessed on the basis of an algorithm that incorporated the reaction times obtained in the congruous, incongruous, and neutral conditions. The measure of interference was calculated in the following manner:

Incongruent RT – [(congruent * neutral)/(congruent + neutral)].

In the Visual Search Task, selective attention is evaluated by having subjects search for a predetermined target (a checkered circle) from among either 0, 2, 4, 6, or 12 distractor shapes, where the target is actually present on 50% of the trials. Targets and distractors could be discriminated from each other on the basis of either one (simple) or two (conjoined) visual characteristics. The relative difference in reaction times and error rates between the simple and conjoined search conditions (collapsed across array size and target-present and target-absent conditions) for each subject served as an overall measure of visual search performance.

(2) Visual-Spatial Motor Abilities: The Clock Drawing Test [35] and the WAIS Block Design Test [34] were used as standardized neuropsychological measures of visual-spatial motor abilities.

The experimental cognitive tests of visual-spatial motor abilities involved a computerized Tracking Test. This test required subjects to manually track a moving target box on a computer screen using a computer mouse while performing an increasingly difficult concurrent secondary task (counting, detecting auditory signals, repeating sets of auditorily presented numbers). Tracking performance was based on the average percentage of time subjects were able to maintain the cursor within the target box across the secondary task conditions.

(3) Short-Term and Working Memory: Three standardized neuropsychological measures of short-term and working memory were administered. These included the Logical Memory I and Digit Symbol subscales of the WAIS [34], and the Visual Memory Span subscales of the Wechsler Memory Scale. The experimental cognitive test included the Brown-Peterson Task [36, 37]. This task required subjects to recall a series of visually presented consonant trigrams after 0-, 5- or 10-second delay intervals. During the 5- and 10-second interval trials, subjects either rehearsed the trigrams, or performed a secondary concurrent verbal task (repeatedly articulating a letter, or a digit reversal task). Memory performance was assessed by calculating the average % correctly recalled items for each subject across the three delay and secondary task conditions.

(4) Learning and Memory: The Visual Memory Span subscale of the Wechsler Memory Scale, the Logical Memory II subscale of the Wechsler Adult Intelligence Scale (WAIS II-R) [38], and the delayed recall index of the Rey Auditory Verbal Learning Test (RAVLT) [39] were used as standardized neuropsychological measures of learning and memory. There was no experimental cognitive test of learning and memory.

(5) Lexical-Semantic Knowledge: Three neuropsychological and five experimental cognitive RT measures were used to test lexical-semantic knowledge. The neuropsychological measures consisted of the Boston Naming Test [40], Letter Word Fluency, and the Similarities subtest of the WAIS [38]. The cognitive RT measures included computerized versions of the PAL (Psycholinguistic Assessment of Language) Picture Naming Test [41], a Lexical Decision Task, a Primed Lexical Decision Task, a Word-to-Picture Matching Test, and Semantic Probes Test [41]. The following provides a brief summary of the computerized cognitive tests.

In the PAL Picture Naming Test, subjects were required to name 32 line drawings of objects sampled from biological (i.e. different items of animals, fruits, or vegetables) and non-biological (i.e. tools, vehicles) categories. The Word-Picture Matching Test required subjects to match as rapidly as possible each of the line drawings presented in the PAL Picture Naming Test to a written word that may or may not correspond to the pictured item. The Semantic Probes Test involved having subjects judge whether auditory statements about biological and nonbiological objects were true or false. The statements pertained to object properties that were either perceptual (e.g. Carrot: 'Is this orange?') or nonperceptual (e.g. Dog: 'Does this eat hay?'). Performance on the PAL picture Naming Test, the Word-Picture Matching Test and the Auditory Probes Test was evaluated by measuring the average reaction time and error rate over all items for each subject in each task.

In the Lexical Decision Task, subjects were asked to decide as quickly as possible whether written-letter sequences were legitimate English words or not. The items included equal numbers of real words and pronounceable non-words. The real words included balanced samples of high and low frequency words. The Primed Lexical-Decision Task required subjects to perform a lexical-decision task to words or non-words that were preceded by semantically associated or nonassociated words (i.e. primes). Previous investigations involving neurologically healthy subjects show that lexical-decision latencies may be significantly reduced when preceded by semantically associated word primes, relative to nonassociated primes [42]. Alzheimer's subjects have been shown to produce abnormal priming effects [43, 44], which are presumed to reflect semantic memory deficits in these individuals. Performance on the Lexical Decision and Primed Lexical Decision tasks were separately assessed by averaging the reaction times and number of errors over all items for each subject within each test. The primary effect in the Primed Lexical Decision task was determined by subtracting the associated prime reaction times and the nonassociated prime reaction times.

Donepezil Therapy and Treatment Assessment

Subjects were treated with donepezil, administered and monitored in the context of an open-label drug trial. An initial dose of 5 mg daily was given for 1 month, and then increased in all cases to 10 mg daily for another 5 months.

Donepezil treatment effects were assessed using the MMSE, ADAS-cog, and CIBIC-plus measures. The three measures were assessed at time 1 (T1) prior to treatment, and time 2 (T2) after 6 months therapy. We calculated a ratio algorithm for each measure, namely T2 score minus T1 score/initial T1 score. For the ADAS-cog, which has a maximum score of 70, we used T1-T2 in order to maintain all deteriorations as negative changes. A percentage change was then calculated for all three measures. Thus, for example, if a subject's MMSE increased from 21 to 24, the ratio score would be (24 minus 21/21) or a 14.3% improvement (positive change). To avoid overweighting the ADAS-cog measure, the denominator was estimated as 70 minus T1 ADAS-cog score. For instance, if the ADAS-cog at T1 was 20 and at T2 was 10, we did not consider this to be a 50% (10/20) improvement, but rather a 20% (10/50) improvement. The CIBIC, by definition, is a change score, with no score assigned at initial presentation. Given that on the CIBIC, a score of 4 = 'no change', 3 = 'mild decline', and 5 = 'mild improvement', we assigned an arbitrary baseline score of 4 at T1. The donepezil response algorithm was based on the mean of the three percentage change values for each subject. Subjects obtaining a score of 0 or greater were considered as being stable or improving and thus were classified as responders. This cutoff score was deemed practical but conservative, given that AD is a degenerative disease marked by progressive cognitive decline. Thus, subjects demonstrating mild decline (i.e. decreases of less than 5%) may have arguably been considered as responding favorably to treatment as well.

Data Analysis

Separate t tests were used to compare responders and nonresponders on each of the neuropsychological and experimental cognitive tests administered at T1. The t tests were evaluated using separate group variances. In order to control for Type I error, analyses within each domain of cognition examined (attention, working memory, visual-spatial motor, learning and memory, lexical semantics) were evaluated using a critical alpha value of $p < 0.05/n$, where n corresponds to the number of comparisons performed within each domain of neuropsychological or RT cognitive tests administered. Analyses of the latency data were based on median reaction times in order to control for latency outliers.

Table 1. Demographic values and scores for the global treatment measure (MMSE, ADAS-cog, CIBIC) for responders and nonresponders

	Responders	Nonresponders
n	18 (7 F–11 M)	12 (9 F–3 M)
Age (range)	74.1 ± 8.2 (54–87)	74.7 ± 8.8 (57–85)
Education (range)	10.6 ± 3.7 (5–20)	11.0 ± 3.4 (5–16)
MMSE (range)	22.8 ± 2.5 (18–26)	23.1 ± 3.0 (18–27)
ADAS-cog (range)	19 ± 5.9 (9–33)	23 ± 6.7 (13–35)
CIBIC (range)	4.8 ± 0.6 (4–6)	3.1 ± 0.7 (2–4)

Results

Of the 34 subjects treated for therapy, 4 discontinued treatment during the course of the study, prior to the final assessment. The reasons for discontinuation were as follows: One subject refused to continue with the study, and dropped out during the course of the 6 months at week 24; a second subject, within 2 months of enrollment, was found to have had an unsuspected pancreatic carcinoma and was discontinued from the study. Two subjects developed side effects. One experienced a decrease in appetite and became fatigued. The event was assessed as 'possibly related' to the study drug. The other patient was discontinued after 12 weeks of study medication after he experienced diarrhea and fecal incontinence. This side effect was assessed as 'probably related' to the study drug. The remaining 30 subjects completed the study, receiving medication for the full 6-month period. None of these subjects reported adverse side effects, or had other serious illness intervene. All tolerated 10 mg of donepezil daily.

On the basis of the response algorithm, 18 (60%) of the 30 subjects were classified as responders, while 12 were classified as nonresponders (table 1). There was no difference in initial age, education, initial MMSE, ADAS-cog, or CIBIC scores between responders and nonresponders. However, men were over-represented among the responders (11/18) vs. nonresponders (3/12).

Table 2. Average scores and SDs for the neuropsychological and cognitive measures in responders and nonresponders

	Responders	Nonresponders level	Significance
Standardized neuropsychological tests			
Attention			
Mental control (/6)	4.3 ± 1.3	3.9 ± 1.6	n.s.
Working memory			
Logical memory 1	3.7 ± 2.5	1.9 ± 2.4	n.s.
Spatial span	10.9 ± 4.0	11.3 ± 4.3	n.s.
Digit symbol	25.2 ± 11.7	17.0 ± 12.1	n.s.
Brown-Peterson (% overall trigrams recalled)	77.6 ± 12.9	80.4 ± 14.7	n.s.
Visual-spatial motor			
Clock drawing	6.9 ± 2.4	5.0 ± 1.6	*
Block design	11.2 ± 8.0	9.3 ± 8.3	n.s.
Learning and memory			
Logical memory delayed	1.0 ± 2.0	0.1 ± 0.3	n.s.
RAVLT delayed recall	1.9 ± 1.7	0.5 ± 0.9	n.s.
Lexical-semantic functioning			
Boston naming test (/60)	41.6 ± 11.0	27.9 ± 14.2	**
Fluency (mean number of items)	34.1 ± 13.5	27.6 ± 14.8	n.s.
Similarities	11.8 ± 6.5	7.4 ± 5.8	n.s.
Reaction time tests			
Attention			
Stroop colored color word RT's	62.6 ± 9.8	78.1 ± 12.8	n.s.
Stroop colored color word error rate, %	25.0 ± 0.06	34.6 ± 0.08	n.s.
Mean simple/choice RT and cued/choice RT	0.83 ± 0.09	0.29 ± 0.08	n.s.
Visual search (conjoined – simple search rates)	74.1 ± 43.6	79.6 ± 43.4	n.s.
Visual search (conjoined – simple error rate %)	11.0 ± 15.7	5.4 ± 5.3	n.s.
Stroop picture naming interference[a]	954.3 ± 481.4	781.7 ± 206.7	n.s.
Stroop picture naming error rate, %	9.1 ± 8.8	9.5 ± 13.1	n.s.
Visual-spatial motor abilities			
Tracking (average % time on target)	49.2 ± 10.3	42.6 ± 7.4	*
Lexical-semantic functioning			
Lexical decision RT, ms	2,012.7 ± 1,626.6	2,032.0 ± 1,135.4	n.s.
Lexical decision error rate, %	10.2 ± 10.4	11.8 ± 12.7	n.s.
Primed lexical decision RT, ms	–16.6 ± 268.1	134.5 ± 93.9	n.s.
Primed lexical decision error rate, %	1.8 ± 2.0	3.0 ± 3.3	n.s.
Picture naming RT, ms	1,491.2 ± 558.0	1,593.5 ± 470.3	n.s.
Picture naming error rate, %	32.9 ± 16.2	44.3 ± 17.5	n.s.
Semantic probes RT, ms	1,824.0 ± 696.5	1,363.3 ± 1,050.9	n.s.
Semantic probes error rate, %	15.3 ± 6.9	16.0 ± 4.0	n.s.
Word-picture matching RT, ms	3,057.1 ± 3,935.4	3,105.7 ± 2,192.7	n.s.

n.s. = Not significant; * $p < 0.05$; ** $p < 0.01$. [a] Interference = (Incongruent RT – [(congruent * neutral)/(congruent + neutral)]; Priming effect = Associated Prime RT – Nonassociated Prime RT.

Three subjects in the nonresponders group showed only mild decline (decrease of 1, 3, and 5%) in overall mean treatment score. It is arguable that these subjects were showing a marginal response to donepezil as well. A more liberal treatment criterion would thus have indicated that 21 (70%) of the 30 subjects responded favorably to the treatment. However, we retain the initial classification of response to treatment.

Neuropsychological Predictors of Donepezil Response

Across the standardized neuropsychological and experimental cognitive measures, an average of 1.7

(range = 0–3) of subjects were not able to complete one or more of the tests. Among the experimental tasks, an additional 12 subject data sets were lost across the Stroop Picture Naming Test (4 subjects), the Visual-Spatial Tracking Test (4 subjects), and the Primed Lexical Decision Test (3 subjects) due to technical problems at testing sessions. All score values (means, medians in the case of the RT measures, and standard deviations) are shown in table 2.

Attention. The t test comparing responders and nonresponders on the mental control measure of attention failed to reveal a significant difference ($p > 0.05$).

Short-Term and Working Memory. The t test comparisons on the neuropsychological tests of working memory were evaluated at alpha = 0.05/3 = 0.017. These tests did not indicate significant differences between responders and nonresponders for either the Logical Memory I Test ($p > 0.05$), the Visual Memory Span Test ($p > 0.05$), or the Digit Symbol Test ($p > 0.05$).

Visual-Spatial Motor Ability. Separate t tests performed on each of the visual-spatial motor abilities tests were evaluated at alpha = 0.05/2 = 0.025. Responders and nonresponders did not differ on the Block Design Test ($p > 0.05$). However, responders were significantly less impaired than nonresponders on the Clock Drawing Test ($t(26.7) = 2.9$, $p < 0.025$).

Learning and Episodic Memory. t test comparisons (at alpha = 0.05/2 = 0.025) indicated that responders and nonresponders did not differ in their performance on either the RAVLT-delayed recall index ($p > 0.05$), or the Logical Memory II Test ($p > 0.05$).

Lexical-Semantic Knowledge. Comparisons between responders and nonresponders on each neuropsychological test (using a critical alpha value of 0.05/3 = 0.017) indicated a significant difference on the Boston Naming Test ($t(17.3) = 2.7$, $p < 0.017$). No significant differences were obtained between responders and nonresponders on either the Letter Word Fluency Test ($p > 0.05$) or the Similarities subtest of the WAIS ($p > 0.05$).

Experimental Cognitive Test Predictors of Donepezil Response

Attention. On all cognitive tests of attention (Visual Search, Stroop, Word-Picture Stroop, Choice Reaction Time), no detectable difference was noted between responders and nonresponders on any of the t tests (using a critical alpha value of 0.05/4 = 0.013).

Short-Term and Working Memory. There was no detectable difference between responders and nonresponders on the Brown-Peterson task ($p > 0.05$).

Visual-Spatial Motor Ability. In the Tracking Task, responders were on target a significantly greater percentage of the time than nonresponders ($t(22.1) = 2.7$, $p < 0.05$).

Lexical-Semantic Knowledge. The t tests comparing responders and nonresponders on the cognitive tests of lexical-semantic knowledge were evaluated at alpha = 0.05/5 = 0.01. None of the tests demonstrated statistically significant differences between responders and nonresponders (all $p > 0.05$). However, there was a nonsignificant trend indicating that responders produced fewer errors than nonresponders on the PAL Picture Naming Test ($t(16.0) = 2.5$, $p < 0.1$). A more detailed inspection of the error data revealed that responders were significantly less impaired than nonresponders for pictures depicting living things ($p < 0.05$).

Assessing Degree of Performance Overlap between Responders and Nonresponders

In order to assess the degree to which the significant predictor measures discriminated between responders and nonresponders, we calculated the percentage of responders that performed more than 1 SD from the mean nonresponder performance, based on the nonresponders' mean and SD. The percentages of responders performing more than one standard deviation away from of nonresponder mean performance on each test were the following: Clock Drawing Test: 56%; Boston Naming Test 40%; Visual-Spatial Tracking Task: 50%.

Discussion

The present study is the first empirical attempt to use a broad range of fine-grained cognitive tests as a means to investigate cognitive predictors of response to cholinergic therapy in a cohort of AD subjects. On the basis of the 6-month donepezil treatment trial, 60% subjects responded favorably to donepezil (i.e. stable or improved global cognitive scores), while a more liberal estimate suggested that 70% were treatment responders. While our numbers were not sufficient to statistically demonstrate a gender effect, there was a predominance of males among donepezil responders. This unexpected finding corroborates a previous cholinergic treatment study using tacrine and galantamine, which showed that men have a 73% greater likelihood of responding than women [15]. Thus, it may be that sex is an important predictor of cholinesterase inhibitor treatment outcome.

We find (within a narrow range of subjects with MMSE greater than 18) no significant differences between re-

sponders and nonresponders on pretreatment MMSE, ADAS-cog, or CIBIC measures. This suggests that while these global measures are able to demonstrate the outcome of treatment effects in studies of individuals treated with cholinesterase inhibitors, individually they do not sufficiently predict treatment outcome.

The main goal of the study was to determine if specific cognitive task performance might be predictive of response to donepezil. On objective neuropsychological and experimental cognitive tests, quite specific cognitive performance was indeed found to be predictive of whether or not an AD subject was a donepezil responder. The measures that showed significant differences between responders and nonresponders were the Clock Drawing Test, a Tracking Speed Test, and the Boston Naming Test. Moreover, there were non-significant trends suggesting that the cognitive measures of picture naming predicted treatment outcome – a trend that was significant when the test was limited to items that depicted biological objects. However, contrary to expectation, better performance on these tasks prior to therapy was associated with a greater likelihood of becoming a donepezil responder. These findings suggest that better task performance in the domains of visual-spatial abilities and lexical-semantic knowledge predict eventual donepezil response. No significant group differences were found on other tests within these domains, or on other tests of attention, learning and episodic memory, or working memory.

In no one cognitive or neuropsychological task, however, was separation clear enough for it to be used alone as a predictor of response. Across the three predictive measures, between 40 and 56% of responders performed outside 1 SD of the nonresponders' average scores. Thus, while statistically significant differences in performance were obtained between responders and nonresponders on the Clock Drawing, Tracking, and Boston Naming tests, the similarity in response scores among the two groups suggests that these tests have a moderate level of sensitivity in predicting treatment response.

We conclude that while global measures of donepezil treatment response are useful in validly capturing general changes in cognition and functioning in AD patients, they fail to predict eventual treatment outcome. In contrast, the results suggest that specific tests of spatial abilities and lexical-semantic knowledge may be more sensitive pretreatment predictors of response to donepezil therapy in these patients. Such tests are applicable in a clinical setting and may help clinicians in assessing which patients are most likely to benefit from donepezil medication. While cognitive performance on these specific tests may not be clear-cut enough to alter a clinician's decision to administer donepezil to a patient, such test scores may nonetheless prove to be useful as adjunct measures in predicting cognitive response to donepezil treatment. It may be fruitful for future investigations to examine cognitive predictors of response with other types of cholinesterase inhibitors.

Acknowledgements

This work was supported by a grant from the Medical Research Council (MRC) [now the CIHR (Canadian Institutes of Health Research)] and the PMAC (Pharmaceutical Manufacturers of Canada) to H. Chertkow. Funding of the PMAC component of the grant originated with Pfizer Canada. H. Chertkow is a chercheur national of the FRSQ. Daniel Saumier was supported by the Alzheimer's Society of Canada.

References

1 Gauthier S, et al: Tetrahydroaminoacridine-lecithin combination treatment in patients with intermediate-stage Alzheimer's disease: Results of a Canadian double-blind cross-over, multicenter study. N Engl J Med 1990;322:1272–1276.

2 Farlow M, et al: A controlled trial of tacrine in Alzheimer's disease. The Tacrine Study Group. JAMA 1992;268:2523–2529.

3 Weinstock M: The pharmacotherapy of Alzheimer's disease based on the cholinergic hypothesis: an update. Neurodegeneration 1995;4:349–356.

4 Rogers SL, Friedhoff LT, the Donepezil Study Group: The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicentre, randomized, double-blind, placebo-controlled trial. The Donepezil Study Group. Dementia 1996;7:293–303.

5 Bryson HM, Benfield P: Donepezil. Drugs Aging 1997;10:234–239.

6 Robbins TW, et al: Cognitive enhancers in theory and practice: studies of the cholinergic hypothesis of cognitive deficits in Alzheimer's disease. Behav Brain Res 1997;83:15–23.

7 Winblad B, et al: A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001;57:489–495.

8 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

9 Rosen W, et al: A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364.

10 Soares JC, Gershon S: THA – historical aspects, review of pharmacological properties and therapeutic effects. Dementia 1995;6:225–234.

11 Parnetti LU, Senin U, Mecocci P: Cognitive enhancement therapy for Alzheimer's disease: the way forward. Drugs 1997;53:752–768.
12 Lanctot KL, Herrmann N, Loulou MM: Correlates of response to acetylcholinersterase inhibitor therapy in Alzheimer's disease. J Psychiatry Neurosci 2003;28:13–26.
13 Poirier J, et al: Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. Proc Natl Acad Sci USA 1995;92:12260–12264.
14 Farlow MR, et al: Treatment outcome of tacrine therapy depends on apolipoprotein genotype and gender of the subjects with Alzheimer's disease. Neurology 1998;50:669–677.
15 MacGowan, SH, Wilcock GK, Scott M: Effect of gender and apolipoprotein E genotype on response to anticholinesterase therapy in Alzheimer's disease. Int J Geriatr Psychiatry 1998;13:625–630.
16 Wilcock GK, Lilienfeld S, Gaens E: Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ 2000;321:1445–1449.
17 Almkvist O, Winblad B: Early diagnosis of Alzheimer dementia based on clinical and biological factors. Eur Arch Psychiatry Clin Neurosci 1999;249(suppl 3):3–9.
18 Schneider LS, et al: Do blood pressure and age predict response to tacrine (THA) in Alzheimer's disease? A preliminary report. Psychopharmacology Bulletin 1991;27:309–314.
19 Pomara ND, Deptula, Singh M: Pre-treatment postural blood pressure drop as a possible predictor of response to the cholinesterase inhibitor velnacrine (HP 029) in Alzheimer's disease. Psychopharmacol Bull 1991;27:301–307.
20 Alhainen K, Riekkinen PJ: Discrimination of Alzheimer patients responding to cholinesterase inhibitor therapy. Acta Neurol Scand 1993;88(suppl 149):16–21.
21 Almkvist O, et al: Responder characteristics to a single oral dose of cholinesterase inhibitor: a double-blind placebo controlled study with tacrine in Alzheimer patients. Dement Geriatr Cogn Dis 2001;12:22–32.
22 Mega MS, et al: The spectrum of behavioral responses to cholinesterase inhibitor therapy in alzheimer disease. Arch Neurol 1999;56:1388–1393.
23 Mega M, et al: Orbital and dorsolateral frontal perfusion defect associated with behavioral response to cholinesterase inhibitor therapy in Alzheimer's disease. J Neuropsychiatry Clin Neurosci 2000;12:208–218.
24 Farlow M, et al: Response of patients with Alzheimer disease to rivastigmine treatment is predicted by the rate of disease progression. Arch Neurol 2001;58:417–422.
25 Whitehouse PJ, et al: Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science 1982;215:1237–1239.
26 Callaway E, Halliday R, Naylor H: Cholinergic activity and constraints on information processing. Biol Psychol 1992;33:1–22.
27 Parasuraman R, Greenwood PM, Alexander GE: Alzheimer disease constricts the dynamic range of spatial attention in visual search. Neuropsychologia 2000;38:1126–1135.
28 Sahakian B, et al: The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the Alzheimer type [see comments]. Br J Psychiatry 1989;154:797–800.
29 Sahakian BJ, Coull JT: Tetrahydroaminoacridine (THA) in Alzheimer's disease: an assessment of attentional and mnemonic function using CANTAB. Acta Neurol Scand Suppl 1993;149:29–35.
30 Sahakian BJ, et al: Further analysis of the cognitive effects of tetrahydroaminoacridine (THA) in Alzheimer's disease: assessment of attentional and mnemonic function using CANTAB. Psychopharmacology 1993;110:395–401.
31 Chertkow H, et al: Cognitive and biological correlates of response to donepezil in Alzheimer's disease. Neurobiol Aging 2000;21(suppl 1):S24.
32 APA: APA Diagnostic and Statistical Manual of Mental Disorders, ed 4: DSM-IV. Washington, American Psychiatric Association, 1994.
33 McKann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health Services Task Force on Alzheimer's disease. Neurology 1984;34:939–944.
34 Wechsler D: Wechsler Adult Intelligence Scale – revised. New York, Psychological Corporation, 1981.
35 Tuokko H, et al: The Clock Test: A sensitive measure to differentiate normal elderly from those with Alzheimer disease. J Am Geriatr Soc 1992;40:579–584.
36 Brown J: Some tests of the decay theory of immediate memory. Q J Exp Psychol 1958;10:12–21.
37 Peterson LR, Peterson MJ: Short term retention of individual verbal items. J Exp Psychol 1959;58:193–198.
38 Wechsler D: Wechsler Memory Scale – revised. San Antonio, Psychological Corporation, 1987.
39 Geffen G, et al: Performance measures of 16- to 86-year-old males and females on the Auditory Verbal Learning Task. Clin Neuropsychol 1990;4:45–63.
40 Kaplan E, Goodglass H, Weintraub S: The Boston Naming Test. Philadelphia, Lea & Febiger, 1983.
41 Caplan D: Language: Structure, Processing, and Disorders. Cambridge, MIT Press, 1992, p 515.
42 De Groot AMB, Thomassen AJ, Hudson PTW: Primed lexical decision: the effect of varying stimulus-onset asynchrony of prime and target. Acta Psychol 1986;16:17–36.
43 Chertkow H, Bruemmer A, Bub DN: Automatic changes in semantic priming in dementia of the Alzheimer's type. Meeting Canadian Association of Gerontology, 1989.
44 Chertkow H, et al: Increased semantic priming in patients with dementia of the Alzheimer's type. J Clin Exp Neuropsychol 1994;16:608–622.