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The effect of cholinesterase inhibitors on decline in multiple functional domains in Alzheimer's disease: a two-year observational study in the Sunnybrook dementia cohort

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ABSTRACT

Background: Despite widespread use of second-generation cholinesterase inhibitors (CHEIs) for the symptomatic treatment of Alzheimer's disease (AD), little is known about possible long-term effects in different functional domains. This study seeks to assess change in activities of daily living (ADLs) over two years in AD patients treated with CHEIs matched to untreated patients in the same longitudinal cohort study.

Methods: This study is based on the two-year prospective cohort study at the Memory Clinic in Sunnybrook Health Sciences Centre, University of Toronto. Probable AD patients (N = 130: untreated = 65, treated = 65) underwent standardized neuropsychological assessments including the Disability Assessment for Dementia Scale (DAD), at baseline, one-year and two-year follow-up. Groups received a careful evaluation of comorbid illnesses, concomitant medication use, and vascular risk factors.

Results: At baseline, there were no significant differences in demographics and characteristics. Treated patients showed less decline in overall function and in instrumental and basic ADLs. Furthermore, less decline was seen in the overall scores for initiation and planning over two years with moderate to large effect sizes.

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Conclusion: These findings have clinical relevance since functional ability has been increasingly recognized as a key outcome variable in AD treatment. It is also of note that the subscores reflecting executive functioning appear to drive these beneficial differences.

Key words: functional decline, instrumental ADL, basic ADL, Disability Assessment for Dementia Scale (DAD), executive function, Alzheimer's disease

Introduction

Alzheimer's disease (AD) is a neuro-degenerative disorder characterized by progressive decline in cognition that is invariably accompanied by functional deterioration. A commonly used indicator of functional impairment is the decline in performance of activities of daily living (ADL). Measures of ADL have been used as secondary outcomes in many clinical trials of three to six months' duration (Tariot *et al.*, 2000). The Federal drug Administration requires that clinical trials demonstrate a beneficial effect on a performance-based cognitive instrument and a global measure of function. Since functional disability in AD is an important determinant of patient and caregiver distress and costs of care, European and Canadian regulatory guidelines have recognized the importance of the function domain and consider it a primary outcome variable when assessing treatment benefits (Mohr *et al.*, 1995). The National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and the Diagnostic and Statistical Manual 4th Edition (DSM-IV) also identify the assessment of functional performance as an important element of a comprehensive diagnostic evaluation for AD (McKhann *et al.*, 1984; American Psychiatric Association, 1994).

Impairment in the ability to perform ADL often develops gradually in AD and may first appear when the cognitive deficits are still mild. In the early stages of AD, complex tasks such as maintaining a job, and instrumental ADL (IADL), such as leisure activities, housework, and finance begin to deteriorate. In later stages, progressive loss of autonomy in basic ADL (BADL) self-care tasks, such as dressing, eating and personal hygiene is observed (Gelinas *et al.*, 1999). The loss of ADL skills has been described in a hierarchy, beginning with spontaneous initiation, then planning and organization, and finally effective performance of a given task. The performance of both IADL and BADL requires the use of one or more executive skills, including the ability to initiate, plan and organize, and effectively execute an activity (Boyle, 2004). These subcomponents are separately scored on the Disability Assessment for Dementia scale (DAD), which has been used in several clinical treatment trials.

This characteristic pattern of loss of IADL and BADL can have a profound impact on both the AD patient and the caregiver. It may lead to feelings of frustration, anxiety, aggression, loss of self-esteem and a poorer quality of life. As a result, the patient may exhibit social withdrawal and be at a greater risk for harm. Furthermore, this progressive functional decline in AD patients

necessitates ever-increasing supervision and assistance from the caregiver. The resulting burden of care may create psychological, emotional and physical stress for the caregiver (Lingler *et al.*, 2005). Functional decline and caregiver burden are critical factors in the decision to institutionalize AD patients (Severson *et al.*, 1994; Geldmacher *et al.*, 2003). Therefore, drugs that can enhance or preserve AD patients' ability to perform IADL and BADL may not only contribute to a better quality of life for the patient but also decreased caregiver burden and reduced costs of patient care.

Three second-generation CHEIs have been on the market for the symptomatic treatment of mild to moderate probable AD. Although there are a few trials over one year, most studies have assessed short-term benefits over 3 to 6 months (Lanctôt *et al.*, 2003). Results suggest treatment benefits in overall functional ability over the short-term compared with placebo. Although these studies demonstrate beneficial effects on overall functional abilities, treatment benefits on specific functional losses have been assessed in a few 6-month studies (Feldman *et al.*, 2001; 2003). Treated AD patients show less decline in IADL and BADL and also in the components of initiation, planning and performance (Feldman *et al.*, 2001; 2003).

Four double-blind, randomized, placebo-controlled trials have investigated the efficacy of continued CHEI treatment over one year (Winblad *et al.*, 2001; Mohs *et al.*, 2001; Karaman *et al.*, 2005) and two years (Courtney *et al.*, 2004). While these studies demonstrated benefits in overall functional abilities in treated patients, treatment effects on the subcomponents were not separately assessed. The non-pharmaceutical sponsored AD2000 study revealed less decline in treated patients on the Bristol activities of daily living scale (BADLS), but did not find a significant difference in loss of functional milestones. The study was hampered by large subject attrition (Courtney *et al.*, 2004), so whether treatment benefits on functional scales continue beyond one year has been less well-determined. The available data are derived from open label extensions that suggest long-term beneficial effects of treatment on overall functional abilities (Raskind *et al.*, 2004). However, a major limitation of these studies is that patients are self-selected to continue treatment and inferences are based on modeling of extrapolated decline rates.

Given that AD has a duration of five to eight years, it is important to assess the potential of CHEIs over longer time periods. Furthermore, given that placebo-controlled trials are no longer ethical due to the apparent efficacy shown, it is necessary to resort to cohort effectiveness studies to investigate the longer-term benefits of these drugs. Moreover, the results may more closely reflect effectiveness of CHEIs under conditions of usual clinical care.

Our previously reported study suggested that executive functions may be more amenable to treatment benefits with CHEIs compared to memory (Behl *et al.*, 2006). These findings may be particularly relevant to ADL that depend on executive functions and require concurrent manipulation of information, even when components of the tasks are well learned (e.g. preparing meals, paying bills, or balancing a checkbook). The current analysis of this cohort aimed to address whether treatment benefits seen in executive cognitive functions corresponded to benefits in everyday ADL. The DAD was used to evaluate

differential treatment effects over one and two years with CHEIs compared to no treatment in matched samples of patients with mild to moderate AD within the same longitudinal cohort study. IADL and BADL subscores were documented and, in addition, each item within these subdomains was separately scored with respect to the subcomponents of initiation, planning and organization, and performance. Detailed review of comorbid illnesses, concomitant medications and vascular risk factors was conducted to assess comparability of the two groups (Behl *et al.*, 2006).

Methods

Cohort selection

Patients meeting NINCDS-ADRDA criteria for mild (baseline Mini-mental State Examination (MMSE) 20–30) or moderate (baseline MMSE 10–19) probable AD were selected from the Cognitive Neurology clinic at Sunnybrook Health Sciences Center, a University of Toronto academic healthcare institution which is part of the Sunnybrook Dementia Study. All subjects were between the ages of 40 and 90, fluent in English and had adequate visual and auditory acuity to complete neuropsychological testing. Patients were excluded if they had other possible secondary causes of dementia, concomitant neurological or psychiatric illness, including a history of significant premorbid or current major depression. All patients underwent standardized neuropsychological, functional and behavioral assessments, including the DAD (Gelinas *et al.*, 1999), as well as magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT). Mean depressive symptomatology scores from the Cornell Scale for Depression in Dementia were computed for both groups, and concomitant use of selective serotonin reuptake inhibitors (SSRIs) was carefully documented. All of these patients were enrolled in a longitudinal observational study using the same standardized protocol either prior to the approval of CHEIs or after treatment became a common clinical option, at which point all patients with mild to moderate probable AD were offered cholinergic therapy, if not contraindicated, and titrated as recommended to a maximum tolerated dose (achieved in $>90\%$ of patients). Financial status was not a factor for those over 65 as the drugs were covered by the provincial healthcare plan.

To be included in this cohort study, baseline assessment could be no sooner than a month prior to, or a month after, the start of therapy with donepezil or two months after the start of therapy with rivastigmine or galantamine. This was based on the titration period needed to achieve a therapeutic dose for the individual drugs. Patients were matched on education and baseline MMSE. Education was categorized into elementary (0–6 years), high school (7–12 years), and post-secondary ($\geq$13 years) education, and MMSE into mild ($\geq$20) and moderate (10–19) categories.

Since the control group was an historical cohort, factors such as the use of concomitant medications, presence of comorbid illnesses, vascular risk

factors (hypertension, diabetes mellitus, hyperlipidimia, coronary artery disease and smoking) and a family history of stroke and presence of vascular end-organ damage could have differed in the two samples. These were collected prospectively and then double-checked by a careful second review of clinic charts (Behl *et al.*, 2006). Another concern with this study design is that patients started on treatment who are lost to follow-up are not considered, potentially leading to a selection bias toward those who continue and benefit from therapy. Reasons for dropping out included progression of disease leading to institutionalization, death, adverse events or lack of compliance. Baseline demographics of all patients seen in the Cognitive Neurology clinic who were given a diagnosis of mild or moderate probable AD and started on treatment between 1997 and 2002 were examined. Patients started on treatment but who dropped out for various reasons were compared to those who stayed on therapy and were followed in the study.

Untreated sample

For the patients in the longitudinal study between 1993 and 1996, Flowchart 1 describes the process of arriving at the study sample of 65 untreated probable AD patients from 80 probable AD patients.

Treated sample

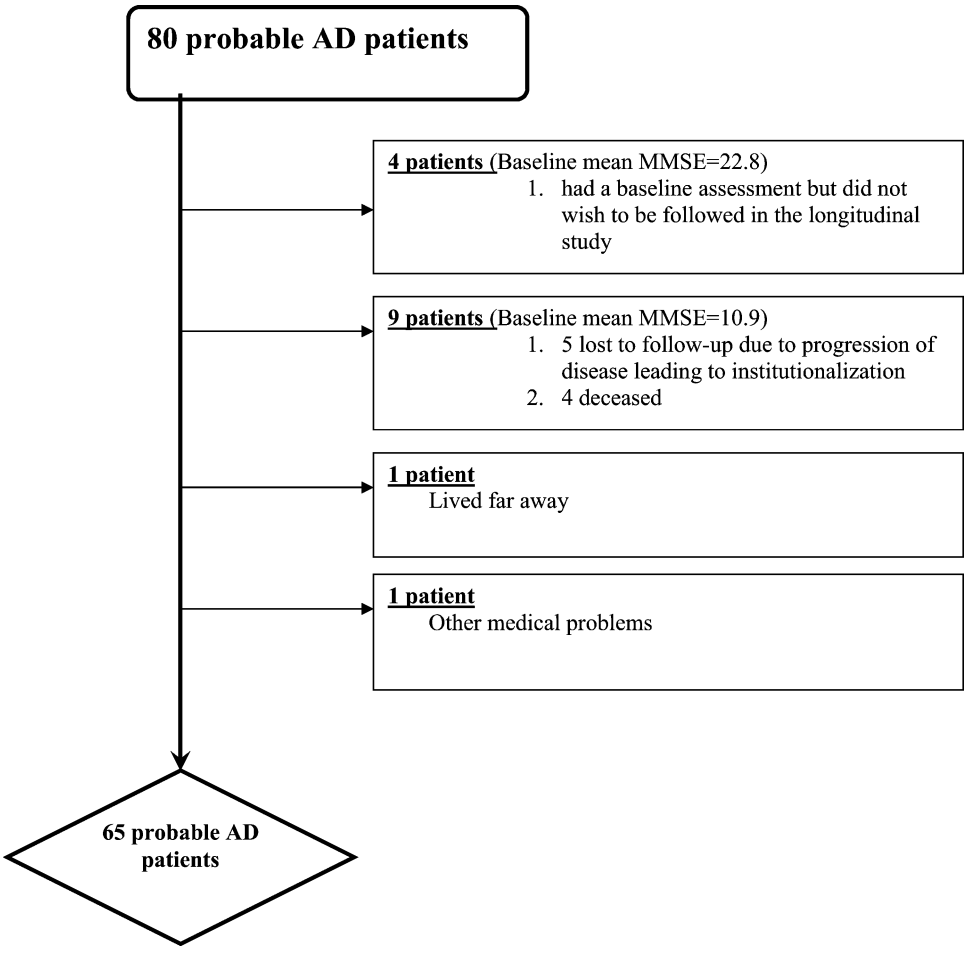
A description of the process used to arrive at the treated study sample of 65 probable AD patients from a total of 211 probable AD patients is shown in Flowchart 2.

One-year cohort

All patients (untreated = 65, treated = 65) underwent standardized neuropsychological and neurobehavioral assessments including the DAD at baseline and one year follow-up. The "one year" follow-up was defined as being no earlier than 11 months and no later than 17 months with a mean follow-up of 14.4 months for the untreated group and 14.6 months for the treated group. There was no significant difference in the follow-up time between the two groups. The untreated group consisted of 15 patients from 1993 and 50 from 1994–1996 and the treated group consisted of 40 patients from 1997–1999 and 25 from 2000–2002.

Two-year cohort

Of the 130 patients, 92 (untreated = 34, treated = 58) had a second-year follow-up. All patients with a second-year follow-up were included, so patients were not one-to-one matched on baseline demographics. Patients had a baseline and a one-year follow-up no earlier than 11 months and no later than 17 months with a mean follow-up of 13.6 months for the untreated group and 14 months for the treated group. The "two year" follow-up was defined as being no earlier than 24 months and no later than 28 months from baseline, with a mean follow-up of 25.2 months for the untreated group and 26 months for the treated group. There

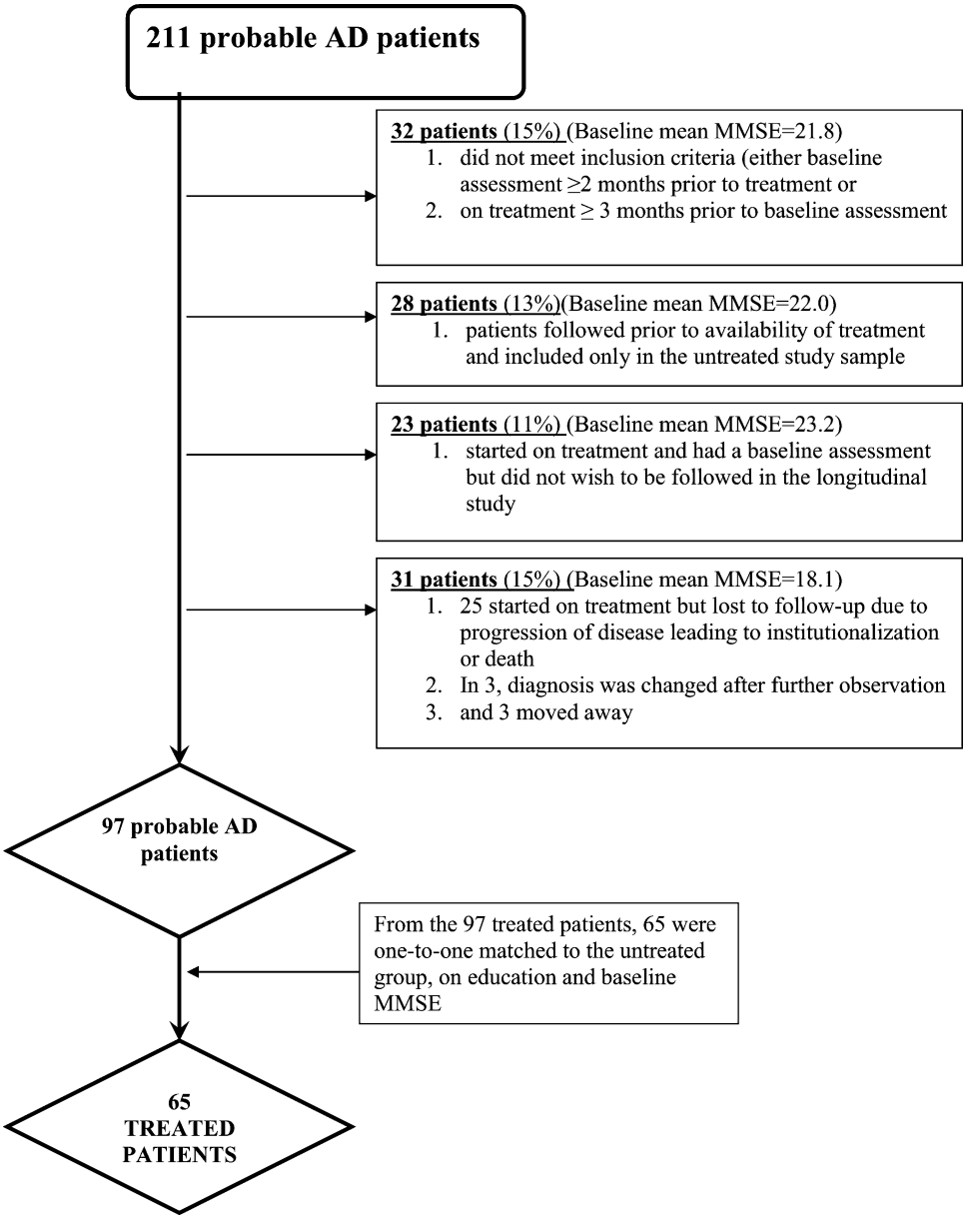


Flowchart 1. Process of arriving at the untreated study sample (N = 65).

was no significant difference in the follow-up time between the two groups. The untreated group consisted of 10 patients from 1993 and 24 from 1994–1996 and the treated group included 30 patients from 1997–1999 and 28 from 2000–2002.

Outcome measures: overall function and functional domains

Functional capacity was assessed with the DAD for activities of daily living, a validated instrument for AD, which provides subscores for IADL and BADL (Gelinas *et al.*, 1999). Additionally, each item within these subscores was further broken down into initiation, planning and organization, and performance components. Global cognitive function was assessed using the total Dementia Rating Scale (DRS) (Mattis, 1976).



Flowchart 2. Process of arriving at the treated study sample (N = 65)
None of the sub-groups started on therapy who dropped out was statistically significantly different from the study sample treated group on age, education or baseline MMSE.

Statistical analysis

Paired-sample t-tests were performed for the one-year cohort to examine differences between the two groups (treated vs. untreated) for the continuous variables of age, education, duration of symptoms, and baseline scores for

MMSE, total DRS, total DAD and total BEHAVE-AD (Behavioral Pathology in Alzheimer's Disease rating scale). Because patients were not one-to-one matched for the two-year cohort, independent sample t-tests were performed to compare these demographic variables. Fisher Exact tests or χ^2 analyses were performed for the one- and two-year cohorts to examine between-group differences in categorical variables such as handedness, sex, non-vascular and vascular disease burden indices, and the use of concomitant medications. Critical values for significance were corrected for multiple comparisons using the Holm correction (Holland and Copenhaver, 1988). The Holm correction, termed a sequentially-rejective Bonferroni method, performs a modified Bonferroni correction that is more powerful than the traditional Bonferroni approach but maintains experiment-wise error rate.

Treatment effect sizes (ES; Cohen's d) were calculated as standardized response means for the one- and two-year cohorts.

$$\frac{(\mathbf{T}_{t2-t1} - \mathbf{U}_{t2-t1})}{(SD)_{pooled}}$$

where **T** is the treated group, **U** is the untreated group, *t2* is the follow-up, *t1* is the baseline, and SD_{pooled} are the standard deviations of the change scores for the two groups.

Repeated measures Multivariate Analysis of Covariance models (MANCOVA), after covarying for the effects of baseline MMSE and education, were performed to determine the relation between CHEI use and the outcome measures for the one- and two-year cohorts. Critical values were corrected for multiple comparisons using Holm's correction (Holland and Copenhaver, 1988).

Distribution of the treated scores (total DRS and total DAD scores) was checked for normality and Pearson correlations between cognitive and functional scores were carried out using the DRS and the DAD to assess the degree of association, if any, between the cognitive and functional change over one year.

Results

One- and two-year cohorts

Baseline demographics and characteristics are provided in Tables 1 and 2. The proportion of men and women was similar between the two groups. There were no significant differences between the two groups on baseline demographics and characteristics. The untreated group was not significantly different from the treated group on baseline functional performance. With regard to the non-vascular and vascular disease burden indices, there were no significant differences for the one- and two-year cohorts at baseline or at follow-ups. More specifically, there were no group differences in any body system or in chemical exposure, alcohol use, allowable neurological problems (such as history of migraine), or remote history of depressive symptoms. There were also no significant differences in the prevalence of cerebrovascular, cardiac and peripheral vascular disease; in

Table 1. Baseline demographics

	UNTREATED	TREATED	χ^2/T TEST (DF)	P VALUE
Males/Females				
1-YEAR COHORT	32/33 = **65**	36/29 = **65**	0.50 (1)	0.500
2-YEAR COHORT	19/15 = **34**	33/25 = **58**	0.94 (1)	0.500
Age				
1-YEAR COHORT	71.4 ± 8.4	71.9 ± 9.9	0.70 (128)	0.700
2-YEAR COHORT	70.9 ± 7.9	69.9 ± 10.9	0.40 (92)	0.700
Education (y)				
1-YEAR COHORT	13.5 ± 3.5	13.3 ± 3.9	0.50 (128)	0.500
2-YEAR COHORT	13.6 ± 3.3	13.5 ± 3.6	0.11 (92)	0.910
Handedness				
1-YEAR COHORT				
Right	60	63	0.40 (1)	0.800
Both	5	2		
Handedness				
2-YEAR COHORT				
Right	32	55	0.021 (1)	0.900
Both	2	3		
Symptoms [duration (y)] 1-YEAR COHORT	3.5 ±2.3	2.8 ±2.3	0.11 (128)	0.800
Symptoms [duration (y)] 2-YEAR COHORT	3.5 ±2.6	2.7 ±2.1	1.60 (92)	0.100

Values are ± SD unless otherwise stated.
Fisher exact test was used for cells with counts less than or equal to 15
df = degrees of freedom
Critical values corrected for multiple comparisons (Holm correction)-no significant difference.

addition, there were no significant differences for the one- and two-year cohorts at baseline or at follow-ups in the use of concomitant medications including statins, antihypertensives and hypoglycemic agents.

None in this study sample was discontinued due to adverse side effects. In general, if side effects occurred, they were successfully switched from one CHEI to another.

One-year cohort

There was a significant effect of Time ($F = 10.3$, $df = 1/111$, $P < 0.001$) and a significant Group by Time interaction ($F = 9.2$, $df = 1/111$, $P = 0.003$) on the overall MANCOVA. Post-hoc analyses were conducted for each of the domains and subdomains as described below.

Overall DAD and subdomains (IADL and BADL): There were significant Group by Time interactions for the IADL ($F = 6.2$, $df = 1/111$, $p = 0.010$) ($ES = 0.5$)

Table 2. Besline Characteristics

	UNTREATED	TREATED	χ^2/T TEST	P VALUE
MMSE				
1-YEAR COHORT				
Mild (20–30)	52	52		
Moderate (10–19)	13	13		
MMSE				
2-YEAR COHORT				
Mild (20–30)	27	51		
Moderate (10–19)	7	7		
MMSE				
1-YEAR COHORT	22.4 ±3.7	23.1 ±3.6	1.1 (128)	0.300
2-YEAR COHORT	22.9 ± 4.0	24.3 ± 3.3	1.80 (92)	0.080
DRS				
1-YEAR COHORT	116.8 ± 11.0	118.8 ± 14.3	0.98 (128)	0.320
2-YEAR COHORT	118.2 ± 12.0	120.5 ± 15.1	0.80 (92)	0.400
DAD				
1-YEAR COHORT	78.9 ± 15.9	82.8 ± 17.3	0.10 (128)	0.900
2-YEAR COHORT	76.0 ± 14.7	80.9 ± 15.8	1.30 (92)	0.200
IADLs				
1-YEAR COHORT	65.9 ± 25.2	72.2 ± 24.6	0.10 (128)	0.920
2-YEAR COHORT	60.1 ± 24.9	69.1 ± 24.4	1.50 (92)	0.140
BADLs				
1-YEAR COHORT	95.8 ± 5.9	95.2 ± 9.1	1.90 (128)	0.060
2-YEAR COHORT	94.6 ± 6.4	95.9 ±6.4	0.90 (92)	0.400
BEHAVE-AD				
1-YEAR COHORT	5.3 ± 3.6	5.6 ± 6.5	0.20 (128)	0.800
2-YEAR COHORT	6.3 ± 3.4	4.2 ± 3.8	1.90 (92)	0.060

BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease rating scale.

and BADL ($F = 10.5$, $df = 1/111$, $P = .002$) ($ES = 0.6$) with treated patients showing less decline compared to untreated patients (Figure 1).

Initiation: Broken down by initiation, there were significant Group by Time interactions on overall DAD ($F = 6.9$, $df = 1/111$, $P = 0.01$) ($ES = 0.5$) and the subdomains of IADL ($F = 8.2$, $df = 1/111$, $P = 0.005$) ($ES = 0.6$) and BADL ($F = 8.5$, $df = 1/111$, $P = 0.004$) ($ES = 0.5$) with treated patients showing significantly less decline in the ability to initiate compared to untreated patients.

Planning and organization: Broken down by planning and organization, there were significant Group by Time interactions on the overall DAD ($F = 7.6$, $df = 1/111$, $P = 0.007$) ($ES = 0.6$) and the subdomain of BADL ($F = 12.6$, $df = 1/111$, $P < 0.001$) ($ES = 0.7$). Treated patients showed significantly less decline in the

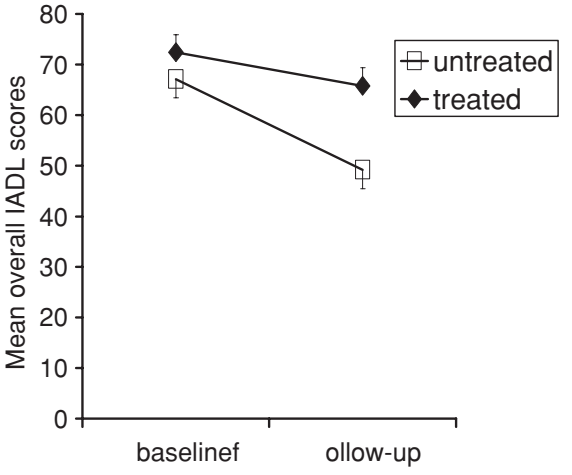


Figure 1. Change in mean overall IADL scores over one year.

ability to plan and organize on the overall DAD score and BADL, but not IADL compared to untreated patients.

Performance: Broken down by performance, there were significant Group by Time interactions on the overall DAD ($F = 8.9$, $df = 1/111$, $P = 0.004$) ($ES = 0.6$) and the subdomain of BADL ($F = 9.1$, $df = 1/111$, $P = 0.003$) ($ES = 0.5$). Treated patients showed significantly less decline in the ability to execute overall and basic ADL but not IADL effectively compared to untreated patients.

Two-year cohort

There was a significant effect of Time ($F = 17.9$, $df = 1/79$, $P < 0.001$) and a significant Group by Time interaction ($F = 18.1$, $df = 1/79$, $P < 0.001$) on the overall MANCOVA. Post-hoc analyses revealed the following results for each of the domains and subdomains.

Overall DAD and subdomains (IADL and BADL): There was a significant Group by Time interaction for the overall DAD ($F = 10.2$, $df = 1/79$, $P = 0.002$) ($ES_{1\text{-year}} = 0.8$; $ES_{2\text{-years}} = 1.0$) and the subdomains of IADL ($F = 17.3$, $df = 1/89$, $P < 0.001$) ($ES_{1\text{-year}} = 0.9$; $ES_{2\text{-years}} = 1.1$) and BADL ($F = 17.4$, $df = 1/79$, $P < 0.001$) ($ES_{1\text{-year}} = 0.4$; $ES_{2\text{-years}} = 0.7$). Treated patients showed less decline in overall function and sudomains compared to untreated patients (Figures 2a–2c).

Initiation: Broken down by initiation, there were significant Group by Time interactions on overall DAD ($F = 16.9$, $df = 1/79$, $P < 0.001$) ($ES_{1\text{-year}} = 0.5$; $ES_{2\text{-years}} = 0.8$) and the subdomains of IADL ($F = 17.0$, $df = 1/79$, $P < 0.001$) ($ES_{1\text{-year}} = 0.6$; $ES_{2\text{-years}} = 0.9$) and BADL ($F = 17.4$, $df = 1/79$, $P < 0.001$)

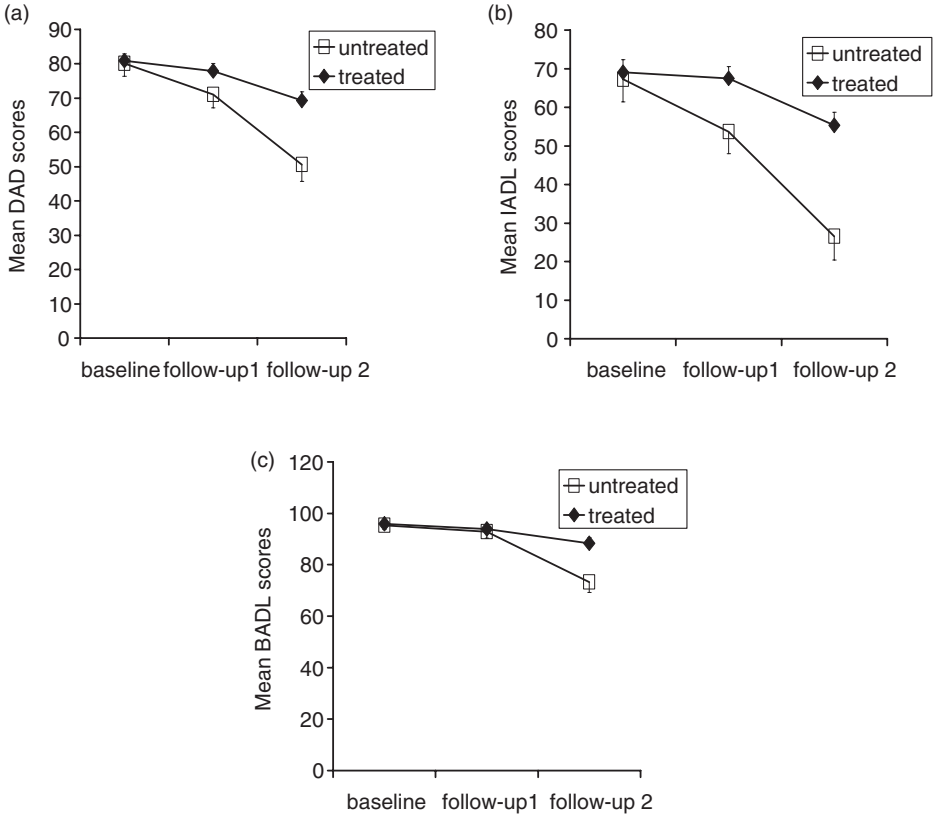


Figure 2. (a) Change in mean overall DAD scores over two years, (b) Change in mean overall IADL scores over two years, (c) Change in mean overall BADL scores over two years.

($ES_{1\text{-year}} = 0.4$; $ES_{2\text{-years}} = 0.7$) with treated patients showing significantly less decline in the ability to initiate compared to untreated patients.

Planning and organization: Broken down by planning and organization, there were significant Group by Time interactions on the overall DAD ($F = 11.1$, $df = 1/79$, $P = 0.001$) ($ES_{1\text{-year}} = 0.8$; $ES_{2\text{-years}} = 1.0$) and the subdomain of BADL ($F = 17.1$, $df = 1/79$, $P < 0.001$) ($ES_{1\text{-year}} = 0.7$; $ES_{2\text{-years}} = 1.0$). Treated patients showed significantly less decline in the ability to plan and organize overall DAD and BADL but not IADL compared to untreated patients.

Performance: Broken down by performance, there were no significant Group by Time interactions on the overall DAD or the subdomains of IADL and BADL.

Correlation between functional and cognitive measure: Results from our previous study demonstrated significantly less decline in treated patients over one year in overall cognition as indexed by the DRS (Behl *et al.*, 2006). Since less decline was noted in both the functional and cognitive domains, Pearson correlations

comparing functional and cognitive change over one year showed a trend toward significance (Pearson's $r = 0.3$; $p = 0.07$).

Discussion

To our knowledge, this is the first observational cohort study to assess longer-term performance of CHEIs in multiple functional domains using a standardized and validated functional measure in mild to moderate probable AD. Our results indicate that differences in the functional domains of the DAD were seen in mild-moderate AD separately for both IADL and BADL as well as for the executive skills (initiation, planning). Performance also differed at one-year follow-up but this difference was not sustained by two years. These differences at one and two years in the functional domains had moderate to large ESs (see Figures 3a and 3b).

Even though cognitive decline is invariably accompanied by functional deterioration, only a few studies have examined the relationship between different cognitive domains, such as memory or executive function, and functional abilities (Teri *et al.*, 1989; Perry and Hodges, 2000; Glosser *et al.*, 2002). Overall disease severity scales such as the DRS and MMSE, rather than tests of specific cognitive ability, have been used in these studies. More specifically, the initiation and memory subscale of the DRS have shown strong correlations with IADL (Teri *et al.*, 1989), but little relationship between DRS scores and BADL has been seen. Others have indicated that functional competence in AD can be predicted from scores of memory, attention, visual perceptual and visuospatial function (Perry and Hodges 2000; Glosser *et al.*, 2002).

More recently, specific neuropsychologic determinants of ADL dysfunction have been analyzed to understand the cognitive deficits most highly associated with functional disability in AD. Executive deficits are highly significant predictors of functional status in AD, even after accounting for dementia severity (Boyle *et al.*, 2003). In addition, ADLs have shown significant positive correlations with the overall pathologic burden in medial temporal and orbital frontal regions (Marshall *et al.*, 2006).

Executive functions are those higher-order cognitive processes that orchestrate the performance of complex, goal-oriented tasks. This goal-directed behavior includes initiation, strategy development and flexibility to change strategy, planning, organization, monitoring appropriate sequences, and inhibition (Perry and Hodges, 1999). The ability to perform ADLs may thus require cognitive flexibility, an important aspect of executive functioning, even when the components of the task are well learned (e.g. preparing meals, brushing teeth, etc.).

Results from our previous study showed that compared to an untreated cohort, treated patients showed less decline in multiple cognitive domains (Behl *et al.*, 2006). In particular, these included executive, language and visuoconstructive tasks. Results further suggest that ADL impairments that also contribute to the disability associated with AD may be manifested due to deficits

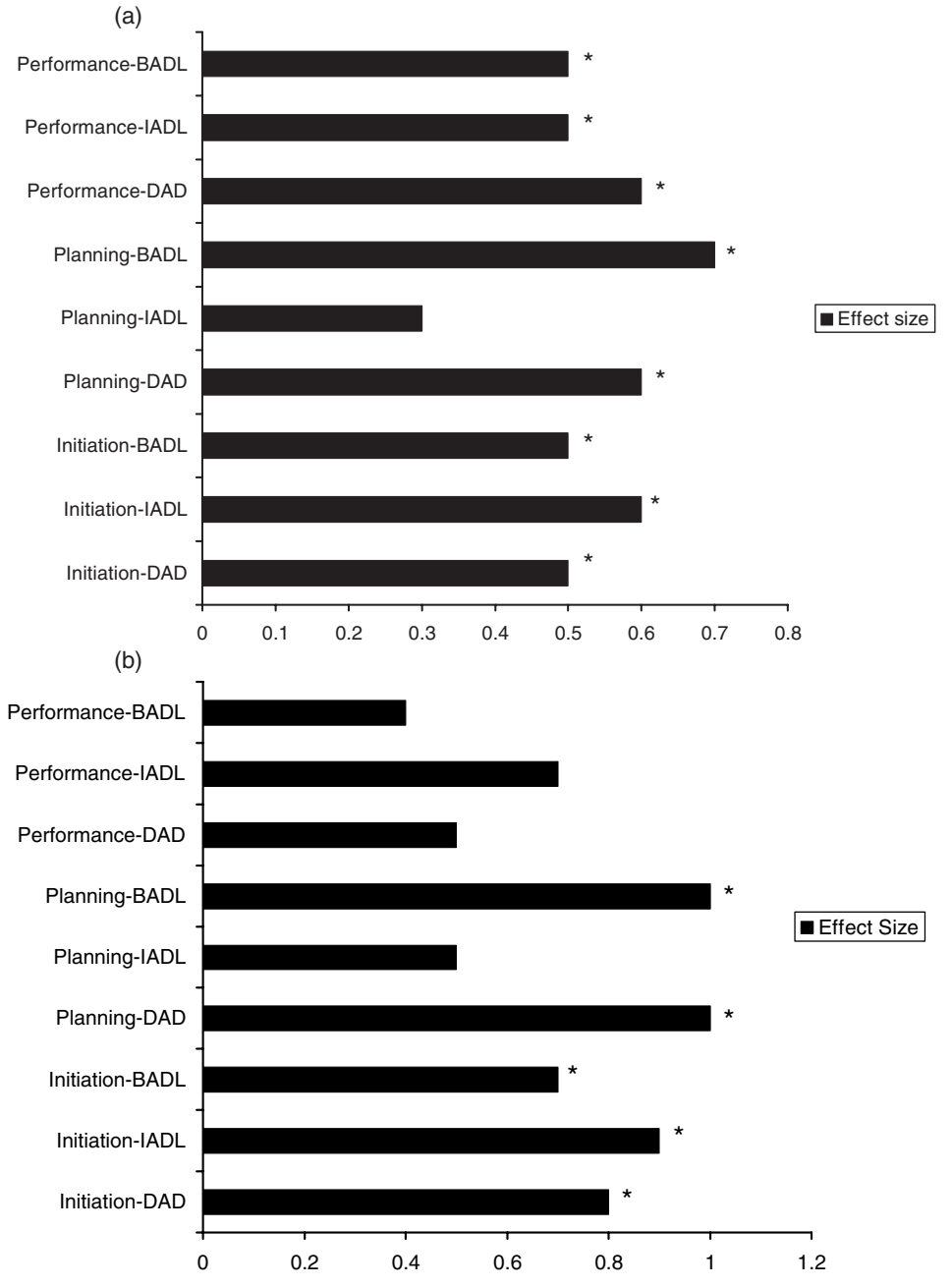


Figure 3. (a) Effect sizes for the one-year cohort, (b) Effect sizes for the two-year cohort.

in executive cognitive functioning. This emerging relationship between executive dysfunction and functional status likely reflects the involvement of a common substrate, i.e. the frontal lobes. Given the known effects of the cholinergic system on attention and executive functions (Mesulam, 2004), it may not be surprising that these functions are particularly responsive to treatment with cholinergic therapy in AD.

Results from our study suggest that the functional differences over two years of follow-up in our treated and untreated cohorts, more likely to be considered clinically relevant, occurred in parallel with cognitive benefits. In a previous publication comparing decline over one year in the same treated and untreated patient sample on the Mattis Dementia Rating Scale (DRS) (Behl *et al.*, 2006), the treated patients showed less decline compared to untreated patients in overall cognition and in all subscores of the DRS except for memory (effect sizes 0.5–0.7) (Behl *et al.*, 2006). In the current study, less decline was seen in treated AD patients across the domains of IADL and BADL, as well as in initiation, planning and execution of some of these activities. These results provide further support for the hypothesis that executive functioning, as in the cognitive domain, may be selectively more responsive to CHEIs over one and two years.

The degree of association between the functional (DAD) and cognitive change (DRS) examined by the Pearson correlation showed a trend towards significance suggesting that improvement was occurring in both groups but the patients who improved in cognition were not the same patients who improved in function.

Assessment of ADL represents an important component in the management and treatment strategies for AD patients since functional status can be a major factor in determining need for institutionalization (Severson *et al.*, 1994). Functional ability loss can also have a profound impact on the quality of life for AD patients and usually must be compensated for by the caregiver. This caregiver burden, including the financial, physical and emotional distress of caring for an adult family member with a mentally disabling condition, often becomes overwhelming and can also contribute to the decision to institutionalize (Khang *et al.*, 2004). There is some evidence that sustained treatment with CHEIs in AD may delay institutionalization (Geldmacher *et al.*, 2003; Lingler *et al.*, 2005) but then no significant benefits were seen in institutionalization in the AD2000 study (Courtney *et al.*, 2004).

One study evaluated the efficacy of metrifonate in mild to moderate AD patients over six months using the DAD scale (Gelinas *et al.*, 2000). Results demonstrated that treatment significantly improved AD patients' ability to perform not only overall ADL but also IADL when compared with placebo. Furthermore, treated patients showed improvements in the subscores of initiation, planning and effective execution of ADL when compared with placebo. In a 24-week, randomized trial of a moderate to severe AD study, treatment was significantly better than placebo on the functional measures of DAD, IADL and the modified Physical Self-Maintenance Scale (PSMS) (Feldman *et al.*, 2001; 2003). Results from our study are consistent with these studies on the efficacy of CHEI for functional ability in randomized, double-blind, placebo-controlled trials (Tariot *et al.*, 2000), the few long-term trials (Mohs *et al.*, 2001; Winblad

et al., 2001; Courtney *et al.*, 2004) and some other cohort studies over one and two years (Lopez *et al.*, 2002; 2005).

There is some evidence from recent clinical trials in probable AD that the placebo groups may be declining less rapidly compared to those in the early 1990s. It has been suggested that this is partly due to factors such as more widespread use of statins, antihypertensive and hypoglycemic agents, and possibly due to greater social support. The available social support services did not differ in our region over this period. In addition, medical histories revealed no significant differences between the two groups over one and two years in the use of concomitant medications including statins, antihypertensive and hypoglycemic agents. There were also no differences in the number of comorbid illnesses, and prevalence of major vascular risk factors, which have been implicated in cognitive decline (Behl *et al.*, 2006).

Attention and executive deficits are usually the first non-memory domains affected in AD. Difficulties in ADL, which occur in even mildly impaired patients correlate with attention and executive deficits. Routine standardized tests in clinical settings do not usually tap into executive dysfunction and have been insensitive to these deficits. Therefore, to better understand executive dysfunction and treatment benefits in AD, tests sensitive to executive as well as other cognitive functions need to be administered. Results from our previous study showed less decline over one year in treated vs. untreated AD patients in overall cognition, executive functioning, naming, and visuospatial tasks with moderate to large ESs (Behl *et al.*, 2006). The present study showed less decline in treated patients across the domains of IADL and BADL, as well as in the executive components of initiation, planning and performance of these activities.

Conclusion

Although patients were not randomized to treatment, this well-matched cohort study, in which numerous potential confounding factors were addressed, provides evidence for the effectiveness of CHEI on functional outcomes in mild to moderate AD over two years. Importantly, results suggest that those functions particularly mediated through the attentional system and frontal lobes may be more responsive to CHEI therapy over the long term. In future trial designs, it would be prudent to incorporate more explicit tests of executive dysfunction as well as scales of ADL that fractionate more executive subcomponents such as the DAD, to better capture treatment benefits in AD patients.

Conflict of interest declaration

This study was conducted independently of any pharmaceutical company sponsorship. Sandra E. Black declares honoraria from CME and ad hoc consulting from Pfizer, Janssen-Ortho, Novartis Pharmaceuticals, Lundbeck and Myriad Pharmaceuticals and operating funds from Pfizer Inc., Janssen Ortho, Novartis Pharmaceuticals, Myriad Pharmaceuticals, Sanofi-Aventis,

Astra-Zeneca, Boehringer Ingelheim and Novo Nordisk. Krista L. Lanctôt declares consultant and speaker honoraria, and contract research funding from Pfizer Inc. and Janssen Ortho.

Description of authors' roles

Drs. Behl and Black formulated the study concept and design, and Drs. Behl, Streiner and Black were responsible for the data analysis and interpretation. All the authors contributed to the preparation of the manuscript and the writing of the final paper.

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