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Cholinesterase inhibitors may not benefit mild cognitive impairment and mild Alzheimer disease dementia

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Abstract

INTRODUCTION: We investigated whether cholinesterase inhibitors (ChEIs) benefit cognitive outcomes in mild cognitive impairment (MCI) due to Alzheimer disease (AD) and in mild AD dementia.

METHODS: Data from 2,242 individuals, clinically diagnosed with MCI due to AD (MCI-AD, Clinical Dementia Rating [CDR] = 0 or 0.5) or with mild AD dementia (ADdem, CDR = 0.5 or 1), were available from the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS). General linear mixed models were used to examine the annual change in the CDR Sum Boxes (CDR-SB) and in neuropsychological performance. We compared slopes before and after ChEI initiation among ChEI users, and also compared change in scores of ChEI users versus non-users.

RESULTS: Thirty-four percent of 944 MCI-AD and 72% of 1,298 ADdem participants were ChEI users. Cognitive decline was greater after ChEI initiation in MCI-AD and ADdem groups (e.g., MCI-AD, CDR-SB: 0.03 points/year before initiation; 0.61 points/year after initiation, $p < 0.0001$). Both MCI-AD and ADdem groups had faster decline after ChEI initiation than non-users (e.g., MCI-AD, CDR-SB: 0.61 points/year, ChEI users; 0.24 points/year, non-users, $p < 0.0001$).

DISCUSSION: This study suggests that ChEI use may not improve the cognitive course in MCI-AD and mild ADdem.

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Conflict of Interests

No other disclosures were reported.

Keywords

Cholinesterase inhibitor; Cognitive outcome; Mild cognitive impairment; Alzheimer disease; Alzheimer disease dementia

Introduction

Cholinesterase inhibitor (ChEI) drugs are approved for the symptomatic treatment of Alzheimer disease (AD) dementia and these agents (e.g., donepezil; rivastigmine; galantamine) have consistently demonstrated modest improvement in cognitive outcomes¹⁻³. Their utility in individuals with mild cognitive impairment (MCI) due to AD⁴ is uncertain, however, as efficacy at this initial stage of symptomatic AD has not been convincingly demonstrated. For example, although trials of ChEIs in persons with MCI have failed to demonstrate efficacy in primary outcome measures, some have showed benefit for secondary outcome measures⁵⁻⁷. One trial of donepezil in MCI found an initial slowing of cognitive decline in the early portion of the trial but not at its conclusion⁸. Another study of galantamine in combination with memantine (a non-ChEI) seemed to show benefit for the combination therapy, although the study was limited by small sample size (N=232)⁹. Finally, a meta-analysis concluded that there was no therapeutic benefit for ChEI use in MCI¹⁰.

The cholinergic hypothesis^{11,12}, which serves as the rationale for ChEI therapy in AD, posits a central cholinergic deficit in AD that contributes to cognitive dysfunction. However, hippocampal and frontal cortical upregulation of choline acetyltransferase (CAT) activity occurs in MCI, which may reduce the efficacy of ChEIs¹³. In contrast, another study showed protective effects of ChEIs for neurodegeneration¹⁴. These minimal and conflicting mechanistic studies of ChEI effects on central nervous systems processes provide an uncertain rationale for the use of ChEIs therapy in MCI.

Nonetheless, use of ChEI in MCI individuals is prevalent in clinical practice¹⁵. To determine whether ChEI use benefits individuals with MCI due to AD, and to ascertain what factors are associated with use of ChEIs in such individuals, we conducted an observational study with data from the Uniform Data Set (UDS)¹⁶ at the National Alzheimer's Coordinating Center (NACC).

Methods

Participants

Data from the UDS are collected at annual visits and are supplemented by standardized Neuropathology (NP) Data Set (NDS) for those who had autopsy. These data accrue from approximately 30 actively-funded National Institute on Aging Alzheimer Disease Centers (ADCs) and are maintained at NACC. Data collection at the ADCs occurs for each participant on an annual basis and includes demographics, medication history, clinical characteristics and diagnoses, neuropsychological test performances, and neuropathological characteristics, using standardized UDS and neuropathology forms. Data collected from September 2005 through August 2016 were included in this study. Details of the participant recruitment in NACC sample and data collection procedures have been described

previously^{16–18}. Institutional review board of each institutions have reviewed and approved the study protocols. Written informed consent was obtained from all participants and informants of this study.

Participants who were naïve to ChEI use at their initial UDS visit were included if they had three or more annual UDS visits and had a primary etiological diagnosis of MCI due to AD (global Clinical Dementia Rating¹⁹ [CDR] of 0 or 0.5) or mild AD dementia (CDR of 0.5 or 1) at baseline; the mild AD dementia group was included as it is recognized that symptomatic AD represents a continuum from its incipient stage (MCI due to AD) through progressively severe stages²⁰. Two groups were compared: *ChEI users* were participants who reported use of any ChEI at any follow-up visit after the initial UDS visit and who had at least one visit subsequent to the one where ChEI use was reported, and *ChEI non-users* were participants who never reported ChEI use at any UDS visit.

Demographic information (eg. sex, age, education level), past self-reported medical history (e.g., stroke, diabetes), family history of cognitive impairment (first degree family member), presence of co-existing problems assessed by clinician (eg. behavior, language) and medication use were collected at each UDS visit. All participants were evaluated using the standardized UDS clinical measures including the CDR and neuropsychological test battery¹⁸. Coexisting mood disorders were evaluated in both subjective self-report of depression and the participant's score on the 15-item Geriatric Depression Scale (GDS)²¹. *Apolipoprotein E (APOE)* genotype was available for the majority of the sample (86%).

Neuropsychological Tests

The cognitive measures in the UDS neuropsychological battery¹⁸ included Mini-Mental State Examination (MMSE) for global cognition, Wechsler Memory Scale Logical Memory - Immediate Recall and Delayed Recall for episodic memory, Wechsler Memory Scale-Revised (WMS-R) Digit Span Forward and Backward for attention, Wechsler Adult Intelligence Scale- Revised Digit Symbol and the Trail Making Test (Part A and B) for measuring processing speed and executive function, Animal and Vegetable list generation for semantic fluency, and Boston Naming Test (30 odd items) for naming. Dementia progression was measured by CDR Sum of Boxes (CDR-SB), which sums the individual scores in the six domains assessed by the CDR: memory, orientation, judgment, home and hobbies, community affairs, and personal care²².

Neuropathology

For participants in this study who died and came to autopsy (N=283), neuropathological data were retrieved from NACC's NDS as described in its standardized Neuropathology Form and Coding Guidebook²³. The NDS has applied the National Institute on Aging-Alzheimer's Association (NIA-AA) Alzheimer's disease neuropathological change (ADNC) guidelines²⁴ which rank AD neuropathology changes in three parameters of an "ABC score" - consisting of "A"- immunohistochemistry of amyloid beta plaque score²⁵, "B" - neurofibrillary tangle (NFT) stage of Braak²⁶, and "C" - neuritic plaque score from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)²⁷. However, ADNC scores were not gathered prior to 2014 [because "A" (Thal Phase) was not done]. To permit an adequate sample size,

and to provide some consistency with the “B” and “C” scores, we used the criteria of moderate to frequent neuritic plaques from CERAD (“C”) and Braak stage III-VI (“B”) to define AD neuropathology.

Statistical Analyses

Using analyses of variance models or Chi-squared tests, ChEI users and non-users in both MCI due to AD (MCI-AD) and mild Alzheimer disease dementia (ADdem) groups were compared on age, education, sex, race, Hispanic ethnicity, presence of *APOE e4* allele, family history of cognitive impairment, and global CDR at the baseline. We also compared total number of UDS visits and presence of AD neuropathology in individuals whom had autopsy. Additionally, we compared age of onset and duration of cognitive decline as reported by the participants, clinician-assessed affected cognitive domains, presence of behavioral problems, self/proxy-reported history of vascular risk factors, other contributing etiologies, initial GDS scores, and antidepressant and memantine use at initial visit in these groups.

In the MCI-AD group, less than 1% of participants had missing data for education and race but 12% were missing *APOE* genotypes. In the ADdem group, less than 2% of participants had missing data for education and race but 16% had missing *APOE* genotypes. The unadjusted logistic regression was used to calculate p-values. Statistical significance was based on alpha level of 0.05.

General linear mixed effects models were used to examine the annual rate of change in the CDR-SB and the neuropsychological test outcomes in both MCI-AD and ADdem groups. Specifically, for the ChEI users, we implemented a piecewise linear growth/decline pattern over time that was linked at the initiation of the ChEI use (treated as time 0). The model then assumed the vector of two slopes (i.e., the annual rates of change prior to and after the initiation of ChEI use) and the performance at the initiation of ChEI use (the intercept) as both random and fixed effects²⁸. For the ChEI non-users, we implemented a simple random intercept and random slope model. Mean slopes were then compared before and after ChEI initiation among ChEI users in the MCI-AD and ADdem groups, and also to the slope of ChEI non-users. Adjusted analyses were performed, controlling for baseline age, sex, education, race, presence of *APOE e4* allele, behavioral problems, and GDS score at baseline. All analyses were done by SAS²⁹.

Results

Demographics and baseline characteristics

A total of 944 MCI-AD participants (322 ChEI users, 622 ChEI non-users) and 1298 mild ADdem participants (932 ChEI users, 366 ChEI non-users) met our eligibility criteria. Baseline characteristics differed in most of the measures between ChEI users and non-users of both MCI-AD and ADdem groups (Table 1). Compared to non-users, ChEI users were more likely to have greater years of education, be of Caucasian race, and have at least 1 *APOE e4* allele. At the initial visit, ChEI users had better global CDR scores compared to the non-users; however, at their first use of ChEI, ChEI users have worse global CDR scores

compared to non-users at the initial visit. ChEI users in both groups more often had family history of dementia. In the ADdem group only, ChEI users were more likely to be younger at initial visit than non-users.

In this sample, 283 had a neuropathological examination (Table 1). The availability of neuropathology data was similar between ChEI users and non-users in the ADdem group, but ChEI users in the MCI-AD group more often had neuropathology data than non-users. In the ADdem group, ChEI users more frequently met neuropathological criteria for AD compared with non-users (135 cases, 86.5% in ChEI users; 54 cases, 76.1% in non-users, p -value = 0.05).

Presence of other diagnoses potentially contributing to cognitive impairment were more prominent in the non-users (Table 2); in particular, cerebrovascular disease was more likely to contribute in both MCI-AD and ADdem non-users. Co-morbid cardiovascular risk factors were also more often present in the ADdem non-users. Compared to ChEI users, ChEI non-users more often reported diabetes in the MCI-AD group and more often reported diabetes, stroke and cardiovascular disease in the ADdem group.

Reported symptoms and medication use related to depression did not differ between the groups (Table 2), but GDS scores were higher in the non-user groups. Use of memantine, a N-Methyl-D-aspartic acid-receptor antagonist approved only for moderate to severe AD dementia, was reported in a small subset of the MCI-AD participants (<2%), and was reported more frequently among the ChEI non-users (18.3%) than ChEI users (8.7%) in the ADdem group. Behavioral problems were reported more frequently in ChEI non-users of ADdem group (62.8%) than ChEI users (51.9%) at their initial visit, but upon initiation of first ChEI use, both MCI-AD (47.2%) and ADdem (67.3%) group showed increased reports of behavioral problems (see Table, Supplementary Digital content 1, which outlines additional clinical symptoms of sample).

Baseline cognitive test scores significantly differed between ChEI users and ChEI non-users (see Table, Supplementary Digital content 6). At the initial visit, ChEI non-users scored worse than ChEI users on all cognitive measures in the ADdem group; ChEI non-users in the MCI-AD group performed worse than ChEI users on Digit Span Forward and Backward and the Boston Naming Test.

Comparisons in rates of cognitive decline before and after ChEI initiation

When we compared rate of cognitive decline before and after the initiation of ChEI in unadjusted analyses, there was an increase in the rate of decline after the initiation of drug (see Table, Supplementary Digital content 2, which shows results from Unadjusted annual change in scores in MCI-AD and AD dementia participants) in both MCI-AD and ADdem groups. After controlling for demographic differences (e.g., age, sex, education, race, *APOE* $\epsilon 4$ status), baseline cognition and symptoms (i.e., presence of behavior problems, GDS score), the annual increase in CDR-SB before ChEI initiation was 0.03 (95% CI: -0.03, 0.09) in MCI-AD, which increased to 0.61 (95% CI: 0.52, 0.69) after ChEI initiation (Table 3, Figure 1). Annual decline in MMSE scores before ChEI initiation in MCI-AD was -0.09 (95% CI -0.20, -0.01) which worsened to -0.68 (95% CI: -0.79, -0.58) after ChEI

initiation. For ADdem group, the annual increase in CDR-SB before ChEI initiation was 0.30 (95% CI 0.24, 0.36), and increased to 1.26 (95% CI 1.20, 1.33) after initiation. In MMSE, rate of decline before initiation was -0.44 (95% CI -0.54 , -0.34) and -1.58 (95% CI -1.68 , -1.48) after initiation. This accelerated rate of cognitive decline after ChEI initiation was observed for almost all cognitive measures in the MCI-AD and ADdem groups, with the exception of Digit Span Backward in the MCI-AD group and Logical Memory Immediate, Delayed in the ADdem group

In a sensitivity analysis (see Table, Supplementary Digital content 3, which shows results from sensitivity analysis in adjusted annual change in CDR-SB in MCI-AD and AD dementia participants before and after begin taking cholinesterase inhibitors, restricting to two years before and after first ChEI use), we focused on the annual change in CDR-SB scores, restricted the analysis to two years before and after first ChEI use, and controlled for demographic differences (e.g., age, sex, education, race, APOE $\epsilon 4$ status), presence of behavior problems and GDS scores. In both MCI-AD and ADdem groups, the rate of cognitive decline increased significantly after ChEI initiation, showing a similar trend compared to the main analysis.

Comparisons in rates of cognitive decline between ChEI users and ChEI non-users

In both the MCI-AD and ADdem groups, compared to non-users, ChEI users after initiation of ChEI had faster decline after controlling for the demographics and baseline cognitive and behavioral symptoms (Table 4). ChEI users showed faster CDR-SB progression than non-users (MCI-AD: 0.24, 95% CI: 0.19, 0.30; ADdem: 1.27, 95% CI: 1.12, 1.43). Similar findings were observed for all of the other measures in both MCI-AD and ADdem groups except for Vegetable naming and Trail making B in ADdem groups. However, when we compared the non-users to ChEI users before initiation, Logical Memory Immediate, Delayed, and Animal naming showed faster decline in ChEI users of MCI-AD groups. In ADdem groups, CDR-SB, MMSE, Boston naming test and Trail Making A showed slower decline than non-users, but faster decline in Logical Memory Immediate and Delayed.

In post-hoc analyses, the adjusted analyses for Tables 3 and 4 were repeated additionally controlling for age of onset of cognitive decline and history of diabetes, stroke, and cardiovascular disease, to control for additional factors that may influence differences in cognitive decline between the groups (Supplementary Digital Content 4 and 5). The overall conclusions remained unchanged.

Discussion

Although ChEI drugs are the major symptomatic therapy for AD, their efficacy in MCI-AD is uncertain. Fewer than half (34%) of MCI-AD participants reported taking ChEIs, as would be expected given the lack of specific recommendations for the drug use at the MCI stage. Seventy-two percent of ADdem participants reported taking ChEIs; although we did not assess reasons for not taking ChEIs, these may include personal preferences, costs, or contraindication due to side effects. In this study, we aimed to determine whether use of ChEI drugs benefit MCI-AD individuals. We compared the rate of cognitive decline prior to

and after the initiation of ChEIs and also compared the overall course of decline of ChEI users and non-users.

We found that initiation of ChEIs seemed to be associated with aggravated cognitive decline. This unexpected observation was consistent across all cognitive outcome measures used in the study in both MCI-AD and in mild AD dementia. Despite demonstrated efficacy of ChEIs in mild-moderate AD dementia (ie, a broader range of dementia severity)¹⁻³, we found significant acceleration in rate of cognitive decline after the initiation of ChEIs in both MCI-AD and mild AD dementia.

It is possible that our observations reflect the natural course of decline in ADdem and MCI-AD, the earliest symptomatic stages of AD, whereas rate of cognitive decline is known to accelerate with disease progression³⁰⁻³². The rate of pre-treatment decline in our study is faster in ADdem group than the MCI-AD group, and the rate of decline after ChEI initiation in the MCI-AD group lies between the pre-treatments decline of MCI-AD and ADdem groups, suggesting that the measured rate of cognitive decline rate in these early symptomatic groups may be affected more by inherent disease progression itself rather than by ChEI treatment.

Another possibility is that the decision to initiate ChEI therapy was made at the inflection point where greater cognitive decline was perceived. Although the baseline cognitive test scores were comparable between ChEI users and non-users in the MCI-AD group, and were significantly higher in the ChEI users of ADdem group (see Table, Supplementary Digital content 6, which shows the unadjusted mean scores at initial visit), at the time of ChEI initiation the cognitive scores of ChEI users in both the MCI-AD and ADdem groups were lower than those of non-users at baseline (see Table, Supplementary Digital content 7, which shows the unadjusted mean scores at first visit reporting ChEI use among ChEI users). If this greater decline was recognized by the individual's physician, it may have prompted initiation of ChEIs in an effort to slow disease progression.

It also is possible that individuals who were not prescribed ChEIs had a perceived slower rate of progression or suspicion of non-AD etiology, hence discouraging the use of ChEIs. There were trends of higher burden of AD pathology in ChEI users in the ADdem group (ADNP: 86.5% in ChEI users, 76.1% in non-users, $p=0.05$), which implies that non-users of ChEI included more non-AD etiologies. Although non-significant, this trend was also seen in the MCI-AD group (ADNP: 72.7% in ChEI users, 65.2% in non-users, $p=0.55$). Although the neuropathological data were drawn from small sample sizes, this suggest that non-users more often had non-AD dementing disorders, which also may have factored into the non-use of ChEIs. In this regard, ChEI non-users in the MCI-AD group showed improved longitudinal performance on the Logical Memory immediate and delayed measures, an unlikely result for the Logical Memory test³³ when the underlying disorder is AD.

However, the immediate change from the two years before ChEI initiation showed an average increase of 0.03 per year on CDR-SB (see Table, Supplementary Digital content 3), yet ChEI was prescribed to participants. Among factors that may have played a role in the

decision to initiate ChEIs, informants may have reported perceived greater memory decline or presence of behavioral problems between initial visit and at the first ChEI use (see Table, Supplementary Digital content 1). Whether this or other factors influenced treatment decisions warrant further investigation.

We noted some use of memantine in the MCI-AD and ADdem participants despite a lack of efficacy for this drug at these early symptomatic stages. We also noted a lower rate of ChEI use in African American participants in our sample compared with Caucasians, consistent with recent Medicare data³⁴ showing health disparities for therapeutic interventions for African-Americans.

We observed overall slower cognitive decline of the study cohort, both in treatment and non-treatment groups compared to prior untreated cohorts. Previous cohorts from pre-ChEI era in 1990s have shown average rate of decline of 3 points per year on the MMSE³⁵, whereas observations from recent studies align with our study, showing slow decline in ChEI treated patients^{36,37}. It may be possible that previous untreated cohorts were mixed population of AD dementia and non-AD dementia, of which AD dementia patients were treated, and for those who did not decline remained as the untreated cohort.

Alternatively, the patient population may have changed over the past few decades, and the change in rate of decline may not be related to use of ChEIs. For example, the most recent cohort from Framingham studies showed decreased incidence of dementia³⁸ regardless of decreased incidence of stroke, atrial fibrillation and heart failure. This indicates the relevance of cardiovascular risk factors with dementia; although results from multi-modality intervention trials have mixed findings^{39,40}, improved control of major cardiovascular risk factors such as hypertension, diabetes mellitus, and hyperlipidemia may have affected overall course of cognitive decline in general population.

Although our results appear to contradict the symptomatic benefit for ChEIs demonstrated in previous clinical trials, trials¹⁻³ had a treatment duration of less than 52 weeks. One trial with a treatment duration of 3 years³⁶ showed no clear efficacy of the ChEI drug compared with the placebo arm.

A major limitation of our findings is that they derive from a retrospective cohort study. Interpretation of results are limited to possible correlations and associations. We tried to overcome this restriction by implementing models that show drug effects prior and after ChEI initiation; however, the factors leading to a physician's decision regarding drug therapy were not available for analysis and thus it is unknown whether perceived underlying disease progression triggered the initiation of ChEIs versus ChEI drugs themselves contributing to worsening cognitive decline. In addition, neuropathology data were missing for a large majority of our sample, so that we could not restrict the study to participants with confirmed AD neuropathology nor could we evaluate the possible effect of co-pathologies.

Although our study does not support the use of ChEI drugs in MCI-AD or mild ADdem, we were unable to control for various factors that may have influenced our findings. Randomized clinical trials are needed to evaluate the efficacy of ChEI use in the prodromal stage of symptomatic AD (MCI due to AD and mild AD dementia).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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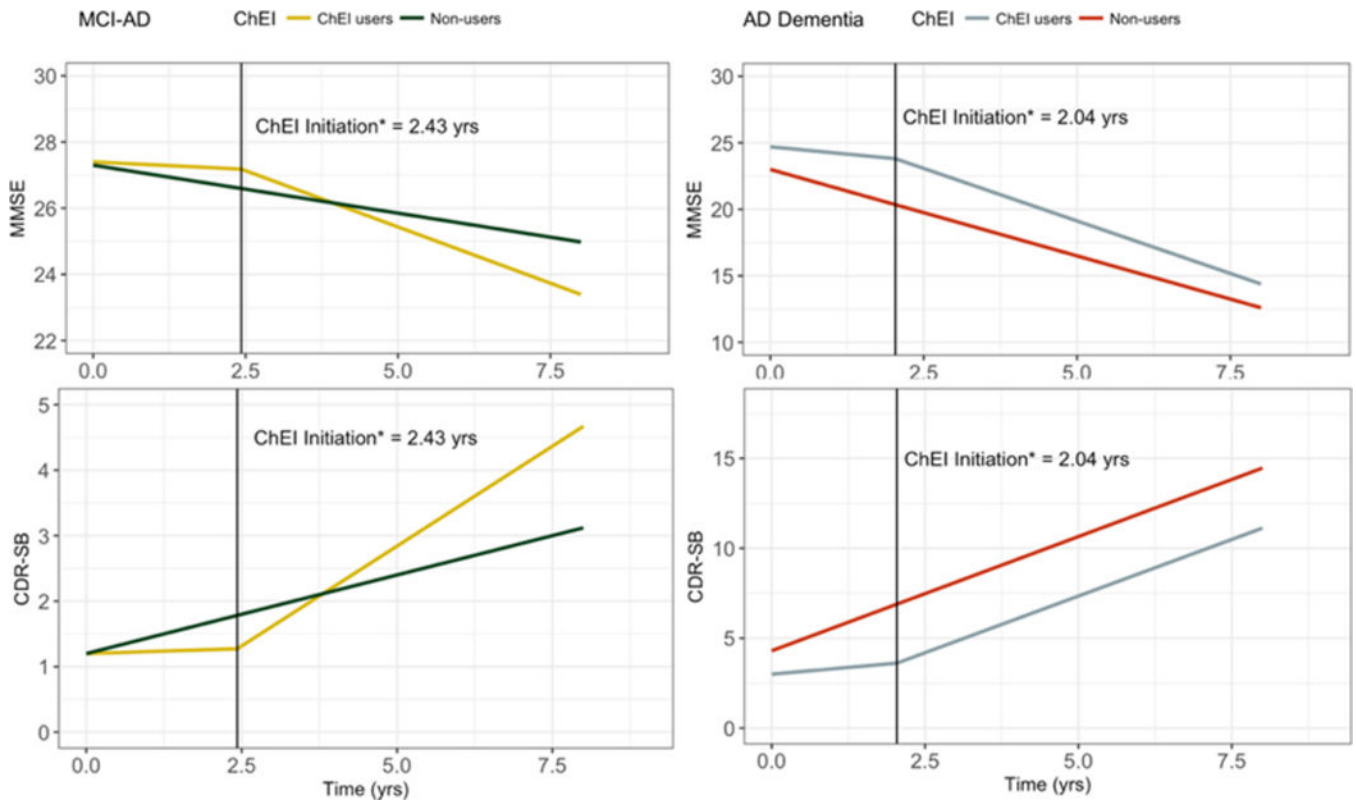


Figure 1. Annual rates of cognitive decline in CDR-SB and MMSE in MCI-AD and AD dementia participants of cholinesterase inhibitor users and non-users. Vertical lines indicate inflection point of ChEI initiation in ChEI users; intercepts of y-axis reflect average scores at the baseline. *ChEI initiation refers to average time in years to ChEI initiation from first visit

Table 1.

Baseline characteristics of sample

Characteristic	MCI-AD*			Mild AD dementia*		
	ChEI users	Never used ChEI	p-value [†]	ChEI users	Never used ChEI	p-value [†]
Sample size, n	322	622	NA	932	366	NA
Age at Initial Visit, mean (SD)	74.1 (8.1)	73.5 (9.1)	0.37	74.7 (8.8)	77.7 (9.7)	<0.0001
Male, n (%)	170 (52.8%)	309 (49.7%)	0.36	411 (44.1%)	166 (45.4%)	0.68
Education (years), mean (SD)	15.8 (2.9)	15.3 (3.4)	0.03	14.7 (3.6)	14.2 (4.0)	0.03
Race, n (%)						
White	288 (90.3%)	474 (77.0%)	Ref.	763 (83.5%)	273 (76.9%)	Ref.
African American	21 (6.6%)	75 (12.2%)	0.003	94 (10.3%)	55 (15.5%)	0.008
Other	10 (3.1%)	67 (10.9%)	< 0.0001	57 (6.2%)	27 (7.6%)	0.25
Hispanic ethnicity, n (%)	16 (5.0%)	45 (7.2%)	0.18	64 (6.9%)	31 (8.5%)	0.32
Number of years of follow-up, mean (SD)	5.4 (2.2)	3.9 (1.6)	< 0.0001	4.8 (2.2)	3.9 (1.9)	< 0.0001
Presence of at least 1 APOE e4 allele, n (%)	151 (53.0%)	225 (41.2%)	0.001	460 (57.4%)	139 (46.6%)	0.0002
Family history of cognitive impairment, n (%)	216 (71.5%)	354 (60.4%)	0.001	557 (66.1%)	184 (58.4%)	0.02
Global CDR at Initial Visit, n (%)						
0	70 (20.8%)	38 (6.0%)	< 0.0001	86 (9.2%)	0 (0.0%)	< 0.0001
0.5	258 (76.8%)	584 (92.7%)		567 (60.8%)	170 (46.5%)	
1	8 (2.4%)	8 (1.3%)		279 (30.0%)	196 (53.6%)	
Global CDR at First ChEI use [‡] , n (%)						
0	5 (1.6%)	38 (6.1%)	0.003	0 (0.0%)	0 (0.0%)	0.02
0.5	317 (98.5%)	584 (93.9%)		365 (39.2%)	170 (46.5%)	
1	0 (0.0%)	0 (0.0%)		567 (60.8%)	196 (53.6%)	
Had neuropathology exam/autopsy, n (%)	33 (10.2%)	23 (3.7%)	0.0002	156 (16.7%)	71 (19.4%)	0.28
ADNP among those with autopsy, n (%)	24 (72.7%)	15 (65.2%)	0.55	135 (86.5%)	54 (76.1%)	0.05

Abbreviations: MCI-AD = Mild cognitive impairment with primary etiologic diagnosis of Alzheimer’s disease; AD = Alzheimer’s disease; ChEI = cholinesterase inhibitor; CDR = Clinical Dementia Rating; APOE = apolipoprotein E; ADNP = moderate to frequent neuritic plaques and Braak Stage III-VI Missing data: MCI-AD (ChEI users, Never used ChEI): Education (n=1, n=1); Race: (n=3; n=6); Hispanic ethnicity (n=1; n=4); APOE genotype (n=37, n=76); Mild AD dementia (ChEI users, Never used ChEI): Education (n=6, n=2); Race: (n=18; n=11); Hispanic ethnicity (n=2, n=0); APOE genotype (n=130, n=68)

* Diagnosis at time of first ChEI use among ChEI users or at Initial Visit for never users

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Used unadjusted logistic regression comparing ChEI users and never users

For those who never used ChEI, providing CDR at Initial Visit

Bolded if statistically significant at $p < 0.05$

Table 2.

Clinical characteristics and symptoms of sample

Characteristic at Initial Visit	MCI-AD*		Mild AD dementia*		p-value [†]
	ChEI users	Never used ChEIs	ChEI users	Never used ChEIs	
Age of onset of cognitive decline, mean (SD)	71.8 (8.7)	70.3 (9.7)	71.8 (9.3)	73.1 (9.7)	0.02
Contributing clinical diagnoses, n (%)					
None	274 (85.1%)	460 (74.0%)	740 (79.4%)	262 (71.6%)	0.003
Lewy body disease including PD	1 (0.3%)	4 (0.6%)	12 (1.3%)	4 (1.1%)	0.78
FTLD including bvFTD and PPA	0 (0.0%)	1 (0.2%)	13 (1.4%)	6 (1.6%)	0.74
Cerebrovascular disease	6 (1.9%)	38 (6.1%)	30 (3.2%)	36 (9.8%)	<0.0001
Other	43 (13.4%)	128 (20.6%)	152 (16.3%)	69 (18.9%)	0.27
History of stroke, n (%)	9 (2.8%)	23 (3.7%)	52 (5.6%)	44 (12.1%)	<0.0001
History of diabetes, n (%)	34 (10.6%)	104 (16.8%)	118 (12.7%)	62 (17.0%)	0.05
History of hypertension, n (%)	166 (51.6%)	357 (57.5%)	503 (54.3%)	215 (58.7%)	0.15
History of hypercholesterolemia, n (%)	175 (55.4%)	345 (55.7%)	486 (52.6%)	179 (49.6%)	0.33
History of cardiovascular disease, n (%)	63 (19.6%)	120 (19.4%)	168 (18.1%)	102 (28.0%)	<0.0001
Depression in past 2 years, self-report, n (%)	75 (23.4%)	168 (27.2%)	293 (31.7%)	128 (35.2%)	0.24
Depression medication use, n (%)	64 (20.1%)	125 (20.2%)	216 (23.5%)	81 (22.6%)	0.75
Geriatric Depression Scale at Initial Visit, mean (SD)	1.8 (2.0)	2.1 (2.3)	2.4 (2.4)	2.7 (2.7)	0.08
Cholinesterase inhibitor at first ChEI use, n (%)					
Donepezil	271 (84.2%)	N/A	710 (76.2%)	N/A	N/A
Rivastigmine	35 (10.9%)	N/A	125 (13.4%)	N/A	N/A
Galantamine	18 (5.6%)	N/A	100 (10.7%)	N/A	N/A
Memantine use, n (%)	4 (1.2%)	11 (1.8%)	81 (8.7%)	67 (18.3%)	<0.0001

Abbreviations: MCI-AD = Mild cognitive impairment with primary etiologic diagnosis of Alzheimer's disease; AD = Alzheimer's disease; ChEI = cholinesterase inhibitor; N/A = Not applicable, not calculated; bvFTD = behavioral variant frontotemporal dementia; PPA = primary progressive aphasia; FTLD = frontotemporal lobar degeneration

Missing data: MCI-AD (ChEI users, Never used ChEI): Family history of cognitive impairment (n=20, n=36); stroke (n=2, n=1); diabetes (n=0, n=1); hypercholesterolemia (n=6, n=3); cardiovascular disease (n=1, n=3); depression (n=2, n=4); depression medications (n=4, n=3); Age of onset of cognitive decline (n=28, n=102); Mild AD dementia (ChEI users, Never used ChEI): Family history of cognitive impairment (n=89, n=51); stroke (n=3, n=2); diabetes (n=3, n=1); hypertension (n=6, n=0); hypercholesterolemia (n=8, n=5); depression (n=9, n=2); depression medications (n=11, n=8); Age of onset of cognitive decline (n=9, n=10)

* Diagnosis at time of first ChEI use among ChEI users or at Initial Visit for never users

Used unadjusted logistic regression comparing ChEI users and never users (analysis of normal cognition at Initial Visit used Fisher's exact chi-square test)

§ Bolded if statistically significant at $p < 0.05$

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Table 3.

Adjusted annual change in scores in MCI-AD and AD dementia participants before and after begin taking cholinesterase inhibitors

Measure [‡]	MCI-AD [*]			Mild AD dementia [*]		
	Before first ChEI use		After first ChEI use	Before first ChEI use		After first ChEI use
	Annual score change (95% CI) [‡]	p-value	Annual score change (95% CI) [‡]	Annual score change (95% CI) [‡]	p-value	Annual score change (95% CI) [‡]
CDR-SB	0.03 (-0.03, 0.09)	<0.0001	0.61 (0.52, 0.69)	0.30 (0.24, 0.36)	<0.0001	1.40 (1.31, 1.49)
Mini Mental State Exam	-0.09 (-0.19, 0.02)	<0.0001	-0.68 (-0.79, -0.58)	-0.44 (-0.54, -0.34)	<0.0001	-1.58 (-1.68, -1.48)
Logical Memory Immediate	-0.04 (-0.23, 0.16)	<0.0001	-0.56 (-0.67, -0.45)	-0.60 (-0.74, -0.47)	<0.0001	-0.76 (-0.82, -0.71)
Logical Memory Delayed	-0.04 (-0.29, 0.22)	0.0001	-0.54 (-0.65, -0.42)	-0.53 (-0.68, -0.39)	0.72	-0.54 (-0.61, -0.48)
Digit Span Forward	-0.07 (-0.15, 0.01)	0.03	-0.16 (-0.20, -0.12)	-0.05 (-0.11, 0.01)	<0.0001	-0.23 (-0.26, -0.19)
Digit Span Backward	-0.13 (-0.19, -0.06)	0.16	-0.18 (-0.23, -0.14)	-0.15 (-0.22, -0.09)	<0.0001	-0.34 (-0.37, -0.31)
Animals	-0.45 (-0.68, -0.23)	0.002	-0.81 (-0.93, -0.68)	-0.70 (-0.85, -0.54)	<0.0001	-1.21 (-1.29, -1.13)
Vegetables	-0.26 (-0.40, -0.11)	<0.0001	-0.67 (-0.77, -0.57)	-0.62 (-0.72, -0.52)	<0.0001	-0.87 (-0.93, -0.81)
Boston Naming Test	-0.12 (-0.25, 0.01)	<0.0001	-0.66 (-0.79, -0.52)	-0.62 (-0.77, -0.46)	<0.0001	-1.46 (-1.59, -1.33)
Trail Making Part A	0.09 (-0.55, 0.73)	<0.0001	2.50 (1.89, 3.11)	2.23 (1.43, 3.04)	<0.0001	7.72 (7.06, 8.39)
Trail Making Part B	1.41 (-1.36, 4.19)	<0.0001	11.08 (9.20, 12.97)	11.50 (8.70, 14.29)	<0.0001	17.61 (16.14, 19.07)
Digit Symbol	-0.55 (-0.80, -0.29)	<0.0001	-1.53 (-1.78, -1.29)	-1.66 (-1.98, -1.33)	<0.0001	-3.08 (-3.29, -2.87)

Abbreviations: MCI-AD = Mild cognitive impairment with primary etiologic diagnosis of Alzheimer’s disease; AD = Alzheimer’s disease; ChEI = cholinesterase inhibitor; CDR-SB = Clinical Dementia Rating Sum of Boxes; CI = Confidence Interval

* Diagnosis at time of first ChEI use among ChEI users or at Initial Visit for never users

‡ Controlling for age, sex, education (years), race (White, African American, other), presence of I APOE e4 allele, behavioral problems, Geriatric Depression Scale score at first visit reported taking ChEI

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Higher test score equates to a better score for all tests, except CDR-SB, Trail Making Part A, Trail Making Part B in which lower score is better score

‡ Bolded if statistically significant at $p < 0.05$

Table 4.

Comparing adjusted annual change in scores over entire follow-up in MCI-AD and AD dementia participants in cholinesterase inhibitor users and non-users

Measure [‡]	MCI-AD*				Mild AD dementia*			
	Never used ChEI	Never used ChEI versus Took ChEI – before first ChEI use	Never used ChEI versus Took ChEI – after first ChEI use	p-value	Never used ChEI	Never used ChEI versus Took ChEI – before first ChEI use	Never used ChEI versus Took ChEI – after first ChEI use	p-value
	Annual score change (95% CI) [†]	Annual score change (95% CI) [†]	Annual score change (95% CI) [†]	p-value	Annual score change (95% CI) [†]	Annual score change (95% CI) [†]	Annual score change (95% CI) [†]	p-value
CDR-SB	0.24 (0.19, 0.30)	0.28	<0.0001	0.28	1.27 (1.12, 1.43)	<0.0001	0.003	<0.0001
Mini Mental State Exam	-0.29 (-0.37, -0.20)	0.74	<0.0001	0.74	-1.30 (-1.49, -1.11)	<0.0001	<0.0001	<0.0001
Logical Memory Immediate	0.11 (0.00, 0.22)	0.02	<0.0001	0.02	-0.42 (-0.56, -0.29)	0.02	0.003	0.003
Logical Memory Delayed	0.25 (0.13, 0.36)	0.0003	<0.0001	0.0003	-0.14 (-0.27, -0.01)	0.0002	0.05	0.05
Digit Span Forward	-0.04 (-0.08, 0.00)	0.42	0.05	0.42	-0.13 (-0.19, -0.06)	0.10	0.04	0.04
Digit Span Backward	-0.03 (-0.07, 0.01)	0.07	0.003	0.07	-0.14 (-0.20, -0.09)	0.99	0.003	0.003
Animals	-0.27 (-0.38, -0.17)	0.05	<0.0001	0.05	-0.79 (-0.96, -0.62)	0.78	0.006	0.006
Vegetables	-0.25 (-0.33, -0.17)	0.35	<0.0001	0.35	-0.66 (-0.79, -0.53)	0.19	0.10	0.10
Boston Naming Test	-0.09 (-0.18, 0.01)	0.18	<0.0001	0.18	-1.16 (-1.40, -0.91)	0.005	0.0001	0.0001
Trail Making Part A	0.93 (0.41, 1.46)	0.10	<0.0001	0.10	5.80 (4.52, 7.08)	0.0003	0.003	0.003
Trail Making Part B	4.19 (2.54, 5.85)	0.91	<0.0001	0.91	11.66 (8.02, 15.29)	0.19	0.19	0.19
Digit Symbol	-0.42 (-0.67, -0.16)	0.19	<0.0001	0.19	-2.08 (-2.54, -1.62)	0.01	0.0005	0.0005

Abbreviations: MCI-AD = Mild cognitive impairment with primary etiologic diagnosis of Alzheimer’s disease; AD = Alzheimer’s disease; ChEI = cholinesterase inhibitor; CDR-SB = Clinical Dementia Rating Sum of Boxes; CI = Confidence Interval

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* Diagnosis at time of first ChEI use among ChEI users or at Initial Visit for never users

[†] Controlling for age, sex, education (years), race (White, African American, other), presence of 1 APOE e4 allele, behavioral problems, Geriatric Depression Scale score at first visit reported taking ChEI

[‡] Higher test score equates to a better score for all tests, except CDR-SB, Trail Making Part A, Trail Making Part B in which lower score is better score

[§] Bolded if statistically significant at $p < 0.05$