Treatment With Cholinesterase Inhibitors and Memantine of Patients in the Alzheimer's Disease Neuroimaging Initiative

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Objectives: To assess the clinical characteristics and course of patients with mild cognitive impairment (MCI) and mild Alzheimer disease (AD) treated with cholinesterase inhibitors (ChEIs) and memantine hydrochloride.

Design: Cohort study.

Setting: The 59 recruiting sites for the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Participants: Outpatients with MCI and AD in ADNI.

Main Outcome Measures: The AD Assessment Scale–cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR) scale, and Functional Activities Questionnaire (FAQ).

Results: A total of 177 (44.0%) of 402 MCI patients and 159 (84.6%) of 188 mild-AD patients were treated with ChEIs and 11.4% of MCI patients and 45.7% of AD patients with memantine at entry. Mild-cognitive-impairment patients who received ChEIs with or without memantine were more impaired, showed greater decline in scores, and progressed to dementia sooner than patients who did not receive ChEIs. Alzheimer-disease patients who received ChEIs and memantine took them longer, were more functionally impaired, and showed greater decline on the MMSE and CDR (but not on the ADAS-cog or FAQ) than those who received ChEIs only.

Conclusions: Academic physicians frequently prescribe ChEIs and memantine earlier than indicated in the US Food and Drug Administration–approved labeling to patients who are relatively more severely impaired or who are rapidly progressing toward cognitive impairment. The use of these medications in ADNI is associated with clinical decline and may affect the interpretation of clinical trial outcomes.

Study Registration: clinicalTrials.gov Identifier: NCT00106899

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MANY PATIENTS WITH mild cognitive impairment (MCI) and mild Alzheimer disease (AD) participating in the National Institutes of Health (NIH) Alzheimer's Disease Neuroimaging Initiative (ADNI)[1] are receiving cholinesterase inhibitors (ChEIs) and memantine hydrochloride. The prescription of the former for MCI and the latter for mild AD is not approved by the US Food and Drug Administration (FDA). Rather, ChEIs are indicated for AD[2] and memantine for moderate to severe AD (defined as AD with Mini-Mental State Examination [MMSE] scores below 15), per FDA-approved labeling.[3]

Clinical trial results do not show efficacy for ChEIs in MCI[4-9] or for memantine in mild to moderate AD.[10-14] In 1 placebo-controlled MCI trial,[4] however, donepezil hydrochloride was associated with small effects on secondary outcomes, including memory and language subscales, as well as a clinical dementia rating (CDR) at 12 to 18 months and an MMSE score at 24 months of treatment that were not maintained.

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We compared MCI and AD patients enrolled in ADNI who were receiving ChEIs and memantine with those who were not receiving those medications on clinical differences at study entry and outcomes over 2 years to assess the medications' potential for efficacy or for affecting clinical outcomes.

METHODS

STUDY OVERVIEW AND PARTICIPANTS

The ADNI is a natural-history, nontreatment, observational study aimed at setting standards for brain imaging and chemical biomarkers for diagnosis and treatment trials.[1] Most of the 59 recruiting sites are academic, from which 188 participants with mild AD (ie, who had MMSE scores from 21 through 26), 402 with MCI (ie, who had MMSE scores from 24 through 30), and 229 with no cognitive impairment were enrolled and followed up with regular clinical, imaging, and biomarker assessments.[1] Inclusion criteria are detailed elsewhere; participants are allowed to continue their use of marketed antidementia medications if they had been taking stable doses for at least 4 weeks prior to entry.[1]

CLINICAL OUTCOMES

The main clinical outcomes in ADNI are the AD Assessment Scale–cognitive subscale (ADAS-cog),[15,16] CDR,[17] MMSE,[18] and Functional Activities Questionnaire (FAQ).[19] Assessments were performed at 6-month intervals during the first 2 years (except month 18 for AD patients). The ADAS-cog[15,16] is a structured scale used to evaluate memory, reasoning, language, orientation, praxis, language, and word-finding difficulty and is scored from 0 to 70, with higher scores indicating worse performance. The CDR[17] is used to rate 5 levels of impairment (0 [not impaired], 0.5, 1, 2, and 3 [severely impaired] in each of 6 categories: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR sum of boxes (CDR-SB) score is used as a measure of severity and outcome, ranging from 0 to 18.

The MMSE[18] is used to evaluate orientation, registration, attention, concentration, recall, language, and visual construction. Scores are the number of correct items, with a range from 0 through 30. The FAQ[19] relies on an interview with a study partner to rate a participant's ability to perform 10 complex activities of daily living (eg, manage finances, shop, prepare a meal, and travel). Each activity is rated on 3 levels (0 = does without difficulty, 1 = needs frequent advice or assistance, and 2 = someone else has taken over the activity); scores range from 0 to 20.

STATISTICAL ANALYSIS

We tested for associations between diagnostic groups (MCI vs AD) at study entry on clinical characteristics and medication use (including dose and previous duration of use) and between treatment groups within diagnoses using the Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables. (We excluded the few MCI patients who received only memantine and the few AD patients who received no medication or memantine only.)

We used linear mixed-effects models to assess the rate of change for each of the 4 clinical outcomes over 24-month follow-up periods between treatment groups. Time was modeled continuously and calculated from participant visit dates. Prior drug exposure was estimated using concurrent medication start and stop dates. Diagnostics for model fit were done by visual inspection of residuals. Imbalances of age, sex, educational level, apolipoprotein E (*APOE*) ε4 carrier status, and family history were assessed among treatment groups. Covariates were included if they were associated with the outcome ($\alpha = .15$) and treatment group ($\alpha = .10$). Estimates were adjusted for age regardless of observed association.

We assessed time to progression from MCI to dementia, defined as change in CDR score from 0.5 through 1.0, using Weibull regression, an interval-censored parametric survival model, because the time could only be known to have occurred between 6-month visits and not on an exact date. Ratios of mean time to progression derived from the survival analysis were used to compare the risk for progression in the medication-treated groups with that in the nontreated group. Covariates were included using the same criteria as the mixed models.

We compared by group the proportions discontinuing their medications during follow-up, the reasons for discontinuation, and serious adverse events (by FDA definition), including deaths. We then assessed the numbers of patients who started these medications after study entry. Data were downloaded from the ADNI database (http://adni.loni.ucla.edu/) on May 7, 2009. Statistical analyses were performed on all participants with available data using R software, version 2.9.2 (http://www.r-project.org).

Table 1. Characteristics and Medication Use for All MCI and AD Patients at Study Entry[a]

Characteristic	MCI (n=402)	AD (n=188)	*P* Value[b]
Age (SD), y	74.8 (7.42)	75.3 (7.56)	.47
Female sex	143 (35.6)	89 (47.3)	.007
Educational level (SD), y	15.7 (3.04)	14.7 (3.14)	<.001
Family history of AD or dementia[c]	170 (49.6)	78 (50.3)	.92
APOE ε4 genotype carriers, 1 or 2 alleles	215 (53.5)	124 (66.0)	.004
GDS score (SD)[d]	1.58 (1.37)	1.67 (1.42)	.50
MMSE score (SD)[d]	27.0 (1.78)	23.3 (2.04)	<.001
ADAS-cog, errors, mean (SD)	11.54 (4.43)	18.72 (6.33)	<.001
CDR-SB score (SD)	1.60 (0.88)	4.36 (1.61)	<.001
FAQ score (SD)	3.88 (4.48)	13.14 (6.84)	<.001
ChEI use	177 (44.0)	159 (84.6)	<.001
ChEI type			.22
Donepezil hydrochloride	150 (84.7)	123 (77.4)	. . .
Galantamine	18 (10.2)	25 (15.7)	. . .
Rivastigmine	9 (5.1)	11 (6.9)	. . .
Prior exposure, median (IQR), y	0.97 (0.41-2.14)	1.42 (0.57-3.01)	.02
Memantine hydrochloride use	46 (11.4)	86 (45.7)	<.001
Prior exposure, median (IQR), y	0.88 (0.30-1.42)	0.94 (0.32-1.93)	.38
ChEI and memantine prescription	36 (9.0)	73 (38.8)	<.001
Neither ChEI nor memantine	215 (53.5)	16 (8.5)	<.001

Abbreviations: AD, Alzheimer disease; ADAS-cog, AD Assessment Scale–cognitive subscale; *APOE*, apolipoprotein E; CDR-SB, Clinical Dementia Rating–sum of boxes subscale; ChEI, cholinesterase inhibitor; ellipses, not applicable; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

[a] Data are given as number (percentage) unless otherwise indicated.

[b] *P* values based on Fisher exact tests for categorical variables and Kruskal-Wallis tests for continuous variables.

[c] Family history of AD or dementia in first-degree relatives was missing for 59 MCI and 33 AD patients.

[d] Inclusion criteria required GDS scores of less than 6 and MMSE scores from 24 to 30 for MCI and from 21 through 26 for mild-AD patients.

RESULTS

MCI COMPARED WITH AD PATIENTS AT STUDY ENTRY

Most of the MCI and AD patients were male (**Table 1**). One-half of MCI and two-thirds of AD patients were *APOE* ε4 carriers. Mild-cognitive-impairment patients showed less

Table 2. Characteristics of MCI Patients by Treatment Groups at Study Entry[a]

Characteristic	None (n=215)	ChEI (n=141)	ChEI and Memantine Hydrochloride (n=36)	*P* Value[b]
Age (SD), y	75.4 (7.60)	74.2 (7.06)	74.0 (8.23)	.30
Female sex	80 (37.2)	52 (36.9)	10 (27.8)	.58
Educational level (SD), y	15.5 (3.15)	15.7 (2.90)	16.7 (2.95)	.08
MCI due to AD	205 (95.3)	132 (93.6)	32 (88.9)	.61
APOE ε4 genotype carrier on 1 or 2 alleles	99 (46.0)	86 (61.0)	25 (69.4)	<.01
Family history of AD or dementia[c]	85 (47.0)	63 (51.2)	18 (62.1)	.29
MMSE score (SD)[d]	27.1 (1.80)	27.1 (1.75)	26.4 (1.70)	.10
ADAS-cog, errors (SD)	10.7 (4.12)	12.2 (4.55)	13.7 (4.54)	<.001
CDR-SB score (SD)	1.45 (0.77)	1.74 (0.93)	1.97 (1.08)	<.001
FAQ score (SD)	2.88 (3.54)	4.60 (4.93)	6.43 (5.58)	<.001
Prior exposure, median (IQR), y				
ChEI		0.90 (0.31-2.09)	1.54 (0.78-2.75)	.02
Memantine		. . .	0.80 (0.33-1.35)	. . .

Abbreviations: AD, Alzheimer disease; ADAS-cog, AD Assessment Scale–cognitive subscale; *APOE*, apolipoprotein E; CDR-SB, Clinical Dementia Rating–sum of boxes subscale; ChEI, cholinesterase inhibitor; ellipses, not applicable; FAQ, Functional Activities Questionnaire; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

[a] Data are given as number (percentage) unless otherwise indicated. Ten MCI patients who received only memantine were excluded.

[b] *P* values based on Fisher exact and Kruskal-Wallis tests.

[c] AD or dementia in first-degree relatives was missing for 59 MCI patients.

[d] Inclusion criteria for MCI patients required MMSE scores from 24 through 30.

impairment on clinical ratings scales. Among MCI patients, 177 (44.0%) received ChEIs; 46 (11.4%), memantine; and 215 (53.5%), neither. Among AD patients, 159 (84.6%) received ChEIs; 86 (45.7%), memantine; and 16 (8.5%), neither. Median duration of prior ChEI use was 0.97 years for MCI and 1.42 years for AD patients (*P*=.02), and duration of prior treatment with memantine was 0.88 and 0.94 years (*P*=.38), respectively.

MCI RESULTS: ChEIs AND MEMANTINE VS NO TREATMENT

Patient Characteristics

There were virtually no differences in age, sex, and educational level between MCI patients who received ChEIs only or ChEIs and memantine and patients who received none (**Table 2**). A total of 93.9% were classified as having MCI due to Alzheimer disease. Carriers of the genotype *APOE* ε4 were more prevalent in the treated groups. The 2 medication-treated groups performed worse on the ADAS-cog, CDR, and FAQ than the no-treatment group, with the group that received a ChEI and memantine performing worse than the ChEI-only group. Median prior treatment with ChEIs was 0.90 years for patients receiving ChEIs only and 1.54 years for those receiving both types of medication; median treatment with memantine was 0.80 years prior to study entry.

Of the 150 donepezil-treated patients, 116 (77.3%) were taking 10 mg/d or higher, 33 (22.0%) were taking 5 mg/d, and 1 (0.7%) was taking 2.5 mg/d. Of the 18 galantamine-treated patients, 14 (77.8%) were taking 16.0 to 24.0 mg/d and 4 (22.2%) were taking 8.0 to 12.0 mg/d. Of the 9 rivastigmine-treated patients, 8 (88.9%) were taking 6.0 to 12.0 mg/d and 1 (11.1%) was taking 3.0 mg/d. Of the 36 memantine-treated patients (not including 10 who were taking memantine only), 30 (83.3%) were taking 20.0 mg/d and 6 (16.7%) were taking 10.0 mg/d.

Change in Rating Scales Scores

Mild-cognitive-impairment patients treated with ChEIs only or with ChEI and memantine showed decline on the ADAS-cog, MMSE, CDR-SB, and FAQ to a greater extent than patients not receiving those medications (**Table 3**, **Figure 1**). The mean differences generally increased from month 6 to month 24. The magnitude of decline was more than 2-fold greater in patients treated with both types of medication than in those treated with ChEIs only on the observed change scores at the 6-, 12-, 18-, and 24-month follow-ups and the model-based change per year (except the ADAS-cog). For example, decline on the MMSE was 0.87 point greater per year in patients treated with ChEIs only and 1.89 points greater per year in those treated with both types of medication compared with patients not treated with either type.

Progression to AD

One hundred twenty-eight MCI patients progressed to having dementia, including 48 (22.3%), 60 (42.6%), and 20 (55.6%) in the nontreated, ChEI-only–treated, and ChEI and memantine–treated groups, respectively. The mean time to dementia for ChEI-only–treated patients was reduced by 29.8% (*P*=.005) and for ChEI and memantine–treated patients by 41.8% (*P*=.003) compared with the no-treatment group, and the risk for progression was higher for patients taking medications (**Figure 2**). Estimates were adjusted for age, *APOE* ε4 genotype carrier status, educational level, and baseline ADAS-cog score.

Duration of Prior Drug Exposure

Duration of exposure to ChEI treatment prior to study entry was not associated with change on the ADAS-cog compared with no treatment (*P*=.57). However, every year

Table 3. Observed Change From Baseline and Modeled Difference in Annual Rate of Decline on Clinical Outcomes by Treatment for MCI Patients (See Figure 1)[a]

Assessment Instrument and Treatment Group	Observed Change From Study Entry, mo				Increase in Rate of Decline[b]	
	6	12	18	24	Compared With None (Points/y)	*P* Value for Model
ADAS-cog						
None	0.49	0.84	1.32	1.83		
ChEI only	0.59	1.00	2.41	3.46	0.78	.03
ChEI and memantine hydrochloride	2.83	3.23	5.74	5.64	0.86	.14
MMSE						
None	–0.32	0.01	–0.54	–0.72		
ChEI only	–0.87	–1.20	–1.55	–2.72	–0.87	<.001
ChEI and memantine	–1.33	–2.56	–3.86	–4.36	–1.89	<.001
CDR–SB						
None	0.22	0.48	0.73	1.10		
ChEI only	0.45	0.77	1.00	1.62	0.26	<.001
ChEI and memantine	0.89	1.45	2.21	2.69	0.72	<.001
FAQ						
None	0.64	1.28	2.36	3.64		
ChEI only	1.12	2.27	3.07	4.46	0.63	.007
ChEI and memantine	3.16	4.29	6.36	8.28	2.29	<.001

Abbreviations: ADAS-cog, AD Assessment Scale–cognitive subscale; CDR-SB, Clinical Dementia Rating–sum of boxes subscale; ChEI, cholinesterase inhibitor; FAQ, Functional Activities Questionnaire; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

[a] Sample sizes for the 3 treatment groups were from 215 to 147 for no treatment, 141 to 92 for ChEI only, and 36 to 25 for ChEI and memantine. Overall sample sizes for the models were 375 to 392 patients.

[b] Model-based estimates compared with the no-treatment group. Estimates were adjusted for age, educational level, *APOE* genotype, and baseline CDR-SB or ADAS-cog score.

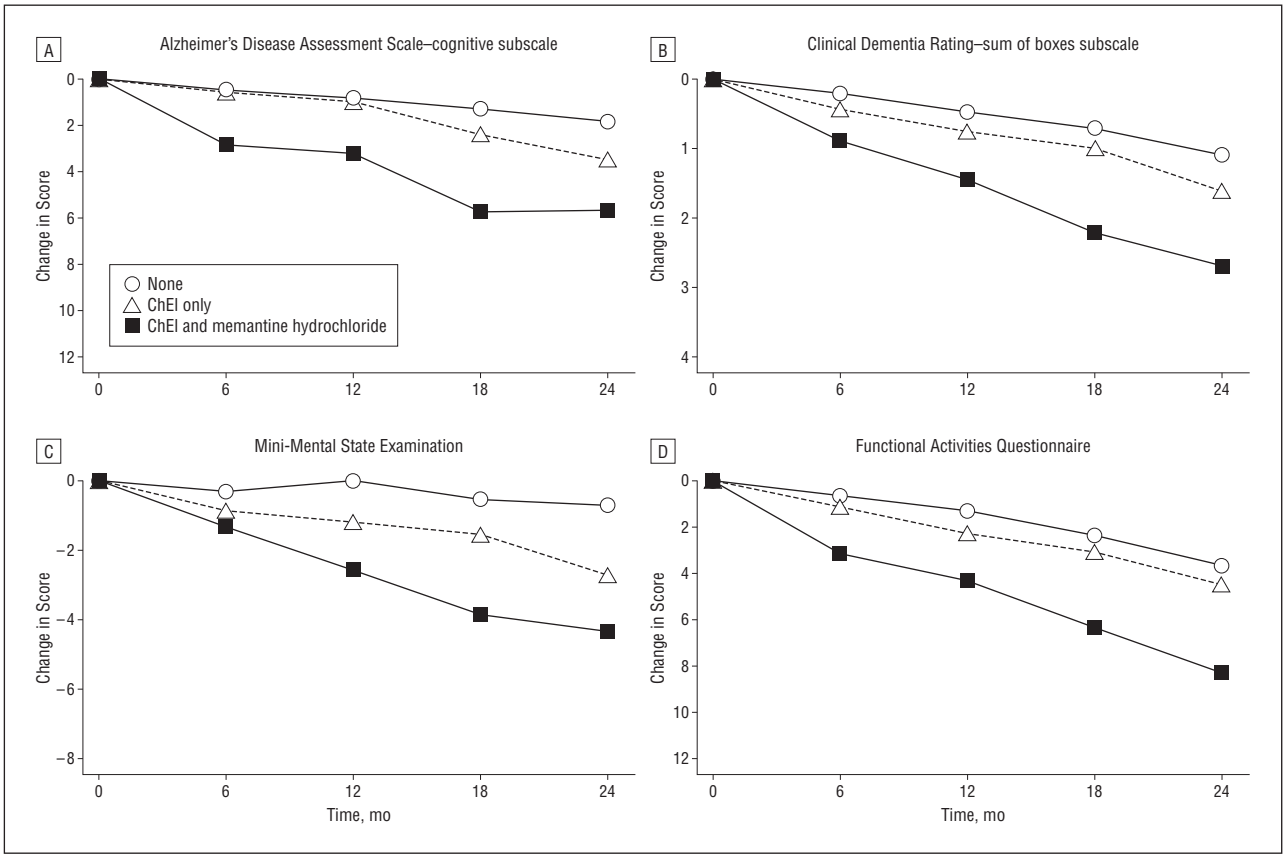

Figure 1. Observed change on clinical outcomes by treatment for patients with mild cognitive impairment. See Table 3 for values. ChEI indicates cholinesterase inhibitor.

of ChEI exposure prior to study entry was associated with a rate of decline of 0.13 point per year slower on the CDR-SB ($P<.001$), 0.12 point per year slower on the MMSE ($P=.04$), and 0.41 point per year slower on the FAQ ($P<.001$) compared with no treatment. For example, during a 2-year period, a participant taking a ChEI

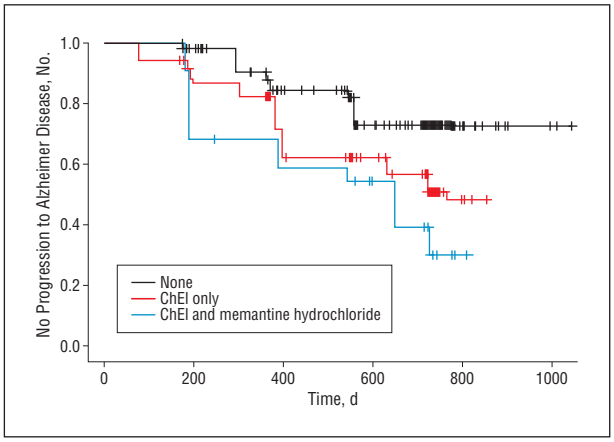

Figure 2. Kaplan-Meier estimates of the rate of progression from mild cognitive impairment to Alzheimer disease, showing the observed estimates for no progression to Alzheimer disease for the 3 treatment groups during follow-up (*P*=.003). ChEI indicates cholinesterase inhibitor.

for 2.5 years at baseline would be expected to show a decline of 0.24 point less on the MMSE than a participant with only 0.5 years of exposure.

Discontinuations, Adverse Events, and Medication Discontinuation and Initiation

Thirty-seven (9.2%) of 402 MCI patients discontinued treatment during follow-up. The main reasons were withdrawal of consent (n=23), loss to follow-up (n=4), and protocol noncompliance (n=2). Virtually no differences were found among treatment groups. Serious adverse events were reported in 59 (27.4%), 30 (21.3%), and 12 (33.3%) (including deaths in 5, 3, and 2 patients) no-treatment, ChEI-only–, and ChEI and memantine–treated patients, respectively. (There was 1 serious adverse event and 0 deaths in the 10 patients treated with memantine only.)

Sixteen (9.0%) of 177 MCI patients taking ChEIs discontinued treatment during follow-up, and 45 (20.9%) of 215 not taking ChEIs started to do so. Five (13.9%) of 36 patients taking memantine at baseline discontinued doing so. Of 356 not taking memantine at baseline, 45 (12.6%) started doing so, with 29 (8.1%) taking it in addition to their ChEI.

AD RESULTS: ChEIs AND MEMANTINE VS ChEI TREATMENT

Patient Characteristics

There were virtually no differences in age, sex, educational level, or family history of AD or dementia between mild-AD patients receiving ChEIs only and those receiving ChEIs with memantine (**Table 4**). Carriers of *APOE* ε4 were somewhat more prevalent in the ChEI-only group than in the group treated with both types of medication (74.4% vs 58.9%). At entry, the group receiving both types of medication performed worse on the CDR and FAQ but not the ADAS-cog (*P*=.11) or MMSE compared with the group receiving only a ChEI. Median duration of prior use of ChEIs was 2.20 years for patients receiving both types of medication and 0.97 years for those receiving only ChEIs. The median duration for prior memantine treatment was 1.03 years.

Overall, 108 (87.8%) of donepezil-treated patients were taking 10 mg/d or greater and 15 (12.2%) were taking 5 mg/d; 23 (92.0%) of galantamine-treated patients were taking 16 to 24 mg/d and 2 (8.0%), 8 mg/d; 10 (90.9%) of rivastigmine-treated patients took 6 to 12 mg/d, and 1 (9.1%) took 3 mg/d. For memantine, 63 (86.3%) were taking 20 mg/d, 8 (11.0%) were taking 10 mg/d, 1 (1.4%) was taking 15 mg/d, and 1 (1.4%) was taking 40 mg/d.

Table 4. Characteristics of AD Patients Taking Antidementia Medications at Study Entry[a]

Characteristic	ChEI Only (n=86)	ChEI and Memantine Hydrochloride (n=73)	*P* Value[b]
Age (SD), y	76.0 (6.69)	74.0 (8.63)	.21
Female sex, No. (%)	38 (44.2)	31 (42.5)	.87
Educational level (SD), y	14.8 (3.05)	15.1 (2.85)	.43
APOE ε4 genotype carrier on 1 or 2 alleles, No. (%)	64 (74.4)	43 (58.9)	.04
Family history of AD or dementia, No. (%)[c]	35 (50)	34 (54)	.73
MMSE score (SD)[d]	23.4 (2.02)	23.1 (2.05)	.35
ADAS-cog, errors (SD)	18.1 (5.87)	19.7 (6.64)	.11
CDR-SB score (SD)	4.15 (1.47)	4.82 (1.64)	.001
FAQ score (SD)	11.7 (6.40)	15.8 (7.05)	<.001
ChEI exposure, median (IQR), y	0.97 (0.33-2.15)	2.20 (1.00-3.66)	<.001
Memantine exposure, median (IQR), y	. . .	1.03 (0.38-1.97)	. . .

Abbreviations: AD, Alzheimer disease; ADAS-cog, AD Assessment Scale–cognitive subscale; *APOE*, apolipoprotein E; CDR-SB, Clinical Dementia Rating–sum of boxes subscale; ChEI, cholinesterase inhibitor; ellipses, not applicable; FAQ, Functional Activities Questionnaire; IQR, interquartile range; MMSE, Mini-Mental State Examination.

[a] Sixteen (8.5%) patients who received no medication and 13 (7.0%) who received memantine only were excluded.

[b] *P* values based on Fisher exact and Kruskal-Wallis tests.

[c] Family history of AD or dementia in 1st-degree relatives was missing for 26 AD patients.

[d] Inclusion criteria for AD patients required MMSE scores from 21 through 26.

Change in Rating Scales

Alzheimer-disease patients treated with ChEIs and memantine showed greater clinical decline than patients treated with only ChEIs on the MMSE and CDR-SB scales, by 0.93 and 0.50 points per year, respectively (**Table 5**, **Figure 3**). There were no significant differences between the groups on the ADAS-cog or the FAQ based on the modeled differences, although at 24 months, patients taking both types of medication had a worse score, by 2 ADAS-cog points, on observed change. Duration of exposure prior to entry was not associated with change on the ADAS-cog (*P*=.60), MMSE (*P*=.05), CDR-SB (*P*=.27), or FAQ (*P*=.76) among AD patients treated only with a ChEI vs treatment with both types of medication.

Table 5. Observed Change From Baseline and Modeled Difference in Annual Rate of Decline on Clinical Outcomes by Treatment for AD Patients (See Figure 3)[a]

Assessment Instrument and Treatment Group	Observed Change From Study Entry, mo				Increase in Rate of Decline[b]	
	6	12	18	24	Compared With ChEI Only (Points/y)	*P* Value for Model
ADAS-cog						
ChEI only	2.35	4.96	. . .	9.25		
ChEI and memantine hydrochloride	2.56	4.44	. . .	11.26	−0.12	.87
MMSE						
ChEI only	−0.64	−2.15	. . .	−4.19		
ChEI and memantine	−1.96	−3.15	. . .	−6.04	−0.93	.005
CDR-SB						
ChEI only	0.59	1.30	. . .	3.02		
ChEI and memantine	0.93	1.86	. . .	4.09	0.50	.007
FAQ						
ChEI only	2.60	5.43	. . .	7.79		
ChEI and memantine	2.22	4.02	. . .	6.74	−0.55	.21

Abbreviations: AD, Alzheimer Disease; ADAS-cog, AD Assessment Scale–cognitive subscale; CDR-SB, Clinical Dementia Rating–sum of boxes subscale; ChEI, cholinesterase inhibitor; ellipses, not applicable; FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental State Examination.

[a] Sample sizes for the 2 treatment groups were from 86 through 54 for ChEI only and between 73 and 49 for ChEI and memantine. Overall, sample sizes for the models were 158 through 149.

[b] Model-based estimates comparing treatment with ChEI and memantine to ChEI only. Estimates were adjusted for age, educational level, *APOE* genotype, and baseline CDR-SB or ADAS-cog score.

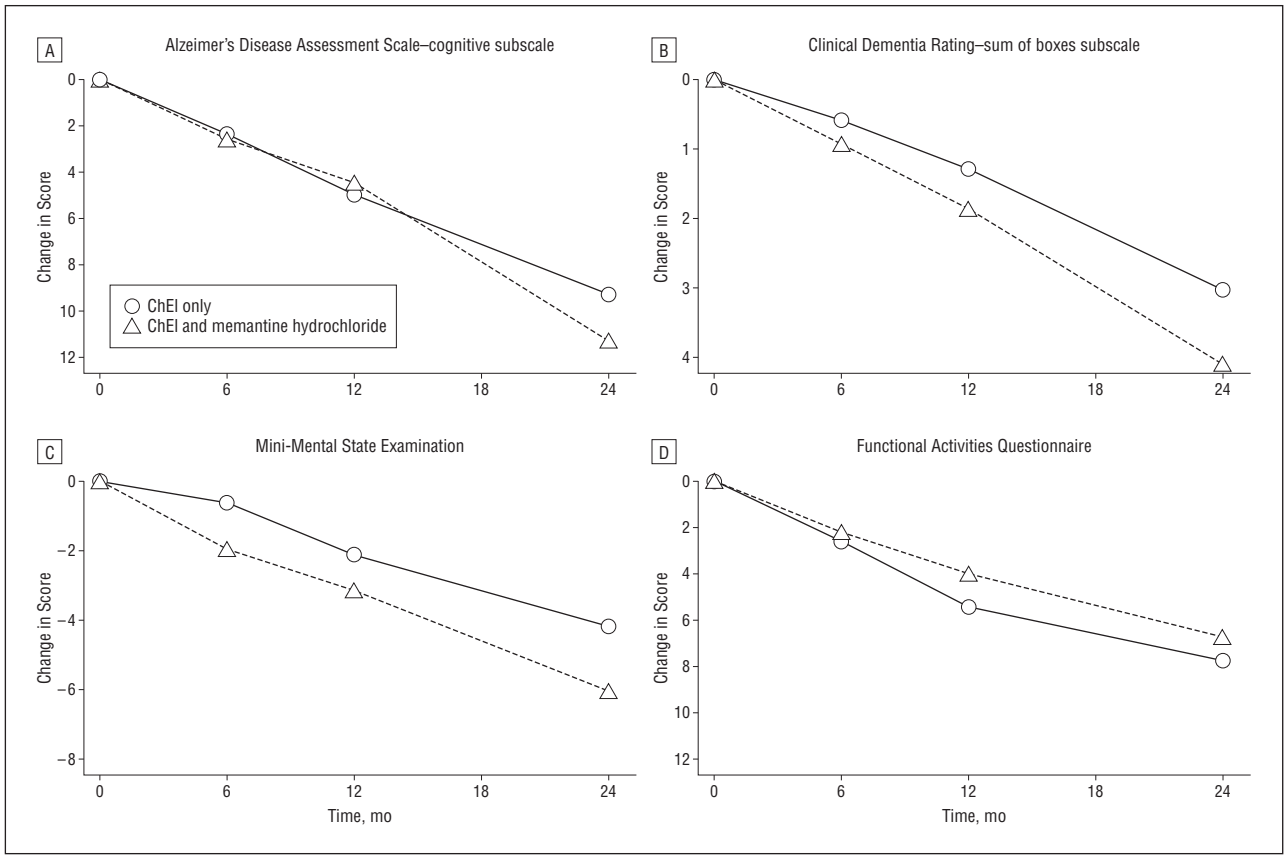

Figure 3. Observed change on clinical outcomes by treatment for mild–Alzheimer Disease patients. See Table 5 for values. ChEI indicates cholinesterase inhibitor.

Discontinuations, Adverse Events, and Medication Discontinuation and Initiation

Sixteen (8.5%) of 188 AD patients discontinued medications during follow-up. The main reasons were withdrawal of consent (n = 10) and protocol noncompliance (n = 3), and there were no significant differences between the groups. Serious adverse events were reported in 18 (20.9%) and 22 (30.1%) (*P* = .02), including deaths in 1 ChEI-only–treated and 2 ChEI and memantine–treated patients, respectively.

Of 159 AD patients taking ChEIs at entry, 25 (15.7%) discontinued taking them during follow-up. Fourteen (19.2%) of 73 patients taking memantine discontinued doing so, and 30 (34.9%) of 86 patients not taking memantine at entry started doing so.

COMMENT

Rates of ChEI (84.6%) and memantine treatment (45.7%) for mild-AD patients among the mostly academic ADNI centers are similar to rates found in recent mild to moderate AD clinical trials conducted from 2003 through 2009, wherein mean ChEI treatment increased from 52.9% to nearly 100% and memantine treatment from 13.5% to 63.4%.[20] Rates were comparable to a recent tarenflurbil trial in mild AD, in which ChEI treatment was 75.1% and memantine treatment was 48.1%.[21] However, rates of treatment with those medications were higher than for similar mild-AD patients registered in the NIH National Alzheimer's Coordinating Center (NACC) during 2009, of whom 152 (58.5%) of 260 received ChEIs and 65 (25.0%) received memantine (Walter Kukull, PhD; oral communication; January 13, 2010).

Cholinesterase inhibitor treatment of 44.0% for MCI patients in ADNI was nearly twice that of MCI patients in the NACC and the California Alzheimer's Disease Centers.[22] Specifically, 23.9% of 351 MCI patients in the NIH centers and 25.1% of 578 MCI patients in the California centers received these medications. Treatment with memantine (at 11.1% and 10.9%, respectively) was similar to that in ADNI (11.4%).

The MCI patients who received ChEIs had, on average, a more severe decline in scores than those who did not, and their scores deteriorated more rapidly. They were very similar to AD patients, as evidenced by lower performance scores; *APOE* ε4 carrier rates of 61.0% to 69.5% similar to AD patients enrolled in clinical trials[20]; and greater rate of worsening of clinical ratings compared with MCI participants from recent trials.[4,8,9] Retrospectively, the study physicians probably considered the patients to have technically fulfilled the MCI criteria used in ADNI while also having AD, as further evidenced by their characterizing 95% of the MCI diagnoses as MCI due to AD. Under these circumstances, use of ChEIs could be expected to be consistent with the treatment of early AD.

Although unlikely, other hypotheses merit consideration, including the possibility that treatment with ChEIs in MCI during 1 to 1.5 years is associated with worse outcomes compared with no treatment. Notably, the approximately 1.5-point ADAS-cog and 0.5- to 1.5-point CDR-SB differences between the treatment and no-treatment groups during 1 to 2 years have the same magnitude as the effect of ChEIs in placebo-controlled AD trials[23] and as the effect sizes expected for experimental drugs in current clinical trials[20,21] but in the opposite (countertherapeutic) direction. This observation is also consistent with the observation herein that the mild-AD patients who received both ChEIs and memantine and received the ChEI for longer than 2 years prior to entering ADNI had greater dementia severity and a worse disease course compared with those who received ChEIs only and had been treated less than half as long. It should be emphasized, however, that none of the placebo-controlled MCI trials of ChEIs suggest cognitive or behavioral toxicity of the medications during the 2- to 4-year trial periods.[4-6]

Although a relatively longer duration of treatment with ChEIs in MCI prior to entering ADNI was associated with less decline compared with no treatment in 3 of 4 outcomes, the effects, such as 0.12 MMSE point per year, were slight. This finding may represent the combination of a group taking medications who had not shown clinical decline and whose medication regimens are maintained on a long-term basis and another group who had recently started taking medications because their symptoms were more severe or their scores were showing more rapid decline.

Evidence for the efficacy of memantine in mild AD is lacking despite its widespread use.[13] The 3 placebo-controlled trials for mild to moderate AD included few mild-AD patients (ie, they allowed only patients with MMSE scores ≤22 in 2 trials and ≤24 in 1) and were not statistically significant overall.[10-13] As with MCI patients, one consideration is that the mild-AD patients who have worsening scores on the assessment measures may have had memantine added to their ChEI regimen with hope of added benefit. In other words, physicians in a predicament may choose to treat early with memantine rather than delay treatment until patients' conditions deteriorate into the severity range for which the medication has been demonstrated effective.[3]

Important limitations to making inferences from these analyses include that ADNI is not a treatment study and not a clinical trial and that medication was not assigned randomly or in a double-blind manner to minimize biased outcomes. As with all observational studies, known and unknown potential biases cannot be fully corrected for by multivariable analysis. As we have discussed herein, physicians at these academic centers could have made treatment decisions based on biomarkers including *APOE* ε4 genotype carrier status, clinical severity, neuropsychological test performance, and clinical course.

The results raise issues regarding MCI diagnoses and in particular whether the diagnosis of MCI due to Alzheimer disease, as used by research physicians in ADNI, is actually early or prodromal AD before or early in the dementia syndrome.[24] Moreover, there are substantial implications for health policy and clinical trial planning and interpretations because MCI and mild-AD patients receiving marketed antidementia medications may have different responses to experimental drugs and different, counterintuitive clinical courses compared with those not receiving medications. It does not necessarily follow, however, that because medication-treated patients show worsening on assessments to a greater extent than nontreated patients, they would be more likely to respond to an experimental drug or that a therapeutic effect to such treatment may be detected more readily. Rather, the opposite could be true. Much more investigation needs to be given to the long-term effects of marketed antidementia medications; the imaging and biomarker studies in ADNI may provide additional information.

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Additional Information: The Alzheimer's Disease Neuroimaging Initiative: Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI, NIA U01 AG024904) database (www.loni.ucla.edu/ADNI). As such, the investigators within ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete list of investigators in ADNI is listed at: http://adni.loni.ucla.edu/about/who-we-are/principal-investigators/. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as to lessen the time and cost of clinical trials.

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