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Off-Label Medication Use in Frontotemporal Dementia

Bei Hu, BS¹, Leslie Ross, PhD², John Neuhaus, PhD³, David Knopman, MD⁴, Joel Kramer, PsyD¹, Bradley Boeve, MD⁴, Richard J. Caselli, MD⁵, Neill Graff-Radford, MD⁶, Mario F. Mendez, MD⁷, Bruce L. Miller, MD¹, and Adam L. Boxer, MD, PhD¹

¹Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA, USA

²Institute for Health and Aging, University of California, San Francisco, CA, USA

³Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA

⁴Department of Neurology, Mayo Clinic, Rochester, MN, USA

⁵Department of Neurology, Mayo Clinic, Scottsdale, AZ, USA

⁶Department of Neurology, Mayo Clinic, Jacksonville, FL, USA

⁷Department of Neurology, University of California, Los Angeles, CA, USA

Abstract

Objective—There are no Food and Drug Administration (FDA)-approved medications indicated for the treatment of frontotemporal dementia (FTD). We sought to determine the most commonly used drugs used to treat behavioral variant FTD (bvFTD) in specialized dementia clinics.

Methods—Medication and demographic data from the Alzheimer's Disease Research Centers of California (ARCC) and a multicenter FTD natural history study (NHS) data set were compared in bvFTD and Alzheimer's disease (AD), and effects of demographic variables were assessed using logistic regression.

Results—Overall, the percentage of patients taking one or more FDA-approved AD or psychiatric medications was similar in bvFTD and AD; however, after controlling for demographic variables, acetylcholinesterase inhibitor (AChI) use was less common in bvFTD, whereas memantine use remained similar in the 2 groups.

Conclusions—Despite lack of evidence for efficacy, the use of AChIs and memantine is common in bvFTD. Clinical trials should be pursued to determine the optimal therapeutic interventions for bvFTD.

Keywords

frontotemporal dementia; Alzheimer's disease; treatment; donepezil; memantine; galantamine; antipsychotic agents

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Corresponding Author: Adam L. Boxer, Memory and Aging Center, Department of Neurology, University of California, San Francisco, Box 1207, San Francisco, CA 94143, USA. aboxer@memory.ucsf.edu.

Declaration of Conflicting Interest

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Introduction

Alzheimer's disease (AD) and frontotemporal dementia (FTD) are common causes of dementia. Frontotemporal dementia is pathologically different from AD, and patients present with dissimilar clinical symptoms, commonly including changes in personality, behavior, and language. Treatment with acetylcholinesterase inhibitors (AChI; donepezil, galantamine, and rivastigmine) or the *N*-methyl-D-aspartate (NMDA)-receptor antagonist memantine is approved by the Food and Drug Administration (FDA) for use in AD, but there are no medications indicated for use in FTD.¹ However, clinical experience suggests that many patients with FTD are treated off-label with AD medications.

Acetylcholinesterase inhibitors and memantine are well tolerated and have modest effects on the symptoms of AD, with a variety of randomized, placebo-controlled clinical trials demonstrating better cognitive, functional, and global outcomes when compared to placebo.² Moreover, combinations of an AChI plus memantine may be more effective than treatment with donepezil alone.³ In addition to AChI and memantine, antipsychotics, antidepressants, and anxiolytics are often used in patients with AD to treat symptoms of agitation, hallucinations, delusions, and other behavioral dysfunctions with varying degrees of success.^{4,5}

A number of medications that affect the function of specific neurotransmitter systems have been studied and may offer modest benefits for the behavioral and cognitive sequelae of behavioral variant (bv) FTD. There is selective vulnerability of serotonergic neurons in FTD, and a meta-analysis of SSRI treatment studies suggests that these medications offer modest benefits for improving the behavioral symptoms of bvFTD.⁶ A randomized, placebo-controlled trial demonstrated that trazodone improves behavior as measured by the neuropsychiatric inventory (NPI) in bvFTD.⁷ Although commonly used to control behavior in bvFTD, antipsychotic agents may be of limited use due to enhanced sensitivity to extrapyramidal side effects in these patients.⁸

Less success has been reported in treating the cognitive symptoms of bvFTD. Unlike AD, cholinergic neurons are relatively preserved in bvFTD, and studies using AChIs have produced mixed results. One open-label study suggested that rivastigmine was well tolerated in bvFTD,⁹ and a recent placebo-controlled study demonstrated a potential benefit of galantamine in logopenic variants of primary progressive aphasia (who may have underlying AD pathology¹⁰); however, experience from a number of FTD-specialty clinics suggests that AChIs frequently worsen behavior in bvFTD patients with more severe behavioral impairments.^{11,12} Three open-label studies of memantine in FTD have been reported, all suggesting that the FDA-approved dose for moderate-severe AD is well tolerated; however, no clear efficacy signals could be identified.¹³⁻¹⁵

Little is known about actual medication use in bvFTD. We compared the use of anti-AD medications, antipsychotics, mood stabilizers, antidepressants, and anxiolytics by patients with bvFTD to patients with AD in a combined cohort derived from the Alzheimer's Research Centers of California (ARCC) database and a multicenter, natural history study (NHS) of FTD.¹⁶

Methods

Medication and demographic data were gathered from the Alzheimer's Disease Research Centers of California (ARCC) Minimum Uniform Data Set (MUDS) and a multicenter FTLN NHS data set.¹⁶ Patients with dementia due to NINCDSADRDA (National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association) probable AD¹⁷ or bvFTD¹⁸ were included in this study. Both AD and

bvFTD cases were included from the ARCC data set. Progressive aphasia cases were not included because there were too few to analyze. Only patients with bvFTD from the NHS data set were included for analysis because these data set contained no patients with AD. Because the University of California, San Francisco (UCSF), and University of California, Los Angeles (UCLA), contributed participants to both the ARCC and the NHS data sets, dates of birth were analyzed to be certain that none of the bvFTD cases were duplicated in the final data set. Because memantine was approved for use in AD in October 2003, patients with a visit date prior to January 2004 were excluded from analysis. For the ARCC data, disease duration was calculated by subtracting the age at onset of symptoms from the age at the date of visit. The disease duration was already included as a variable in the FTLN NHS data set.

The study cohort consisted of 616 participants. Of these patients, 569 patients were from the ARCC data set, who had primary diagnoses of probable AD (n = 528) or bvFTD (n = 41). Forty-seven patients with bvFTD were from the FTLN NHS data set. Patient visits occurred between 2004 and 2008, and data came from 13 centers: 93 from UCSD, 67 from USC/Rancho Los Amigos, 45 from UC Davis/Sacramento, 44 from UC Davis/Martinez, 57 from UCSF, 67 from Stanford, 66 from UCSF/Fresno, 39 from UC Irvine, 19 from UCLA, 96 from USC/Los Angeles, 10 from Mayo Rochester, 9 from Mayo Jacksonville, and 4 from Mayo Scottsdale.

Variables Analyzed

Variables that were analyzed included original data set, education level, age of onset, number of years symptoms present, date of visit, date of birth, gender, race, Mini-Mental State Examination (MMSE) score, anti-AD medication, and all other medication use were recorded. Because memantine was approved for use in AD in October 2003, patients with a visit date prior to January 2004 were excluded from analysis. Race was coded as Caucasian, African American, Asian/Pacific Islander, Native American, Hispanic/Latino, other, and unknown for the baseline characteristics analysis. However, for some analyses (eg, logistic regression), the patient race was coded as either non-Hispanic white or non-white to increase sample size. Age was calculated using the patients' date of birth and the date of the visit.

Use of 5 different anti-AD medications and 15 other psychoactive medications (either over-the-counter or prescription) were recorded based on Multum drug codes. Alzheimer's disease medications analyzed were memantine or AChIs donepezil, galantamine, and rivastigmine. Psychiatric medications were categorized as antipsychotic, mood stabilizer, antidepressant, and anxiolytic medications. Use of the following *antipsychotic agents* was recorded: promethazine, risperidone, olanzapine, quetiapine, quetiapine, haloperidol, clozapine, prochlorperazine, aripiprazole, and perphenazine. *Mood stabilizers* included carbamazepine, valproic acid, or lithium. *Antidepressants* included citalopram, sertraline, mirtazapine, trazodone, paroxetine, venlafaxine, maprotiline, amitriptyline, fluoxetine, duloxetine, nortriptyline, doxepin, clomipramine, fluvoxamine, escitalopram, and bupropion. *Anxiolytic* medications consisted of lorazepam, clonazepam, alprazolam, temazepam, zolpidem, eszopiclone, doxylamine, flurazepam, midazolam, phenobarbital, triazolam, chlordiazepoxide, oxazepam, buspirone, diphenhydramine, hydroxyzine, meprobamate, and ramelteon.

Statistical Analysis

Because 2 different databases were the source of our bvFTD sample, we conducted descriptive analyses on the variables that would be used in the larger analysis to determine whether the ARCC and NHS bvFTD samples could be combined. To assess whether there were differences between the bvFTD groups, a multivariate analysis of variance (MANOVA) was used to examine group differences between age, years of education and MMSE, and χ^2 tests to analyze bivariate and categorical variables such as the number of anti-AD medications, gender, race, and AD and psychiatric medication use.

Results of the bvFTD group comparison are shown in supplementary table (available at <http://aja.sagepub.com/supplemental>). The ARCC bvFTD participants had lower MMSE scores than the NHS bvFTD participants (21.4 ± 1.22 vs 25.1 ± 0.6 , $P = .005$), however, there were no significant differences in medication-related variables. For this reason, we elected to combine the ARCC and the NHS data sets to increase sample size but included original data set as an additional covariate in subsequent logistic regression models comparing medication use in the AD versus bvFTD groups.

After the 2 bvFTD samples were combined, similar analyses, MANOVA, t tests, and χ^2 analyses were conducted comparing the AD and bvFTD groups on the demographic and descriptive data.

Logistic regression models (enter method) were constructed to investigate possible roles of gender, age, MMSE score, years of education, race, and original data set (ARCC or NHS) in medication use among the 2 diagnostic groups (AD vs FTD). However, due to small sample sizes within the non-white race/ethnicity categories, race/ethnicity was coded as either non-Hispanic white or non-white. The Homer and Lemeshow test¹⁹ and regression diagnostics measured how well the model fit the data; if $P < .05$, then the model was rejected and the variable that was least significant was removed until logistic regression model best fit the data.

Results

Demographics for the combined bvFTD group as compared to the AD group are shown in Table 1. The patients with bvFTD were younger ($P < .001$) and were more highly educated ($P < .001$) than the patients with AD. The AD participants had lower MMSE scores than the patients with bvFTD ($P < .001$) and a higher proportion of AD participants were female than the bvFTD group ($P < .001$). The mean total number of all medications was higher in the patients with AD than in patients with bvFTD ($P = .023$).

FDA-Approved AD Medications

The percentage of patients taking any AD medication (donepezil, galantamine, rivastigmine, or memantine) was comparable between the bvFTD and the AD groups, and there was no difference in the mean number of FDA-approved AD medications taken ($P = .075$) between the bvFTD and the AD groups (Table 1). The most frequently used AD medication was donepezil, followed by memantine. Logistic regression analysis (Table 2) suggested that differences in all AD medication use were explained by differences in MMSE score between the 2 groups. Mini-Mental State Examination was inversely associated with the use of any anti-AD medication; that is, adjusted for diagnosis, patients were less likely to take any anti-AD medication if they had a higher MMSE score (odds ratio [OR]: 0.94, 95% confidence interval [CI]: 0.91–0.97, $P < .001$). Patients treated with AD medications had a mean MMSE score of 18.6 ± 0.4 as compared to 20.4 ± 0.4 for those who were not ($P < .001$).

Acetylcholinesterase inhibitor use, driven by the use of donepezil, was higher in AD ($P = .010$ for AChI and $P = .007$ for donepezil; Table 1) than in bvFTD. Galantamine, rivastigmine, and memantine use was similar between the 2 groups. After adjusting for demographic variables (Table 2), the odds of AChI use (donepezil, galantamine, and rivastigmine) were higher in patients with AD than in patients with bvFTD even when other variables such as age, gender, race, education level, and MMSE scores were included in the model (OR for bvFTD: 0.45, 95% CI: 0.25–0.82). The most commonly used AChI was donepezil, and the logistic regression for donepezil analysis showed similar results.

There was no difference in the odds of memantine use between patients with AD and bvFTD (OR: 1.12, 95% CI: 0.58–2.16, $P = 0.727$). In all participants combined, memantine use was

associated with more education (OR: 1.08, 95% CI: 1.02–1.14; $P = .008$) and lower MMSE scores (OR: 0.93, 95% CI: 0.90–0.96; $P < .001$). Individuals who took memantine had a mean of 13.9 ± 0.3 years of education as compared to 13.0 ± 0.2 years in those who did not take memantine and had mean MMSE scores of 17.9 ± 0.5 as compared to 19.9 ± 0.3 in those who did not.

Psychiatric Medications

Psychiatric medication use was comparable between patients with AD and bvFTD even when controlling for age, gender, race, education level, and MMSE score (Table 3). Adjusted for diagnosis, men were less likely to use psychiatric medications than women (OR: 0.65, 95% CI: 0.45–0.95; Table 3). There was a nonsignificant trend for younger patients to be more likely to take psychiatric medications ($P = .014$). Those who were taking any type of psychiatric medication had a mean age of 75.0 ± 0.7 as compared to those who were not, who had a mean age of 77.0 ± 0.6 .

Antidepressant use was higher in patients with bvFTD than AD ($P = .014$; Table 1). However, after controlling for demographic variables, diagnosis was not associated with antidepressant use (OR: 1.29, 95% CI: 0.70–2.38; Table 3). In all participants combined, treatment with antidepressants was less likely if the patient was older (OR: 0.98, 95% CI: 0.96–1.0 $P = .012$) or male (OR: 0.55, 95% CI: 0.37–0.83; $P = .004$). The average age of individuals taking an antidepressant was 74.2 ± 0.8 as compared to 77.0 ± 0.5 individuals not taking antidepressants. Males made up only 31.6% of the population taking antidepressants.

Antipsychotic medication use was similar between the diagnostic groups ($P = .213$); 10.0% of patients with AD and 4.5% of patients with bvFTD took at least 1 antipsychotic. In the logistic regression, diagnosis did not predict antipsychotic use ($P = .236$). Individuals with higher MMSE scores were less likely use an antipsychotic (OR: 0.9, 95% CI: 0.86–0.95; $P < .001$). Patients taking an antipsychotic had mean MMSE score of 150.58 ± 1.02 and those who did not had mean MMSE score of 19.71 ± 0.27 . Mood stabilizer and anxiolytic medication use was similar between the bvFTD and the AD groups.

Other Medications

On average, patients with AD took a greater number of medications than patients with bvFTD ($P = .023$; Table 1). The most common non-AD/psychiatric medications used in patients with AD were aspirin (31.4% of participants), followed by multivitamins (25.8%), calcium carbonate (15.2%), and levothyroxine (13.4%). The most frequently used non-AD/psychiatric medications in bvFTD were aspirin (39.8%), multivitamin (31.8%), vitamin C (17.0%), and vitamin E (15.9%).

Discussion

Although FDA-approved AD medications are not indicated for use in bvFTD, we found that overall the use of such medications is as common in bvFTD as in AD in specialized dementia clinical and research centers. Moreover, despite concerns regarding efficacy and worsening of FTD-related behaviors by AChIs,^{1,12} 40.9% of patients with bvFTD took an AChI. Although AChI use, particularly donepezil, was more common in AD than bvFTD, memantine use was nearly identical in the 2 groups. Similarly, prescription psychiatric medication use was similar between the AD and bvFTD groups, although antidepressant use was higher in the bvFTD than AD groups. This difference may have been accounted for by the younger age in the bvFTD group, because younger age was more strongly associated than diagnosis with antidepressant use when data from both groups were combined (Table 3).

We identified a number of interesting trends in medication use across all participants, irrespective of diagnosis. A lower MMSE score was associated with higher odds of use of antipsychotics, AD medications (as a class), an AChI, or memantine, regardless of diagnosis. We speculate that the association of MMSE scores with medication use may reflect greater certainty about a dementia diagnosis for AD medications and worsening behavior with increasing disease severity for antipsychotics. However, medication use was not associated with disease duration in either group. This may reflect the difficulty in accurately determining disease onset, heterogeneous rates of decline, or an inconsistent relationship between disease duration and severity in each of the groups.

The odds of using memantine were increased with higher education levels, and there was a nonsignificant trend for greater odds of any AD medication use in individuals with higher levels of education ($P = .117$). Memantine was first made available in January 2004, and all data in this study reflect visits from 2004 to 2008. Patients with a higher education level might have been more likely to be prescribed this medication, due to a greater knowledge of newly available therapies, or possibly due to a higher socioeconomic status, leading to a greater ability to afford new medications.

There were important limitations in conducting this study. First, the number of patients with bvFTD in our analysis was small in comparison to the number of patients with probable AD. This may have limited our ability to detect differences in the pattern of medication use.¹⁹ Overall, the small number of patients taking antipsychotics, mood stabilizers, and anxiolytic medications also limited our ability to detect disease-specific differences in the use of these medications. Moreover, because dosage information was not available for analysis, differences in AD medication dose between groups may have been missed. In addition, because the medication data were derived from 2 different data sets with few common neuropsychological or functional assessments, we were forced to rely on MMSE as a measure of disease severity, which may have underestimated the relative disease severity of the patients with bvFTD.²⁰ Finally, the retrospective nature of the data may have introduced a variety of unknown biases that were not accounted for in our analyses.

It is not clear from our study why such a large proportion of patients with bvFTD are treated with FDA-approved AD medications. The treatment of bvFTD patients with AD medications might reflect uncertainties about underlying diagnosis, patient or caregiver preference, or a general bias to medicate demented individuals. Because the bvFTD cases were not autopsy-confirmed, it is possible that some may have had underlying AD pathology with some clinical features of AD that contributed to diagnostic uncertainty. Although AChI use was higher in AD than in bvFTD, memantine use was similar in the 2 groups. This may reflect conflicting published reports on effects of AChIs in bvFTD, which include both “positive” open-label studies, suggesting improved behavior⁹ and “negative” studies documenting adverse effects of cholinesterase inhibitors.¹² In contrast, open-label studies of memantine have suggested either possible mild benefits^{13,15} or no effects.¹⁴ The higher percentage of patients with bvFTD taking antidepressants is likely to reflect the published literature on bvFTD treatment, including a placebo-controlled trial of trazodone⁷ and other open-label studies, which suggest benefits of SSRIs in bvFTD.^{1,6}

Our analysis shows that off-label use of antidementia and psychiatric medications is common in bvFTD, despite little evidence to support such treatment. Larger and more comprehensive studies are needed to understand the reasons for current treatment practices. More importantly, randomized, placebo-controlled clinical trials of antidementia medications should be pursued in bvFTD to allow for evidence-based decision making in determining the treatment of patients with this common form of dementia.

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Table 1Demographics and Medication Use in AD Versus bvFTD^a

	Probable AD	bvFTD	P Value
Number	528	88	N/A
Gender	34.3%	63.6% male	<.001
	Male 65.7% female	36.4% female	
Age	78.3 ± 0.4	62.9 ± 1.0	<.001
Years of education	12.9 ± 0.2	15.1 ± 0.3	<.001
MMSE	18.7 ± 0.3	23.45 ± 0.7	<.001
Disease duration (years)	5.0 ± 0.2	4.1 ± 0.3	.139
Race	65.7%	83.0%	
White	6.0%	0%	.011
Black	20.2%	9.1%	NS
Hispanic	6.7%	8.0%	NS
Asian/Pacific Islander	0.5%	0%	NS
American Indian	0.2%	0%	NS
Other/unknown			NS
Total no medications	6.3 ± 0.2	5.3 ± 0.4	.023
% Using any AD medication	59.3%	54.5%	.393
Mean no AD medications taken	0.9 ± 0.04	0.7 ± 0.08	.075
Percentage using			
Any cholinesterase inhibitor	55.3%	40.9%	.012
Donepezil	50.6%	35.2%	.007
Galantamine	5.3%	4.5%	.764
Rivastigmine	3.6%	2.3%	.524
Memantine	28.4%	29.5%	.835
Percentage using			
Any psychiatric medication	41.3%	48.9%	.188
Antidepressant	29.9%	43.2%	.014
Anxiolytic	11.4%	6.8%	.200
Antipsychotic	10.0%	4.5%	.099
Mood stabilizer	1.1%	3.4%	.101

Abbreviations: AD, Alzheimer's disease; FTD, frontotemporal dementia; MMSE, Mini-Mental State Examination.

^aMean ± SEM values shown.

Table 2

Factors Associated With AD Medication Use in all Participants Combined

		OR	95% CI	P Value
Any AD medication	Age	0.99	0.97–1.01	.390
	Gender	1.24	0.85–1.78	.262
	Race	1.35	0.88–2.07	.162
	Education	1.04	0.99–1.10	.117
	MMSE	0.94	0.91–0.97	<.001
	bvFTD Diagnosis	0.80	0.44–1.45	.464
	Disease duration	1.02	0.98–1.06	.287
Any acetylcholinesterase inhibitor	Age	0.99	0.97–1.01	.205
	Gender	1.26	0.87–1.81	.225
	Race	1.26	0.83–1.92	.284
	Education	1.04	0.99–1.09	.159
	MMSE	0.95	0.92–0.98	<.001
	bvFTD Diagnosis	0.45	0.25–0.82	.010
	Disease duration	1.01	0.97–1.04	.674
Donepezil	Age	0.99	0.97–1.01	.461
	Gender	1.26	0.87–1.81	.218
	Race	1.22	0.80–1.86	.363
	Education	1.03	0.98–1.08	.322
	MMSE	0.95	0.92–0.98	.001
	bvFTD Diagnosis	0.47	0.25–0.86	.014
	Disease duration	1.00	0.97–1.04	.776
Memantine	Age	0.99	0.97–1.01	.354
	Gender	1.05	0.69–1.58	.824
	Race	1.54	0.94–2.53	.087
	Education	1.08	1.02–1.15	.008
	MMSE	0.93	0.90–0.96	<.001
	bvFTD Diagnosis	1.12	0.58–2.16	.727
	Disease duration	1.00	0.96–1.04	.964

Abbreviation: AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio.

Table 3

Factors Associated With Psychiatric Medication Use in all Participants Combined

		OR	95% CI	P Value
Psychiatric medications	Age	0.98	0.96–1.00	.014
	Gender	0.65	0.45–0.95	.024
	Race	1.17	0.76–1.79	.472
	Education	1.03	0.98–1.09	.200
	MMSE	0.98	0.95–1.01	.212
	Diagnosis	1.09	0.60–1.97	.776
	Disease duration	1.00	0.97–1.04	.792
Antidepressants	Age	0.98	0.96–0.99	.012
	Gender	0.55	0.37–0.83	.004
	Race	1.05	0.67–1.65	.828
	Education	1.04	0.98–1.09	.231
	MMSE	1.00	0.97–1.03	.857
	Diagnosis	1.29	0.70–2.38	.410
	Disease duration	1.01	0.98–1.05	.564
Anxiolytics	Age	1.03	1.00–1.07	.080
	Gender	0.87	0.48–1.58	.652
	Race	1.16	0.57–2.32	.687
	Education	1.02	0.94–1.11	.670
	MMSE	0.99	0.94–1.04	.620
	Diagnosis	0.87	0.28–2.62	.797
	Disease duration	0.97	0.89–1.05	.429
Antipsychotics	Age	0.97	0.94–1.00	.056
	Sex	0.84	0.43–1.67	.627
	Race	0.89	0.42–1.87	.752
	Education	1.06	0.97–1.16	.174
	MMSE	0.91	0.87–0.96	<.001
	Diagnosis	0.46	0.14–1.56	.213
	Disease duration	1.00	0.94–1.07	.890
Mood stabilizers	Age	0.97	0.90–1.05	.508
	Gender	0.77	0.15–4.02	.752
	Race	0.75	0.11–4.87	.759
	Education	0.95	0.74–1.22	.689
	MMSE	1.10	0.93–1.29	.270
	Diagnosis	2.71	0.31–23.43	.365
	Disease duration	1.03	0.96–1.12	.407

Abbreviation: AD, Alzheimer's disease; CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio.