ELSEVIER

Alzheimer's & Dementia 8 (2012) 180–187

Alzheimer's & Dementia

Effects of Food and Drug Administration-approved medications for Alzheimer's disease on clinical progression

Michelle M. Mielke[a,*], Jeannie-Marie Leoutsakos[a], Chris D. Corcoran[b,c], Robert C. Green[d], Maria C. Norton[b,e,f], Kathleen A. Welsh-Bohmer[g], JoAnn T. Tschanz[b,e], Constantine G. Lyketsos[a]

[a]*Department of Psychiatry, Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[b]*Division of Epidemiologic Studies, Utah State University, Logan, UT, USA*
[c]*Department of Mathematics and Statistics, Utah State University, Logan, UT, USA*
[d]*Departments of Neurology, Medicine (Genetics), and Epidemiology, Boston University Schools of Medicine and Public Health, Boston, MA, USA*
[e]*Department of Psychology, Utah State University, Logan, UT, USA*
[f]*Department of Family, Consumer and Human Development, Utah State University, Logan, UT, USA*
[g]*Department of Psychiatry and Behavioral Sciences and the Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University, Durham, NC, USA*

Abstract

Background: Observational studies suggest that cholinesterase inhibitors and/or memantine may delay clinical progression of Alzheimer's disease (AD) in 40% of individuals taking the medications. Given this response and existence of side effects, we sought to quantify medication use and benefits in a population-based study of incident AD cases.

Methods: The Cache County Dementia Progression Study enrolled and followed a cohort of 327 incident AD cases for a maximum of 9 years. Drug exposure was expressed using a persistency index (PI), calculated as total years of drug use divided by total years of observation. Linear mixed-effects models examined PI, and interactions with sex and apolipoprotein E (*APOE*) as predictors of clinical progression on the Mini-Mental State Examination and Clinical Dementia Rating-Sum of Boxes.

Results: A total of 69 participants (21.1%) reported having ever used cholinesterase inhibitors or memantine. There was a strong three-way interaction between PI, sex, and time. Among women, a higher PI (i.e., greater duration of use) of cholinesterase inhibitors was associated with slower progression on the Mini-Mental State Examination and Clinical Dementia Rating-Sum of Boxes, particularly among those with an *APOE* ε4 allele. In contrast, higher PI was associated with faster progression in males.

Conclusion: A low percentage of individuals with AD in the community are taking cholinesterase inhibitors or memantine. This study suggests that women, particularly those with an *APOE* ε4 allele, may benefit the most from these medications. With the newly approved increased dose of donepezil, it will be imperative to determine whether a higher dose is needed in men or whether other factors warrant consideration.

Keywords: Cholinesterase inhibitor; Memantine; Incident Alzheimer's disease; Population-based; Disease progression; Sex; *APOE*

J.T.T. and C.G.L. are co-last authors.

All other authors have no disclosures.

The corresponding author had full access to all the data in the study and had final responsibility of the decision to submit for publication.

The authors had access to the data at all times and retain the data. Funding was obtained from NIH grants. All participants provided informed consent and the study was approved by the Johns Hopkins University, Utah State University, and Duke University Institutional Review Boards.

Constantine Lyketsos: Grant support (research or CME)—NIMH, NIA, Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, Glaxo-Smith-Kline, Eisai, Pfizer, Astra-Zeneca, Lilly, Ortho-McNeil, Bristol-Myers, Novartis; Consultant/Advisor—Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Genentech; Honorarium or travel support—Pfizer, Forest, Glaxo-Smith Kline, Health Monitor.

*Corresponding author. Tel.: 443-326-5174; Fax: 410-550-1407.

E-mail address: mmielke1@jhmi.edu

1552-5260/$ - see front matter
doi:10.1016/j.jalz.2011.02.011

1. Introduction

Although there is currently no cure for Alzheimer's disease (AD), current therapeutic strategies with the aim to treat disease symptoms and delay cognitive and functional decline include the use of second-generation cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the *N*-methyl-D-aspartate receptor antagonist, memantine. Studies conducted in specialized clinical settings and nursing homes suggest a high prevalence of dementia medication use among patients with AD [1–4]. However, this is likely an overestimate of use because many persons with AD in the United States do not seek specialized treatment and thus are not diagnosed [5]. A study of community-dwelling Medicare beneficiaries reported that only 26% of persons with dementia were prescribed a cholinesterase inhibitor or memantine between 2001 and 2003 [6]. Although claims data include information on prescription medications, they lack clinical information and are subject to misclassification biases due to diagnostic errors, especially underdiagnosis. A population-based study of well-characterized participants with incident AD is preferred to characterize patterns of medication use among AD patients.

Cholinesterase inhibitors and memantine are regarded as having very moderate symptomatic benefits on cognition and functioning, but are not disease modifying. Observational studies suggest that these drugs may have symptomatic effects that delay cognitive progression for up to a year and may delay the time to nursing home placement [7,8]. However, only 40% are thought to be improved [9,10]. Given this low response and the existence of side effects, it is important to quantify their benefits in real world settings and to identify predictors of treatment response. Although several clinical trials and clinical observational studies have examined such predictors, these have not been examined in a population-based study of well-characterized incident dementia cases. Clinical studies and randomized trials have more stringent criteria for inclusion and findings may therefore not be generalizable to the vast majority of individuals with AD.

The Cache County Dementia Progression Study (DPS) has enrolled and followed a population-based cohort of incident dementia cases for more than 9 years. Participants were originally diagnosed from the population-based Cache County Study on Memory and Aging. The aims of the present analyses were to (1) describe patterns of use for Food and Drug Administration (FDA)-approved AD dementia medications (cholinesterase inhibitors and memantine) in this unique population-based sample of incident dementia cases; (2) determine whether persistency of medication use (defined later) is associated with slower dementia progression, as assessed by the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating-Sum of Boxes (CDR-Sum); and (3) examine whether specific participant characteristics previously reported in clinical studies, including *APOE* ε4 genotype, sex, and onset age, affect response to these medications in this cohort.

2. Methods

2.1. Participants and dementia diagnosis

The design and sampling methods of the study have previously been described in detail [11,12]. The DPS originated from the longitudinal, population-based Cache County Study on Memory in Aging (CCSMA), which has examined the prevalence, incidence, and risk factors of dementia in a U.S. county recognized for the longevity of its residents. In its first wave, CCSMA enrolled 90% of the 5677 county residents aged ≥65 years. Three triennial incidence waves were subsequently completed, as described previously [11,12]. Briefly, using state-of-the-art diagnostic assessments involving cognitive screening and in-home evaluation by a trained team, a study geropsychiatrist and neuropsychologist reviewed data from each participant at each CCSMA wave and assigned preliminary diagnoses of dementia according to Diagnostic and Statistical Manual (DSM)-III-R criteria [13]. Neuroimaging and laboratory studies were used as part of the diagnostic work-up to further define dementia type. The age of dementia onset was the age when the participant unambiguously met DSM-III-R criteria for dementia. Dementia severity was rated on the Clinical Dementia Rating (CDR) [14] and health status according to the General Medical Health Rating [15]. A panel of experts consisting of neurologists, geropsychiatrists, neuropsychologists, and a cognitive neuroscientist reviewed all available clinical and neuropathological data, and possible and probable AD was diagnosed according to National Institutes of Neurological Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria [16]. All study procedures were approved by the institutional review boards of Utah State, Duke, and the Johns Hopkins University.

All participants and their caregivers/proxy informants surviving as of 2002 were recruited to participate in the DPS, a longitudinal study of dementia progression. Participants and their caregivers/proxy informants were visited semiannually by a nurse and psychometric technician. Participants completed a battery of neuropsychological tests including the MMSE, and underwent a brief physical examination including height and weight check and standardized measurement of blood pressure. A CDR was administered to participants and caregivers. Caregivers were also interviewed regarding the functional status of the care-recipient, and they provided updated information related to the participant's health history, psychiatric symptoms, family history of memory problems, medications, quality of life, and use of formal and informal services.

Of the original 581 individuals diagnosed with incident dementia in the CCSMA, 358 had at least one follow-up visit either through procedures of the CCMSA or the DPS. The

DPS enrolled 88% of the surviving cases of dementia (n = 337) and has followed them semiannually over the past 8 years. Attrition has been primarily because of death, with <5% of subjects refusing follow-up. Participants diagnosed with possible or probable AD were included in the present analyses.

2.2. Measures of dementia progression

Outcomes reflecting progression of AD dementia were the MMSE [17] and the CDR-Sum [14]. The MMSE is a global measure of cognition that is widely used in clinical trials that assess potential treatments on AD progression [18]. Similar to methods previously used in DPS [12,19], a sensory/motor MMSE-adjusted score was calculated by discarding items missed due to sensory/motor impairment (e.g., severe vision or hearing loss, motor weakness, tremor, etc.), calculating the percent correct, and rescaling the final score on a 30-point scale.

The CDR [14] examines functioning in six domains: memory, orientation, judgment/problem solving, community affairs, home/hobbies, and personal care. The CDR is assessed with a semistructured interview and has excellent reliability and validity [20]. Scores include a composite score (CDR-composite) and Sum of Boxes (CDR-Sum), which is the sum of ratings in each of the six domains with a range of 0 (no impairment) to 30 (maximum impairment in all domains). CDR-Sum was chosen as the principal outcome here, instead of the composite, because of its greater range, and demonstrated sensitivity to change in mild cognitive impairment and AD as demonstrated [21].

2.3. Medication ascertainment and calculation of persistency index

Ascertainment of medications in this study has been previously described [22] and relied on visual inspection of all available medication vials at each follow-up. When participants were institutionalized, this information was obtained from nursing home records. We classified current dementia medication use as regular if a medication was being used ≥4 times per week. We focused on FDA-approved medications: cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the *N*-methyl-D-aspartate receptor antagonist, memantine. As the various cholinesterase inhibitors have been shown to have similar efficacy despite different pharmacological properties, we examined this drug category rather than each specific drug.

Because accumulation of exposure to AD dementia medications may be important to progression, drug exposure was estimated using the persistency index (PI) [23]. The PI was calculated as the total years of drug use divided by the total years of observation since AD diagnosis by the study investigators, and ranged from 0 to 1. A PI of 1 indicates that the person has been taking an AD medication over the entire study duration, whereas a PI of 0.5 would indicate the person was taking it only over half the study duration. Because the DPS sample is an incident sample, all participants with AD had been assessed before the onset of dementia. The use of these medications was first assessed at the visit when dementia was diagnosed. Time in the study was from the initial baseline visit (e.g., from the visit of the dementia diagnosis) onward, and in multivariate models, we adjusted for the duration of dementia at the time of the diagnostic visit that was determined by the age of onset estimated at the consensus conference. A PI was calculated for any dementia medication use and just for cholinesterase inhibitors (excluding participants ever taking memantine). We did not calculate a PI for memantine-only users because of insufficient numbers.

Because we did not have information on medication use between visits, if a person was taking a medication at consecutive visits, we assumed she/he was taking it over the entire period between these visits. If an individual was taking the medication at one visit but not at the next consecutive visit, we estimated that the time of drug use was half the time between visits. This method was supported by our observation in this study that no individuals went on drug, off drug, and then back on drug over three consecutive visits. Hence, once they started a dementia medication, they tended to stay on a dementia medication, although they may have changed to a different cholinesterase inhibitor or memantine at subsequent visits.

2.4. Statistical analyses

Differences in baseline demographic and health-related characteristics between those who ever regularly used a dementia medication versus irregular (<4 times/week) or never users were examined using Fisher's exact test for categorical variables and Student's *t* test for continuous variables. Similarly, these same tests were used to estimate differences between those with only a baseline visit and those with one or more follow-up visits.

To model nonlinear effects of medication use (PI) on dementia progression, we examined average change in MMSE and CDR-sum from the visit at which dementia was first diagnosed, using mixed-effects models, treating subject-specific intercepts and linear change with time as random effects. This approach, used previously in DPS [12], allows us to assess the effects of key fixed factors, such as age, on average rate of change, while accounting for the dependence between within-subject repeated measures and for *nonlinear* change with respect to time. Because our analysis revealed significant nonlinear time effects for both the MMSE and CDR-sum, and as we have done before in similar analyses, we included a time-squared term and appropriate time-squared terms in all examined interactions.

Some variables have previously been found to be associated with progression in MMSE and CDR-sum in this population of AD participants [12]. Therefore, they were included as covariates in the current models; these variable include baseline age, sex, education, duration of dementia

at the time from the age of onset to the age when diagnosis was made, and presence of one or two *APOE* ε4 alleles. Education, sex, and *APOE* genotype were determined at wave 1 of the CCSMA. *APOE* genotype was determined from buccal DNA, using standard protocol [11]. In addition, we also examined three-way interactions between the PI, time, and sex. The interaction terms were retained in the models if the comparison between likelihood ratio (LR) test statistics between models with and without the interaction terms was significant ($P < .05$). All analyses were conducted using STATA Version 10.0 (StataCorp, College Station, TX).

3. Results

3.1. Descriptive

The current analyses included 327 participants diagnosed with incident AD and who had information on medication use. The majority were female (65.8%), Caucasian (99.1%), and had mild impairment (mean global CDR = 1.1, standard deviation [SD] = 0.6) at the time of diagnosis. At baseline, 36 (11.0%) were regularly taking a cholinesterase inhibitor and/or memantine: 32 (9.8%) were regularly only taking a cholinesterase inhibitor. Over the course of the follow-up, an additional 26 (8.0%) individuals initiated regular cholinesterase use and 7 (2.1%) initiated regular memantine use (Table 1 for cross-sectional use of dementia medications at each follow-up visit and at which visit each drug was first taken). For persons who took dementia medications at multiple visits, all visits were consecutive (i.e., no person was on a drug at one time point, off at another time point, then back on the medication again at the next time point).

Sixty-nine participants (21.1%) ever used a cholinesterase inhibitor or memantine from the time of diagnosis to the last follow-up. Differences in baseline demographic and other health-related characteristics between the 69 persons who ever regularly took a cholinesterase inhibitor and/or memantine during the study and the 258 who did not are shown in Table 2. Those who ever took an FDA-approved AD medication were younger (81.2 vs 87.1, $P < .001$), had more years of education (14.0 vs 13.0, $P = .014$), and were more likely to be *APOE* ε4 allele carriers (68.1% vs 39.1%, $P < .001$), compared with those who never regularly used a cholinesterase inhibitor and/or memantine. There were no differences in baseline MMSE or CDR-Sum scores, dementia duration, or other health-related characteristics, including medical comorbidities.

Of the 327 participants at baseline, 216 had at least one follow-up visit and could be analyzed longitudinally; 191 were included in the calculation of the cholinesterase inhibitor-only PI after excluding those ever taking memantine. Of the total, 111 (33.9%) individuals lacked any follow-up, the majority (n = 88, 79.3%) because of death. As previously reported [12], these individuals were older and had a lower MMSE at diagnosis compared with those with follow-up data. Of the 216 participants with follow-up data, average time in the study was 3.3 years (SD = 2.2; maximum = 9.9 years) with 4.2 study visits (SD = 2.4; maximum = 11 visits). The mean (SD) of the overall PI among the 62 persons in the longitudinal sample taking any FDA-approved AD medication was 0.64 (SD = 0.31, range: 0.07–1.0), which means that they were taking such a medication for 64% of the time under observation. For the 37 participants only taking a cholinesterase inhibitor (excluding anyone taking memantine), the mean PI was 0.63 (SD = 0.31, range = 0.07–1).

3.2. Persistency index

For individuals taking any FDA-approved AD medication or for those taking cholinesterase inhibitors only, a higher PI (i.e., use of one of these medications for longer periods under observation) was not associated with better performance over time on either the MMSE or CDR-Sum (Table 3). However, there was a strong three-way interaction between PI,

Table 1
Regular use and starting visit of cholinesterase inhibitors and memantine over the DPS follow-up

Dementia medication	Baseline (n = 327) n (%)	Visit 2 (n = 216) n (%)	Visit 3 (n = 140) n (%)	Visit 4 (n = 110) n (%)	Visit 5 (n = 84) n (%)	Visit 6 (n = 60) n (%)	Visit 7 (n = 35) n (%)	Visit 8 (n = 23) n (%)	Visit 9 (n = 16) n (%)	Visit 10 (n = 11) n (%)	Visit 11 (n = 3) n (%)
Cholinesterase inhibitor only											
Use	32 (9.8%)	33 (15.3%)	27 (19.3%)	22 (20.0%)	14 (16.7%)	7 (11.7%)	2 (5.7%)	1 (4.4%)	0	0	0
Visit started	32 (9.8%)	14 (6.5%)	7 (5.0%)	4 (3.6%)	0	1 (1.7%)	0	0	0	0	0
Memantine only											
Use	1 (0.3%)	2 (0.9%)	3 (2.1%)	2 (1.8%)	2 (2.4%)	2 (3.3%)	1 (2.9%)	0	1 (6.3%)	0	0
Visit started	1 (0.3%)	2 (0.9%)	2 (1.4%)	1 (0.9%)	1 (1.2%)	1 (1.7%)	0	0	0	0	0
Both											
Use	3 (0.9%)	3 (1.4%)	7 (5.0%)	8 (7.3%)	9 (10.7%)	8 (13.3%)	4 (11.4%)	2 (8.7%)	2 (12.5%)	2 (18.2%)	1 (33.3%)
Visit started	3 (0.9%)	2 (0.9%)	6 (4.2%)	2 (1.8%)	4 (4.8%)	2 (3.3%)	0	0	1 (6.3%)	0	0
Any medication use	36 (11.0%)	38 (17.6%)	37 (27.2%)	32 (29.0%)	25 (29.8%)	17 (28.3%)	7 (20.6%)	3 (13.6%)	3 (18.8%)	2 (18.2%)	1 (33.3%)

Abbreviation: DPS, Dementia Progression Study.

Table 2
Baseline characteristics of regular dementia medication users at any examination over the follow-up and nonusers

	Regular use (n = 69)	No/irregular use (n = 258)	
Baseline variable	n (%) or mean (SD)	n (%) or mean (SD)	*P* value
Age (years)	81.2 (5.4)	87.1 (5.9)	<.001
Female	42 (60.9%)	173 (67.1%)	.392
Education	14.0 (3.0)	13.0 (2.9)	.014
APOE ε4 allele	47 (68.1%)	100 (39.1%)	<.001
Stroke	1 (1.5%)	15 (5.8%)	.209
CABG	3 (4.4%)	16 (6.2%)	.774
MI	10 (14.5%)	36 (14.0%)	1.000
Diabetes	7 (10.1%)	47 (18.2%)	.143
Antihypertensive medication use	35 (50.7%)	119 (46.3%)	.587
Dementia duration	1.9 (1.2)	1.6 (1.3)	.099
GMHR			
Poor	0	1 (0.4%)	.371
Fair	18 (26.1%)	91 (35.3%)	
Good	44 (63.8%)	134 (51.9%)	
Excellent	7 (10.1%)	32 (12.4%)	
MMSE	22.6 (4.3)	21.7 (4.7)	.168
CDR-Sum	6.1 (3.3)	5.9 (3.4)	.696

Abbreviations: *APOE*, apolipoprotein E; CABG, coronary artery bypass surgery; MI, myocardial infarction; GMHR, General Medical Health Rating scale; MMSE, Mini-Mental State Examination; CDR-Sum, Clinical Dementia Rating Scale—Sum of boxscores; SD, standard deviation.

sex, and time, particularly when examining cholinesterase inhibitor use only (MMSE LR: $\chi^2 = 9.26$, 2 *df*, $P < .01$; CDR-Sum LR: $\chi^2 = 6.40$, 2 *df*, $P < .05$), for which there was more power, because of the greater number of individuals taking these medications as compared with memantine (Table 4). Women with a PI of 1 compared with PI of 0 did better on the MMSE and CDR-Sum over time. In contrast, men with a PI of 1 compared with PI of 0 did worse over time.

We further explored the effect of the *APOE* ε4 allele on the three-way interaction, stratifying the earlier models by the presence of any versus none ε4 alleles. Although the results are based on a small sample number (19 females and 10 males) with a PI > 0 and an ε4 allele, the relationship between cholinesterase inhibitor use and MMSE and CDR trajectories appeared to be limited to ε4 carriers for each sex, such that women with a high PI did better over time if they had an ε4 allele while men did worse. Table 5 shows this association in greater detail and displays the amount of progression on both the MMSE and CDR-Sum at 1, 3, and 5 years after baseline. For example, after 5 years, women with a PI of 1 and an *APOE* ε4 allele had a 2.6-point decline (95% confidence interval: −9.11, 3.96) on the MMSE, which was significantly less than the 20.9-point decline among women with a PI of 1 and without an *APOE* ε4 allele. Similarly, after 5 years, men with a PI of 1 and an *APOE* ε4 allele had a 19.7-point MMSE decline (95% confidence interval: −28.87, −10.22), which was significantly more than the 6.4-point decline among men with a PI of 1 and without an *APOE* ε4 allele.

4. Discussion

In this population-based study of an incident cohort of individuals with AD we found that: (1) only 21.1% of persons diagnosed with AD ever regularly used a cholinesterase inhibitor or memantine; (2) participants who used these medications tended to be younger, were more highly educated,

Table 3
Examination of the dementia medication PI as a predictor of progression on the MMSE and CDR-Sum

		MMSE*,†			CDR-Sum*,†	
PI	n	β (95% CI)	LR test	n	β (95% CI)	LR test
Any dementia medication	200			216		
PI*time		0.01 (−0.98, 1.00)	$\chi^2 = 1.26$, 2 *df*, $P = .533$		0.01 (−0.82, 0.84)	$\chi^2 = 3.28$, 2 *df*, $P = .194$
PI*time^2		0.06 (−0.08, 0.21)			−0.09 (−0.21, 0.04)	
Cholinesterase inhibitor only	175			191		
PI*time		0.25 (−1.20, 1.71)	$\chi^2 = 0.27$, 2 *df*, $P = .874$		−0.19 (−1.43, 1.05)	$\chi^2 = 0.12$, 2 *df*, $P = .941$
PI*time^2		−0.07 (−0.35, 0.20)			0.01 (−0.22, 0.25)	

Abbreviations: PI, persistency index; CI, confidence interval.
*Using mixed-effects regression, all models adjusted for time, time^2, baseline age, sex, education, dementia duration at baseline, and any *APOE* ε4 allele.
†A positive coefficient for MMSE represent a better performance whereas a negative coefficient for CDR-Sum represents a better performance.

Table 4
Examination of an interaction between the dementia medication persistency index (PI) and sex as a predictor of progression on the MMSE and CDR-Sum

		MMSE*,†			CDR-Sum*,†	
PI	n	β (95% CI)	LR test	n	β (95% CI)	LR test
Any dementia medication	200			216		
PI*Male*time		0.94 (−1.05, 2.94)	$\chi^2 = 3.54$, 2 *df*, $P = .171$		−0.49 (−2.16, 1.17)	$\chi^2 = 3.29$, 2 *df*, $P = .193$
PI*Male*time^2		0.10 (−0.20, 0.39)			−0.11 (−0.36, 0.15)	
Cholinesterase inhibitor only	175			191		
PI*Male*time		1.02 (−2.08, 4.14)	$\chi^2 = 9.26$, 2 *df*, $P = .010$		0.71 (−2.02, 3.44)	$\chi^2 = 6.40$, 2 *df*, $P = .041$
PI*Male*time^2		0.42 (−0.18, 1.03)			−0.52 (−1.06, 0.03)	

*Using mixed-effects regression, all models adjusted for time, time^2, baseline age, sex, education, dementia duration at baseline, and any *APOE* ε4 allele.
†A positive coefficient for MMSE represent a better performance whereas a negative coefficient for CDR-Sum represents a better performance.

and were more likely to have an *APOE* ε4 allele, but they were no more or less likely to have medical comorbidities; (3) among all participants, a higher PI was not significantly associated with progression in the MMSE or CDR-Sum. However, among women, longer periods of cholinesterase inhibitor use were associated with slower progression on both the MMSE and CDR-Sum, particularly among those women with an *APOE* ε4 allele. In contrast, among men, longer periods of cholinesterase inhibitor use were associated with a faster progression, particularly among those with an *APOE* ε4 allele.

Some studies from clinical settings have reported a high prevalence of dementia medication use [1,4]. For example, Zhu et al [4] reported that almost 80% of persons in the predictors 2 cohort used cholinesterase inhibitors or memantine. In contrast, in this population-based cohort of incident AD, just over 21% of participants used one of these FDA-approved AD medications. Our finding is similar to a study of Medicare beneficiaries, which reported that 26% of individuals with an AD diagnosis had filled prescriptions for either type of medication [6]. Because claims data often underestimate the prevalence of dementia, the percentage of

Table 5
Amount of progression on the MMSE and CDR-SB at 1, 3, and 5 years after baseline by sex, ε4 status, and PI

	After 1 year	After 3 years	After 5 years
Sex, ε4 status, and PI	β (95% CI)	β (95% CI)	β (95% CI)
MMSE			
Male			
No ε4 allele			
PI = 0	−0.50 (−1.30, 0.30)	−2.20 (−4.28, −0.11)	−4.82 (−8.05, −1.58)
PI = 1	−1.12 (−4.90, 2.66)	−3.59 (−10.89, 3.71)	−6.36 (−19.28, 6.55)
1 or 2 ε4 alleles			
PI = 0	−0.96 (−1.88, −0.04)	−3.38 (−5.82, −0.95)	−6.50 (−10.41, −2.59)
PI = 1	−1.36 (−3.71, 0.99)	−7.91 (−13.23, −2.59)	−19.55 (−28.87, −10.22)
Female			
No ε4 allele			
PI = 0	−2.43 (−3.02, −1.84)	−6.99 (−8.49, −5.50)	−11.16 (−13.49, −8.83)
PI = 1	−0.95 (−5.30, 3.40)	−7.69 (−15.66, 0.27)	−20.89 (−39.12, −2.65)
1 or 2 ε4 alleles			
PI = 0	−1.44 (−2.12, −0.76)	−5.38 (−7.18, −3.58)	−10.72 (−13.66, −7.79)
PI = 1	−1.03 (−2.55, 0.49)	−2.32 (−6.17, 1.52)	−2.58 (−9.11, 3.96)
CDR-Sum			
Male			
No ε4 allele			
PI = 0	0.40 (−0.29, 1.09)	1.66 (−0.15, 3.47)	3.54 (0.74, 6.33)
PI = 1	1.19 (−2.13, 4.51)	0.90 (−5.42, 7.22)	−2.93 (−14.12, 8.27)
1 or 2 ε4 alleles			
PI = 0	1.10 (0.37, 1.84)	3.38 (1.53, 5.23)	5.74 (2.91, 8.57)
PI = 1	0.27 (−1.74, 2.28)	6.04 (1.90, 10.18)	18.79 (11.83, 25.75)
Female			
No ε4 allele			
PI = 0	1.68 (1.18, 2.18)	5.05 (3.79, 6.31)	8.46 (6.50, 10.41)
PI = 1	−0.76 (−3.83, 2.31)	0.76 (−5.82, 7.34)	6.34 (−5.26, 17.93)
1 or 2 ε4 alleles			
PI = 0	0.77 (0.23, 1.32)	3.44 (2.08, 4.80)	7.60 (5.47, 9.74)
PI = 1	1.31 (0.10, 2.52)	3.21 (0.25, 6.17)	4.14 (−0.66, 8.95)

persons with dementia who were taking a dementia medication is likely lower than 26%. Thus, there is a large discrepancy between the prevalence of use in clinical observational studies and use at the population level. Notably, the study of Medicare beneficiaries described usage between 2001 and 2003, and the DPS began enrolling incident dementia cases in 2002. Thus, it is possible that the low frequency could be attributable to the timing of the medication assessments because rivastigmine and galantamine were only approved in 2000 and 2001, respectively. However, as the Predictors 2 cohort recruited the majority of participants before 2002, and median follow-up was 4 years, this timing cannot completely explain the differences in percentages.

Although reasons for this discrepancy are not readily clear, it is not surprising that persons who are younger and more educated are more likely to be on a medication. However, because *APOE* ε4 status obtained in the Cache County Study was not released to any community physician or participant at any point in the study, and information on *APOE* ε4 status was not included in the clinical consensus diagnosis of dementia type, it is surprising that individuals with an *APOE* ε4 allele were almost twice as likely to have taken a dementia medication. It is possible ε4 allele carriers were more clear-cut cases of AD and, thus, easier for physicians to recognize. However, there were no differences between ε4 allele carriers and noncarriers in the prevalence of vascular factors and other comorbidities at baseline, which may complicate the diagnosis of AD. Although African Americans and Hispanics have a lower prevalence of dementia medication use [6,24], this factor cannot explain the finding in this study because 99% of participants were Caucasian. Thus, additional research examining factors associated with use of dementia medications in community settings are needed.

We used the PI [23] to quantify exposure to FDA-approved AD medications during the study. The PI is the total years of drug use divided by the total years of observation. The advantage of using this index was twofold—it allowed for the quantification of the medication duration of exposure and accounted for variations in the period of observation because of the high rate of mortality-related attrition. Rountree et al [23] previously reported that higher PIs were associated with better performance on cognitive and functional outcomes. In this study, we did not find an association between PI and decline among the entire sample. However, there was a strong sex interaction such that women with a higher PI had a slower decline compared with women not taking these medications, particularly women carrying an *APOE* ε4 allele. This is interesting in light of the fact that women with AD have been found to have a faster decline than men when cholinesterase use is not considered [12,25]. In contrast, men with a high PI and an *APOE* ε4 allele did significantly worse compared with men with a low PI or with men, regardless of PI, with no *APOE* ε4 allele. This explains our lack of finding when a gender interaction was not included. Further, this suggests that only subgroups of the population may be benefiting from these drugs at the currently approved doses. Given that some side effects do exist, it is important to further determine the people who might most benefit from these medications, in additional population-based studies.

Although reasons for the slower decline among women with a higher PI are not exactly known, this sex-specific benefit of these medications has been reported in some clinical trials [26], but not others [27]. In animal studies, sex differences have been found for nearly all cholinergic markers including acetylcholinesterase activity, acetylcholine, and acetylcholine-receptor distribution [28–31]. Further, testosterone may interfere with the effects of cholinesterase inhibitors by decreasing the amount of drug that reaches the brain or by modifying the interaction of the cholinesterase inhibitor with cholinesterase [32,33]. Thus, it is possible that men either have less benefit overall or would need a higher dose to have the same benefit from the medications as women. In light of recent approval of a higher dose of donepezil by the FDA, it would be interesting to find out whether there are sex differences in tolerability and efficacy. It is also notable that women only taking cholinesterase inhibitors benefitted, compared with those taking memantine.

Limitations in this study warrant consideration. First, we did not have information on pharmacy claims to directly ascertain whether an individual was a regular user and continuously refilled their prescription. Thus, we may have either overestimated or underestimated the medication use if it was started and stopped between waves. Second, we did not have information on dose. However, it is unlikely that doses for women would have been higher than men, and thus explain the beneficial effect in women on this basis; if at all, we might expect women to be on lower doses due to less tolerability of higher doses because of smaller body size. Third, the number of women and men who were *APOE* ε4 carriers and taking cholinesterase inhibitors was quite small and necessitates the need for replication in a larger study of incident AD cases. Finally, the Cache County population is primarily Caucasian and of northern European descent. Thus, these results may not generalize to populations with different ethnic representation. Strengths of the study include its population base, its focus on incident cases, the extended follow-up after dementia onset, and the high participation rates observed in dementia ascertainment and over the period of observation.

In conclusion, a low percentage of individuals with AD in the community are taking cholinesterase inhibitors or memantine for treatment. As these drugs may benefit a subset of AD patients [9,10], it is important to further ascertain the reasons for the low prevalence of use. Finally, this study suggests that women on dementia medications have a slower decline compared with men. With the newly approved increased dose of donepezil, it will be imperative to determine whether a higher dose is needed in men or whether other factors warrant consideration.

Acknowledgments

This research was supported by the following grants from the National Institute on Aging: R01AG21136, R01AG11380, R01AG18712 and the Bryan Alzheimer Disease Research Center (AG 028377).

References

[1] Dybicz SB, Keohane DJ, Erwin WG, McRae T, Shah SN. Patterns of cholinesterase-inhibitor use in the nursing home setting: a retrospective analysis. Am J Geriatr Pharmacother 2006;4:154–60.

[2] Herrmann N, Lanctot KL. Pharmacologic management of neuropsychiatric symptoms of Alzheimer disease. Can J Psychiatry 2007; 52:630–46.

[3] Mucha L, Shaohung S, Cuffel B, McRae T, Mark TL, Del Valle M. Comparison of cholinesterase inhibitor utilization patterns and associated health care costs in Alzheimer's disease. J Manag Care Pharm 2008;14:451–61.

[4] Zhu CW, Livote EE, Kahle-Wrobleski K, Scarmeas N, Albert M, Brandt J, Blacker D, Sano M, Stern Y. Longitudinal Medication Usage in Alzheimer Disease Patients. Alzheimer Dis Assoc Disord (in press).

[5] Black BS, Kasper J, Brandt J, Shore AD, German P, Burton L, et al. Identifying dementia in high-risk community samples: the memory and medical care study. Alzheimer Dis Assoc Disord 2003;17:9–18.

[6] Zuckerman IH, Ryder PT, Simoni-Wastila L, Shaffer T, Sato M, Zhao L, et al. Racial and ethnic disparities in the treatment of dementia among Medicare beneficiaries. J Gerontol B Psychol Sci Soc Sci 2008; 63:S328–33.

[7] Lopez OL, Becker JT, Wisniewski S, Saxton J, Kaufer DI, DeKosky ST. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002; 72:310–4.

[8] Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc 2003;51:937–44.

[9] Foster RH, Plosker GL. Donepezil. Pharmacoeconomic implications of therapy. Pharmacoeconomics 1999;16:99–114.

[10] Mega MS, Masterman DM, O'Connor SM, Barclay TR, Cummings JL. The spectrum of behavioral responses to cholinesterase inhibitor therapy in Alzheimer disease. Arch Neurol 1999; 56:1388–93.

[11] Breitner JC, Wyse BW, Anthony JC, Welsh-Bohmer KA, Steffens DC, Norton MC, et al. APOE-epsilon 4 count predicts age when prevalence of AD increases, then declines: the Cache County Study. Neurology 1999;53:321–31.

[12] Tschanz JT, Corcoran CD, Schwartz S, Treiber K, Green R, Norton MC, et al. Progression of cognitive, functional and neuropsychiatric symptom domains in a population cohort with Alzheimer's dementia: The Cache County Dementia Progression Study. J Am Geriatr Soc (in press).

[13] APA. Diagnostic and statistical manual of mental disorders. 3rd edn Rev. ed. , Washington, DC: American Psychiatric Association; 1987.

[14] Hughes C, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Dement 1982;140:566–72.

[15] Lyketsos CG, Galik E, Steele C, Steinberg M, Rosenblatt A, Warren A, et al. The General Medical Health Rating: a bedside global rating of medical comorbidity in patients with dementia. J Am Geriatr Soc 1999;47:487–91.

[16] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–44.

[17] Folstein MF, Folstein SE, McHugh PR. "Mini-Mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[18] Mohs RC, Schmeidler J, Aryan M. Longitudinal studies of cognitive, functional and behavioural change in patients with Alzheimer's disease. Stat Med 2000;19:1401–9.

[19] Mielke MM, Rosenberg PB, Tschanz J, Cook L, Corcoran C, Hayden KM, et al. Vascular factors predict rate of progression in Alzheimer disease. Neurology 2007;69:1850–8.

[20] Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 1997;9(Suppl 1):173–6. discussion 177–8.

[21] Pavlik VN, Doody RS, Massman PJ, Chan W. Influence of premorbid IQ and education on progression of Alzheimer's disease. Dement Geriatr Cogn Disord 2006;22:367–77.

[22] Zandi PP, Anthony JC, Hayden KM, Mehta K, Mayer L, Breitner JC. Reduced incidence of AD with NSAID but not H2 receptor antagonists: the Cache County Study. Neurology 2002;59:880–6.

[23] Rountree SD, Chan W, Pavlik VN, Darby EJ, Siddiqui S, Doody RS. Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease. Alzheimers Res Ther 2009;1:7.

[24] Mehta KM, Yin M, Resendez C, Yaffe K. Ethnic differences in acetylcholinesterase inhibitor use for Alzheimer disease. Neurology 2005; 65:159–62.

[25] Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B. Prognostic factors in very old demented adults: a seven-year follow-up from a population-based survey in Stockholm. J Am Geriatr Soc 1998;46:444–52.

[26] Ferris S, Lane R, Sfikas N, Winblad B, Farlow M, Feldman HH. Effects of gender on response to treatment with rivastigmine in mild cognitive impairment: a post hoc statistical modeling approach. Gend Med 2009;6:345–55.

[27] Rigaud AS, Traykov L, Latour F, Couderc R, Moulin F, Forette F. Presence or absence of at least one epsilon 4 allele and gender are not predictive for the response to Donepezil treatment in Alzheimer's disease. Pharmacogenetics 2002;12:415–20.

[28] Rhodes ME, O'Toole SM, Wright SL, Czambel RK, Rubin RT. Sexual diergism in rat hypothalamic-pituitary-adrenal axis responses to cholinergic stimulation and antagonism. Brain Res Bull 2001;54:101–13.

[29] Luine VN, Renner KJ, McEwen BS. Sex-dependent differences in estrogen regulation of choline acetyltransferase are altered by neonatal treatments. Endocrinology 1986;119:874–8.

[30] Avissar S, Egozi Y, Sokolovsky M. Studies on muscarinic receptors in mouse and rat hypothalamus: a comparison of sex and cyclical differences. Neuroendocrinology 1981;32:295–302.

[31] Hortnagl H, Hansen L, Kindel G, Schneider B, el Tamer A, Hanin I. Sex differences and estrous cycle-variations in the AF64A-induced cholinergic deficit in the rat hippocampus. Brain Res Bull 1993; 31:129–34.

[32] Wang RH, Schorer-Apelbaum D, Weinstock M. Testosterone mediates sex difference in hypothermia and cholinesterase inhibition by rivastigmine. Eur J Pharmacol 2001;433:73–9.

[33] Wang RH, Bejar C, Weinstock M. Gender differences in the effect of rivastigmine on brain cholinesterase activity and cognitive function in rats. Neuropharmacology 2000;39:497–506.