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Memantine is Associated with Longer Survival than Donepezil in a Veterans Affairs Prescription Database, 1997 to 2008

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Abstract. Alzheimer's disease (AD) shortens life-expectancy, but the effects of pharmacological treatments for this disorder on mortality have not been studied. We compared two commonly prescribed medications, donepezil and memantine, with respect to the length of survival of veterans presumed to have AD. The Computerized Medical Records System at the Veterans Affairs Palo Alto Health Care System (VAPAHCS) was used to identify all patients prescribed these medications between 1997 and 2008. The VAPAHCS approved donepezil in 1997 and memantine in 2004. Kaplan-Meier and Cox regression analyses were used to test for chronological and drug-related associations with survival in 2,083 male veterans aged 55 years and older receiving prescriptions for donepezil, memantine, or both. Overall patient mortality decreased in the 2004 to 2008 era, compared with the 1997 to 2003 era, pre-memantine (HR: 0.75; 95% CI: 0.63, 0.89; $p = 0.001$). In analyses confined to the 2004 to 2008 era, patients prescribed memantine alone survived significantly longer than those prescribed donepezil alone (HR: 2.24; 95% CI: 1.53, 3.28; $p < 0.001$) or both donepezil and memantine (HR: 1.83; 95% CI: 1.14, 2.94; $p = 0.012$). While this study has several limitations, these findings suggest that memantine treatment is associated with an increased life-expectancy relative to donepezil treatment. Additional research is needed to replicate these unexpected findings and identify potential mechanisms to explain this apparent association, to establish if the relationship applies to other cholinesterase inhibitors, and to discover whether the findings generalize to women and patient populations with characteristics different from those of the veterans in this study.

Keywords: Alzheimer's disease, anticholinesterase drugs, database, donepezil, life-expectancy, memantine, mortality, pharmacy, survival analysis

INTRODUCTION

Alzheimer's disease (AD), the most common cause of dementia, is associated with decreased life-expectancy compared to the general population [1–3]. Medications approved by the Food and

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Drug Administration (FDA) for the treatment of AD—the acetyl-cholinesterase inhibitors (AChEIs) and memantine, a moderate affinity N-methyl-D-aspartate receptor modulator—are widely used and provide modest benefits for cognition, daily function, and behavior [4–9]. Donepezil, the most often prescribed AChEI, was approved by the FDA in December 1996 and memantine was approved in October 2003.

An important factor in making prescription decisions is the effect of medication on life-expectancy. Knowledge of life-expectancy is also important for resource planning at both the individual and public policy levels [10]. A large number of the estimated 4 to 6 million Americans who suffer from AD are either undiagnosed or are untreated with these FDA-approved medications [11]. Estimates of the survival benefits of current AD medications are needed to guide diagnostic and treatment practices and public policy.

Since it is unknown whether cholinesterase inhibitors and memantine affect life-expectancy in AD patients, we addressed this issue by studying a large pharmacy database of prescriptions written for patients of a single Veterans Affairs Health Care System.

MATERIALS AND METHODS

Study population

We conducted a retrospective analysis of the pharmacy database of the Veterans Affairs Palo Alto Health Care System (VAPAHCS), which serves a population of approximately 370,000 veterans in a 10 county area in northern California. Primary, secondary, and tertiary care is provided in 3 hospitals and 6 community-based clinics. Over 100,000 veterans have both medical and pharmacy records in the system. Donepezil has been in the VAPAHCS formulary since March 4, 1997 and memantine since January 27, 2004. Between 2005 and 2008, the VAPAHCS clinicians used an algorithm based on the Functional Assessment Staging (FAST) score [12] that restricted donepezil prescription to patients with mild or moderate dementia (FAST score 4–6) and memantine to patients with moderate to severe dementia (FAST score 5–7). The algorithm also discourages clinician prescription of these medications for patients unlikely to have AD.

VAPAHCS pharmacists review the clinicians' prescriptions and whether the patients meet the algorithm's criteria for their use, and then enter the medication name, dose, and date into VistA-CPRS (the Veterans Health Information Systems and Technology Architecture - Computerized Patient Record System) at the time that prescriptions are filled. Mortality data are entered into the database when information becomes available about a veteran's death. The Decedent Affairs Office of the VAPAHCS usually receives notification of a patient's death from a local hospital, coroner, or family member within 20 days, though that office estimates that 25% of deaths might be unreported (verbal communication with the Director of that office, November, 2012). This study retrieved data on all veterans for whom one or more prescriptions for donepezil, memantine, or both were filled between March 4, 1997 and April 30, 2008. There were 70 patients prescribed another AChEI (predominantly galantamine, sometimes in combination with memantine), who were excluded from this study. Data were initially retrieved through April 30, 2007 and subsequently augmented with data from the following twelve months. In our initial data, only 54 of 1,599 veterans were women (3.4%), so women were excluded from the study. Analyses also excluded 27 men whose first prescription for an AD medication occurred before age 55 years of age, to reduce potential confounding by diagnoses other than AD.

Statistical analysis

We classified patients according to drug treatment group, based on prescription history, as receiving donepezil alone, memantine alone, or both drugs (at the same or different times). We classified treatment initiation as pre-memantine or memantine era according to whether the first prescription for either medication was filled prior to or after January 27, 2004. Some patients, whose treatment was classified as pre-memantine era on this basis, had follow-up into the memantine era.

Survival analyses were implemented using Kaplan-Meier plots and the Cox proportional hazards model in Stata v.11. Survival was defined as time to death measured from initial prescription date. Survival times for patients alive on April 30, 2008, the end of the study, were treated as censored. We used two-sided Wald hypothesis tests and a 0.05 significance level. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. The first set of analyses examined changes in prescription practice and mortality during the study period, without specifically examining differential drug effects. We regressed age of first prescription on calendar day of first prescription, without covariates, to examine whether the patient age at which physicians initiated treatment with AD medications changed over time. Next, we conducted a Cox model survival analysis comparing all pre-memantine

era patients to all memantine-era patients to determine whether length of survival changed at the time that VAPAHCS approved memantine use. To identify overall population effects, we adjusted this analysis for age at first prescription, but not drug treatment group. We then repeated the same survival analysis on the donepezil-only treatment group to determine whether there was a change in survival unrelated to memantine treatment.

A second set of analyses focused on differences in mortality associated with specific AD medications. We restricted this set of analyses to memantine-era patients only, in order to avoid confounding by possible differences between the pre-memantine and memantine eras. We conducted a Cox model survival analysis with drug treatment group as a predictor, adjusting date of initial prescription and age at initial prescription to account for both age-related mortality and possible changes in the patient population or physician practice between 2004 and 2008. We also carried out a separate analysis to estimate two year survival rates in the memantine era for each drug treatment group as simple proportions. For this analysis, we included only subjects who began treatment early enough in the memantine era to allow two complete years of follow-up prior to the end of the study (i.e., those beginning treatment before April 30, 2006). Since less than 50% of these subjects died within two years, we could not directly calculate median survival from these data. Accordingly, we used the following approximations to compare the survival rates of this study era to median survival times reported by earlier studies. To approximate two-year survival rates in those earlier studies, we used linear extrapolation of the reported median survival times, assuming a constant number of deaths per year. This approximation is intermediate between the Gompertz and Makeham models of age-related mortality [13, 14]. To approximate median survival times for the present study, we used the same assumption and linear extrapolation based on the observed two-year survival rates.

This study was approved by the Internal Review Board of the VAPAHCS at Stanford University and complied with all human experimentation guidelines. Written consent was not required since studies did not use individually identifiable information.

RESULTS

In the PAVAHCS, 2,083 men aged 55 years and older received a prescription for donepezil ($n = 1{,}533$, 73.6%), memantine ($n = 284$, 13.6%), or both ($n = 266$, 12.8%), and 669 (32.1%) men died during the observation period. The number beginning treatment increased steadily from 55 in 1998, the first complete year in the study, to a high of 342 in 2004 (Table 1). In the three complete years observed since the introduction of memantine, the number of newly treated patients ranged from 298 in 2005 to 279 in 2007.

Table 1
Number of veterans beginning treatment with "Either" AD medication and number of first-time prescriptions of "Donepezil" and "Memantine". The "Either" group includes those individuals who began an "initial" AD medication (i.e., "Donepezil" or "Memantine") for the first time in that year. These numbers include individuals 55 years of age and older

Year	Either Number (Median Age)	Donepezil Number	Memantine Number
1997*	46 (75.8)	46	0
1998	55 (78.2)	55	0
1999	88 (77.6)	88	0
2000	105 (77.9)	105	0
2001	123 (79.5)	123	0
2002	182 (79.9)	182	0
2003	207 (79.8)	207	0
2004	342 (80.4)	275	136
2005	298 (80.4)	229	132
2006	252 (81.6)	198	110
2007	279 (81.9)	213	121
2008*	106 (82.7)	78	51
Total	2083 (80.2)	1799	550

*Year includes data for fewer than 12 months.

During the study period, the mean age at which an AD medication was first prescribed increased significantly by an annual rate of 0.48 years (95% CI: 0.37, 0.59, $p < 0.001$) from an estimated 76.6 in 1997 to an estimated 81.9 in 2008 (Fig. 1).

The 1,277 veterans who began treatment in the memantine era had significantly lower mortality rates than the 806 veterans who began treatment in the pre-memantine era (HR: 0.75; 95% CI: 0.63, 0.89; $p = 0.001$; Fig. 2). Older age at treatment initiation was associated with an increased risk of death (HR: 1.05 per year; 95% CI: 1.04, 1.07; $p < 0.001$). To clearly distinguish a period effect from a memantine effect, we repeated the same analysis restricting the sample to the donepezil-only patients (excluding patients receiving memantine alone or in combination with donepezil). We found that donepezil-only patients who began treatment during the memantine era also had lower mortality rates than donepezil-only patients in the pre-memantine era (HR: 0.81; 95% CI: 0.67, 0.98; $p = 0.034$). Note that 657 veterans in the pre-memantine cohort continued to receive treatment in the memantine era. Of these, 91 eventually received memantine, of whom 35 died (38%), while 566 never

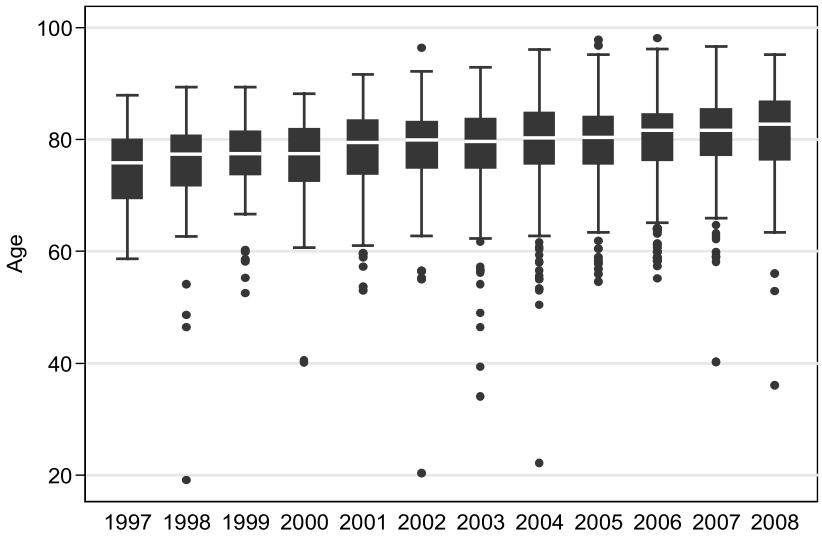

Fig. 1. Age at initial prescription by calendar year for individuals shown in column 1 of Table 1. Box plots show medians (horizontal bar), inter-quartile ranges (box), ranges of non-outliers (whiskers), and outliers (circles). The statistical analysis excluded Veterans below 55 years of age when beginning treatment. (See "Either" column in Table 1 for numbers.)

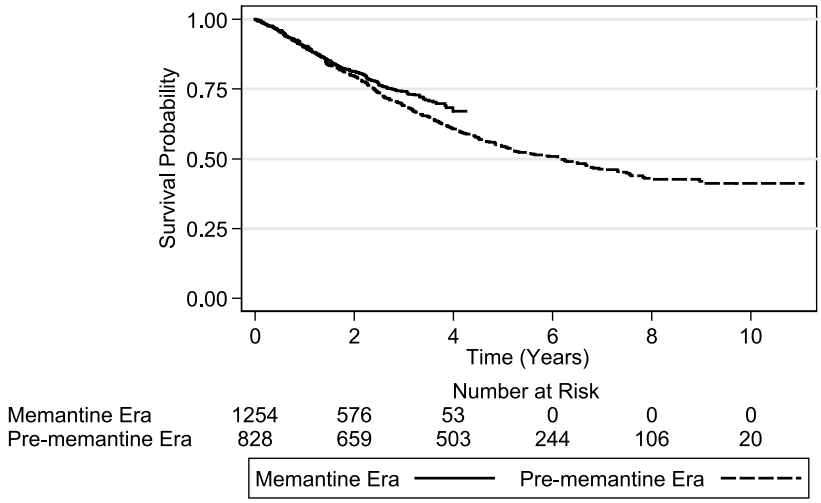

Fig. 2. Kaplan-Meier Curves by era (all drugs)

received memantine, of whom 205 died (36%). These 657 were excluded from the subsequent memantine-era analyses.

To examine whether longer survival in individuals prescribed memantine could explain in part the overall decrease in mortality in the memantine era, a second analysis tested drug effects (donepezil, memantine, or both) within the 1,255 subjects whose treatment began in the memantine era. By the end of the study, April 30, 2008, 242 (19.3%) memantine-era subjects had died (172/798 = 21.6% for donepezil alone; 31/284 = 10.9% for memantine alone; 39/173 = 22.5% donepezil plus memantine). Drug group was significantly associated with survival (Wald statistic: 17.33; df: 2; $p = 0.0002$; Fig. 3). Both the donepezil-only group and the donepezil plus memantine group had significantly higher mortality rates than the memantine-only group (HR: 2.24; 95% CI: 1.53, 3.28; $p < 0.001$, and HR: 1.83; 95% CI: 1.14, 2.94; $p = 0.012$, respectively). Survival of donepezil-only patients did not differ significantly from that of donepezil plus memantine patients ($p = 0.26$). In this model, each additional year of age at time of initial prescription was associated with an increased mortality rate (HR: 1.09; 95% CI:

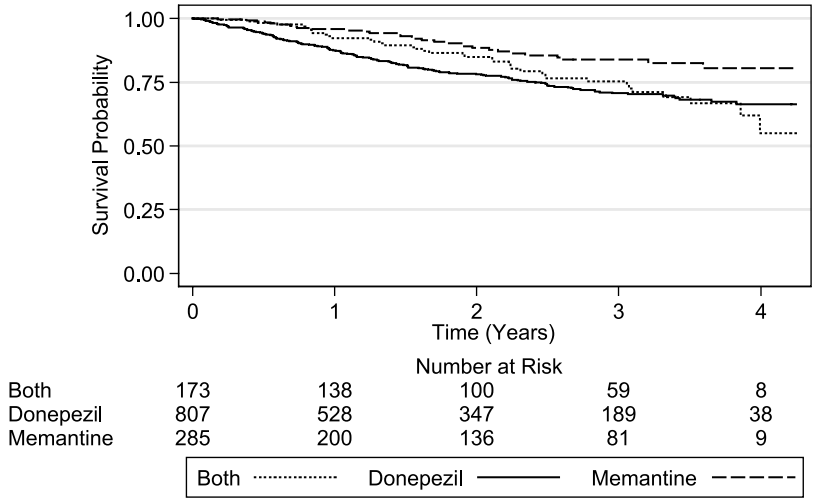

Fig. 3. Kaplan-Meier Curves by era (memantine-era patients only).

1.06, 1.11; $p < 0.001$). Date of initial prescription was not significant ($p = 0.41$). During the memantine era, memantine-only patients were on average slightly, but not significantly ($p = 0.22$), older at the beginning of treatment (80.8 years) than donepezil-only patients (79.9 years) and donepezil plus memantine patients (80.4 years).

To estimate two-year survival within drug treatment groups, we considered only patients who began treatment in the memantine era early enough to have at least two years of follow-up. The two-year survival rate was higher in the memantine-only group than in the donepezil-only group (88.8% versus 78.2%). Two-year survival was intermediate for patients from the same cohort who received both drugs at some point in time (85.5%; Table 2). There were too few deaths in this group to calculate median survival time directly. However, linear extrapolation from the two-year survival rate suggested that the median survival time of patients prescribed memantine alone may be nearly twice that of those prescribed donepezil alone (8.9 years versus 4.6 years; Table 2). An interesting observation was that the mortality pattern among identified veterans (Figs. 2 and 3) appeared to follow a Makeham model (decay curve) as opposed to a Gompertz model (survival curve), typical of age-associated mortality [13, 14] and dementia incidence [15].

Survival in the VAPAHCS cohort was within the range of that reported in prior studies. Wolfson et al. [2] finds a 74.2% two-year survival rate in men with AD, similar, but slightly less than the estimated survival of veterans treated with donepezil-alone in this study (78.2%, Table 2). Since mortality increases exponentially with age from 30 to 100 years old, we determined linearly interpolated estimates of two-year survival, based on the results in Brookmeyer et al. [3], which included data from the Baltimore Longitudinal

Table 2
Comparison of memantine era (2004–8) estimates with previous reports, for individuals 55 years of age and older

Current Study Memantine Era	n	Median Survival Time Years[1]	2-year Survival Rate % (95% CI[2])
Donepezil	436	4.6	78.2 (74.0, 82.0)
Both	117	6.9	85.5 (77.8, 91.3)
Memantine	152	8.9	88.8 (82.7, 93.3)
Males from Table 1 of Brookmeyer et al. [3] Age (years)		Median Survival Time Years	2-year Survival Rate %[3]
AD			
60		9.3	89.2
70		6.5	84.6
80		4.6	78.3
90		3.2	68.8
BLSA (recruited sample)			
60		28.5	96.5
70		18.7	94.7
80		10.3	90.3
90		5.1	80.4
Life tables (U.S. Population)			
60		20.0	95.0
70		12.4	91.9
80		6.7	85.1
90		3.3	69.7

[1]Extrapolated median based on 2-year survival rate, mean age of initial prescription: 80.0 in 2004 to 81.9 in 2008. [2]Exact confidence intervals for binomial proportions. [3]Interpolated survival rate based on median survival time.

Study of Aging (BLSA) and US Life Tables. Since the VAPAHCS veterans were generally closest to 80 years old, the most relevant comparisons are to the 80-year old men of that publication: 78.3% in men with AD, 90.3% for men in the BLSA, and 85.1% for men in the US Life Tables. The 2-year survival rate for normal individuals was similar to the estimated two-year survival in our memantine-only group (88.8%), while the values for AD patients are similar to the estimated survival found in our donepezil-only subjects (78.2%). In an additional sensitivity analysis (not shown), we considered the effect on estimated two-year survival rates if 25% of deaths were unreported. Sensitivity adjusted two-year survival rates under this assumption were 3.7% to 7.3% lower (memantine only, 85.1%; donepezil only, 70.9%; and donepezil and memantine, 80.7%). These comparisons are made between approximations derived from very different populations and methodologies, so their demographic relevance is uncertain.

DISCUSSION

The striking finding in this observational study is that male veterans with a presumptive diagnosis of AD survived longer when treated with memantine alone than with donepezil alone or donepezil in combination with memantine (Fig. 3). The present study provides estimates of survival for these veterans that are comparable to published values from other elderly and AD populations [2, 3, 16, 17]. Median survival times and the 2-year survival rates were similar for donepezil-treated patients and a reference AD population, while the values for memantine-treated patients were similar to normal populations, and the values for patients treated with both memantine and donepezil were intermediate (Table 2).

We also found longer overall survival in patients who began treatment during the era from 2004 to 2008 than from 1997 to 2003 (Fig. 2). To understand this finding, we analyzed age of first prescription and found that this age increased progressively throughout the study period (Fig. 1), which would be expected to lead to shorter survival. This effect was present even when controlled by studying only patients treated with donepezil without memantine. There are many possible reasons for this improvement, including advances in health care, general increases in life-expectancy, treatment of healthier individuals, and treatment at an earlier stage of dementia. The finding of increased age of first prescription could itself be related to the aging of the World War II Veterans, who comprise the majority of patients in this sample. Further, treatment might have begun earlier in the dementia course in the latter time period, despite the increased age of first prescription. The latter possibility could be related to numerous other factors, such as increased recognition of dementia in older individuals, particularly since it is exponentially more common with increasing age, and perception of dementia as a treatable condition in older individuals is improving over time. In any case, the aging of the treatment population would not increase survival, so alternative explanations are required for the observation of longer survival of patients in the later era.

It is unknown how AD medications affect survival. There is evidence that patients treated with AChEIs have slower cognitive decline and delayed nursing home placement relative to untreated patients [4, 18], though not necessarily longer life-expectancy [19]. Furthermore, the combination of donepezil and memantine acts synergistically in AD patients to improve cognition [6, 20] and delay nursing-home placement [21]. In contrast, we did not find a synergistic effect of donepezil and memantine on survival.

While this study did not include an untreated comparison group, comparison of the present data to previous life-expectancy reports suggests that survival rates in patients treated with memantine might be similar to rates in a general U.S. population (data from years 1985 to 1999 [3]), as well as other normal populations which have significantly greater longevity than people with a clinical diagnosis of dementia [16, 17]. However, general survival rates, veteran characteristics, and prescribing patterns may have changed since the time of the reference studies. Therefore, it is important to determine the precise effects of these medications and the issues of their separate and combined actions in directly compared populations. These findings suggest that the underlying interactions of these drugs needs to be further understood.

The mortality rate after prescription, particularly with donepezil, declines with a decay curve (Fig. 2 and donepezil curve of Fig. 3), as would be found with a constant mortality rate (Makeham Law) as opposed to a survival curve, which is based on an exponentially increasing mortality rate (Gompertz Law). The finding of a decay curve suggests that mortality occurs as a phenomenon with invariant probability, influencing the chance of mortality more strongly than normal causes of mortality. Since the risk of dementia increases more rapidly with age than mortality, dementia likely contributes substantially to risk of death beyond that of age.

In these data, the contribution of dementia to mortality is more apparent for patients treated with donepezil than memantine.

There are plausible hypotheses that both AChEIs and memantine may be disease modifying. There is laboratory evidence that AChEIs beneficially modulate the cleavage of the amyloid-β protein precursor and block the formation of hyperphosphorylated tau, both considered related to the pathological cascade leading to dementia [22, 23]. However, there may be a physiologic response to increase cholinesterase enzyme levels, which blunts the benefit over time [24]. By partially antagonizing N-methyl-D-aspartate receptors, memantine protects neurons from excessive excitotoxicity [25], and memantine may lower glutamate levels in the brain directly [26]. However, both drugs are also associated with side effects that can potentially reduce life-expectancy. AChEIs are reported to increase rates of syncope, bradycardia, pacemaker insertion, and hip fracture [27]; memantine may cause psychosis [28].

We cannot exclude potential confounding by factors that could influence physician selection of AD medication for patients with different life-expectancies. However, between 2005 and 2008, the VAPAHCS used an algorithm that restricted donepezil to patients with mild or moderate dementia presumably due to AD and memantine to patients with moderate to severe dementia presumably due to AD. That algorithm also discouraged treatment with these medications for patients unlikely to have AD. Selective prescribing of memantine to more severely demented patients would have biased survival negatively with respect to donepezil, in the opposite direction of what was observed. Selective prescribing of donepezil to patients with mild dementia or mild cognitive impairment would also have biased survival in the opposite direction to what was observed.

Characteristics associated with decreased survival in patients with AD include age, male gender, genetic polymorphisms, degree of cognitive impairment, extrapyramidal signs, mood and behavioral disturbances, anti-psychotic medications, comorbid medical conditions, and psychosocial variables such as multiple caregivers [1, 16, 17, 29–31]. Some of these factors may have confounded prescription patterns. In addition, memantine or donepezil could have affected survival by exacerbating or ameliorating such factors.

This study has other limitations. All participants were male veterans, and the findings may not apply to women and may not generalize to men in other settings. Diagnoses of AD were inferred, and some patients receiving drugs approved for AD treatment could have had disorders other than AD. While it is unlikely such misclassification would have been biased, it is also possible that complicating diagnoses such as dementia with Lewy bodies/Parkinson dementia or vascular dementia and other guidelines for alternative use of cholinesterase medications and memantine could have influenced prescribing practices. We cannot distinguish between improved survival with memantine or reduced survival with donepezil, since we had no reference group of untreated patients presumed to have AD. Prescription records may not reflect patient compliance. Exposure misclassification could also have occurred if some veterans obtained anti-dementia treatment outside the VAPAHCS. The donepezil-only group and the memantine-only group may therefore have included patients receiving both drugs. Veterans with access to two healthcare systems may have been healthier, and misclassification would most likely have biased findings toward better survival in the donepezil-only group. Short follow-up and a relatively small number of deaths of memantine-era patients make it impossible to calculate median survival time or life-expectancy directly, reducing the power to detect trends over time following the introduction of memantine. However, the VA collects data from veterans nationally, so the findings can be validated in future studies involving larger populations of veterans.

Our findings, which suggest an association between survival and type of dementia treatment, do not establish a causal relationship and do not have immediate practice implications. It is unknown whether similar differences would be obtained for comparisons between memantine and AChEIs other than donepezil. However, the possibility of differential survival between memantine and donepezil should be further examined in other cohorts of dementia patients and in laboratory models. These findings, if validated, would have important implications for the treatment of patients with dementia due to AD.

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