

Featured Article

Alzheimer's disease medication and risk of all-cause mortality and all-cause hospitalization: A retrospective cohort study

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Abstract

Introduction: Identifying Alzheimer's disease (AD) pharmacologic treatment options that effectively reduce the risk of mortality and hospitalization in real-world settings is critical.**Methods:** We compared donepezil, galantamine, memantine, oral rivastigmine, and transdermal rivastigmine with regard to all-cause mortality and all-cause hospitalization risk among fee-for-service Medicare beneficiaries with AD (aged ≥ 65 years) using a retrospective cohort study design. Our primary analysis was based on intention to treat (ITT), but we also present as-treated analysis.**Results:** In our final study sample ($N = 21,558$), significant difference in survival among index AD medication groups were observed with donepezil being associated with better survival than memantine, and oral and transdermal forms of rivastigmine for both ITT and as-treated analysis. Difference in hazards of all-cause hospitalization among index AD medication groups was observed in ITT analysis but not in as-treated analysis.**Discussion:** Significant differences exist in terms of mortality and hospitalization risk with different AD medication initiation in real-world setting.© 2019 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords:

Alzheimer's disease medications; Safety; All-cause mortality; All-cause hospitalization; Survival analysis; Inverse probability of treatment weighting

1. Introduction

Alzheimer's disease (AD) is the 6th leading cause of death in the United States [1], and mortality due to AD has approximately doubled from 2000 and 2014 [2]. Moreover,

individuals with AD have a significantly higher risk of hospitalization, falls, fractures, and other complications than those without AD [3]. Pharmacological therapies approved for AD treatment include acetylcholinesterase inhibitors [AChEIs: donepezil, rivastigmine (oral and transdermal), and galantamine] and the N-methyl-D-aspartate antagonist (memantine) [4].

Existing studies synthesizing findings from randomized controlled trials (RCTs) and long-term observational controlled studies found that AD medications have modest benefit in cognitive decline, patient functioning and behavior, and global clinical change compared with no

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treatment [5,6]. AD medications remain the mainstay of AD treatment with existing reviews suggesting benefits with AD medication treatment compared with no treatment. Hence, examining safety and effectiveness of individual AD medications is critical to help health care providers make informed decisions when selecting AD medications in real-world settings. However, existing studies examining the safety and effectiveness of AD medications are inconsistent. Few studies have observed increased risk of mortality [7,8] and hospitalization [9,10] with AD medication use, whereas other studies have observed favorable outcomes with the use of AD medications [11–15]. These existing studies using various study designs (such as RCT, long-term observational controlled study) were limited by small sample size, lacked generalizability, had short follow-up period, mostly compared only two or three AChEIs, did not differentiate between oral and transdermal forms of rivastigmine, and did not use robust study design to address selection bias. Moreover, except one study [10], none of the other studies provided comparative benefits of memantine with other AD medications.

To address these gaps in the existing literature, we compared AD medications with regard to all-cause mortality and all-cause hospitalization risks among older adults with AD by using a retrospective cohort study design utilizing a US national sample of Medicare beneficiaries.

2. Methods

A retrospective cohort study was conducted using Medicare 5% sample claims data (2011–2015), Long Term Care Minimum Data Set (MDS) 3.0 (2011–2015) and Area Health Resources File (AHRF) data sets.

We used all the standard analytic files (inpatient, outpatient, skilled nursing facility, carrier, hospice care, home health, part D events, Medicare Beneficiary Summary File and durable medical equipment) from Medicare claims data (5% random sample) [16]. MDS 3.0 comprises a standardized assessment tool to comprehensively assess every nursing home resident in US federally certified facilities [17]. The MDS was used to identify older adults with AD who had at least one nursing home stay before initiating AD medication. The AHRF is a US county-specific database that contains more than 6000 variables (e.g., health professions representation; environmental characteristics). The AHRF data set is maintained at the county level and contains geographic codes and descriptors that enable linkage to other files and facilitates aggregation into various geographic groupings. We linked AHRF data to Medicare data using Social Security Administration codes to include socioenvironmental factors as covariates at the person level.

Our study sample consisted of fee-for-service Medicare beneficiaries aged ≥ 65 years with AD. Individuals with AD were identified based on the Centers for Medicare and Medicaid Services Chronic Conditions Data Warehouse Condition Categories algorithm [18]. The first prescription claim

for an AD medication was defined as the “index-date” and six months before index-date was considered to be the baseline period. To be included in the study and to establish a washout period, beneficiaries had to be continuously enrolled in Medicare part A (hospital coverage), B (medical coverage), and D (prescription drug coverage) for at least six months before the index date. Beneficiaries were excluded if they (1) enrolled in Health Maintenance Organizations or other Medicare Advantage health plans during baseline; (2) had end-stage liver disease during the baseline; (3) had end-stage renal disease during index AD medication prescription year; (4) had initiated more than one AD medication on the “index-date”; (5) had missing age, gender, race/ethnicity, or AHRF variable information; or (6) had inconsistencies in date of birth across different study years. End-stage renal disease was identified from the Medicare Beneficiary Summary File, whereas end-stage liver disease was identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 155.0 and 571.xx [19]. Rivastigmine is also approved by the US Food and Drug Administration for mild to moderate dementia associated with Parkinson's disease (PD) [20]. To minimize the chances of indication bias, we excluded individuals with PD at the baseline. Beneficiaries with PD were identified using validated ICD-9-CM code of 332.xx [21,22]. A minimum of six-month “washout period” before the AD medication initiation was used to limit the analysis to new initiators of AD medication to minimize prevalent user bias.

Two outcomes of interest of this study included time to (1) all-cause mortality (identified from the Medicare Beneficiary Summary File) and (2) first all-cause hospitalization (identified from the inpatient claims data sets) after initiation of an AD medication. The exposure variable for this study was an AD medication (donepezil, oral rivastigmine, transdermal rivastigmine, galantamine, or memantine) initiation. Medications of interest were identified using National Drug Codes from the part D events files. Our study sample was categorized as donepezil, oral rivastigmine, transdermal rivastigmine, galantamine, or memantine initiators based on the first AD medication received.

To control for confounding, inverse probability of treatment weighting (IPTW) analyses [23] were conducted to assess the comparative safety of individual AD medications after adjusting for individual-level variables. Individual-level factors included in the propensity score calculation were age; gender; race/ethnicity; receipt of public assistance (indicated by Medicare premiums and deductibles that were subsidized for the enrollee by the state); density of neurologists in the beneficiary's geographic area; natural logarithm of the median household income where the enrollees resided; census region; metropolitan residency status; burden of comorbidities measured by previously validated [24,25] Elixhauser comorbidity index; and baseline medication use. Despite the lack of an appropriate measure of severity of AD in claims database, it can be argued that older adults with AD who had nursing home

stay may have a higher severity of AD. Hence, we included baseline nursing home stay as a proxy measure for AD severity as one of the variables to generate propensity score. Details of the categorization of each variable are presented in [Table 1](#). Propensity scores were estimated using multinomial logistic regression. We considered standardized mean difference (SMD) of <0.20 [26] as an indicative of achieving good balance after IPTW adjustment, and calculated pairwise and average SMDs of the five AD medications before and after IPTW adjustment.

From 1st October 2015, diagnosis claims in Medicare data were coded using ICD-10-CM instead of ICD-9-CM codes. To accommodate this change, we have used previously validated ICD-10-CM codes for Elixhauser comorbidity index calculation and for other conditions (e.g., PD and end-stage liver disease) from 1st October through 31st December 2015 [24,27].

In this study, we used two approaches: our primary analysis was based on intention to treat (ITT), but we also used a per-protocol analysis or as-treated analysis. For both ITT and as-treated analysis, subjects were followed up until the event (hospitalization or mortality) or censoring occurred. The difference between these approaches was the criteria for censoring. For ITT analysis, subjects were censored at the time of the earliest of these events if they (1) did not have continuous Medicare part A/B/D eligibility; (2) added Health Maintenance Organizations coverage; or (3) reached study end period. In the as-treated analysis, in addition to the censoring criteria of the ITT analysis, subjects were censored at the time of (1) they were prescribed an AD medication other than the index medication during the follow-up period (switching); (2) they discontinued or (3) they were nonadherent to the “index” AD medication. Apart from switching to another AD medication from the index AD medication, we also considered that the individual switched if they initiated Namzaric (approved for AD treatment in 2014 [28]) while on the index AD medication. Discontinuation was defined as subjects having no additional prescription for AD treatment after the index medication run-out date and no switch to other AD treatment occurred before the run-out date [29]. To assess adherence, we used a 30-day moving average of proportion of days covered for the index AD medication. Older adults with AD were considered to be nonadherent if the 30-day moving average of proportion of days covered fell below 80%. Detailed explanation of the algorithm used to compute prescription coverage days is provided in [Supplementary document](#) (see Page 31).

In our analysis, we considered death before hospitalization as a competing risk rather than a censoring event. We initially intended semiparametric methods to analyze all-cause mortality (Cox proportional hazards model) and all-cause hospitalization (Fine-Gray proportional subdistribution hazards model) with mortality as the competing event. However, diagnostic tests (drug-time interaction terms were statistically significant, $P < .05$) indicated violation of proportionality assumption of these methods and

reporting a constant relative effect (e.g., hazard ratio for pairs of AD medications) would not appropriately reflect the differences in outcomes among the AD medication groups. Therefore, we opted to use fully nonparametric methods. To compare survival curves for all-cause mortality among the five index drugs, we used the adjusted Kaplan-Meier estimator and weighted log-rank test [30] with IPTW. To compare cumulative incidence functions (CIFs) of all-cause hospitalization with mortality as the competing event, we modified the test statistic in Gray's test [31] to account for IPTW and tested for significance using a randomized permutation test (see [Supplement section](#) Page 32-45 for the overview of the algorithm used to conduct the modified Gray's test and the R code used). For both of these analyses, if the overall test was significant (P value $< .05$), post hoc tests were conducted on each pair of treatments.

To quantify effect sizes, in addition to presenting Kaplan-Meier survival and CIF plots, we present point estimates and 95% confidence intervals for proportion survival and cumulative incidence of hospitalization at 365, 730, 1095, and 1460 days as well as the 1st quartile and median time to event for each outcome.

An *a priori* α level of 0.05 was used to establish statistical significance. We also checked for missing data in our sample. We conducted two sensitivity analyses to assess the robustness of our findings. First, we included age as a continuous variable (rather than categorical variable) in the propensity score model, as age is one of the strongest predictors of mortality and hospitalization. Second, we used one-year washout period (rather than six-month washout period). The Institutional Review Board of the University of Arizona approved this study and determined that human subjects review was not required.

3. Results

[Supplementary Fig. 1](#) shows the development of the final study sample. After applying all study inclusion/exclusion criteria, we had 21,558 Medicare beneficiaries with AD in our final study cohort. As the number of subjects excluded for missing/inconsistent data in our study sample was very low ($n = 173$; $<1\%$ of our study sample), we considered it to have inconsequential effect and hence did not use any imputation to address missing data. The cohort consisted of 13,837 donepezil initiators, followed by 4884 memantine, 2235 transdermal rivastigmine, 355 galantamine, and 247 oral rivastigmine initiators. [Table 1](#) presents the baseline characteristics and their differences before IPT-weighting and the P values after IPT-weighting among the five groups. After the IPT-weighting, all of the baseline characteristics were considered balanced as evidenced from all pairwise and average SMDs of <0.20 after IPT-weighting (see [Supplementary Table 3](#)). [Supplementary Fig. 2](#) shows the propensity score distribution for AD medication actually initiated, whereas [Supplementary Fig. 3](#) shows the distribution of the inverse probability of treatment weights. In

Table 1
Summary statistics of baseline characteristics and *P* values of unweighted and IPT-weighted analysis

Characteristics	Donepezil (N = 13,837), N (%)	Galantamine (N = 355), N (%)	Memantine (N = 4884), N (%)	Oral rivastigmine (N = 247), N (%)	TD rivastigmine (N = 2235), N (%)	Unweighted <i>P</i> value	IPT- weighted <i>P</i> value
Age group							
65-74 years	2074 (14.99)	39 (10.99)	589 (12.06)	40 (16.19)	278 (12.44)	<.01	>.99
75-84 years	6168 (44.58)	155 (43.66)	2173 (44.49)	100 (40.49)	925 (41.39)		
85+ years	5595 (40.43)	161 (45.35)	2122 (43.45)	107 (43.32)	1032 (46.17)		
Gender							
Male	4181 (30.22)	152 (42.82)	1487 (30.45)	70 (28.34)	636 (28.46)	<.01	.94
Race/ethnicity							
White	11,881 (85.86)	324 (91.27)	4211 (86.22)	221 (89.47)	1928 (86.26)	.08	>.99
African American	1285 (9.29)	24 (6.76)	430 (8.80)	14 (5.67)	199 (8.90)		
Others	671 (4.85)	7 (1.97)	243 (4.98)	12 (4.86)	108 (4.84)		
Public assistance							
Yes	3368 (24.34)	68 (19.15)	1276 (26.13)	71 (28.74)	713 (31.90)	<.01	.72
Elixhauser comorbidity index							
0	2526 (18.26)	77 (21.69)	849 (17.38)	40 (16.19)	314 (14.05)	<.01	>.99
1	2740 (19.80)	83 (23.38)	846 (17.32)	49 (19.84)	358 (16.02)		
2	2355 (17.02)	70 (19.72)	805 (16.48)	41 (16.60)	383 (17.14)		
≥3	6216 (44.92)	125 (35.21)	2384 (48.82)	117 (47.37)	1180 (52.80)		
Baseline nursing home stay							
Yes	2724 (19.69)	62 (17.46)	1203 (24.63)	62 (25.10)	630 (28.19)	<.01	>.99
Baseline medication use							
ACE inhibitors	3697 (26.72)	74 (20.85)	1070 (21.91)	65 (26.32)	541 (24.21)	<.01	.94
ARBs	2121 (15.33)	44 (12.39)	674 (13.80)	31 (12.55)	315 (14.09)	.03	.97
Anticoagulants	1507 (10.89)	33 (9.30)	481 (9.85)	27 (10.93)	238 (10.65)	.31	.96
Antidepressants	5438 (39.30)	118 (33.24)	2032 (41.61)	102 (41.30)	1021 (45.68)	<.01	.99
Antidiabetics	2403 (17.37)	36 (10.14)	736 (15.07)	33 (13.36)	394 (17.63)	<.01	.99
Antipsychotics	1957 (14.14)	42 (11.83)	966 (19.78)	49 (19.84)	533 (23.85)	<.01	>.99
Anxiolytics	2108 (15.23)	42 (11.83)	811 (16.61)	45 (18.22)	440 (19.69)	<.01	.79
Statins	6026 (43.55)	122 (34.37)	1675 (34.30)	91 (36.84)	810 (36.24)	<.01	.79
Beta-blockers	5415 (39.13)	99 (27.89)	1642 (33.62)	84 (34.01)	847 (37.90)	<.01	.95
CCBs	3551 (25.66)	74 (20.85)	1064 (21.79)	62 (25.10)	528 (23.62)	<.01	.91
Diuretics	4645 (33.57)	90 (25.35)	1438 (29.44)	74 (29.96)	755 (33.78)	<.01	.95
PPIs	3490 (25.22)	69 (19.44)	1164 (23.83)	50 (20.24)	619 (27.70)	<.01	.82
Metropolitan status							
Yes	11,127 (80.41)	290 (81.69)	3959 (81.06)	197 (79.76)	1770 (79.19)	.43	.86
Region							
Northeast	2787 (20.14)	74 (20.85)	883 (18.08)	47 (19.03)	370 (16.55)	<.01	1.00
South	5730 (41.41)	141 (39.72)	2130 (43.61)	118 (47.77)	1113 (49.80)		
Midwest	3429 (24.78)	87 (24.51)	1156 (23.67)	57 (23.08)	538 (24.07)		
West	1891 (13.67)	53 (14.93)	715 (14.64)	25 (10.12)	214 (9.58)		
Density of neurologists							
0	2591 (18.73)	50 (14.08)	872 (17.85)	58 (23.48)	456 (20.40)	<.01	>.99
1	3730 (26.96)	87 (24.51)	1345 (27.54)	64 (25.91)	598 (26.76)		
2	3662 (26.47)	101 (28.45)	1416 (28.99)	73 (29.55)	590 (26.40)		
3	3854 (27.84)	117 (32.96)	1251 (25.62)	52 (21.05)	591 (26.44)		
Mean (±SD) in median household income (natural log scale)	10.82 (±0.26)	10.85 (±0.27)	10.82 (±0.25)	10.82 (±0.25)	10.80 (±0.26)	<.01	.99

NOTE: Based on 21,558 older adults with AD.

Abbreviations: SD, standard deviation; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCB, calcium channel blockers; PPI, proton pump inhibitors.

addition, summary statistics of propensity scores and IPTW are provided in [Supplementary Table 4](#).

In our primary ITT analysis, total number of deaths during the follow-up was 7249, whereas in our secondary as-treated analysis, total number of deaths during the follow-up was 1015 (details provided in [Supplementary Table 1](#)). In the ITT analysis, donepezil had the highest point estimate of survival at each of the four times points ([Table 2](#)) as well as nearly consistently across the entire study time

([Fig. 1](#)). Point estimate of the median survival time was longest for donepezil (1330 days) in the ITT analysis ([Table 3](#)). The weighted log-rank test revealed a statistically significant difference in survival curves among index AD medication groups with donepezil being associated with better survival than memantine, and oral and transdermal forms of rivastigmine for both the ITT (*P* value < .001, [Fig. 1](#)) and as-treated analysis (*P* value = .003, [Supplementary Fig. 4](#)). Post hoc pairwise comparisons are presented in [Table 4](#).

Table 2
Survival estimates (95% CI) for all-cause mortality and cumulative incidence estimates (95% CI) for all-cause hospitalization at 365, 730, 1095, and 1460 days

	ITT	As-treated analysis
Survival estimates (95% CI) for all-cause mortality		
365 days		
Donepezil	0.844 (0.837–0.850)	0.906 (0.897–0.915)
Galantamine	0.801 (0.745–0.846)	0.898 (0.813–0.946)
Memantine	0.819 (0.807–0.830)	0.882 (0.859–0.901)
Oral rivastigmine	0.807 (0.743–0.856)	0.906 (0.814–0.954)
TD rivastigmine	0.806 (0.787–0.823)	0.874 (0.839–0.902)
730 days		
Donepezil	0.705 (0.696–0.714)	0.827 (0.808–0.845)
Galantamine	0.654 (0.587–0.713)	0.818 (0.663–0.906)
Memantine	0.655 (0.639–0.671)	0.771 (0.724–0.811)
Oral rivastigmine	0.628 (0.548–0.699)	0.797 (0.619–0.898)
TD rivastigmine	0.652 (0.628–0.675)	0.780 (0.701–0.840)
1095 days		
Donepezil	0.577 (0.566–0.588)	0.738 (0.703–0.770)
Galantamine	0.528 (0.450–0.600)	0.818 (0.663–0.906)
Memantine	0.504 (0.485–0.523)	0.669 (0.595–0.733)
Oral rivastigmine	0.466 (0.375–0.552)	NA
TD rivastigmine	0.538 (0.509–0.565)	0.733 (0.629–0.811)
1460 days		
Donepezil	0.464 (0.449–0.479)	0.618 (0.535–0.691)
Galantamine	0.378 (0.278–0.478)	0.663 (0.176–0.908)
Memantine	0.398 (0.373–0.423)	0.637 (0.523–0.731)
Oral rivastigmine	0.440 (0.342–0.533)	NA
TD rivastigmine	0.435 (0.398–0.471)	0.478 (0.176–0.731)
Cumulative incidence estimates (95% CI) for all-cause hospitalization		
365 days		
Donepezil	0.417 (0.409–0.426)	0.409 (0.395–0.422)
Galantamine	0.410 (0.282–1.000)	0.438 (0.000–1.000)
Memantine	0.406 (0.391–0.419)	0.433 (0.406–0.462)
Oral rivastigmine	0.383 (0.288–0.576)	0.342 (0.202–0.586)
TD rivastigmine	0.403 (0.381–0.426)	0.423 (0.378–0.467)
730 days		
Donepezil	0.571 (0.562–0.580)	0.579 (0.558–0.598)
Galantamine	0.563 (0.311–1.000)	0.611 (0.000–1.000)
Memantine	0.567 (0.550–0.583)	0.581 (0.540–0.623)
Oral rivastigmine	0.551 (0.403–0.704)	0.669 (0.458–0.884)
TD rivastigmine	0.558 (0.535–0.583)	0.648 (0.583–0.718)
1095 days		
Donepezil	0.663 (0.652–0.673)	0.676 (0.649–0.701)
Galantamine	0.604 (0.385–1.000)	0.686 (0.000–1.000)
Memantine	0.645 (0.629–0.661)	0.654 (0.611–0.704)
Oral rivastigmine	0.641 (0.523–0.891)	0.669 (0.458–0.884)
TD rivastigmine	0.636 (0.611–0.661)	0.699 (0.625–0.774)
1460 days		
Donepezil	0.722 (0.710–0.734)	0.715 (0.680–0.747)
Galantamine	0.677 (0.449–1.000)	0.894 (0.000–1.000)
Memantine	0.691 (0.671–0.710)	0.697 (0.634–0.765)
Oral rivastigmine	0.731 (0.609–0.927)	0.669 (0.458–0.884)
TD rivastigmine	0.698 (0.668–0.727)	0.735 (0.645–0.825)

NOTE: A point estimate and/or upper limit to the confidence interval will not be available when all the remaining individuals got censored.

Adjusting for death as competing event, in the ITT analysis, there were 11,707 hospitalizations, 1864 death before hospitalization, and 7987 censored observations. However, for the as-treated analysis, there were 4737 hospitalizations, 426 death before hospitalization, and 16,395 censored observations (see [Supplementary Table 2](#)). CIFs for each of the

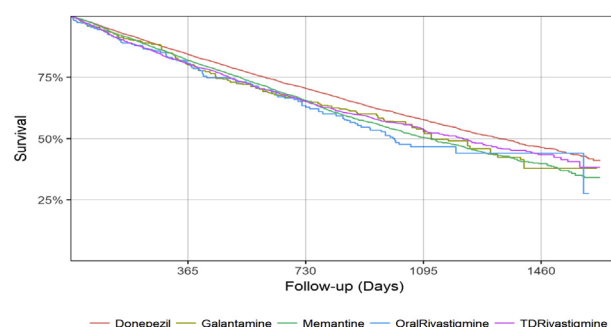


Fig. 1. IPT-weighted Kaplan-Meier curve for all-cause mortality (intention to treat analysis). Weighted log-rank $P < .001$. Abbreviation: IPT, inverse probability of treatment.

five AD medications are illustrated in [Fig. 2](#) for the ITT analysis and [Supplementary Fig. 5](#) for the as-treated analysis. Although the modified Gray's test indicated the hazard of hospitalization was not constant over time among the five AD medications for the ITT analysis (P value = .014), post hoc pairwise comparisons only revealed a difference between donepezil and memantine (P value = .029, [Table 4](#)). However, the difference in median time to all-cause hospitalization was relatively small: 538 days (donepezil) versus 561 days (memantine) (see [Table 3](#)). In the as-treated

Table 3
Median and first quartile survival times (95% CI) in days for all-cause mortality and time to hospitalization (95% CI) in days for all-cause hospitalization

	ITT	As-treated analysis
Time to mortality (95% CI) in days for all-cause mortality		
1st quartile		
Donepezil	605 (580–629)	1040 (909–1178)
Galantamine	452 (358–597)	1397 (496–NA)
Memantine	526 (492–552)	779 (697–859)
Oral rivastigmine	423 (360–637)	891 (372–977)
TD rivastigmine	492 (455–536)	762 (615–1245)
Median		
Donepezil	1330 (1291–1379)	1608 (1509–NA)
Galantamine	1119 (974–1407)	NA (1397–NA)
Memantine	1121 (1054–1178)	NA
Oral rivastigmine	1006 (846–NA)	977 (891–NA)
TD rivastigmine	1219 (1102–1308)	1245 (1099–NA)
Time to hospitalization (95% CI) in days for all-cause hospitalization		
1st quartile		
Donepezil	144 (137–150)	150 (142–157)
Galantamine	173 (23–255)	183 (128–NA)
Memantine	164 (151–177)	153 (133–165)
Oral rivastigmine	175 (54–284)	210 (53–403)
TD rivastigmine	155 (136–177)	154 (139–175)
Median		
Donepezil	538 (517–556)	529 (496–580)
Galantamine	507 (91–NA)	586 (128–NA)
Memantine	561 (522–589)	552 (439–613)
Oral rivastigmine	602 (147–967)	434 (120–NA)
TD rivastigmine	569 (508–635)	455 (389–589)

NOTE: A point estimate and/or upper limit to the confidence interval will not be available where an insufficient number of events have occurred.

Table 4

P values for post hoc (pairwise) weighted log-rank tests for all-cause mortality and for post hoc (pairwise) modified Gray's tests (IPT-weighted) for all-cause hospitalization

	Donepezil	Galantamine	Memantine	Oral rivastigmine	TD rivastigmine
All-cause mortality					
Donepezil		0.068	<0.001	0.026	<0.001
Galantamine	0.795		0.879	0.649	0.859
Memantine	0.047	0.746		0.638	0.482
Oral rivastigmine	0.030	0.213	0.207		0.506
TD rivastigmine	0.001	0.381	0.128	0.459	
All-cause hospitalization					
Donepezil		0.150	0.029	0.480	0.085
Galantamine			0.512	0.707	0.547
Memantine				0.869	0.917
Oral rivastigmine					0.949
TD rivastigmine					

NOTE: The upper-diagonal gives values from the intention-to-treat (ITT) analysis. The lower diagonal gives values from the per-protocol analysis or as-treated analysis.

The overall *P* values for ITT and as-treated analysis approach for all-cause mortality were <.0001 and .0029, respectively.

For all-cause hospitalization, the overall *P* value for ITT approach was .0142. Post hoc (pairwise) Gray's tests (IPT-weighted) were not calculated for the as-treated analysis, as the overall *P* value (*P* = .627) was not statistically significant.

analysis, there was no statistically significant difference in the hazard of hospitalization among the five AD medications (*P* value = .627). Point estimates for median time to hospitalization ranged from 507 days (galantamine) to 602 days (oral rivastigmine) for the ITT analysis and from 434 days (oral rivastigmine) to 586 days (galantamine) for the as-treated analysis, but there was considerable overlap in confidence intervals for both analyses (Table 3).

Sensitivity analyses using age as a continuous covariate in the propensity score model and one-year washout period revealed consistent findings to our base case analysis (details provided in Supplementary Tables 5-18).

4. Discussion

To the best of our knowledge, this is one of the largest studies using a national database that demonstrated a difference in mortality risk among AD medications. The key finding of this study is that compared with other pharmacological agents for AD (memantine, oral and transdermal rivastigmine), donepezil was associated with lower risk of all-cause mortality.

While we present findings from both ITT and as-treated analysis, it should be noted that findings from as-treated analysis usually provide lower level of evidence compared with ITT analysis [32]. Hence, it is important to keep in mind the strengths and weaknesses of ITT and as-treated analysis while interpreting the study findings. Advantages of ITT analysis include elimination of bias, preserving sample size, and closely reflect "effectiveness" of the intervention rather than "efficacy" [33]. Even though ITT analysis is the preferred method of analysis, it is sometimes considered to be "too conservative" and has the possibility of exposure misclassification [33,34]. To address these issues, we conducted secondary analysis using as-treated analysis that censored individuals who did not adhere to the protocol

strictly. However, drawbacks of common as-treated analysis include not accounting for postrandomization confounding and selection bias, not mimicking real-life situation, possibility of demonstrating an overstated treatment effect and probability of informative censoring and time-dependent confounding bias [33,34].

Our finding is consistent with previous investigations showing reduced mortality in donepezil-treated outpatients [14], nursing home residents [35], and hospitalized patients with pneumonia [36]. However, none of these previous studies compared donepezil with other AD agents. Our study findings are consistent with Kazmierski et al. study that demonstrated higher risk of mortality with rivastigmine compared with donepezil [8]. Our study findings provides further information showing survival benefits of donepezil compared with both oral and transdermal rivastigmine. However, our study findings are inconsistent with a study based on US Department of Veterans Affairs that found that donepezil was associated with a higher mortality

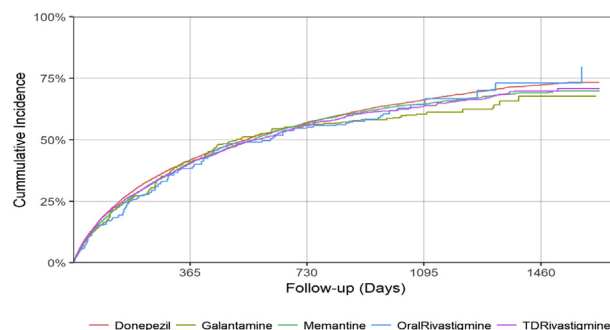


Fig. 2. IPT-weighted cumulative incidence function of hospitalization, adjusting for death before hospitalization as a competing risk (intention to treat analysis). Modified Gray's test *P* = .014. Abbreviation: IPT, inverse probability of treatment.

compared with memantine [37]. Some of the limitations (e.g., diagnosis of AD was inferred, and individuals with PD were not identified or excluded) of the Veterans Affairs study might contribute to this inconsistency.

Although existing placebo controlled trials [5,38] have assessed changes in the measures of cognition, physical functional, behavioral, or global assessment among individuals with AD, important real-world outcomes (such as mortality and hospitalization) have not been examined. The use of subjective scales and inventory, along with lack of power, minimized the chance to detect important real-world outcomes. Thus, the present study findings fill a research gap by directly comparing AD agents with respect to their associations to mortality and hospitalization. Even though the relationship between donepezil use and mortality among individuals with AD is not well understood, it can be speculated that vagotonic [39] and anti-inflammatory properties [40–42] of donepezil on atherosclerosis might be associated with lower risk of myocardial infarction and mortality. Moreover, survival benefits of donepezil have been demonstrated in an animal study via pump failure prevention and cardiac remodeling in congestive heart failure model in mice [43].

There have been very few trials that have directly compared AChEI for the treatment of AD [38]. A 12-week comparative open-label trial ($n = 111$), in which individuals with mild to moderate AD were randomized to receive donepezil or rivastigmine, showed no significant difference in cognitive symptom improvement between the two groups, with more patients in the donepezil group completing the study compared with those in the rivastigmine group (89% vs. 69%, $P = .009$) [44]. The authors concluded that donepezil was tolerated better by patients than rivastigmine and resulted in fewer drug discontinuations [44]. This study suggested a potential advantage in favor of donepezil, which is consistent with our findings.

Bullock et al. [45] randomized 998 patients with moderate to severe AD to receive donepezil or rivastigmine and demonstrated a similar change in cognitive function with donepezil (-9.9 ± 1.1) and rivastigmine (-9.3 ± 1.1) on the Severe Impairment Battery. Interestingly, rivastigmine showed superior efficacy compared with donepezil with respect to global deterioration ($P = .049$) and activities of daily living ($P = .007$). Unfortunately, outcomes from our study cannot be directly compared with those of Bullock et al. trial [45] and it was conducted outside US, potentially limiting extrapolation to the Medicare population. Finally, it should be noted that while the trial by Wilkinson et al. [44] was funded by the manufacturers of donepezil, the trial by Bullock et al. [45] was funded by the manufacturers of rivastigmine.

There have also been conflicting clinical trial results involving direct comparisons of donepezil versus galantamine assessing cognition and function of patients with AD [46,47]. These studies were limited by small sample size, open-label design, and unbalanced groups. A recent pragmatic randomized trial ($n = 196$) showed rates of

discontinuation at 18 weeks of 39% with donepezil, 53% with galantamine, and 59% with rivastigmine ($P = .063$) [48]. Overall in the study by Campbell et al. [48], approximately 81% of caregivers reported adverse events with the use of acetylcholinesterase inhibitors. These rates of discontinuation favor donepezil and could have led to lower all-cause mortality shown in our study.

Memantine is indicated for moderate to severe AD [49] and existing literature suggests that memantine may have a favorable safety and tolerability profile compared with AChEI [37,50,51]. However, memantine had lower survival benefits than donepezil in our study.

Interestingly in our study, we observed a difference between donepezil and memantine in terms of all-cause hospitalization (median time to hospitalization for donepezil and memantine initiators was 538 and 561 days, respectively) in our ITT analysis. Even though delaying hospitalization among individuals with AD has important clinical and economic implications, but the relatively small difference of 23 days in median time to hospitalization between donepezil and memantine initiators limits the appropriate interpretation of this finding. Future studies evaluating the clinical and economic benefits from delayed hospitalization among individuals with AD are warranted to shed light on this issue. Inconsistencies between the ITT and as-treated analysis for all-cause hospitalization can potentially be attributed to adherence to index AD medication with lower risk of hospitalization as observed in other chronic conditions [52].

Limitations of this study were restricted to variables in claims data; lack of the information including provider preference, time of AD diagnosis, severity of AD over time; unavailability of clinical measures of AD symptoms related to cognition, function, or behavior progression or change; Namzaric approved in 2014 not included; adherence was estimated based on prescription refills which does not guarantee medication consumption and findings not generalizable to populations outside Medicare beneficiaries with AD (such as Medicare Advantage enrollees or those having commercial insurance).

5. Conclusion

Notwithstanding the limitations of this study, we observed that donepezil was associated with a lower risk of all-cause mortality compared with memantine, oral rivastigmine, and transdermal rivastigmine. Overall all-cause hospitalization risk was significantly different for the ITT analysis, but did not differ for the as-treated analysis. Future studies should evaluate mortality and hospitalization risk associated with AD medications used in different stages of AD, along with their dosing and formulation used, and examine the safety and effectiveness of the combination product in real-world settings. Additional studies that can elucidate underlying causes of mortality and hospitalization would be valuable to determine the direct effects of AD medications and/or AD on mortality and hospitalization.

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.trci.2019.05.005>.

RESEARCH IN CONTEXT

1. Systematic review: Existing literature was reviewed using PubMed. Our search indicated that there was a dearth of head-to-head comparison of Alzheimer's disease (AD) medications in controlled trial settings and also no real-world comparative safety study of AD medications was available. Relevant studies have been cited in our study.
2. Interpretation: Our study findings indicate differences in survival benefits as well as hospitalization risks associated with different AD medication initiation.
3. Future directions: Future studies should evaluate mortality and hospitalization risk associated with AD medications used in different stages of AD, along with their dosing and formulation used, and examine the safety and effectiveness of the combination product in real-world settings. Additional studies that can elucidate underlying causes of mortality and hospitalization would be valuable to determine the direct effects of AD medications and/or AD on mortality and hospitalization.

References

- [1] Kochanek KD, Xu J, Tejada-Vera B. Deaths: Final Data for 2014. National Vital Statistics Report. Available from: https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf, 2016. Accessed September 26, 2018.
- [2] Alzheimer's Association. 2017 Alzheimer's Disease Facts and Figures. Available from: https://www.alz.org/documents_custom/2017-facts-and-figures.pdf, 2017. Accessed August 24, 2018.
- [3] Malone DC, McLaughlin TP, Wahl PM, Leibman C, Arrighi HM, Cziraky MJ, et al. Burden of Alzheimer's disease and association with negative health outcomes. *Am J Manag Care* 2009;15:481–8.
- [4] Massoud F, Gauthier S. Update on the pharmacological treatment of Alzheimer's disease. *Curr Neuropsychopharmacol* 2010;8:69–80.
- [5] Bond M, Rogers G, Peters J, Anderson R, Hoyle M, Miners A, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. *Health Technol Assess* 2012;16:1–470.
- [6] Rountree SD, Atri A, Lopez OL, Doody RS. Effectiveness of antedementia drugs in delaying Alzheimer's disease progression. *Alzheimers Dement* 2013;9:338–45.
- [7] Sheldon T. Study of rivastigmine for delirium in intensive care is stopped after deaths. *BMJ* 2010;340:c2895.
- [8] Kazmierski J, Messini-Zachou C, Gkioka M, Tsolaki M. The Impact of a Long-Term Rivastigmine and Donepezil Treatment on All-Cause Mortality in Patients With Alzheimer's Disease. *Am J Alzheimers Dis Other Dement* 2018;33:385–93.
- [9] Kroger E, Berkers M, Carmichael PH, Souverein P, van Marum R, Egberts T. Use of rivastigmine or galantamine and risk of adverse cardiac events: a database study from the Netherlands. *Am J Geriatr Pharmacother* 2012;10:373–80.
- [10] Francois M, Sicsic J, Pelletier Fleury N. Drugs for Dementia and Excess of Hospitalization: A Longitudinal French Study. *J Alzheimers Dis* 2018;61:1627–37.
- [11] Ballard C, Lane R, Barone P, Ferrara R, Tekin S. Cardiac safety of rivastigmine in Lewy body and Parkinson's disease dementias. *Int J Clin Pract* 2006;60:639–45.
- [12] Sato K, Urbano R, Yu C, Yamasaki F, Sato T, Jordan J, et al. The effect of donepezil treatment on cardiovascular mortality. *Clin Pharmacol Ther* 2010;88:335–8.
- [13] Nordstrom P, Religa D, Wimo A, Winblad B, Eriksdotter M. The use of cholinesterase inhibitors and the risk of myocardial infarction and death: a nationwide cohort study in subjects with Alzheimer's disease. *Eur Heart J* 2013;34:2585–91.
- [14] Meguro K, Kasai M, Akanuma K, Meguro M, Ishii H, Yamaguchi S. Donepezil and life expectancy in Alzheimer's disease: a retrospective analysis in the Tajiri Project. *BMC Neurol* 2014;14:83.
- [15] Wattmo C, Londo E, Minthon L. Longitudinal associations between survival in Alzheimer's Disease and Cholinesterase inhibitor use, progression, and community-based services. *Dement Geriatr Cogn Disord* 2015;40:297–310.
- [16] Centers for Medicare and Medicaid Services. National Claims History (NCH) Standard Analytical Files. Available from: <https://aspe.hhs.gov/centers-medicare-medicare-services>. Accessed July 20, 2018.
- [17] Mor V. A comprehensive clinical assessment tool to inform policy and practice: applications of the minimum data set. *Med Care* 2004;42:III50–9.
- [18] Centers for Medicare and Medicaid Services. Chronic Conditions Data Warehouse: Condition Categories. Available from: <https://www.ccwdata.org/web/guest/condition-categories>, 2015. Accessed July 20, 2018.
- [19] Perez A, Anzaldúa M, McCormick J, Fisher-Hoch S. High frequency of chronic end-stage liver disease and hepatocellular carcinoma in a Hispanic population. *J Gastroenterol Hepatol* 2004;19:289–95.
- [20] Novartis Pharmaceutical Corporation. Exelon (rivastigmine tartrate) Capsules and Oral Solution. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/019872Orig1s001.pdf.

- fda.gov/drugsatfda_docs/label/2006/020823s016,021025s0081bl.pdf, 2006. Accessed August 15, 2018.
- [21] Bhattacharjee S, Metzger A, Tworek C, Wei W, Pan X, Sambamoorthi U. Parkinson's disease and home healthcare use and expenditures among elderly medicare beneficiaries. *Parkinsons Dis* 2015;2015:606810.
 - [22] Noyes K, Liu H, Holloway R, Dick AW. Accuracy of medicare claims data in identifying Parkinsonism cases: comparison with the Medicare current beneficiary survey. *Mov Disord* 2007; 22:509–14.
 - [23] Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;34:3661–79.
 - [24] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–9.
 - [25] Zhu CW, Cosentino S, Ornstein KA, Gu Y, Andrews H, Stern Y. Interactive effects of dementia severity and comorbidities on medicare expenditures. *J Alzheimers Dis* 2017;57:305–15.
 - [26] Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Lawrence Erlbaum Associates, Publishers; 1988.
 - [27] Bauer K, Schwarzkopf L, Graessel E, Holle R. A claims data-based comparison of comorbidity in individuals with and without dementia. *BMC Geriatr* 2014;14:10.
 - [28] Highlights Of Prescribing Information - Namzaric. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/2064391bl.pdf, 2014. Accessed August 10, 2018.
 - [29] Bent-Enakhil N, Coste F, Xie L, Aigbogun MS, Wang Y, Kariburyo F, et al. A Real-world analysis of treatment patterns for cholinesterase inhibitors and memantine among newly-diagnosed Alzheimer's disease patients. *Neurol Ther* 2017;6:131–44.
 - [30] Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Stat Med* 2005;24:3089–110.
 - [31] Gray RJ. A Class of K-Sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141–54.
 - [32] Intention to treat analysis and per protocol analysis: complementary information. *Prescrire Int* 2012;21:304–6.
 - [33] Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: Intention-to-treat versus per-protocol analysis. *Perspect Clin Res* 2016;7:144–6.
 - [34] Park Y, Bateman BT, Kim DH, Hernandez-Diaz S, Paterno E, Glynn RJ, et al. Use of haloperidol versus atypical antipsychotics and risk of in-hospital death in patients with acute myocardial infarction: cohort study. *BMJ* 2018;360:k1218.
 - [35] Gasper MC, Ott BR, Lapane KL. Is donepezil therapy associated with reduced mortality in nursing home residents with dementia? *Am J Geriatr Pharmacother* 2005;3:1–7.
 - [36] Abe Y, Shimokado K, Fushimi K. Donepezil is associated with decreased in-hospital mortality as a result of pneumonia among older patients with dementia: A retrospective cohort study. *Geriatr Gerontol Int* 2018;18:269–75.
 - [37] Lazzeroni LC, Halbauer JD, Ashford JW, Noda A, Hernandez B, Azor V, et al. Memantine is associated with longer survival than donepezil in a Veterans Affairs prescription database, 1997 to 2008. *J Alzheimers Dis* 2013;36:791–8.
 - [38] Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clin Interv Aging* 2008;3:211–25.
 - [39] Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. *Circulation* 2004;109:120–4.
 - [40] Pollak Y, Gilboa A, Ben-Menachem O, Ben-Hur T, Soreq H, Yirmiya R. Acetylcholinesterase inhibitors reduce brain and blood interleukin-1beta production. *Ann Neurol* 2005;57:741–5.
 - [41] Reale M, Iarlori C, Gambi F, Feliciani C, Salone A, Toma L, et al. Treatment with an acetylcholinesterase inhibitor in Alzheimer patients modulates the expression and production of the pro-inflammatory and anti-inflammatory cytokines. *J Neuroimmunol* 2004;148:162–71.
 - [42] Reale M, Iarlori C, Gambi F, Lucci I, Salvatore M, Gambi D. Acetylcholinesterase inhibitors effects on oncostatin-M, interleukin-1 beta and interleukin-6 release from lymphocytes of Alzheimer's disease patients. *Exp Gerontol* 2005;40:165–71.
 - [43] Handa T, Katare RG, Kakinuma Y, Arikawa M, Ando M, Sasaguri S, et al. Anti-Alzheimer's drug, donepezil, markedly improves long-term survival after chronic heart failure in mice. *J Card Fail* 2009; 15:805–11.
 - [44] Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, et al. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. *Int J Clin Pract* 2002;56:441–6.
 - [45] Bullock R, Touchon J, Bergman H, Gambina G, He Y, Rapatz G, et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. *Curr Med Res Opin* 2005;21:1317–27.
 - [46] Jones RW, Soiminen H, Hager K, Aarsland D, Passmore P, Murthy A, et al. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;19:58–67.
 - [47] Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, et al. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging* 2003;20:777–89.
 - [48] Campbell NL, Perkins AJ, Gao S, Skaer TC, Li L, Hendrie HC, et al. Adherence and Tolerability of Alzheimer's Disease Medications: A Pragmatic Randomized Trial. *J Am Geriatr Soc* 2017;65:1497–504.
 - [49] United States Food & Drug Administration. Memantine (Namenda) FDA labeling 2003. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021487s010s012s014,021627s0081bl.pdf. Accessed March 21, 2018.
 - [50] Jones RW. A review comparing the safety and tolerability of memantine with the acetylcholinesterase inhibitors. *Int J Geriatr Psychiatry* 2010;25:547–53.
 - [51] Thomas SJ, Grossberg GT. Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias. *Clin Interv Aging* 2009;4:367–77.
 - [52] Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care* 2005;43:521–30.