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Pharmaceutical Treatment for Alzheimer’s Disease and Related Dementias: Utilization and Disparities

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Abstract

Background: Four prescription drugs (donepezil, galantamine, memantine, and rivastigmine) are approved by the US FDA to treat symptoms of Alzheimer’s disease (AD). Even modest effectiveness could potentially reduce the population-level burden of AD and related dementias (ADRD), especially for women and racial/ethnic minorities who have higher incidence of ADRD.

Objective: Describe the prevalence of antidementia drug use and timing of initiation relative to ADRD diagnosis among a nationally representative group of older Americans, and if there are disparities in prevalence and timing by sex and race/ethnicity.

Methods: Descriptive analyses and logistic regressions of Medicare claims (2008–2016) for beneficiaries who had an ADRD or dementia-related symptom diagnosis, or use of an FDA approved drug for AD. We investigate prevalence of use and timing of treatment initiation relative to ADRD diagnosis across time and beneficiary characteristics (age, sex, race/ethnicity, socioeconomic status, comorbidities).

Results: Among persons diagnosed with ADRD or related symptoms, 33.3% used an approved drug over the study period. Odds of use was higher among Whites than non-Whites. Among ADRD drug users, 40% initiated use within 6 months of the initial ADRD or related symptoms diagnosis, and 16% initiated prior to a diagnosis. We observed disparities by race/ethnicity: 28% of Asians, 24% of Hispanics, 16% of Blacks, and 15% of Whites initiated prior to diagnosis.

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SUPPLEMENTARY MATERIAL

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Conclusions: The use of antidementia drugs is relatively low and varies widely by race/ethnicity. Heterogeneity in timing of initiation and use may affect health and cost outcomes, but these effects merit further study.

Keywords

Acetylcholinesterase inhibitors; Alzheimer's disease and related dementias; disparities; donepezil; galantamine; memantine; rivastigmine

INTRODUCTION

Alzheimer's disease and related dementias (ADRD) have a large, growing, and disparate burden on the afflicted individuals, their caregivers, and the health system as a whole. In the United States, there are approximately 7 million individuals aged 65 and older living with ADRD, and this number is projected to grow to 12 million by 2040 [1]. While there are no drugs that can stop or reverse the progression of dementia, four FDA-approved molecules and five marketed products are currently indicated for treatment of Alzheimer's disease (AD) [2]. These are acetylcholinesterase inhibitors (AChEIs: donepezil, galantamine, and rivastigmine) and memantine, which have shown modest effectiveness in reducing the symptoms of AD [2].

Treatment with antidementia drugs may help delay cognitive decline and maintain daily functioning in some patients, with some evidence showing benefits for functional decline, neuropsychiatric symptoms, nursing home placement, and cognition [3–13]. Other evidence shows a lack of effects for the aforementioned outcomes, and no evidence supports long term benefits [3, 10, 14]. When effective, however, even short-term gains in these outcomes could improve both patient and caregiver quality of life, by possibly delaying the need for a higher level of care. The burden of ADRD care is substantial, estimated at \$290 billion in 2019 [2]. This motivated the passage of the National Alzheimer's Project Act (NAPA), which calls for research identifying interventions that preserve normal neural function, reduce symptoms, and maintain independent functioning for AD patients as long as possible [15].

Despite mixed evidence of effectiveness of AChEIs and memantine, the potential for improved quality of life for patients and caregivers has led these drugs to be recommended in guidelines for AD treatment (AChEIs for mild to moderate disease, and memantine for moderate to severe disease). They are not indicated for non-AD dementia (except rivastigmine for Parkinson's disease) or mild cognitive impairment [3, 16]. Accordingly, much of the existing evidence on prevalence of use for these drugs focuses on individuals with AD [17–21]. However, some studies suggest that off-label use of antidementia medications is common [22, 23], and focusing strictly on beneficiaries with AD ignores the difficulties of distinguishing etiologic subtypes of dementia and prevalence of mixed dementias. Indeed, etiologic subtype at diagnosis is often unspecified and diagnoses change over time [24], which suggests that it is important to include a broader set of diagnoses (i.e., ADRD and related symptoms) when assessing antidementia treatment in order capture all potential patients. A few studies have examined likelihood of initiation [25], likelihood of

use [26], and patient and setting characteristics [27] in this broader set of diagnoses, but a comprehensive picture of contemporary use and users is critically lacking. Furthermore, limited research has examined the extent to which treatment patterns vary across patient sex and race/ethnicity [20, 21, 26]. A notable exception is a study which found that among a representative sample of possible AD drug users, Hispanics were more likely to initiate AChEIs and memantine than Black and White beneficiaries [25]. Research on disparities in use of antedementia medications is particularly germane, given the higher incidence of ADRD and significant burden of ADRD-related care for women and racial and ethnic minorities [28–30].

This paper addresses these gaps by examining treatment patterns of AChEIs and memantine across sex and race/ethnicity in a nationally representative sample of older adults enrolled in Medicare from 2008–2016. These data provide a comprehensive view of recent use of antedementia drugs by older Americans and include a broad set of demographic characteristics and diagnostic history that can be leveraged to identify the timing of diagnosis and treatment in diverse sub-groups. Given the uncertainty faced by physicians in distinguishing between dementia subtypes, one of our objectives was to evaluate the prevalence of use of antedementia drugs for a broad set of ADRD-related diagnoses, including relevant symptoms; to our knowledge, this is the first study to do so. We also examined the timing of treatment initiation, and variations in use of antedementia drugs over time and by sex and race/ethnicity. A better understanding of disparities in ADRD care is critical to improving care practices and working toward reducing the burden of ADRD, especially for patient sub-groups most at risk.

MATERIALS AND METHODS

Data and study population

We used claims data from a random 20% sample of Medicare beneficiaries to examine the utilization of four antedementia drugs (donepezil, galantamine, rivastigmine, and memantine) in the years 2008–2016. The branded version of the combination donepezil and memantine (Namzaric), was only introduced in 2015 and was not included. The analytic samples varied for our different analyses; all were composed of individuals who either used one of the four drugs, or received a diagnosis related to ADRD (specified below). In each year of observation t , we required that the individuals be enrolled in fee-for-service (FFS) Medicare and Part D for three consecutive years (years $t-2$, $t-1$, and t). This ensures observation of any relevant diagnoses and all prescription drug utilization for each individual. When describing users of the drugs, we required a minimum amount of use of one of the four drugs (specified below). In analyses of medication use among individuals with a diagnosis, we required individuals to have a diagnosis of AD, non-AD dementia, and/or dementia-related symptoms (defined below). Additionally, in analyses that evaluate drug initiation timing, we required the presence of both a diagnosis and a drug claim, and at least 36 months of observability after the earlier of these two events. This restriction ensures that no one was censored through death or attrition during the observation period; in doing so, it removes individuals who die within 36 months of an ADRD diagnosis. The study was approved by the University of Southern California Institutional Review Board.

Measures and outcomes

Main outcomes were the percent of diagnosed individuals using each of the four antedementia drugs, and the timing of initiation relative to dementia-related diagnoses as determined by ICD-9 (International Classification of Diseases) or ICD-10 codes. The diagnoses of interest were AD, non-AD dementia, and a set of dementia-related symptoms (amnesia, aphasia, other symbolic dysfunctions, apraxia, agnosia, and mild cognitive impairment) (Supplementary Material). These symptoms were included because the four drugs are sometimes prescribed for patients exhibiting them [22], and they represent a set of symptoms that occur even in the early stages of cognitive impairment [31–33]. Prescribing AChEIs and memantine for dementia-related symptoms may reflect the difficulties of establishing a definitive diagnosis, which can sometimes require multiple encounters between a physician and patient [24].

Antedementia drug use was first defined as at least seven possession days and one claim within a calendar year. Drugs were identified using the National Drug Code (NDC) associated with each drug on a Part D claim. Seven days was chosen as a minimum threshold in order to capture nearly all users of the drugs, including those who only used for a short period. Secondary definitions required higher adherence thresholds (90, 180, and 270 possession days, along with 2 claims) to be considered a medication user; non-adherence to treatment is often a barrier to effective therapy in AD [34], and these thresholds reflect levels of adherence that may provide better effectiveness. Combination use on the same day (e.g., possessing both memantine and an AChEI on the same day) was only counted as a single possession day. We also examined total possession days per year for each of the drugs, and initiation of use, defined as an antedementia drug claim with no prior observed use.

The investigation included characteristics of AChEI and memantine use (possession days, timing of initiation, drug name, prescribing physician, out-of-pocket cost), and characteristics of the medication users (sex, race/ethnicity, age, socioeconomic status [dual eligibility and low-income subsidy status], and comorbidities ever diagnosed). Dementia specialists were defined as neurologists, psychiatrists, geriatricians, neuropsychiatrists, and geriatric psychiatrists. Race/ethnicity was determined using the beneficiary race code in CMS enrollment data and with the application of a name-based identification algorithm from the Research Triangle Institute [35]. The comorbidity index used was the Centers for Medicaid and Medicare Services-Hierarchical Condition Category (CMS-HCC), an index based on health status from diagnostic data and demographics, in which higher numbers indicate worse health [36].

Statistical analyses

We examined the proportion of individuals diagnosed with ADRD or related symptoms who had ever used antedementia drugs, across sex and race/ethnicity, and calculated descriptive statistics (means and percentages) for the characteristics of drug use. This included details on the timing of their drug initiation, relative to different types of dementia-related diagnoses. We summarized the distribution of the length of time between diagnosis and drug initiation in six-month intervals, with negative values for this length of time corresponding to initiations that preceded diagnoses; we compared this distribution across race and

ethnicity. These analyses used a sample restricted to individuals with both a diagnosis and drug use, with full observability for at least 36 months after the earlier of their index diagnosis and drug initiation.

We performed person-year level logistic regressions to determine the degree to which sex and race/ethnicity are associated with AChEI or memantine use among diagnosed individuals, while adjusting for other beneficiary and setting characteristics. We tested four binary dependent variables (measures of drug use), defined by four adherence thresholds of AChEI or memantine use within a year: 7 possession days and 1 claim, 90 days and 2 claims, 180 days and 2 claims, and 270 days and 2 claims. These regressions used clustered standard errors at the beneficiary zip code level, and regressed an indicator for AChEI or memantine use within the year on the following independent variables: sex, age, age squared, race/ethnicity, AD diagnosis, non-AD dementia diagnosis, HCC comorbidity index quartile indicators, dual eligible indicator, low-income subsidy indicator, year fixed effects (2008–2016), outpatient physician utilization (quartiles of number of visits per year), an indicator having seen a dementia specialist physician (neurologists, psychiatrists, geriatricians, neuropsychiatrists, and geriatric psychiatrists), months since diagnosis, and comorbidity indicators for conditions that may be related to the prescribing of AChEIs and memantine (chronic obstructive pulmonary disease, asthma, chronic kidney disease, hypertension, heart failure, glaucoma, acute myocardial infarction, atrial fibrillation, and ischemic heart disease).

RESULTS

Sample description and prevalence of antedementia drug use

Table 1 describes the sample of individuals with use of an antedementia drug, or a diagnosis for ADRD or dementia-related symptoms during 2008–2016, according to their demographic characteristics, health care utilization, dementia-related diagnoses, antedementia drug use, and comorbidities. Figure 1 displays the unadjusted use rates of AChEIs or memantine, by sex and race/ethnicity for those with a diagnosis of ADRD or dementia-related symptoms before 2016. Among these individuals, 33.3% used any of the four drugs in 2008–2016. The unadjusted rates of drug use were highest for Hispanics (females 42.5%, males 37.5%), followed by Asians (females 40.6%, males 36.7%). White and Black females had similar use rates (White females 33.3%, Black females 33.6%), but White males were more likely to use (31.5%) than Black males (28.2%). While prevalence of use among the diagnosed remained mostly stable during the study period, rates of initiation in the six months following diagnosis declined from 21.0% in 2008 to 15.6% in 2016 (Supplementary Table 1).

Antedementia drug initiation timing

We investigated the length of time between index diagnosis date and drug initiation date among individuals with both a diagnosis and antedementia medication use; values less than zero correspond to drug use that began prior to a diagnosis. Figure 2 shows the distribution of this timing by race/ethnicity relative to the date of the first diagnosis of ADRD or dementia-related symptoms. Forty percent of antedementia drug initiations occurred in the

six months after their initial diagnosis, and 16% initiated treatment prior to diagnosis (as represented by the sum of the bars to the left of 0 on the horizontal axis in Fig. 2). More specifically, 3.1% initiated more than 2.5 years prior to a diagnosis, and 22% initiated drug use at least 2.5 years after diagnosis.

Initiation rates within six months after diagnosis varied across race/ethnicity groups (41% for Whites, 37% for Blacks, 34% for Hispanics, and 38% for Asians). There was a large disparity in the rates of drug use by undiagnosed individuals. Figure 2 shows that 28% of Asians and 24% of Hispanics initiated their drug use before any diagnosis of any type, as compared to 16% of Blacks and 15% of Whites (all differences statistically significant). A similar disparity existed for very early pre-diagnosis use: 2% of Blacks and 3% of Whites initiated drug use at least 2.5 years before their first dementia-related diagnosis of any type; the rate was 5% for Hispanics and 8% for Asians.

Association of antedementia drug use and patient characteristics

Table 2 presents the results from person-year level logistic regressions that identify the association between use of one of the four drugs within a year and sex and race/ethnicity, adjusted for beneficiary and setting characteristics, among individuals with an ADRD or dementia-related symptom diagnosis. Females had similar odds of antedementia drug use to males (odds ratio (OR) = 0.98, 95% confidence interval (CI) = 0.97–0.99). Compared to White beneficiaries, Black and Asian individuals were significantly less likely to use antedementia drugs at all adherence thresholds, with greater disparities at greater adherence thresholds ($p < 0.001$). Hispanic individuals were less likely to use antedementia drugs at higher adherence thresholds. For example, the OR for the association between 7 days/1 claim of use and beneficiary race/ethnicity was 0.90 for Blacks and 0.92 for Asians (compared to the reference group, White); the OR for the association between 270 days/2 claims of use and beneficiary race/ethnicity was 0.78 for Blacks, 0.79 for Hispanics, and 0.79 for Asians. In sensitivity analyses, we restricted the sample for the same logistic regressions to individuals who had been diagnosed with ADRD (Supplementary Table 2) and AD (Supplementary Table 3). These results show no meaningful differences from those depicted in the main analyses (Table 2).

Individuals with a higher comorbidity index were less likely to use drugs than those with lower values. For example, the OR of the association between 7 days/1 claim of use was 0.83 (CI = 0.82–0.84) for the second quartile of the index, 0.83 (CI = 0.82–0.84) for the third quartile, and 0.78 (0.77–0.79) for the fourth quartile, as compared to individuals in the first quartile (the healthiest). Dual eligible individuals were more likely to use antedementia drugs, especially at higher levels of adherence (270 days/2 claims OR = 1.22, CI = 1.21–1.24).

Antedementia drug use across time

Table 3 displays trends in the characteristics of medication users in 2008, 2010, 2012, 2014, and 2016, including persons both with and without a diagnosis. Odd years are omitted for space, but they matched the trends in the neighboring even years. Donepezil was by far the most common drug (69–72% of users), followed by memantine (45–48%), rivastigmine (12–

16%), and galantamine (2–7%). Among users, 30–34% used both an AChEI and memantine in combination. Across time, the relative prevalence of each drug was mostly stable, except a decline in the use of galantamine. The mean out-of-pocket cost for a 30 day supplies of the drugs ranged from \$30–39 in 2008 to \$4–34 in 2016, partially reflecting the timing of generic availability (donepezil (Aricept) 2011, galantamine (Razadyne) 2008, rivastigmine (Exelon) 2007, memantine (Namenda) 2010) [37]. The mean number of possession days increased from 233 to 241 per year across the entire study period.

A small portion of users had received no diagnosis for any type of dementia, or any dementia-related symptom, despite receiving an anticholinesterase drug (2–5% of users). This group became smaller over time but remained 2.3% of users in 2016 (representing approximately 19,000 individuals in the continuously enrolled Medicare Part D population). While the racial/ethnic composition was relatively stable across time, users were healthier in 2016 than earlier, with their mean HCC comorbidity index declining from 1.67 to 1.45, and mean age of initiation declining from 82.3 in 2008 to 80.8 in 2016. Over the same years, the portion of initiations that were prescribed by a specialist increased from 21% to 29%.

DISCUSSION

In this study, we examined Medicare FFS and Part D drug claims for the four drugs currently approved for the treatment of AD (donepezil, galantamine, rivastigmine, and memantine) from 2008–2016. We examined the factors associated with use versus non-use among individuals with ADRD or a dementia-related diagnosis, as well as characteristics of the medication users. We found that approximately one-third of beneficiaries diagnosed with ADRD or dementia-related symptoms used at least one of the drugs. After adjusting for beneficiary and setting characteristics, use of anticholinesterase drugs was more common for White individuals than for Black and Asian individuals at all adherence levels, and also more common than for Hispanic individuals at higher levels of adherence. Beneficiaries with greater comorbidity were less likely to use drugs, and individuals with dual eligibility (Medicare and Medicaid) were more likely. Only 40% of users initiated therapy in the six months following diagnosis; 44% initiated later, and 16% initiated use before their first diagnosis. Pre-diagnosis initiation was much more common for Asians and Hispanics than for Blacks and Whites. Among diagnosed individuals, prevalence of use remained stable from 2008–2016, despite declines in out-of-pocket costs, and initiation rates declined.

Our findings show that use of AChEIs and memantine is relatively low in a population of older adults who were diagnosed with ADRD or dementia-related symptoms. While these drugs are only indicated for AD (except for rivastigmine for Parkinson's disease), recent work suggests that dementia etiological subtype at initial diagnosis is often unspecified, due to etiologic uncertainty at that time, and also that the diagnosis subtype changes over time [2, 24]. This lack of diagnostic certainty across dementia subtypes and potential underdiagnosis of AD suggest that some individuals with claims for non-AD dementia and dementia-related symptoms, who may actually have AD, may possibly receive some benefits from use of these drugs, including delayed functional decline. While the effects of the drugs might be modest, even small delays in loss of cognition and functional decline are important for the afflicted individuals and their caregivers [3].

After adjusting for beneficiary characteristics, we found that Black and Asian beneficiaries were less likely to use antedementia drugs, with a larger disparity at high levels of adherence relative to low levels of adherence. Hispanic beneficiaries were also less likely to use these drugs than Whites at higher levels of adherence. Given that poor adherence is a barrier to reaching any potential benefit of antedementia drugs [34], this implies that these patient subgroups are benefitting less than other beneficiaries. The burden of dementia is disproportionately higher for racial/ethnic minorities, and the demonstrated disparities in the use of these drugs might increase overall disparities in the large and growing burden of this condition [30]. Earlier research on disparities in antedementia drug use showed that Hispanics with ADRD had higher odds of initiation than Whites and Blacks in the second half of 2009 [25]; our analyses, which focused on prevalent use, rather than initiation rates, showed lower adjusted odds of prevalent use at higher adherence levels for non-Whites from 2008–2016. Additionally, our results showing higher odds of antedementia drug use for people with less comorbidity are supportive of earlier evidence [38].

We also show that initiation of drug therapy often precedes diagnoses, sometimes by several years. There are several factors that may contribute to a physician's decision to prescribe before giving a diagnosis. For example, physicians may be hesitant to diagnose one type of dementia because of uncertainty regarding the etiology. It is difficult to distinguish between AD, non-AD dementia, and mixed dementias without detailed longitudinal neuropsychological evaluation information, which is often not available to general practitioners who prescribe these drugs [2]. Despite hesitancy to give a specific diagnosis, physicians may offer pharmaceutical treatments for observed cognitive impairment, as evidenced in earlier research [22]. In addition to etiologic uncertainty, there may be societal factors that influence use of antedementia drugs without a diagnosis of AD. For example, societal stigma against dementia may cause beneficiaries and their families to resist such diagnoses, while still desiring treatment [39, 40]. Stigma may vary across different racial and ethnic groups and may in part explain the differential pre-diagnosis use of drugs that we observed [41]. One implication of our study is that Asians and Hispanics may have higher rates of underdiagnosis of ADRD than Black and White individuals, as evidenced by their higher rates of pre-diagnosis use of AChEIs and memantine.

Given the prevalence of AD medication use prior to the diagnosis of any related condition or symptom, it is clear that health care providers often observe evidence of cognitive decline well before this information is registered via claims as diagnoses. Claims data remain an important resource for ADRD research, but as has been shown in a related study, it is important for researchers to incorporate drug utilization data into their studies as a source of information on otherwise undocumented cognitive decline [42, 43].

Limitations

The Medicare claims data provide a comprehensive perspective on the use of donepezil, galantamine, rivastigmine, and memantine in the United States, and are a robust dataset for examining prescription drug utilization. A limitation, however, is that these data do not include individuals enrolled in Medicare Advantage or FFS without Part D. Additionally, claims for these drugs do not necessarily reflect use of the drugs; however, this study's aim

was to examine treatment patterns, which is a different construct than medication adherence. We use the term “adherence” for convention. Another limitation is measurement error in the timing and presence of dementia-related diagnoses; claims-based diagnoses have no information about disease severity, and can be inconsistent across providers. Indeed, some dementia is undiagnosed, which is why this study also included antedementia drug users who did not have any dementia-related diagnoses. While we acknowledge the likelihood of diagnostic measurement error, we note that recent evidence found diagnosis of dementia has improved over time and concordance with cognitive test-based measures of dementia is high [42, 43]. We also note that despite the potential for underdiagnosis and etiologic imprecision of ADRD diagnoses in claims, this study aims to describe the treatment patterns in the real-world context of diagnostic imprecision. Understanding these treatment patterns can aid in the development and implementation of interventions to improve treatment and dementia management. One other limitation is that these analyses omit combination donepezil/memantine (branded as Namzaric); this product was only approved by the FDA in late December 2014 [37], and had low levels of use during the two years that overlap with our sampling period (2015 and 2016).

Conclusions

Rates of pharmaceutical treatment are low and disparate in the Medicare population diagnosed with ADRD and dementia-related symptoms. Additionally, the timing of therapy initiation relative to diagnosis varies widely across race/ethnicity, suggesting differences in diagnostic and treatment practices across patient sub-groups. Pharmaceutical treatment with donepezil, galantamine, rivastigmine, and memantine has modest effectiveness, but for some people may delay the cognitive and functional decline associated with ADRD, and is recommended in treatment guidelines. Tailored prescribing for interested patients has potential value to individuals, families, and society, even if the delays to decline are brief. ADRD has a large burden that is expected to grow [1], and racial/ethnic differences in overall utilization and timing of utilization may exacerbate disparities in the burden. Future research should examine how these differences in use and timing of use affect outcomes of care in diverse populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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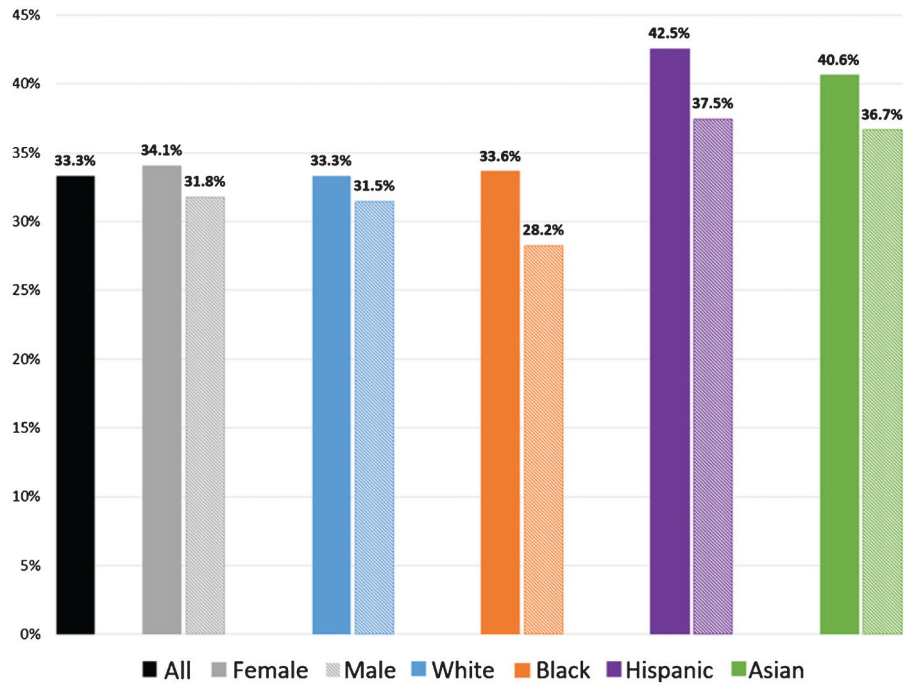


Fig. 1. Percent using an antidementia drug, among individuals diagnosed with Alzheimer’s disease, non-AD dementia, or dementia-related symptoms, by sex and race/ethnicity. 2008–2016 Medicare claims data (20% sample) for 613,970 individuals aged 67+, with 3 consecutive years of enrollment in fee-for-service and Part D, and one of the diagnoses before 2016. Drug use defined as at least 7 days and 1 claim for any of the 4 AD drugs (3 AChEIs (donepezil, galantamine, rivastigmine) and memantine). AD, Alzheimer’s disease; AChEI, acetylcholinesterase inhibitor; ADRD, AD and related dementias. Dementia-related symptoms are amnesia, aphasia, other symbolic dysfunctions, apraxia, agnosia, and mild cognitive impairment.

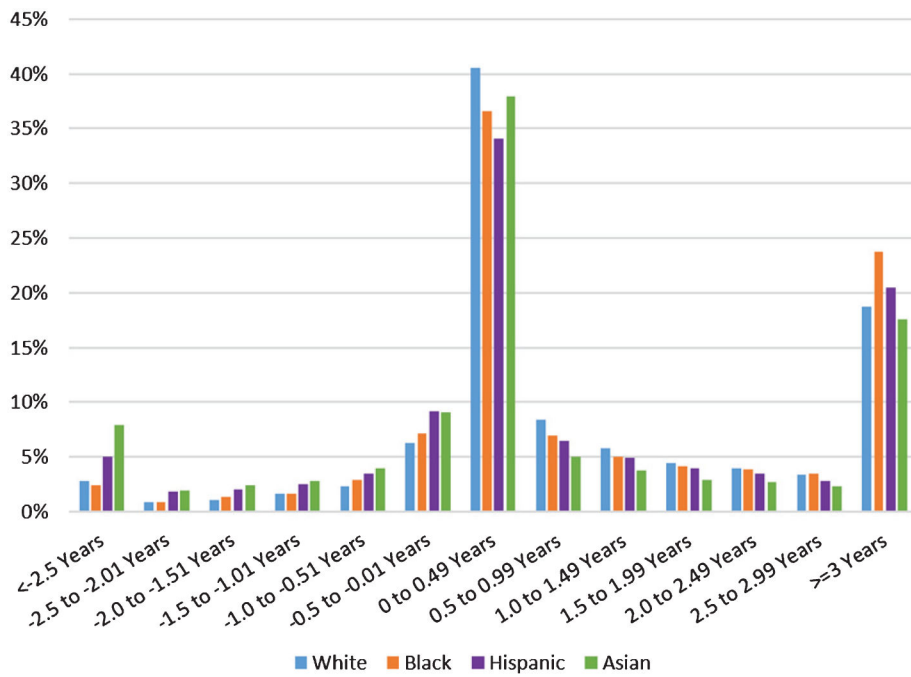


Fig. 2. Timing of antedementia drug initiation, relative to date of ADRD or dementia-related symptom diagnosis, among individuals with both a diagnosis and medication use. 2008–2016 Medicare claims data (20% sample) for 73,161 individuals with an observed index diagnosis, and observed drug initiation for at least 1 of the 4 AD drugs (3 AChEIs (donepezil, galantamine, rivastigmine) and memantine). We require at least 36 months of observation from the index diagnosis or drug initiation, whichever came first, and that individuals are aged 67+, with 3 consecutive years of enrollment in fee-for-service and Part D. AD, Alzheimer’s disease; AChEI, acetylcholinesterase inhibitor; ADRD, AD and related dementias. Dementia symptoms are amnesia, aphasia, other symbolic dysfunctions, apraxia, agnosia, and mild cognitive impairment.

Table 1

Sample description of individuals with use of an antideementia drug, or a diagnosis of AD, non-AD dementia, or dementia-related symptoms (2008–2016)

N	721,878
Patient Characteristics	
Female (N, %)	477,641 (66.2%)
Age at index date (mean, SD)	80.40 (7.77)
White (N, %)	600,358 (83.2%)
Black (N, %)	57,412 (8.0%)
Hispanic (N, %)	44,082(6.1%)
Asian (N, %)	20,026 (2.8%)
Dual eligible (N, %)	225,783 (31.3%)
Low income subsidy (N, %)	35,593 (4.9%)
Physician visits in year of index date (mean, SD)	10.09 (8.95)
HCC (mean, SD)	1.90(1.47)
Ever saw a specialist (N, %)	255,213 (36.5%)
Dementia-related diagnoses (N, %)	
Alzheimer's disease	197,561 (27.4%)
Non-AD dementia	514,633 (71.3%)
Dementia-related symptoms	420,987 (58.3%)
Used antideementia drug without diagnosis	11,558 (1.6%)
Antideementia drug use (N, %)	
Any AChEI	208,731 (28.9%)
Any AChEI & Memantine	70,880 (9.8%)
Donepezil	187,076 (25.9%)
Galantamine	6,059 (0.8%)
Memantine	99,556 (13.8%)
Rivastigmine	42,484 (5.9%)
Comorbidities, ever diagnosed (N, %)	
Chronic obstructive pulmonary disease	341,695 (47.3%)
Asthma	166,987 (23.1%)
Chronic kidney disease	407,612 (56.5%)
Hypertension	686,880 (95.2%)
Heart failure	422,864 (58.6%)
Glaucoma	229,025 (31.7%)
Acute myocardial infarction	90,192(12.5%)
Atrial fibrillation	246,688 (34.2%)
Ischemic heart disease	535,606 (74.2%)

2008–2016 Medicare claims data (20% sample) for individuals aged 67+, with 3 consecutive years of enrollment in fee-for-service and Part D. Drug use defined as at least 7 days and 1 claim for any of the 4 AD drugs [3 AChEIs (donepezil, galantamine, rivastigmine) and memantine]. Index date is first diagnosis, or first antideementia drug use. AD, Alzheimer's disease; AChEI, acetylcholinesterase inhibitor; ADRD, AD and related dementias; HCC, hierarchical condition category; dx, diagnosis. Dementia-related symptoms are amnesia, aphasia, other symbolic dysfunctions, apraxia, agnosia, and mild cognitive impairment.

Association between antideementia drug use and patient characteristics, among individuals diagnosed with AD, non-AD dementia, or dementia-related symptoms

Table 2

Use threshold for dependent variable	7 days & 1 claim	90 days & 2 claims	180 days & 2 claims	270 days & 2 claims
Female	0.98 (0.97–0.99)	1.00 (0.99–1.01)	1.01 (1.00–1.02)	1.02 (1.01–1.03)
White (reference)	–	–	–	–
Black	0.90 (0.89–0.92)	0.86 (0.85–0.88)	0.83 (0.82–0.85)	0.78 (0.77–0.82)
Hispanic	0.98 (0.94–1.01)	0.91 (0.88–0.94)	0.86 (0.83–0.89)	0.79 (0.77–0.82)
Asian	0.92 (0.89–0.95)	0.86 (0.83–0.89)	0.83 (0.80–0.86)	0.79 (0.77–0.82)
Comorbidity quartile 1 (reference)	–	–	–	–
Comorbidity quartile 2	0.83 (0.82–0.84)	0.77 (0.77–0.78)	0.71 (0.71–0.72)	0.68 (0.67–0.69)
Comorbidity quartile 3	0.83 (0.82–0.84)	0.80(0.79–0.81)	0.76 (0.76–0.77)	0.73 (0.72–0.74)
Comorbidity quartile 4	0.78 (0.77–0.79)	0.80(0.80–0.81)	0.82(0.81–0.83)	0.76 (0.75–0.77)
Dual eligible	1.10(1.08–1.11)	1.15 (1.14–1.16)	1.17 (1.15–1.18)	1.22(1.21–1.24)
Low-income subsidy	1.02(1.00–1.04)	1.01 (0.98–1.03)	0.99 (0.97–1.02)	0.98 (0.95–1.00)
N meeting use threshold	1,379,112	1,154,673	968,857	746,794

Odds ratios and 95% confidence intervals from logistic regressions of 4,685,826 person-years (1,403,076 unique beneficiaries) with indicator dependent variable for if the individual used one of the four AD drugs (donepezil, galantamine, rivastigmine, and memantine) in that year. Drug use defined in column title. Sample is person-years of Medicare beneficiaries in the years $t = 2008-2016$ with a diagnosis of Alzheimer’s disease (AD), non-AD dementia, or dementia-related symptoms (amnesia, aphasia, other symbolic dysfunctions, apraxia, agnosia, and mild cognitive impairment). Sample restricted to those aged 67+, with 3 consecutive years of enrollment in fee-for-service and Part D. All regressions feature controls for age, age squared, comorbidity index quartiles, AD diagnosis, non-AD dementia diagnosis, socioeconomic status, year fixed effects, physician utilization, dementia specialist utilization, months since diagnosis, comorbidity indicators (chronic obstructive pulmonary disease, asthma, chronic kidney disease, hypertension, heart failure, glaucoma, acute myocardial infarction, atrial fibrillation, and ischemic heart disease). Standard errors clustered at zip code level.

Table 3

Trends in antideMENTIA drug use, irrespective of diagnosis, 2008–2016

	2008	2010	2012	2014	2016
Total antideMENTIA drug users	155,498	158,584	158,961	155,995	164,580
Any AChEI	87%	87%	86%	85%	84%
Any AChEI & memantine	32%	34%	33%	32%	30%
Donepezil	72%	70%	69%	69%	72%
Galantamine	7%	4%	3%	3%	2%
Memantine	45%	48%	47%	47%	46%
Rivastigmine	12%	16%	16%	16%	12%
Out of pocket costs (mean, 30-day supply)					
Donepezil	\$30	\$36	\$6	\$4	\$4
Galantamine	\$37	\$22	\$19	\$19	\$18
Memantine	\$31	\$33	\$27	\$33	\$24
Rivastigmine	\$39	\$40	\$33	\$36	\$34
Patient characteristics					
Female	73%	73%	71%	69%	66%
White	81%	79%	79%	80%	83%
Black	10%	9%	10%	9%	8%
Hispanic	7%	8%	9%	8%	6%
Asian	2%	3%	3%	3%	3%
No dementia diagnosis or related symptoms	5%	4%	3%	3%	2%
HCC (mean)	1.67	1.65	1.67	1.55	1.45
Use characteristics					
Initially prescribed by dementia specialist	21%	22%	24%	27%	29%
Possession days per year (mean)	233	238	243	242	241
Still using 12–24 months after initiation*	76%	73%	74%	70%	-
Age at initiation (mean)	82.3	82.0	81.5	81.1	80.8

Medicare claims data (20% sample) for individuals aged 67+, with 3 consecutive years of enrollment in fee-for-service and Part D. Drug use defined as at least 7 days and 1 claim for any of the 4 AD drugs (3 AChEIs (donepezil, galantamine, rivastigmine) and memantine). The sample is prevalent users in the column year. Odd years omitted for space. Dementia specialists are neurologists, psychiatrists, geriatricians, neuropsychiatrists, and geriatric psychiatrists.

* Calculation of percent still using 12–24 months after initiation is restricted to individuals who survive 24 months (not observable in 2016). AD, Alzheimer’s disease; AChEI, acetylcholinesterase inhibitor; ADRD, AD and related dementias), HCC, hierarchical condition category. Dementia-related symptoms are amnesia, aphasia, other symbolic dysfunctions, apraxia, agnosia, and mild cognitive impairment.

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