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Effect of medications on physical function and cognition in nursing home residents with dementia

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Abstract

Objectives—To assess effectiveness of medications used in management of Alzheimer’s Disease and Related Dementias (ADRD) on cognition and activities of daily living (ADL) trajectories and to determine whether sex modifies these effects.

Design—Two-year (2007–2008) longitudinal study

Setting—Medicare enrollment and claims data linked to the Minimum Dataset 2.0

Participants—18,950 older nursing home (NH) residents with newly-diagnosed ADRD

Measurements—Exposures included four medication classes: anti-dementia medications (ADM), antipsychotics, antidepressants, and mood stabilizers. Outcomes included ADLs and cognition [Cognitive Performance Scale (CPS)]. Marginal structural models were employed to account for time-dependent confounding.

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Authors’ contributions

Sarah K. Dutcher, Patricia Langenberg, Gail B. Rattinger, and Ilene H. Zuckerman were involved in the study concept and design, analysis and interpretation of data, and preparation of the manuscript. Pankdeep T. Chhabra, Loreen D. Walker, and Christine S. Franey were involved with the study design and concept and analysis of data. Xinggang Liu and Jeannie-Marie Leoutsakos were involved with the analysis and interpretation of data. Paul Rosenberg was involved with the interpretation of data and preparation of the manuscript. Linda Simoni-Wastila was involved with the interpretation of data. All authors were involved with revision of the manuscript and approved the final version.

Results—The mean age was 83.6 years and 76% of the sample was female. Baseline use for ADMs, antidepressants, antipsychotics, and mood stabilizers was 15%, 40%, 13% and 3%, respectively. The mean baseline ADL and CPS scores were 16.6 and 2.1, respectively. ADM use was not associated with a change in ADLs over time but was associated with a slower CPS decline (slope difference: -0.09 points/year, 99% CI $-0.14, -0.03$). Antidepressant use was associated with slower declines in ADL (slope difference: -0.36 points/year, 99% CI $-0.58, -0.14$) and CPS (slope difference: -0.12 points/year, 99% CI $-0.17, -0.08$). Sex modified the effect of both antipsychotic and mood stabilizer use on ADLs; female users declined most quickly. Antipsychotic use was associated with slower CPS decline (slope difference: -0.11 points/year, 99% CI $-0.17, -0.06$), while mood stabilizer use had no effect.

Conclusion—Despite the observed statistically significant slower declines in cognition with ADMs, antidepressants, and antipsychotics, and the slower ADL decline found with antidepressants, these benefits are not likely of clinical significance.

Keywords

Alzheimer's disease; dementia; nursing home; psychotropic medication; activities of daily living; cognition

INTRODUCTION

Among individuals with Alzheimer's disease and related dementias (ADRD) in the United States, 30%–40% reside in long term care (LTC) facilities.¹ In the nursing home (NH) population, estimates for ADRD prevalence reach 64%.¹ Anti-dementia medications (ADM), including acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine, an N-Methyl-D-Aspartate receptor antagonist, are used commonly to manage ADRD symptoms and delay declines in cognitive, behavioral and functional performance.^{2–5} While ADMs have demonstrated statistically significant delays in cognitive decline in placebo-controlled clinical trials,^{3–9} effect sizes are modest and efficacy may not translate to clinically meaningful effectiveness.²

To manage behavioral and psychological symptoms of ADRD, patients often are treated with psychotropic medications, including antidepressants, antipsychotics, sedative-hypnotics, and anticonvulsants.^{10–12} However, these agents have received mixed reviews regarding their benefits relative to their adverse effects.^{2,12,13} Increased risk of falls, syncope, and hip fractures, have been associated with most psychopharmacological medications,¹⁴ acetylcholinesterase inhibitors,¹⁵ and antidepressants, respectively.¹⁶ Furthermore, antipsychotics have been associated with both increased mortality^{17,18} and poorer cognition.¹⁹ Significant changes in treatment experienced by dementia patients as they transition into a NH setting,²⁰ as well as differences in their drug receipt once residing in NHs,^{10,11} demonstrate important treatment decisions that clinicians must make in the face of increasing disease progression.

ADRD symptom presentation varies by sex. Barnes *et al.* found clinical disease development to be more likely in women displaying Alzheimer's disease (AD) pathology than in men.²¹ Men often display more physically aggressive, apathetic, and regressive

behaviors, while women tend to demonstrate depression, anxiety, and agitation through verbal means.^{22,23} However, little is known about sex differences in response to ADMS^{24,25} or psychopharmacologic medications, with one study reporting sex differences in response of AD patients to sertraline.²⁶

Given the high prevalence of medication use in NH patients with ADRD,^{10–12} questions about efficacy and adverse events, differential symptom expression between the sexes, and the paucity of information regarding heterogeneity in treatment effectiveness, investigation is warranted to identify NH residents with ADRD who are most likely to realize benefits from medications used to manage ADRD symptoms. In this study, we sought to measure the associations of medications commonly used in ADRD management with ADL functioning and cognition over time in NH residents and whether the associations of these medications with functional and cognitive outcomes vary by sex.

METHODS

Study Design

This retrospective cohort study used a two-year (2007–2008) longitudinal design. We used data from the Chronic Conditions Data Warehouse (CCW), including the NH Minimum Dataset 2.0 (MDS) and Medicare administrative data and fee-for-service claims for the years 2006 through 2008. CCW is provided by the Centers for Medicare & Medicaid Services and contains data for a 5% random sample of Medicare beneficiaries.²⁷

Cohort selection

Our cohort consisted of Medicare beneficiaries with newly-diagnosed ADRD in 2007–2008 who resided in a NH during at least part of the two-year study period. A beneficiary's index diagnosis was identified using the first ADRD claim based on the CCW algorithm for ADRD^{27,28} or MDS assessment with evidence of ADRD between 1/1/2007 and 12/31/2008. The look-back period for ensuring ADRD was a new diagnosis was 12 months. A CCW claim with an ADRD diagnosis (ICD-9-CM codes: 331.0, 331.1×, 331.2, 331.7, 290.0, 290.1×, 290.2×, 290.3, 290.4×, 294.0, 294.1, 294.1×, 294.8, 797) could arise from a hospital, skilled nursing facility (SNF), home health agency, hospital outpatient, or carrier (physician) claim. The first MDS assessment on or after a beneficiary's index ADRD diagnosis was identified as the index assessment.

Our sample included beneficiaries at least 66 years old who had fee-for-service Medicare Parts A, B, and D prescription drug plan (PDP) coverage. Beneficiaries were required to have Medicare Parts A and B coverage: for 12 months before their index diagnosis to ensure that an index diagnosis based on medical claims was the patient's first ADRD diagnosis, and for 12 months before their index assessment to determine baseline information on comorbidity burden (modified Charlson comorbidity index). Additionally, to obtain complete medication utilization information, individuals were required to have Medicare PDP coverage during the 3 months before and in the month of the index assessment. Subsequent assessments were included if there was PDP coverage in the time period before that assessment, back to the previous assessment.

This study was approved by the University of Maryland Baltimore Institutional Review Board.

Measures

Outcomes—The two primary outcomes were activities of daily living (ADL) functioning and cognition and were assessed using each NH resident's MDS assessments. All assessments with available information to measure outcomes were included: admission, annual, significant change in resident status, quarterly, and those required for the Medicare Prospective Payment System or by the state. ADL functioning was determined using the MDS ADL-long form scale developed by Morris *et al.*²⁹ This scale's total score ranges from 0 to 28; higher scores indicate greater dependence. The ADL-long form is sensitive to small changes over time²⁹ and is an appropriate tool to detect clinically meaningful changes in functioning in NH residents with ADRD.³⁰

Cognition was assessed using the Cognitive Performance Scale (CPS).³¹ CPS classifies NH residents into seven categories ranging from 0 (cognitively intact) to 6 (very severely impaired). CPS has been validated against the Mini-Mental State Examination (MMSE) the Global Deterioration Scale, and the staff rating on the Psychogeriatric Dependency Rating Scale Orientation scale.^{32–35}

Medication Exposures—We assessed exposure to four medication classes commonly used in ADRD management: ADMs [acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine], antipsychotics (typical and atypical), antidepressants (selective-serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, trazodone, tricyclics, mirtazapine, bupropion, monoamine oxidase inhibitors), and mood stabilizers (valproic acid, carbamazepine, oxcarbazepine). Use of each of the four classes was measured during the time period immediately before each MDS assessment, back to the previous assessment. Also, use was measured during the three months immediately before the index assessment. Medication use was captured using Medicare Part D PDP claims. If a beneficiary had a prescription that covered any days during an assessment period, the beneficiary was considered to have used that medication during that period.

Covariates—Sex was considered a potential effect modifier. Time-invariant covariates included age at index assessment, race, geographic region, low-income subsidy (LIS) status, dual (Medicare/Medicaid) eligibility, marital status, maximum education level attained, and length of time between the index diagnosis and index assessment. Time-varying covariates included a modified Charlson comorbidity index (CCI) measured over the 12 months before each assessment, number of hospital admissions during the month of the current assessment, an indicator for the use of each of the other drug classes of interest, and an indicator for the use of medication with anticholinergic properties.³⁶ All time-varying medication use covariates were measured during the period prior to each MDS assessment, back to the previous assessment.

To control for confounding by indication (Table 1), Aggressive Behavior Scale (ABS) scores were used to create time-varying indicators of aggressive behavior.³⁷ The ABS has

been shown to be valid and reliable compared to the Cohen-Mansfield Agitation Inventory.^{35,37} A score >0 was considered aggressive behavior. An indicator based on the MDS Depression Rating Scale (DRS)³⁸ was incorporated as a time-varying measure of depression, also to control for confounding by indication. The MDS DRS ranges from 0 to 14 and we used a score ≥ 3 as an indicator for depression since this cut-point has the highest sensitivity and specificity when validated against the Hamilton Depression Rating Scale and the Cornell Scale for Depression in Dementia.³⁸

Statistical Analysis

Univariable and bivariable analyses were used to describe the cohort and to examine the cross-sectional associations between exposures and sex at the index assessment. Continuous variables are reported as mean and standard deviation ($\pm$ SD) and categorical variables are reported as number and percent.

Repeated measures general linear models were used to determine the multivariate relationship between use of each of the four drug classes and each of the two outcomes. A separate model was developed for each outcome and each drug class, resulting in eight models. Each full or quarterly MDS assessment was treated as an observation. As MDS assessments are unevenly spaced, time was measured in days. In all models, a correlation structure was estimated to account for within-subject correlation. A three-way interaction (drug_use $\times$ sex $\times$ days) was included in all models to determine if the effect of each drug class on ADL or CPS over time varied by sex. If not significant, the two-way interaction between drug use and time (drug_use $\times$ days) was examined to determine the effect of drug use on ADL or CPS over time. Models included all relevant base interactions and non-significant interactions were removed from each model.

Given the possibility of time-dependent confounding, we performed analyses using marginal structural models. Marginal structural models are used to estimate the effect of a time-dependent exposure when time-dependent covariates may confound the relationship between exposure and outcome and that also are affected by prior exposure.^{39–41} In our study we hypothesize that cognition (measured by CPS) may be a time-dependent confounder in the relationship between ADM use and ADL functioning, as cognition may influence both the likelihood of someone being prescribed ADMs as well as ADL performance.

Simultaneously, cognition may be affected by prior use of ADMs. Marginal structural models use inverse probability-of-treatment weighted estimators to address time-dependent confounding.^{39–41} We used marginal structural models to estimate the effect of each of the four drug classes on ADLs and the effects of ADMs and antidepressants on CPS. Since lagged variables are needed to predict future levels of a variable, we used data from the first assessment to create lagged variables and modeled data from the second assessment forward. Therefore, these models excluded those with only one MDS assessment. We did not identify time-dependent confounding as an issue for the effect of antipsychotics or mood stabilizers on CPS. For these two analyses, we employed fixed effects models that modeled the mean trajectories over time, also limited to the second assessment forward, for individuals with more than one assessment. Table 1 presents the models used and the hypothesized time-varying confounders.

As secondary analyses, we developed fixed effects models using all assessments, including those individuals with only one assessment. These analyses served two purposes: 1) to assess if results were influenced by excluding from the main analysis sample those individuals with only one assessment, and 2) to assess if time-dependent confounding played a large role by comparing results from single fixed effects models versus the two-stage marginal structural models. Given the large sample sizes in all analyses, we considered an alpha level of 0.01 as significant for all models. Analyses were conducted using SAS/STAT software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Overall, 18,950 Medicare beneficiaries with ADRD met the study inclusion criteria, contributing 81,466 MDS assessments. Over three-fourths of the sample was female and the mean ($\pm$ SD) age at the index assessment was 83.6 ($\pm$ 7.8) years (Table 2). A majority (86%) of the sample was white and 54% received LIS. The median (range) number of assessments per beneficiary was 3 (1–29) and 18% of beneficiaries contributed only one assessment. One-third (34%) of beneficiaries died during the study period. Compared to males, females were significantly older, were more likely to be white race and less likely to die during the study period (all $p < 0.001$).

During the 3 months prior to each beneficiary's index assessment, 15%, 40%, 13% and 3% used ADMs, antidepressants, antipsychotics, and mood stabilizers, respectively. At the index assessment, females were more likely to use ADMs and antidepressants (both $p < 0.001$), while males were significantly more likely to use mood stabilizers ($p = 0.002$). There was no difference in antipsychotic use by sex at the index assessment ($p = 0.42$). At the index assessment, the mean ($\pm$ SD) ADL score was 16.6 ($\pm$ 6.5) and the mean ($\pm$ SD) CPS score was 2.1 (1.5). A significantly higher proportion of men had ADL scores at the extremes (i.e., ADL score < 10 , > 20), while women more often had ADL scores in the middle of the range. Females had significantly higher CPS scores, indicative of higher levels of cognitive impairment, at their index assessments compared to men.

Results of the multivariate longitudinal models on the effects of each of the four drug classes on ADL functioning over time are presented in Figure 1 and Appendix Table 1 ($n = 62,516$ assessments). Use of ADMs was not associated with a change in ADLs over time for men or women (overall slope difference: 0.04 ADL points/year, 99% CI -0.24 – 0.32).

Antidepressant users declined more slowly versus non-users (overall slope difference: -0.36 ADL points/year, 99% CI -0.58 – -0.14), and this effect was consistent for males and females. Although the drug use $\times$ sex $\times$ days interaction was not significant in the above two models, sex modified the effect of both antipsychotic and mood stabilizer use on ADL over time. For antipsychotics, female users declined most quickly, followed by male non-users, female non-users, and male users (slope difference among males, users vs. non-users: -0.66 ADL points/year, 99% CI -1.29 – -0.03 ; slope difference among females, users vs. non-users: 0.56 ADL points/year, 99% CI 0.23 – 0.90). Results were similar for mood stabilizers (slope difference among males, users vs. non-users: -0.51 ADL points/year, 99% CI -1.51 – 0.49 ; slope difference among females, users vs. non-users: 0.90 ADL points/year, 99% CI

0.23–1.56). These results suggest that antipsychotics and mood stabilizers were associated with a faster ADL decline in women but not men.

Analyses for the association between drug use and cognition are presented in Figure 2 and Appendix Table 2. Sex did not modify the effect of use of any of the four studied drug classes on CPS. ADM use was associated with a slower decline in cognition (slope difference: -0.09 CPS points/year, 99% CI -0.14 – -0.03). Antidepressant users demonstrated a slower decline in cognition compared to nonusers (slope difference: -0.12 CPS points/year, 99% CI -0.17 – -0.08). Similarly, antipsychotic users had a slower cognitive decline versus nonusers (slope difference: -0.11 CPS points/year, 99% CI -0.17 – -0.06). Mood stabilizer use had no effect on CPS decline (slope difference: -0.06 points/year, 99% CI -0.16 – 0.04).

In general, secondary analyses using fixed effects models performed on the entire cohort ($n=18,950$ beneficiaries, 81,466 assessments) demonstrated results consistent with the main analyses. One difference was in the model for the effect of antipsychotics on ADL functioning: whereas marginal structural models suggested an effect modification of sex, secondary analyses found that antipsychotic users declined more quickly in their ADLs compared to non-users (slope difference: 0.37 ADL points/year, 99% CI 0.13 – 0.62), regardless of sex. The second difference was for the cognition outcome, where secondary analyses demonstrated effect modification of sex on the response to ADM use such that female non-users declined most quickly in their cognition, followed by male users, male non-users, and female users, suggesting that females benefited from ADM use with respect to cognition as measured by CPS, although men did not. All other fixed effects model results based on the full sample (secondary analyses) were consistent with the main marginal structural model results.

DISCUSSION

In a LTC setting, we examined the association of exposure to medications commonly used for ADRD management with cognition and ADLs over time. ADM, antidepressant, and antipsychotics were associated with slower rates of cognitive decline, while antidepressants were associated with a slower rate of ADL decline. Poorer outcomes were only observed for associations between some medication classes and ADLs, where results suggest sex differences in response to antipsychotics and mood stabilizers. However, all effect sizes were relatively small and may not reflect clinically noticeable differences in cognition or function.

ADM users exhibited smaller increases in CPS scores over time, indicative of slower cognitive decline, and secondary analyses suggested this effect may be stronger among women. These results are consistent with previous clinical trials showing small, yet significant, effects on cognitive function with ADM use across stages of ADRD severity.^{2–9} One clinical trial extension study examined the effect of sex on response to donepezil in those with mild to moderate AD and found sex did not impact response to donepezil.²⁵ However, a recent observational study reported that the association of ADMs with better cognitive outcomes in AD was stronger in females.⁴² While our main results using marginal

structural models demonstrated a small positive effect of ADM use overall, our secondary analysis, which used a larger cohort found this beneficial effect for females only (slope difference: -0.10 points/year, 99% CI -0.16 – -0.04). The three-way interaction may be non-significant due to removal of time-varying confounding by marginal structural modeling or the high prevalence of women in the cohort (77%) that causes overall results to mimic the results for females.

Antidepressant users exhibited slower increases in both ADL and CPS scores over time. Prior studies have given mixed results for the effect of antidepressants on cognition and ADLs in patients with AD. Use of sertraline was beneficial for cognition in female patients with Alzheimer's disease in one double-blind placebo-controlled clinical trial,²⁶ but had no influence on cognition in another trial, regardless of effectiveness in depression remission.⁴³ In contrast, sertraline was found to improve ADLs but not cognition in another randomized placebo-controlled trial in patients with AD.⁴⁴ However, in an observational study of community-dwelling dementia patients in Cache County, Utah, antidepressant use was found to worsen cognitive performance.¹² In the current study, use of antidepressants was associated with a slower decline in both ADL functioning and cognition, suggesting a potential beneficial effect. Needing assistance with ADLs was shown to be associated with depression in a study of a sample of older adults residing in assisted living facilities,⁴⁵ suggesting that remission from depression by antidepressant treatment may contribute to our observed ADL benefit.

We observed that antipsychotic and mood stabilizer use had a negative impact on ADL scores over time in females, although this negative effect was found for both sexes in secondary analyses. However, use of antipsychotics resulted in smaller increases in CPS scores (i.e., slower cognitive decline) over time regardless of sex. Several prior studies have shown deleterious effects associated with the use of these medications in community dwelling cohorts of dementia patients,^{12,19,46} although some studies demonstrate null or positive effects.^{47,48} Vigen *et al.* followed outpatients with AD in the CATIE-AD randomized trial and found overall cognitive decline was greater in patients receiving antipsychotic medications over the 36-week study period.¹⁹ An observational study among individuals with AD in Cache County, Utah found that use of antipsychotic medications was associated with more rapid functional decline. Typical antipsychotics were associated with more rapid cognitive decline, although atypical antipsychotics were not.¹² Notably, in a retrospective study of outpatients with mild to moderate AD, atypical antipsychotic users had no significant cognitive change over six months and demonstrated significant improvements in ADLs and IADLs during the same time frame.⁴⁷ One potential rationale for our results is the difference between our sample of NH patients and community-dwelling samples in most previous studies. Our population of NH residents likely has greater physical care demands and more need for psychopharmacological treatment of symptoms of depression, which both may contribute to the different results regarding psychotropic agent use. In addition, the larger sample size and longer average follow-up time in our study could better allow for observation of small benefits.

The most significant limitation of this study is the possibility of confounding by indication (e.g., dementia severity and symptoms). Though we attempted to control for this potential

bias by using marginal structural models and conducting secondary analyses, residual confounding and selection bias due to unmeasured confounders such as severity of dementia remain possible. We could not determine disease severity with the data available (i.e., ICD-9-CM codes), but restricting the sample to those with newly-diagnosed ADRD likely resulted in a cohort of individuals in earlier stages of disease. Also, though the CPS and MDS-ADL long form have considerable data supporting their reliability and validity,^{29,31–35} they are derived from the MDS which is a clinical measure recorded by NH care staff with resultant variance and errors in reporting. Two previous studies examining the ability of the MDS-ADL Long Form Scale to detect change over time found average declines of 1.3 points over 12 months²⁹ and 1.8 points over 6 months³⁰; our models predicted an approximate 0.9 point decline over 1 year in our sample. The smaller decline in our study is likely due to the more heterogeneous nature of our sample; for example, Carpenter *et al.* restricted their study to long-stay residents with at least moderate dementia (CPS = 3) and few comorbid conditions. Despite debate over accuracy of the CPS versus MDS-COGS for measuring cognitive status, these measures are highly correlated and both have similar validity to the MMSE.^{33,34} We chose to use the CPS because it is composed solely of MDS elements measured at quarterly assessments whereas some MDS-COGS elements are captured only at full assessments. Other limitations include those commonly associated with studies that use administrative data, including potential measurement and ascertainment errors, in particular those related to disease diagnosis. Identification of those with ADRD using Medicare claims has shown to have a sensitivity of 0.85 and a specificity 0.89.⁴⁹ While information on actual medication ingestion was not available using Medicare claims or the MDS, NH residents have their medications administered by staff. Consequently medication use is likely to be reliable. We determined medication use with prescription fill and refill patterns, which have been shown to validly measure medication use.⁵⁰ Last, although we identified our sample from a 5% random sample of Medicare beneficiaries, our results may not be generalizable to all Medicare patients with dementia due to study exclusion criteria associated with Medicare plan coverage.

To our knowledge this is the first study in a LTC population with ADRD to examine the impact of these medications on two key outcomes over time since Medicare Part D implementation and as such will be of interest to both clinicians and health policy decision makers. A major strength was that our study was conducted using a large, nationally representative sample of adults residing in NHs with recently diagnosed ADRD. Given the potential for treatment selection bias with many of these medications, we used marginal structural models to control for time-dependent confounding, specifically confounding by indication. Further, since this population uses multiple medications,¹⁰ we controlled for simultaneous use of these medications.

Conclusion

This study documents the effect of ADMs and psychotropic medications on cognitive and functional declines in a “real-world” NH population with ADRD over time. While we observed associations of selected medication classes with slower rates of cognitive and ADL decline, and some heterogeneity in treatment effect by sex, effect sizes were relatively small and not likely of clinical significance. As such, our findings are not strong enough to support

the long-term use of these medications in the NH setting. Use of these medications to manage ADRD patients in LTC facilities should be carefully considered by clinicians when weighed against their side effects, especially with projected increases in ADRD prevalence as the United States population ages and as effective treatment options remain elusive.

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Conflict of interest

- At the time the study was conducted, Gail B. Rattinger was supported by a National Institutes of Health Institutional Career Development Grant (Building Interdisciplinary Research Careers in Women's Health, K12 HD043489) at the University of Maryland Baltimore.
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APPENDIX

Table 1

Effects of medications on activities of daily living* over time (N=15,538; 62,516 assessments)^{†‡}

Variable	Anti-dementia medications [§]			Antidepressants [§]			Antipsychotics [§]			Mood Stabilizers [§]		
	Coefficient	SE	p-value	Coefficient	SE	p-value	Coefficient	SE	p-value	Coefficient	SE	p-value
Drug use	−0.03	0.09	0.70	0.46	0.06	<0.001	0.64	0.19	<0.001	−0.13	0.33	0.70
Days	0.005	0.0003	<0.001	0.005	0.0003	<0.001	0.005	0.0003	<0.001	0.005	0.0003	<0.001
Sex (ref: male)	−0.05	0.10	0.58	−0.06	0.10	0.56	0.008	0.10	0.94	0.30	0.12	0.02
Drug use × days	0.0001	0.0003	0.71	−0.001	0.0002	<0.001	−0.002	0.0007	<0.01	−0.001	0.001	0.19
Drug use × sex	NS	-	-	NS	-	-	−0.61	0.21	0.004	0.008	0.40	0.98
Sex × days	−0.0007	0.0003	0.01	−0.0009	0.0003	0.001	−0.001	0.0003	<0.001	−0.0008	0.0003	<0.01
Drug use × days × sex	NS	-	-	NS	-	-	0.003	0.0008	<0.001	0.004	0.001	<0.01

* Activities of daily living (ADL) functioning was assessed using the MDS ADL-long form scale; scores range from 0 to 28, with higher scores indicating greater dependence.

[†] Models adjusted for: age at index assessment, race, region, education level, marital status, CCI, number of hospital admissions in the month, days between index diagnosis and index assessment, use of other drug classes; non-significant interactions were removed from the models; non-significant covariates were removed from some models to allow the models to converge, if necessary.

[‡] Due to the small number of observations with missing components of ADL score, 19 missing observations were imputed using the mean of each person's ADL scores or the sample mean score of 16.

[§] Multivariate models used marginal structural modeling techniques to account for time-dependent confounding.

APPENDIX

Table 2

Effects of medications on cognition* over time (N=15,468; 62,173 assessments)^{†‡}

Variable	Anti-dementia medications [§]			Antidepressants [§]			Antipsychotics			Mood Stabilizers		
	Coefficient	SE	p-value	Coefficient	SE	p-value	Coefficient	SE	p-value	Coefficient	SE	p-value
Drug use	0.06	0.02	<0.001	0.05	0.01	<0.001	0.18	0.02	<0.001	0.06	0.03	0.07
Days	0.001	0.00003	<0.001	0.001	0.00003	<0.001	0.001	0.00005	<0.001	0.001	0.00003	<0.001
Sex (ref: male)	−0.04	0.02	0.02	−0.05	0.02	<0.01	−0.03	0.02	0.08	−0.03	0.02	0.15
Drug use × days	−0.0002	0.00006	<0.001	−0.0003	0.00005	<0.001	−0.0003	0.00006	<0.001	−0.0002	0.0001	0.14
Drug use × sex	NS	-	-	NS	-	-	NS	-	-	NS	-	-
Sex × days	NS	-	-	NS	-	-	NS	-	-	NS	-	-

Variable	Anti-dementia medications [§]			Antidepressants [§]			Antipsychotics			Mood Stabilizers		
	Coefficient	SE	p-value	Coefficient	SE	p-value	Coefficient	SE	p-value	Coefficient	SE	p-value
Drug use × days × sex	NS	-	-	NS	-	-	NS	-	-	NS	-	-

* Cognition was assessed using the Cognitive Performance Scale (CPS); scores range from 0 to 6, with higher scores indicating greater cognitive impairment.

[†] Models adjusted for: age at index assessment, race, region, education level, marital status, CCI, number of hospital admissions in the month, days between index diagnosis and index assessment, use of other drug classes; non-significant (NS) interactions were removed from the models; non-significant covariates were removed from the models to allow some models to converge, if necessary.

[‡] 343 observations had missing answers for components of the CPS and therefore CPS could not be calculated.

[§] Multivariate models used marginal structural modeling techniques to account for time-dependent confounding.

Figure 1.

Effects of medications on activities of daily living* over time†‡

*Activities of daily living (ADL) functioning was assessed using the MDS ADL-long form scale; scores range from 0 to 28, with higher scores indicating greater dependence.

†Multivariate models were performed using day as the time variable, but time was scaled to 1 year in the graphs for ease of interpretation.

‡Lines represent an individual with the following characteristics: female (ADM and antidepressant models only), age 80 years, white race, South region, high school education, married, 2 comorbid conditions (CCI) at the index assessment, 0 hospitalizations in the month of the index assessment, receiving LIS at the index assessment, dually eligible for Medicaid at the index assessment, 0 days between the index diagnosis and the index assessment, ADL score 8–14 at the index assessment, CPS score 2–3 at the index assessment, ABS score of 0 at the index assessment, MDSDRS score of 0 at the index assessment, non-user of other studied medications over time.

Figure 2.

Effects of medications on cognition* over time†‡

*Cognition was assessed using the Cognitive Performance Scale (CPS); scores range from 0 to 6, with higher scores indicating greater cognitive impairment.

†Multivariate models were performed using day as the time variable, but time was scaled to 1 year in the graphs for ease of interpretation.

‡Lines represent an individual with the following characteristics: female, age 80 years, white race, South region, high school education, married, 2 comorbid conditions (CCI) at the index assessment, 0 hospitalizations in the month of the index assessment, receiving LIS at the index assessment, dually eligible for Medicaid at the index assessment, 0 days between the index diagnosis and the index assessment, ADL score 8–14 at the index assessment, CPS score 2–3 at the index assessment, ABS score of 0 at the index assessment, MDSDRS score of 0 at the index assessment, non-user of other studied medications over time.

Table 1

Time-varying confounders and measures used in multivariable analyses

Dependent Variable	Independent variable	Hypothesized main time-varying confounder	Measure used to capture time-varying confounder	Model used
ADL	ADM use	Cognition	CPS	MSM
ADL	Antidepressant use	Depression	DRS	MSM
ADL	Antipsychotic use	Psychiatric conditions, aggressive behavior	ABS	MSM
ADL	Mood stabilizer use	Psychiatric conditions, aggressive behavior	ABS	MSM
CPS	ADM use	Cognition	Prior CPS	MSM
CPS	Antidepressant use	Depression	DRS	MSM
CPS	Antipsychotic use	None	N/A	Fixed effects models
CPS	Mood stabilizer use	None	N/A	Fixed effects models

ABS: Aggressive Behavior Scale; ADL: Activities of daily living; ADM: anti-dementia medications; CPS: Cognitive Performance Scale; DRS: Depression Rating Scale; MSM: marginal structural model

Table 2

Cohort Characteristics at the Index Assessment

Characteristic	Total			Female			Male			p-value
	N	%		N	%		N	%		
Sample Size	18,950	100.0		14,299	75.5		4,651	24.5		
ADRD diagnosis source										
CCW	16,428	86.7		12,435	87.0		3,993	85.9		
MDS	2,457	13.0		1,816	12.7		641	13.8		0.153
CCW and MDS	65	0.3		48	0.3		17	0.4		
Age at index assessment, years										
mean ($\pm$ SD)	83.6	(± 7.8)		84.4	(± 7.5)		81.1	(± 7.8)		
66–74	2,687	14.2		1,638	11.5		1,049	22.6		
75–84	7,003	37.0		5,093	35.6		1,910	41.1		<0.001
85	9,260	48.9		7,568	52.9		1,692	36.4		
Race										
White	16,337	86.2		12,525	87.5		3,822	82.2		
Black	1,809	9.6		1,272	8.9		537	11.6		<0.001
Other	804	4.2		512	3.6		292	6.3		
Region										
Northeast	4,143	21.9		3,166	22.1		977	21.0		
Midwest	5,283	27.9		4,089	28.6		1,194	25.7		
South (includes Other)	7,175	37.9		5,400	37.8		1,775	38.2		<0.001
West	2,349	12.4		1,644	11.5		705	15.2		
Education										
Less than high school	3,995	21.1		2,967	20.8		1,028	22.1		
High school	4,922	26.0		3,877	27.1		1,045	22.5		
At least some college	2,499	13.2		1,748	12.2		751	16.2		<0.001
Missing	7,534	39.8		5,707	39.9		1,827	39.3		
Marital Status										
Never married	1,360	7.2		825	5.8		535	11.5		
Married	3,594	19.0		1,717	12.0		1,877	40.4		

Characteristic	Total		Female		Male		p-value
	N	%	N	%	N	%	
Widowed	10,662	56.3	9,309	65.1	1,353	29.1	<0.001
Separated/Divorced	1,512	8.0	1,037	7.3	475	10.2	
Missing	1,822	9.6	1,411	9.9	411	8.8	
Original reason for entitlement							
Age	16,464	86.9	12,667	88.6	3,797	81.6	<0.001
Disability/ESRD	2,486	13.1	1,632	11.4	854	18.4	
LIS*	10,312	54.4	7,861	55.0	2,451	52.7	0.007
Dual eligibility*	9,433	49.8	7,193	50.3	2,240	48.2	0.011
Baseline Charlson Comorbidity Index score							
0	3,241	17.1	2,658	18.6	583	12.5	
1	3,675	19.4	2,962	20.7	713	15.3	
2	3,455	18.2	2,680	18.7	775	16.7	<0.001
3	8,579	45.3	5,999	42.0	2,580	55.5	
Died during 2007–2008	6,366	33.6	4,493	31.4	1,873	40.3	<0.001
Time between index diagnosis and index assessment, days							
0	2,867	15.1	2,124	14.9	743	16.0	
1–30	9,588	50.6	7,209	50.4	2,379	51.2	
31–180	4,318	22.8	3,294	23.0	1,024	22.0	0.071
181–730	2,177	11.5	1,672	11.7	505	10.9	
Time to end of follow up, days [†]							
0–30 [‡]	2,344	12.4	1,630	11.4	714	15.4	
31–180	6,385	33.7	4,736	33.1	1,649	35.5	
181–365	4,991	26.3	3,798	26.6	1,193	25.7	<0.001
366–720	5,230	27.6	4,135	28.9	1,095	23.5	
Number of assessments per person							
1 assessment (index)	3,345	17.7	2,442	17.1	903	19.4	
2–3 assessments	6,304	33.3	4,707	32.9	1,597	34.3	
4–5 assessments	3,751	19.8	2,828	19.8	923	19.9	<0.001
6 assessments	5,550	29.3	4,322	30.2	1,228	26.4	

Characteristic	Total		Female		Male		p-value
	N	%	N	%	N	%	
Drug use [§]							
Anti-dementia medications	2,832	14.9	2,223	15.6	609	13.1	<0.001
Antidepressants	7,520	39.7	6,015	42.1	1,505	32.4	<0.001
Antipsychotics	2,552	13.5	1,942	13.6	610	13.1	0.419
Mood stabilizers	571	3.0	399	2.8	172	3.7	0.002
Activities of Daily Living score (range 0–28)							
0–7 (independent)	1,996	10.5	1,441	10.1	555	11.9	
8–14	4,174	22.0	3,199	22.4	975	21.0	
15–21	9,017	47.6	6,937	48.5	2,080	44.7	<0.001
22–28 (dependent)	3,752	19.8	2,715	19.0	1,037	22.3	
missing	11	0.1	7	0.1	4	0.1	
Cognitive Performance Scale score (range 0–6)							
Relatively intact (0–1)	6,090	32.1	4,689	32.8	1,401	30.1	
Mild-moderate impairment (2–3)	10,387	54.8	7,890	55.2	2,497	53.7	<0.001
Severe impairment (4–6)	2,316	12.2	1,612	11.3	704	15.1	
missing	157	0.8	108	0.8	49	1.1	

ADRD: Alzheimer’s disease and related dementias; CCW: Chronic Condition Data Warehouse; ESRD: end-stage renal disease; LIS: low-income subsidy; SD: standard deviation; MDS: Minimum Data Set

* LIS and dual eligibility were assessed during the 12 months prior to the index assessment

[†] Follow-up from index assessment to end of study period or death

[‡] Includes 107 people whose index assessment was on their date of death or 12/31/2008 and 3 people who died during the 7 days prior to the date of their index assessment

[§] Medication use in the 3 months prior to the index assessment