CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

# Antidepressant Use and Cognitive Decline: The Health and Retirement Study

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## ABSTRACT

**BACKGROUND:** Depression is associated with cognitive impairment and dementia, but whether treatment for depression with antidepressants reduces the risk for cognitive decline is unclear. We assessed the association between antidepressant use and cognitive decline over 6 years.

**METHODS:** Participants were 3714 adults aged 50 years or more who were enrolled in the nationally representative Health and Retirement Study and had self-reported antidepressant use. Depressive symptoms were assessed using the 8-item Center for Epidemiologic Studies Depression Scale. Cognitive function was assessed at 4 time points (2004, 2006, 2008, 2010) using a validated 27-point scale. Change in cognitive function over the 6-year follow-up period was examined using linear growth models, adjusted for demographics, depressive symptoms, comorbidities, functional limitations, and antidepressant anticholinergic activity load.

**RESULTS:** At baseline, cognitive function did not differ significantly between the 445 (12.1%) participants taking antidepressants and those not taking antidepressants (mean, 14.9%; 95% confidence interval, 14.3-15.4 vs mean, 15.1%; 95% confidence interval, 14.9-15.3). During the 6-year follow up period, cognition declined in both users and nonusers of antidepressants, ranging from −1.4 change in mean score in those with high depressive symptoms and taking antidepressants to −0.5 change in mean score in those with high depressive symptoms and not taking antidepressants. In adjusted models, cognition declined in people taking antidepressants at the same rate as those not taking antidepressants. Results remained consistent across different levels of baseline cognitive function, age, and duration of antidepressant use (prolonged vs short-term).

**CONCLUSIONS:** Antidepressant use did not modify the course of 6-year cognitive change in this nationally representative sample.

 • *The American Journal of Medicine (2015) 128, 739-746*

**KEYWORDS:** Antidepressants; Cognition; Depression; Epidemiology

Depression is associated consistently with cognitive impairment and an increased risk for dementia in clinical and epidemiologic studies of older adults.[1-8] A meta-analysis of case-control and prospective studies concluded that a history of depression approximately doubled the risk for dementia.[1] However, whether treatment for depression can reduce the rate of cognitive impairment and dementia is unclear.[9-17]

**Funding:** See last page of article.

**Conflict of Interest:** See last page of article.

**Authorship:** See last page of article.

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0002-9343/$ -see front matter 
http://dx.doi.org/10.1016/j.amjmed.2015.01.007

Research to date on the effects of antidepressants on the rate of decline in cognitive function has been limited by small sample sizes (<100 patients), short (<12 months) follow-up, lack of a comparison group, and selected subgroups of patients, such as those who responded to therapy (ie, those whose depressive symptoms decreased after treatment).[11-17] A number of studies have also examined whether antidepressant treatment can slow the rate of cognitive decline or progression of dementia among patients with preexisting cognitive impairments or dementia.[15,18-20] From these studies, it has been difficult to disentangle the association between antidepressant treatment and long-term cognitive outcomes in a broadly representative population of individuals with a wide range of cognitive function, from nonimpaired to moderately impaired, when depression is assessed.

**CLINICAL SIGNIFICANCE**

- Cognitive function did not differ at baseline between antidepressant users and nonusers.
- Rate of decline in cognitive function over 6 years did not differ between antidepressant users and nonusers.
- Treatment with antidepressant medication use does not seem to modify the well-established association between depression and cognitive decline.

Little work has been done on the relationship between antidepressant use and cognition in population-based samples. One study of 595 patients found that antidepressant use was associated with an increased risk of cognitive decline over 4.5 years among depressed patients without cognitive impairment.[10] Within the Women's Health Initiative Memory Study, antidepressant use was associated with a 70% increased risk of incident mild cognitive impairment over 7.5 years.[9] Of note, although the Women's Health Initiative Memory Study collected information on the type of antidepressant taken, neither study assessed the anticholinergic activity of antidepressants. Medications with anticholinergic effects, including amitriptyline, doxepin, paroxetine, and nortriptyline among others, can block muscarinic receptors causing impairment in various cognitive functions, including memory, executive function, and processing speed.[21]

We examined whether antidepressant use was associated with cognitive decline over a 6-year period using data from the nationally representative Health and Retirement Study (HRS) and the HRS Prescription Drug Study (PDS), which include serial assessments of cognitive function, depressive symptoms, and antidepressant treatment. We hypothesized that treatment with antidepressant medications would be associated with slower rates of cognitive decline.

## MATERIALS AND METHODS

### Data Source

Study data were drawn from the 2004, 2006, 2008, and 2010 waves of the HRS, and from the 2005 and 2007 waves of the PDS. The HRS is a longitudinal, nationally representative survey of US residents aged 51 years and older that includes assessments of depressive symptoms and cognitive function. The HRS began in 1992, and participants are re-interviewed every 2 years with high follow-up rates (90%-95%).[22] The PDS was a mail survey distributed to a subsample of the HRS, drawn from respondents to the 2004 HRS wave, designed to track changes in prescription drug use among beneficiaries as Medicare Part D was phased in. The PDS sample includes HRS respondents born in 1942 or earlier (age ≥65 years in 2007) or those who were already covered by Medicare or Medicaid between 2002 and 2004. This analysis starts with the 2004 data to correspond with the first wave of the PDS. This study was approved by the University of Michigan Institutional Review Board; participants provided informed consent at enrollment.

The current study included all PDS respondents born before 1943 who were community dwelling, self-respondents providing cognitive function and depressive symptom assessments in the 2004 HRS interview. Participants' cognitive function was assessed at each wave through the 2010 survey, with up to 4 total assessments. Our primary analyses focus on change in cognitive function in patients who were, compared with those who were not, taking antidepressants according to the PDS.

### Assessment of Cognitive Function

At each HRS wave, cognitive function was assessed using a previously described and validated 27-point scale based on a battery of tests that included tests of memory, serial 7 subtractions, and naming.[23] This battery is a subset of an expanded battery (range, 0-35) administered to participants aged ≥65 years in the HRS; the expanded battery includes measures of orientation.[24] Participants requiring proxy interviews (because of cognitive or physical impairments that limited their ability to self-respond) were excluded from this analysis. Cut points for cognitive function were based on prior studies with the HRS data,[25,26] as well as methods used for the Aging, Demographics, and Memory Study, a supplemental study of dementia in the HRS.[27] These cut points defined a level of cognitive function that was generally consistent with normal function (12-27 points), cognitive impairment but no dementia (7-11 points), and dementia (0-6 points).[28]

### Assessment of Depression

Baseline depression status was based on the 2004 wave of the HRS using an 8-item version of the Center for Epidemiologic Studies Depression Scale.[29,30] This version of the

Center for Epidemiologic Studies Depression Scale included the following questions with "yes/no" response options: Much of the time during the last week, I felt depressed. I felt everything I did was an effort. My sleep was restless. I was happy (reverse coded). I felt lonely. I enjoyed life (reverse coded). I felt sad. I could not "get going." The total number of "yes" responses were summed to calculate an overall depression score (range, 0-8); participants with scores ≥4 were considered to have high depressive symptomatology.[30]

## Assessment of Antidepressant Use

Antidepressant use was assessed using the 2005 and 2007 PDS. Respondents were asked to list all medications prescribed and directed to provide the information on drug name and dosage directly from the prescription bottle label. Medications were then matched to the American Hospital Formulary System, a database of all prescription drugs. Respondents were considered to be taking an antidepressant if any of their medications were matched to therapeutic class code 28:16.04, which includes selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, other novel antidepressants (eg, bupropion), tricyclic antidepressants, and monoamine oxidase inhibitors.

## Other Study Variables

The following sociodemographic variables from the 2004 HRS survey were included as covariates: age, sex, education (less than high school vs high school or more), race (non-Hispanic-white, non-Hispanic-black, Hispanic, and other), chronic conditions (count of 7 self-reported conditions, including high blood pressure, diabetes, heart disease, stroke, lung disease, cancer, and arthritis), self-reported visual or hearing impairment, dependence in Activities of Daily Living,[31] and self-reported duration of antidepressant use. We also included a measure of baseline anticholinergic burden (based on the Anticholinergic Drug Scale),[32] because anticholinergic activity is high in some antidepressant medications and is associated with cognitive decline.[33]

## Analyses

Baseline (2004) characteristics were compared for participants who were taking antidepressants as assessed by the 2005 PDS compared with those who were not taking antidepressants using the chi-square test for categoric variables and analysis of variance analyses for continuous variables. A linear latent growth model was used to examine change on the 27-point cognitive battery over the 6-year follow-up. In this model, time is measured as years since baseline (2004), and random effects are used to capture individual differences in baseline levels (intercepts) and rates of change (slopes). We adjusted for depression, age, sex, education, race, hearing/visual impairment, comorbidity burden, and Activities of Daily Living impairment. We also adjusted for anticholinergic activity load of medications reported in the 2005 PDS.

We conducted several sensitivity analyses: one in which we stratified the analysis on the basis of cognitive function at baseline (no impairment, moderate impairment, dementia) and a second one in which we stratified the analysis on the basis of age at baseline (61-74 vs ≥75 years) to examine whether the association between antidepressant use and change in cognitive function varied according to level of cognitive function or age. In additional sensitivity analyses, we restricted the sample to those taking antidepressants at baseline (n = 445) and examined the effect of self-reported antidepressant use >1 year at baseline compared with shorter-term use and the effect of continuous antidepressant use over the entire follow-up period compared with discontinuation. All analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary NC) and MPlus version 7.1.

# RESULTS

Medication data from the 2005 PDS were available for 4320 individuals. Participants born after 1942 (n = 185), those who required a proxy respondent (n = 373), and those with incomplete data on the Center for Epidemiologic Studies Depression Scale (n = 48) were excluded from the study sample, resulting in an analytic sample of 3714 participants.

Of the 3714 eligible respondents, 445 (12%) were taking antidepressants in 2005. Participants taking antidepressants were more likely to be female, to drink alcohol daily, and to be white in contrast to participants not taking antidepressants (**Table 1**). Those taking antidepressants had a higher burden of comorbidity; they were more likely to need assistance with Activities of Daily Living and Instrumental Activities of Daily Living and more likely to have hearing and visual impairments. As expected, participants taking antidepressants were more likely to report a higher level of depressive symptoms than participants not taking antidepressants. Age, education, marital status, and smoking status did not differ according to antidepressant use (**Table 1**).

## Antidepressant Use and Cognitive Function

**Table 2** shows unadjusted cognitive performance by baseline antidepressant use and depressive symptoms. At baseline, no significant differences were detected in average cognition scores between the 445 (12.1%) participants taking antidepressants and those not taking antidepressants (mean 14.9, 95% confidence interval [CI], 14.3-15.4 vs mean 15.1%; 95% CI, 14.9-15.3). During the 6-year follow-up period, both users and nonusers of antidepressants experienced cognitive decline ranging from −1.4 change in mean score (95% CI, −1.1 to −1.7) in people with high depressive symptoms and taking antidepressants to −0.5 change in mean score (95% CI, −0.6 to −0.3) in people with high depressive symptoms and not taking antidepressants.

In our initial linear growth model, adjusted for age and depressive symptoms, there was a nonsignificant negative association between antidepressant use and baseline cognitive

**Table 1** Sample Characteristics by 2005 Antidepressant Use

| Measure | Antidepressant Use | | *P* Value |
|---|---|---|---|
| | No (n = 3269) % (95% CI) | Yes (n = 445) % (95% CI) | |
| Baseline age, mean, y (95% CI) | 72.0 (71.7-72.4) | 71.9 (70.4-72.8) | .72 |
| Sex, % female | 56.7 | 69.3 | <.001 |
| Education less than high school, % | 23.6 | 20.7 | .91 |
| White | 85.0 | 93.9 | |
| Black | 8.1 | 2.3 | |
| Hispanic/other | 6.9 | 3.8 | <.001 |
| Married, % | 57.4 | 52.3 | .09 |
| Current smoker, % | 10.1 | 13.5 | .042 |
| Intake of 1+ drinks per day, % | 12.3 | 10.8 | .41 |
| CES-D, mean (95% CI) | 1.3 (1.2-1.4) | 2.3 (2.0-2.6) | <.001 |
| CES-D depression* % | 12.0 | 26.6 | <.001 |
| No. of chronic conditions, % | | | |
| 0 | 13.4 | 8.3 | |
| 1 | 26.3 | 20.8 | |
| 2 | 29.8 | 30.1 | |
| 3+ | 30.5 | 40.8 | <.001 |
| Chronic conditions, mean (95% CI) | 1.9 (1.9-2.0) | 2.3 (2.1-2.5) | <.001 |
| Visual impairment | 19.2 | 25.8 | .006 |
| Hearing impairment | 23.2 | 25.7 | .34 |
| 2005 AA load | | | |
| 0 | 64.8 | 14.3 | |
| 1 or 2 | 26.1 | 52.8 | |
| 3+ | 9.1 | 33.0 | <.001 |
| 2005 AA load, mean (95% CI) | 0.8 (0.7-0.8) | 2.1 (2.0-2.3) | <.001 |
| ADL, % any dependence | 15.2 | 28.9 | <.001 |
| IADL, % any dependence | 11.9 | 23.0 | <.001 |
| Duration antidepressant use, % ≥1 y | — | 89.8 | |

AA = anticholinergic activity; ADL = Activities of Daily Living; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; IADL = Instrumental Activities of Daily Living.
*CES-D ≥4.

function (Intercept; Table 3, Model 1), but a significant decline in cognitive function over the 6-year study period in antidepressant users (Slope; Table 3, Model 1). Depression and age were both negatively associated with baseline level of function, but only age was associated with change (decline) in cognitive function over time. In subsequent models, we found a nonsignificant negative association between antidepressant use and change in cognitive function when we further adjusted for sex, education, race, Activities of Daily Living impairments, comorbidity burden (Table 3, Model 2), and anticholinergic load (Table 3, Model 3). Figure 1 presents unadjusted model-based estimates by baseline depressive symptom status (high/low) and antidepressant use corresponding to Model 1 (Table 3) for ages 72 years (2004) to 78 years (2010).

## Subgroup and Sensitivity Analyses

We conducted several sensitivity analyses. First, we examined whether the association between antidepressant use and change in cognitive function varied by baseline level of cognitive function or by age. In linear growth models adjusted for age and depression, antidepressant use was associated with a significant decline in cognitive function among participants with normal cognitive function at baseline (n = 2817; Slope = −0.094 [standard error = 0.04], $P < .05$) but nonsignificant decline in cognitive function among participants with cognitive impairment but no dementia (n = 721; Slope = −0.095 [0.10]) and those who were demented (n = 176; Slope = −0.133 [0.17]). Of note, although the association between antidepressant use and cognitive decline was significant in the participants with normal cognitive function at baseline and not in the 2 cognitively impaired groups, we observed a negative association between antidepressant use and cognitive change across levels of baseline cognitive function. In additional models and similar to findings in the overall cohort, there was a nonsignificant association between antidepressant use and cognitive decline in younger participants (age 61-74 years, n = 2398; Slope = −0.065 [standard error = 0.05]) and older participants (age 75+ years, n = 1316; Slope = −0.133 [standard error = 0.08]).

We also conducted sensitivity analyses among participants taking antidepressants at baseline (n = 414) to examine

**Table 2** Changes in Cognitive Functioning Over 6-Year Period by Baseline Antidepressant Use

| | Baseline (95% CI) | Time 1 (95% CI) | Time 2 (95% CI) | Time 3 (95% CI) |
|---|---|---|---|---|
| Low depressive symptoms and not taking antidepressants | | | | |
| Normal, % | 81.3 (79.6-83.0) | 79.8 (77.6-81.9) | 78.2 (75.9-80.5) | 73.2 (70.9-75.4) |
| Borderline, % | 15.6 (13.8-17.4) | 15.0 (13.3-16.7) | 16.3 (14.4-18.3) | 17.9 (16.2-19.5) |
| Impaired, % | 3.0 (2.4-3.6) | 5.3 (4.4-6.1) | 5.5 (4.4-6.5) | 9.0 (7.7-10.2) |
| Mean score | 15.3 (15.1-15.6) | 15.1 (14.9-15.4) | 15.0 (14.7-15.2) | 14.5 (14.3-14.8) |
| n | 2832 | 2673 | 2424 | 2071 |
| Low depressive symptoms and taking antidepressants | | | | |
| Normal, % | 80.6 (75.0-86.3) | 74.4 (69.7-79.0) | 72.4 (65.8-79.0) | 68.7 (61.8-75.7) |
| Borderline, % | 14.8 (9.8-19.7) | 16.6 (12.5-20.7) | 15.8 (10.4-21.3) | 20.6 (15.4-25.8) |
| Impaired, % | 4.6 (1.8-7.4) | 9.0 (5.4-12.6) | 11.8 (7.8-15.8) | 10.6 (6.3-14.9) |
| Mean score | 15.1 (14.4-15.8) | 14.6 (14.0-15.2) | 14.5 (13.8-15.3) | 14.4 (13.8-15.1) |
| n | 324 | 302 | 262 | 219 |
| High depressive symptoms and not taking antidepressants | | | | |
| Normal, % | 64.0 (57.9-70.1) | 62.6 (56.9-68.2) | 60.1 (52.5-67.7) | 58.0 (51.8-64.3) |
| Borderline, % | 29.3 (24.3-34.4) | 25.8 (20.8-30.7) | 28.1 (21.8-34.5) | 25.1 (19.7-30.5) |
| Impaired, % | 6.7 (3.5-9.8) | 11.7 (7.7-15.6) | 11.8 (8.2-15.3) | 16.9 (11.6-22.1) |
| Mean score | 13.1 (12.6-13.6) | 13.1 (12.5-13.6) | 13.2 (12.5-13.8) | 12.6 (11.9-13.3) |
| n | 437 | 401 | 341 | 257 |
| High depressive symptoms and taking antidepressants | | | | |
| Normal, % | 74.1 (65.2-83.0) | 67.4 (56.7-78.2) | 69.8 (58.1-81.5) | 54.2 (40.6-67.9) |
| Borderline, % | 19.5 (11.9-27.1) | 23.1 (14.0-32.2) | 19.7 (10.3-29.2) | 29.9 (19.3-40.6) |
| Impaired, % | 6.4 (1.7-11.1) | 9.4 (3.7-15.2) | 10.4 (3.6-17.2) | 15.9 (7.0-24.7) |
| Mean score | 14.2 (13.3-15.1) | 13.6 (12.4-14.7) | 13.7 (12.5-14.8) | 12.8 (11.6-14.0) |
| n | 121 | 114 | 93 | 71 |

CI = confidence interval.

the effect of duration and discontinuation of antidepressant use. In linear growth models adjusted for depressive symptoms and age, duration of antidepressant use at baseline and continuity of antidepressant use over the follow-up period were nonsignificantly associated with cognitive change (Slope for >1 year use = 0.103 [standard error = 0.10]) (Slope for continuous use = 0.026 [standard error = 0.09]).

## DISCUSSION

In a nationally representative cohort of older adults, we found that antidepressant use was not associated with changes in cognitive function over a 6-year period, adjusting for depressive symptoms, comorbidity burden, and anticholinergic load. Findings were consistent across levels of baseline cognitive function (normal function, mild cognitive impairment, and dementia). The results suggest that pharmacologic treatment for depression does not modify the negative association observed between depression and cognitive decline in clinical and epidemiologic studies.

Many clinical trials (mostly small) have been conducted to assess the association between antidepressant treatment and cognitive decline, and findings have been mixed. When responders and nonresponders are examined separately, responders to treatment tend to show improvements in cognitive function,[11-13] whereas nonresponders show no improvement[12] or decline.[13] Other studies have shown only modest improvements in cognition after treatment with antidepressants, equal to the practice effects observed in cognitive performance in control groups.[14-17] One study found that treatment with antidepressants decreased the risk of dementia, but only among patients with mild cognitive impairment at baseline.[15]

Little work has been published on treatment with antidepressants and cognitive trajectories in population-based studies. However, the findings suggest that, among nonimpaired participants, antidepressant use is associated with an increased risk of incident mild cognitive impairment in up to 7.5 years of follow-up.[9,10] We found a nonsignificant decline in cognitive function over a 6-year follow-up period among participants taking antidepressants at baseline. Our sample was not restricted to cognitively healthy participants at baseline, and results were similar across strata of baseline cognitive function (normal, mild cognitive impairment, and dementia).

To our knowledge, the effect of anticholinergic activity load has not been controlled or accounted for in previous studies of the longitudinal association between antidepressant use and cognitive decline. High anticholinergic activity

**Table 3** Linear Latent Growth Models of 2004-2008 Health and Retirement Study 27-Point Cognition Measure (n = 3714)

| | Model | | |
|---|---|---|---|
| | 1<br>Coefficient (SE) | 2<br>Coefficient (SE) | 3<br>Coefficient (SE) |
| Intercept | | | |
| Antidepressant use | −0.11 (0.25) | −0.39 (0.24) | −0.36 (0.26) |
| CES-D 4+ | −1.72‡ (0.23) | −0.54‡ (0.20) | −0.54‡ (0.20) |
| Age | −0.18‡ (0.01) | −0.16‡ (0.01) | 0.16‡ (0.01) |
| Female | | 0.42† (0.14) | −0.43† (0.14) |
| <12 y of school | | −2.72‡ (0.16) | −2.72‡ (0.16) |
| Black | | −2.84‡ (0.27) | −2.85‡ (0.27) |
| Hispanic | | −2.44‡ (0.26) | −2.45‡ (0.27) |
| Impaired vision | | −0.28 (0.19) | −0.27 (0.18) |
| Impaired hearing | | −0.68‡ (0.16) | −0.67‡ (0.16) |
| Chronic conditions (range, 0-7) | | −0.11 (0.07) | −0.10 (0.06) |
| 1 ADL impairment | | −0.65† (0.21) | −0.64† (0.21) |
| 2+ ADL impairments | | −1.04† (0.32) | −1.03† (0.32) |
| AA load of 1 or 2 | | | −0.03 (0.16) |
| AA load of 3+ | | | −0.13 (0.20) |
| Mean | 17.40‡ (0.16) | 18.39‡ (0.16) | 18.40‡ (0.16) |
| Residual variance | 11.33‡ (0.42) | 8.10‡ (0.37) | 8.10‡ (0.37) |
| Slope | | | |
| Antidepressant use | −0.09* (0.04) | −0.8 (0.04) | −0.08 (0.05) |
| CES-D 4+ | 0.002 (0.04) | −0.01 (0.05) | −0.01 (0.05) |
| Age | −0.02‡ (<0.01) | −0.02‡ (<0.01) | −0.02‡ (<0.01) |
| Female | | −0.02 (0.03) | −0.02 (0.03) |
| <12 y of school | | −0.01 (0.03) | −0.01 (0.03) |
| Black | | 0.02 (0.04) | 0.02 (0.04) |
| Hispanic | | 0.16† (0.05) | 0.16† (0.05) |
| Impaired vision | | −0.02 (0.03) | −0.02 (0.03) |
| Impaired hearing | | 0.04 (0.03) | 0.04 (0.03) |
| Chronic conditions | | 0.02 (0.01) | 0.02 (0.01) |
| 1 ADL impairment | | 0.01 (0.04) | <0.01 (0.04) |
| 2+ ADL impairments | | 0.01 (0.05) | 0.01 (0.06) |
| AA load of 1 or 2 | | | −0.01 (0.03) |
| AA load of 3+ | | | −0.02 (0.04) |
| Mean | −0.07† (0.02) | −0.12‡ (0.03) | −0.10‡ (0.03) |
| Residual variance | 0.07‡ (0.01) | 0.06‡ (0.01) | 0.06‡ (0.01) |

AA = anticholinergic activity; ADL = Activities of Daily Living; CES-D = Center for Epidemiologic Studies Depression; SE = standard error.
*$P < .05$.
†$P < .01$.
‡$P < .001$.

load is recognized increasingly for its association with negative cognitive effects, and anticholinergic activity is present, often in high doses, in many antidepressants. We were surprised by the small effect of anticholinergic activity load on baseline cognitive function and cognitive decline in our study. A number of population-based studies have examined anticholinergic activity load and cognitive decline, with significant associations observed in some,[33-36] but not all,[37-39] studies. The association between anticholinergic activity and cognitive decline may be related to level of cognitive function at baseline. For example, in a study of more than 13,000 patients, the strongest association between anticholinergic activity load and decline on the Mini Mental State Exam was in participants with scores in the "normal" range (26-30).[33] We found that antidepressant use was associated with a decline in cognitive function across all levels of baseline cognitive function (normal, cognitive impairment no dementia, and dementia) and that the association was strongest among participants with normal cognitive function at baseline and before and after adjustment for anticholinergic activity load of antidepressants.

## Study Strengths and Limitations

The present study has a number of strengths. The HRS is a nationally representative cohort, and our analysis was not

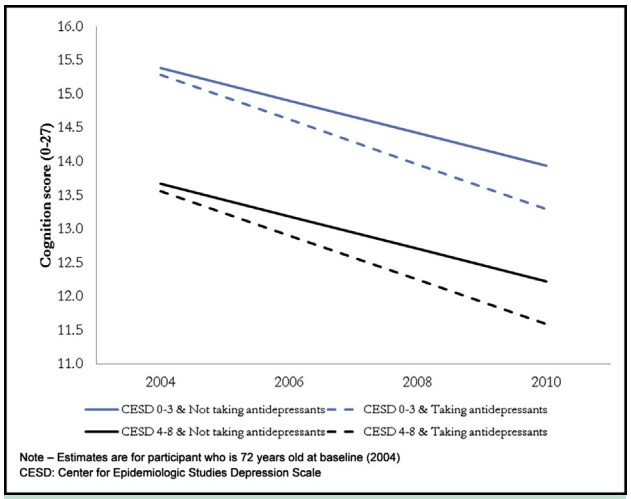


**Figure 1** Linear growth model of antidepressant use, depression, and cognition. Estimates are for participant who is aged 72 years at baseline (2004). CESD = Center for Epidemiologic Studies Depression Scale.

restricted to select subgroups of patients, such as those who responded to therapy or those without preexisting cognitive impairment. The PDS medication data, although self-reported, collects detailed information on medications used, so therapeutic class code can be determined by matching with the American Hospital Formulary System. As a result, we were able to code medications for anticholinergic activity load and examine the effect of high anticholinergic activity load on cognitive trajectories that has been missing from previous studies.

There are several potential limitations to our study. We did not look at specific classes of antidepressants and do not know whether patients were taking antidepressants for depression or other indications, such as weight loss. Our study was not designed to examine responsiveness to antidepressant treatment; however, we controlled for depressive symptoms in our analyses. Duration of antidepressant use was self-reported and thus could have resulted in misclassification, particularly among cognitively impaired participants. The battery of cognitive tests allowed us to examine global cognitive function but not individual cognitive domains, and it did not provide a clinical diagnosis of dementia. However, we used cut points that have been validated against clinical diagnosis of dementia.[26] Likewise, the Center for Epidemiologic Studies Depression Scale assesses depressive symptoms rather than providing a clinical diagnosis of depression; however, we used a well-established cut point that has been validated against clinical diagnosis of depression.[30]

## CONCLUSIONS

In this large nationally representative cohort of older adults, we found that antidepressant use was not significantly associated with 6-year change in cognitive function. These results were consistent across baseline levels of cognitive function and age, and did not change when we controlled for the anticholinergic activity load of antidepressants. Because depression is a well-known risk factor for cognitive decline and dementia, consideration of nonpharmacologic approaches to treatment for depression that also are related to cognitive function (eg, social engagement, physical activity, and diet) may be used in combination with pharmacologic approaches to address cognitive function and depressive symptoms.

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**Funding:** The Health and Retirement Study is funded by the National Institute on Aging (U01 AG09740). JSS was supported in part by funding from the National Institute on Aging (K01AG33643) and the National Heart, Lung, and Blood Institute (U01HL105268). This research was supported in part by P01AG031098 from the National Institute on Aging and the Department of Veterans Affairs, Health Services Research and Development (CD2 07-206-1 and VA IIR 10-176-3).

**Conflict of Interest:** None.

**Authorship:** All authors had access to the data and played a role in writing this manuscript.