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Depressive symptoms, antidepressant use, and future cognitive health in postmenopausal women: the Women's Health Initiative Memory Study

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Abstract

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Conflict of interest

None.

Description of authors' roles

J. S. Goveas, M. A. Espeland, J. M. Kotchen, A. Tummala, N. F. Woods, and S. Wassertheil-Smoller gave final approval to the paper. M. A. Espeland and P. Hogan were engaged in data analysis. J. S. Goveas worked on the initial draft of the paper and provided guidance with data analysis. N. L. Denburg, M. A. Espeland, J. S. Goveas, P. E. Hogan, J. M. Kotchen, J. E. Manson, W. J. Mysiw, J. Ockene, J. Smoller, A. Tummala, S. Wassertheil-Smoller, and N. F. Woods were involved in study design, data acquisition, analysis, and/or interpretation of data. N. L. Denburg, M. A. Espeland, J. S. Goveas, P. E. Hogan, J. M. Kotchen, J. E. Manson, W. J. Mysiw, J. Ockene, J. Smoller, A. Tummala, S. Wassertheil-Smoller, and N. F. Woods provided assistance and were involved in critical revision of the manuscript for important intellectual content.

Background—Antidepressants are commonly prescribed medications in the elderly, but their relationship with incident mild cognitive impairment (MCI) and probable dementia is unknown.

Methods—The study cohort included 6,998 cognitively healthy, postmenopausal women, aged 65–79 years, who were enrolled in a hormone therapy clinical trial and had baseline depressive symptoms and antidepressant use history assessments at enrollment, and at least one postbaseline cognitive measurement. Participants were followed annually and the follow-up averaged 7.5 years for MCI and probable dementia outcomes. A central adjudication committee classified the presence of MCI and probable dementia based on extensive neuropsychiatric examination.

Results—Three hundred and eighty-three (5%) women were on antidepressants at baseline. Antidepressant use was associated with a 70% increased risk of MCI, after controlling for potential covariates including the degree of depressive symptom severity. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) were both associated with MCI (SSRIs: hazard ratios (HR), 1.78 [95% CI, 1.01–3.13]; TCAs: HR, 1.78 [95% CI, 0.99–3.21]). Depressed users (HR, 2.44 [95% CI, 1.24–4.80]), non-depressed users (HR, 1.79 [95% CI, 1.13–2.85]), and depressed non-users (HR, 1.62 [95% CI, 1.13–2.32]) had increased risk of incident MCI. Similarly, all three groups had increased risk of either MCI or dementia, relative to the control cohort.

Conclusions—Antidepressant use and different levels of depression severity were associated with subsequent cognitive impairment in a large cohort of postmenopausal women. Future research should examine the role of antidepressants in the depression–dementia relationship and determine if antidepressants can prevent incident MCI and dementia in individuals with late-life depression subtypes with different levels of severity.

Keywords

antidepressants; selective serotonin reuptake inhibitors; late-life depression; cognitive decline; mild cognitive impairment; dementia

Introduction

The societal impact of late-life depression (LLD) is enormous since it is associated with poorer outcomes of comorbid medical disorders, accelerated cognitive and functional decline, and increased mortality risk (Alexopoulos, 2005; Almeida *et al.*, 2010). LLD increases the future incidence of mild cognitive impairment (MCI) and probable dementia, including Alzheimer’s disease (AD), in a subset of older adults (Ownby *et al.*, 2006; Goveas *et al.*, 2011). In the Women’s Health Initiative Memory Study (WHIMS), depressive symptoms were independently associated with incident MCI and probable dementia, after a mean follow-up of 5.4 years (Goveas *et al.*, 2011). While several studies have provided evidence of the detrimental effects of depression on future cognitive function, the relationship between antidepressant use and subsequent cognitive decline, including MCI and probable dementia, is less clear.

Antidepressants are among the most widely prescribed medications in older adults. Antidepressants are efficacious in the acute and maintenance therapy of LLD, thus decreasing disability and improving the quality of life of depressed elderly persons

(Alexopoulos, 2005; Rajji *et al.*, 2008; Smoller *et al.*, 2009). However, antidepressants frequently cause adverse effects in elderly persons and are associated with increased risk of incident falls, lower bone mineral density and fractures, hyponatremia, cardiovascular morbidity, subclinical and clinical strokes, and all-cause mortality (Smoller *et al.*, 2009; Woolcott *et al.*, 2009; Wright *et al.*, 2009; Haney *et al.*, 2010; Coupland *et al.*, 2011; Mark *et al.*, 2011). Furthermore, despite some studies reporting that the cognitive deficits seen in depressed older adults may improve with antidepressant treatment, especially when taking selective serotonin reuptake inhibitors (SSRIs), these findings are not universal (Knegtering *et al.*, 1994; Lee *et al.*, 2007; Bhalla *et al.*, 2009; Culang *et al.*, 2009). Moreover, the magnitude of cognitive improvement seen in patients with LLD is greater in treatment responders (Culang *et al.*, 2009). Depressed patients who have persisting deficits in the memory and executive function domains after effective treatment may be at higher risk for conversion to dementia (Steffens *et al.*, 2004).

Prospective population-based studies that evaluate the association between depressive symptoms, antidepressant use, and the future incidence of MCI and probable dementia are essential because certain antidepressants, mainly SSRIs, reportedly have neuroprotective properties (Nelson *et al.*, 2007). Furthermore, antidepressant treatment may reduce cognitive decline and even improve cognition in older persons with MCI and AD, though these results are controversial (Mossello *et al.*, 2008; Ravaglia *et al.*, 2008; Weintraub *et al.*, 2010). Therefore, in the WHIMS, a large, multisite study, we examined the prospective relationship of antidepressant use and specific antidepressant class on cognition, in healthy postmenopausal women. We also investigated the association between antidepressant use and subsequent cognitive decline based on the baseline depressive symptom status.

Materials and methods

WHIMS study design and sample

WHIMS, an ancillary study to the Women's Health Initiative randomized clinical trials (WHI-CT), was designed to examine the risks and benefits of postmenopausal hormone therapy on cognition and memory in healthy women aged 65 years and older at baseline. Thirty-nine of the 40 WHI clinical centers participated in the WHIMS and a total of 7,479 community-dwelling postmenopausal women were enrolled beginning in May 1996. Written informed consent was obtained, and the National Institutes of Health (NIH) and institutional review boards of the participating institutions approved the WHI-CT and WHIMS protocols. The study design, eligibility criteria, recruitment procedures, and the results from the WHI-CT have been published previously (Shumaker *et al.*, 1998; 2004). Annual follow-up of the WHIMS participants continued after WHI-CT termination. Women gave consent for extended follow-up, which continued until September 2007. Results from initial WHIMS enrollment to the end of extended follow-up are presented here; these show a higher number of incident MCI and dementia cases than previously reported (Shumaker *et al.*, 2004). The analytic cohort for this study included the WHIMS participants whose history of current antidepressant use was available, had completed the eight-item Burnam depression screen (Borhani *et al.*, 1991), and had attended at least one follow-up visit. After excluding 481 participants who did not meet the above criteria, 6,998 women were included in the analysis.

Assessment of medication use

Participants were asked to bring all current medications to their baseline interview in their original bottles. Medication information was directly entered from the containers into a medications database that assigned codes using the Master Drug Data Base (MDDDB; Medi-Span, Indianapolis, IN, USA). Women were classified into current antidepressant users or non-users based on the baseline medication use. Use of antidepressants was classified into the four mutually exclusive categories of SSRIs, tricyclic antidepressants (TCAs), other/multiple antidepressants, or none.

Depression measurement

Depressive symptoms were measured using the Burnam screening algorithm (Borhani *et al.*, 1991). This consists of six items from the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) and two items from the National Institute of Mental Health's Diagnostic Interview Schedule (DIS), as described elsewhere (Borhani *et al.*, 1991; Goveas *et al.*, 2011). The Burnam screen, initially developed for the National Study of Medical Care Outcomes, uses a logistic regression algorithm and provides a composite score between 0 and 1. A score of 0.06 or higher on the Burnam screen, which has shown excellent sensitivity and specificity for detecting depressive disorder during the past month, was used to define the presence of depressive symptoms.

In order to fully explore the joint relationship between depressive symptoms and antidepressant use and its potential impact on cognitive decline, we created a composite variable consisting of four groups: (1) depressed users (i.e. women with depressive symptoms and antidepressant use, likely representative of undertreated women and poor responders); (2) depressed non-users (i.e. women with depressive symptoms and no antidepressant use, reflective of the untreated group); (3) non-depressed users (i.e. women on antidepressants but without depressive symptoms, which is the remitted depression group); and (4) non-depressed, non-users (i.e. women without depressive symptoms and antidepressant use, which is the reference cohort). This approach permits a more in-depth examination of these groups regarding risk of future cognitive decline for data exploration and hypothesis-generation.

Other covariates

Baseline data including demographic information, medical history (including history of cardiovascular and cerebrovascular disease), and lifestyle variables (including alcohol use and smoking history) were primarily obtained by self-report and clinical measurements using standardized study forms as detailed elsewhere (Shumaker *et al.*, 1998; Goveas *et al.*, 2011). Body mass index (BMI) was calculated as weight (kg) / height² (m²). Physical exercise was defined as moderate or strenuous activity based on 20 minutes or more duration with the metabolic equivalent score of at least 4.0. Cognitive function was measured using the Modified Mini-Mental State (3MS) Examination at baseline and annually, by centrally trained and certified technicians (Shumaker *et al.*, 1998; Goveas *et al.*, 2011).

Outcome measures

The WHIMS protocol for detecting MCI and probable dementia has been described previously (Shumaker *et al.*, 1998; 2004). Centrally trained and certified technicians who were re-certified semi-annually collected the WHIMS-related data. The protocol was divided into four phases. In *phase 1*, 3MS was administered to all participants as a screening assessment of global cognitive functioning during baseline and then at annual follow-up visits. Women who advanced to phases 2 and 3 were scheduled for completion of these phases within three months of phase 1. In phase 2, the certified technician administered the modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery, standardized interviews to assess for acquired cognitive and mental disorders, and a standardized set of 36 questions to assess the participant's acquired cognitive and behavioral changes. In phase 3, a local physician (geriatrician, neurologist, or geriatric psychiatrist) with experience in diagnosing dementia evaluated the participants. After reviewing all available data and completing a structured medical history, and a physical and neuropsychiatric examination, the participants were classified as having probable dementia, MCI, or no dementia, based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. MCI was diagnosed based on the accepted criteria at the time when the WHIMS was initiated, and was operationally defined as poor performance (10th or lower percentile based on CERAD norms on at least one CERAD test, some decline in instrumental activities of daily living (IADL) due to cognitive impairment, intact basic activities of daily living (ADL) reported by a reliable informant, no evidence of medical or psychiatric disorders that can explain the decline in cognitive function, and the absence of adjudicated dementia). For the diagnosis of probable dementia, functional impairment had to be secondary to cognitive impairment and could not be explained by medical etiologies. Women who were suspected of having probable dementia underwent phase 4 evaluation that included a non-contrast computed tomography (CT) brain scan and necessary laboratory blood tests to rule out possible reversible causes of cognitive decline and dementia. Subsequently, the physician was required to provide the most probable etiology of dementia based on the DSM-IV criteria for AD, vascular dementia, and other dementia-related classifications. Finally, the clinical and test data were transmitted to the WHIMS clinical coordinating center for review and central adjudication of MCI and probable dementia. The central adjudication process is described in detail elsewhere (Shumaker *et al.*, 1998; 2004).

Statistical analysis

Women classified as antidepressant users at baseline versus non-users were compared with respect to demographic, lifestyle, cognitive, and clinical characteristics at the time of randomization to the WHI Hormone Therapy (HT) trials using χ^2 tests for categorical variables and t tests for continuous variables. Cox proportional hazards regression was conducted separately for our three outcomes of interest: time until (1) MCI, (2) probable dementia, and (3) either MCI or probable dementia. Time to event was defined as the number of days from randomization into the WHI trials until the date of the 3MS that triggered the referral for additional cognitive testing resulting in the first postrandomization diagnosis of MCI or probable dementia. Participants without an event were censored at the time of their last 3MS testing.

The predictors of primary interest included baseline antidepressant use, a composite variable jointly representing antidepressant use and depression, and antidepressant use by class. Although we chose to treat depressive symptoms as a dichotomous variable, we also used the underlying score as a continuous variable to characterize and compare depression levels among the four groups using median scores and non-parametric tests (Wilcoxon rank-sum and Kruskal–Wallis tests). We fitted unadjusted Cox models focused on our single predictors of interest and adjusted for potential confounders (all baseline variables in Table 1 including baseline depressive symptoms). The effect of antidepressant use was assessed with unadjusted and adjusted hazard ratios (HR) and nominal 95% confidence intervals, and significance with asymptotic Wald tests. In each adjusted model, we examined the interaction between antidepressant use and baseline depressive symptoms, 3MS, and age. We plotted cumulative hazard functions to depict incidence over time by the predictors of primary interest. All statistical analyses were performed with SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC).

Results

Of the total sample of 6,998 participants, 5% ($N=383$) were on antidepressants at baseline: 170 (44%) were on SSRIs; 160 (42%) were on TCAs; and 53 (14%) were on other/multiple antidepressants. Use of trazodone, which is typically prescribed adjunctively in low doses to promote sleep, was not an exclusion criterion for the SSRI and TCA categories: six women were taking an SSRI with trazodone, and none were taking a TCA with trazodone.

Compared to non-users, women on antidepressants were more likely to be depressed and to have lower family income and global cognitive function, have a past history of smoking and alcohol use, and were less likely to exercise. In addition, users tended to have a higher number of vascular risk factors, a history of cardiovascular and cerebrovascular disease, and a prior history of hormone therapy (Table 1).

A total of 331 women (4.7%) developed MCI, 216 women (3.1%) developed probable dementia, and 471 participants (6.7%) developed MCI/probable dementia (76 women who initially developed MCI converted to probable dementia during follow-up). Follow-up time averaged 7.6 years each for MCI and probable dementia, and 7.5 years for MCI/probable dementia. After adjusting for multiple covariates, baseline antidepressant use was associated with incident MCI (HR, 1.70 [95% CI, 1.14–2.54]), and incident MCI/probable dementia (HR, 1.55 [95% CI, 1.09–2.20]). Anti-depressant use was not significantly associated with incident probable dementia (Table 2). There were no significant interactions between antidepressant use and depressive symptoms ($p = 0.37$), baseline 3MS scores ($p = 0.71$) or age ($p = 0.15$). Table S1, available as supplementary material attached to the electronic version of this paper at www.journals.cambridge.org/jid_IPG, includes scores on the CERAD measures for antidepressant users and non-users grouped by incident MCI, probable dementia, and MCI/probable dementia.

In the fully adjusted analysis, use of SSRIs was associated with incident MCI (HR, 1.78 [95% CI, 1.01–3.13]), when compared with no antidepressant use. The TCA use was associated with incident MCI (HR, 1.78 [95% CI, 0.99–3.21]) and MCI/probable dementia

(HR, 1.75 [95% CI, 1.05–2.91]) (Table 3). Although TCAs appear to show an increased risk for incident dementia compared to SSRIs, these findings were not statistically significant. Among women treated with multiple/other antidepressants, there were no significant associations (Table 3). In both unadjusted and adjusted analyses, statistically significant association between antidepressant use and incident MCI and MCI/probable dementia persisted even after using depression scores as a continuous covariate.

Depressed users were found to have a higher median level of depressive symptom severity than the depressed non-users (median values: 0.355 versus 0.213; $p = 0.004$). Likewise, not depressed users reported a higher medial level of depressive symptoms than not depressed non-users (median values: 0.0022 versus 0.0017; $p < 0.0001$). In a fully adjusted model, all three groups were associated with incident MCI (depressed user: HR, 2.44 [95% CI, 1.24–4.80]; non-depressed user: HR, 1.79 [95% CI, 1.13–2.85]; depressed non-user: HR, 1.62 [95% CI, 1.13–2.32]) and MCI/probable dementia (depressed user: HR, 2.34 [95% CI, 1.27–4.32]; non-depressed user: HR, 1.60 [95% CI, 1.06–2.41]; depressed non-user: HR, 1.65 [95% CI, 1.20–2.26]), relative to the reference cohort (Table 4 and Figure 1). The risk of probable dementia associated with the three groups did not reach statistical significance.

Discussion

This is the largest prospective study to examine the association between antidepressant use and incident cognitive impairment in elderly women. First, we found a significant relationship between antidepressant use and incident cognitive impairment. In comparison to women not on antidepressants, users had a 70% increased risk of MCI, after controlling for several potential covariates. Second, the risk of incident MCI and MCI/probable dementia was similarly increased in both SSRI and TCA users, with no specific antidepressant class showing a greater risk. Finally, depressed antidepressant users (undertreated depressed cohort) showed the highest risk for incident cognitive impairment, followed by non-depressed users (remitted depression group) and depressed non-users (untreated depressed women).

Antidepressants, regardless of the class, were associated with an increased risk of MCI and MCI/probable dementia in this study, suggesting a direct link between antidepressant use and incident cognitive impairment in postmenopausal women. Several possible mechanisms may explain the relationship between antidepressants and cognitive decline. The presence of baseline depressive symptoms, lower cognitive function, vascular risk factors, or cardiovascular and cerebrovascular disease may increase the risk of subsequent cognitive impairment (Alexopoulos, 2005; Ownby *et al.*, 2006; Steffens *et al.*, 2006; Goveas *et al.*, 2011). The severity of vascular risk factors, poor baseline cognitive performance, and increased subclinical cerebrovascular disease predicts poor antidepressant response in LLD (Sheline *et al.*, 2010). However, the WHIMS cohort was cognitively healthy at baseline and the detrimental effects of antidepressants persisted even after controlling for the above-mentioned confounding variables. Also, the relationship between antidepressant exposure and incident cognitive impairment persisted even after controlling for the level of depressive symptoms. Another possibility is that antidepressants may increase the risk of subclinical cerebrovascular disease, thus accelerating cognitive decline. In the Cardiovascular Health

Study (CHS), while individuals on TCAs showed greater worsening of white matter disease, those on serotonergic antidepressants had an insignificant worsening of subclinical cerebrovascular disease (Steffens *et al.*, 2008). Also, the antiplatelet aggregating activity of serotonergic antidepressants may increase the risk of hemorrhagic stroke in postmenopausal women (Smoller *et al.*, 2009).

On the contrary, chronic treatment with SSRIs in non-human primates is shown to promote hippocampal neurogenesis and modulate the signal pathways involved in neuroplasticity and survival, thereby alleviating depressive symptoms and improving cognitive performance (Santarelli *et al.*, 2003). SSRIs also reduce *N*-methyl-D-aspartate (NMDA) receptor function, suppress pro-inflammatory cytokine production, exhibit antithrombotic properties, and may protect against amyloid and tau pathology (Nelson *et al.*, 2007; Hashioka *et al.*, 2009; Aboukhatwa *et al.*, 2010). Several studies in human primates have shown beneficial effects of SSRIs on cognitive performance, but these findings may be more pronounced in treatment responders and in individuals without baseline cognitive impairment and less vascular disease (Sheline *et al.*, 2010). Finally, SSRI antidepressants have different anticholinergic activity. Paroxetine that has greater anticholinergic properties may cause impaired delayed verbal memory recall, whereas sertraline is associated with improved verbal fluency and delayed memory recall and citalopram with better memory consolidation, in healthy elderly volunteers (Knegtering *et al.*, 1994). The potential benefits may have been masked by the enrollment in this study of participants on SSRIs with more anticholinergic activity.

Our findings of depressed antidepressant users showing the highest risk for incident cognitive decline and MCI are consistent with the Conselice Study of Brain Aging (CSBA) findings (Ravaglia *et al.*, 2008). Similar to the CSBA, the indications for antidepressant use and duration and adequacy of treatment were not assessed in the WHIMS. It is also not clear if the depressed antidepressant users were undertreated or had recurrent or treatment refractory depression. The CSBA was limited by the small number of antidepressant users and incident MCI cases, predominance of TCAs (71%) among users, and exclusion of participants who subsequently developed dementia (Ravaglia *et al.*, 2008). While a deleterious effect of SSRIs in treatment non-responders in verbal learning and psychomotor speed measures is seen, treatment responders show significant improvement in visuospatial functioning and psychomotor speed relative to non-responders (Culang *et al.*, 2009). Regardless, our findings that older adults with a greater degree of depressive symptoms may be at highest risk for incident MCI and dementia should be a focus of future investigations.

The increased risk of cognitive impairment seen in the treatment responders was an unexpected finding. However, these results are consistent with previous mixed gender studies that found that over 40% of older adults with remitted LLD met the criteria for a cognitive disorder diagnosis, the majority of whom had MCI (Lee *et al.*, 2007; Bhalla *et al.*, 2009; Reynolds *et al.*, 2011). Conversely, our findings are not consistent with results from shorter term randomized controlled trials that have shown a positive impact of antidepressants on cognitive function (Culang *et al.*, 2009), albeit these studies did not carefully assess for a cognitive disorder diagnosis posttreatment. Since TCAs were more commonly prescribed in our remitted depression cohort (47% vs. 41%) ($p=0.002$), it is

plausible that the differential assignment of antidepressant classes may have masked the neuroprotective effects of SSRIs in this group.

The lack of antidepressant use in the depressed women did not decrease the risk for cognitive decline, suggesting that there are complex pathophysiological mechanisms that may explain the relationship between depression and dementia. Several mechanistic links including vascular risk factors and disease, medial temporal lobe (MTL) and frontal regional atrophy, increased white matter hyperintensities, AD neuropathological lesion load, and APOE ϵ 4 status are proposed and require rigorous investigation (Steffens *et al.*, 2000; 2006; Butters *et al.*, 2008; Irie *et al.*, 2008).

The strengths of the study include: a large cohort of postmenopausal women; medication ascertainment; a thorough baseline assessment of several confounding variables, including depression screen; and a rigorous protocol to diagnose incident MCI and dementia cases, including extensive neuropsychiatric examination and a central adjudication process. This is the first prospective study to show a significant relationship between depressive symptoms, antidepressant use, and incident cognitive impairment in healthy, ethnically diverse, older postmenopausal women.

However, the study has limitations. The indication and duration of antidepressant use, and the precise dosages and medication compliance history were not available. While we are perplexed by the significantly higher number of antidepressant users being prescribed tricyclics (42%), this percentage is significantly lower than the one observed in the CSBA (71% of users) (Ravaglia *et al.*, 2008). While TCAs are no longer widely prescribed to treat depression in the elderly, our findings highlight the continued disproportionate use of this group of medications in managing non-mental health-related illnesses including chronic persistent pain and urinary incontinence. WHIMS also did not assess if women were receiving antidepressants alone or in combination with psychotherapeutic interventions, for treatment of LLD. Depressive symptoms that were assessed using the eight-item Burnam screen have excellent sensitivity and specificity to diagnose syndromal depression but have poor positive predictive value (Tuunainen *et al.*, 2001). This screening instrument is not a replacement for the clinician-administered Structured Clinical Interview for DSM-IV disorders (SCID) and could have resulted in an inaccurate estimation of the percentage of women with syndromal depression. Even though we used depression score as a continuous covariate, it is still possible that our findings of antidepressant use-cognitive impairment relationship is due to residual confounding by depression and we are unable to fully unravel the specific effects of antidepressant use from that of depression. While the lack of antidepressant class differences (i.e. our findings that both SSRI and TCA antidepressant use are associated with incident cognitive impairment) may also be taken as evidence of residual confounding by depression, this concern is somewhat mitigated by the fact that we did not see an increased risk in the multiple/other antidepressant group (Table 3). In addition, the age of onset, number of prior depressive episodes, and the duration of current depressive symptoms are not known. It is also important to note that depressive symptoms and antidepressant use status were defined based on cross-sectional assessments at baseline. Therefore, the changes in these exposure variables during follow-up could have resulted in misclassification of true exposure prior to the event, though this might have resulted in a bias

toward null. The operational definition of MCI has continued to evolve since WHIMS was initiated and the women classified as MCI could include individuals with both amnesic and non-amnesic MCI. Our findings are based on women who volunteered and were eligible for a hormone therapy trial, and may not generalize to other cohorts. Finally, the results reported here should be interpreted in the context of an observational study and are not a substitute for randomized double blind, clinical trials.

Our results should not discourage use of antidepressants, rather they further underline the need for the judicious use of these pharmacologic agents to treat LLD. Our study also highlights the complexities of managing depression in late-life using antidepressants. First, antidepressants have beneficial effects in acute and maintenance treatment of LLD (Rajji *et al.*, 2008). However, suboptimal treatment is common in LLD and appropriate dosage, medication adherence, and adequate duration of treatment are essential to achieve remission. On the other hand, older adults using antidepressants are more likely to have other comorbid physical and psychiatric diseases, and be prescribed a wide variety of non-psychotropic and psychotropic medications that can cause synergistic side effects and have drug–drug interactions with antidepressants (Mark *et al.*, 2011). Although at the outset, antidepressant drugs can be perceived as being detrimental to future cognitive health in postmenopausal women, our findings also point to the fact that different gradations of depressive symptom severity may be associated with variable risk of incident cognitive impairment. Since less than 50% of older depressed patients on antidepressant therapy achieve full remission (Alexopoulos, 2005; Rajji *et al.*, 2008; Reynolds *et al.*, 2011), it is critical to augment medications with non-pharmacologic interventions for adequate treatment of LLD. These strategies may also be crucial for preventing MCI and dementia in cognitively intact depressed older adults. Our findings further suggest the need for ongoing monitoring of cognitive function in the depressed elderly. Second, early-onset and late-onset depression may be associated with cognitive decline via different pathophysiological mechanisms. History of depression increases the risk of developing AD approximately twofold, supporting a causal factor hypothesis (Ownby *et al.*, 2006). Younger age of onset and longer duration of untreated depression can result in excessive stress hormone exposure of the MTL structures leading to atrophy (Sapolsky, 2000). Interestingly, antidepressant-induced hippocampal neurogenesis is suggested as an essential component needed for the clinical benefits of antidepressants (Santarelli *et al.*, 2003). In contrast, depressive symptoms may be the earliest non-cognitive manifestation of AD and may be a marker of incipient dementia, suggesting a reverse causality hypothesis (Alexopoulos, 2005; Steffens *et al.*, 2006). Adequate antidepressant treatment of early-onset and mid-life depression, prevention of recurrent episodes, and shortening the duration of untreated depression may prevent future cognitive decline and development of dementia.

In summary, antidepressant use was associated with subsequent cognitive impairment in a large cohort of postmenopausal women. While we are unable to fully disentangle the specific effects of depression and antidepressant use in this study, different levels of depressive symptom severity were associated with varying trajectories with respect to the development of incident cognitive impairment. Moreover, while antidepressant use in women with remitted depression did not prevent subsequent cognitive decline, our results suggest a decreased risk of incident cognitive decline with optimal treatment of depression.

Further research is essential to elucidate the role of antidepressant use in the depression–dementia relationship and to examine if newer generation antidepressants can prevent dementia in mid- and late-life depression subtypes with different levels of symptom severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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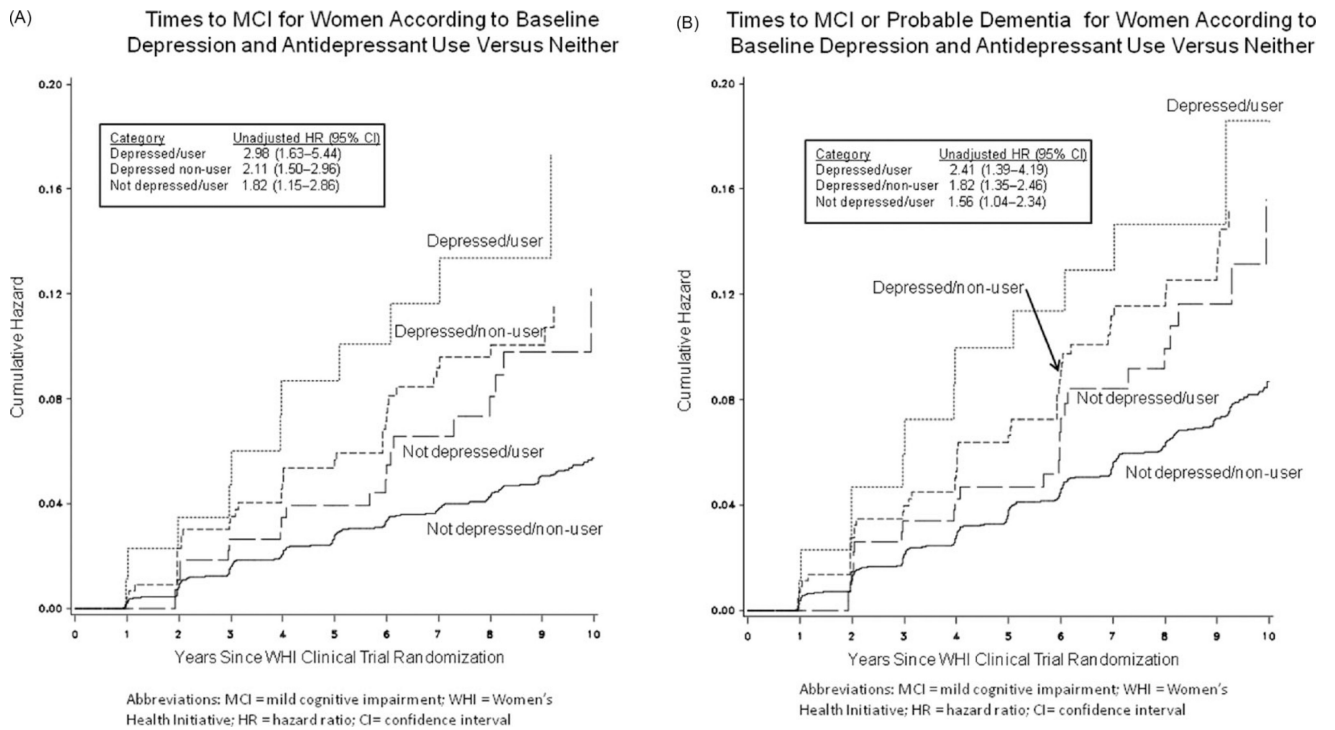


Figure 1. Adverse cognitive outcomes according to baseline depression and antidepressant use. (A) Incidence of mild cognitive impairment; (B) incidence of mild cognitive impairment/probable dementia.

Table 1Baseline characteristics based on antidepressant use ($N = 6,998$)

VARIABLE	BASELINE ANTIDEPRESSANT USE <i>N</i> = NUMBER (%)		P VALUE ^a
	NO <i>N</i> = 6,615 (95)	YES <i>N</i> = 383 (5)	
Age in years mean, standard deviation	70.9, 3.8	71.0, 3.9	0.8996
Ethnicity, <i>n</i> (%)			0.0528 ^b
White	5,777 (87)	350 (91)	
African American	464 (7)	16 (4)	
Hispanic	142 (2)	9 (2)	
Asian	116 (2)	2 (1)	
American Indian	21 (0)	2 (1)	
Other/unknown	95 (1)	4 (1)	
Education, <i>n</i> (%)			0.2967
< high school grad/GED	479 (7)	34 (9)	
High school grad/GED	1,449 (22)	89 (23)	
Some college	2,665 (40)	158 (41)	
College graduate	2,014 (30)	101 (26)	
Family income, \$, <i>n</i> (%)			0.0044
<20,000	1,586 (24)	100 (26)	
20,000–34,999	1,942 (29)	127 (33)	
35,000–49,999	1,302 (20)	64 (17)	
50,000+	1,406 (21)	59 (15)	
Unreported	379 (6)	33 (9)	
Marital status, <i>n</i> (%)			0.6941
Never married	222 (3)	13 (3)	
Divorced/separated	815 (12)	49 (13)	
Widowed	2,010 (30)	126 (33)	
Married/marriage-like relationship	3,553 (54)	194 (51)	
Smoking, <i>n</i> (%)			0.0236
Never	3,527 (54)	177 (47)	
Past	2,567 (39)	171 (45)	
Current	434 (7)	30 (8)	
Alcohol use, <i>n</i> (%)			<0.0001
Non-drinker	875 (13)	33 (9)	
Past drinker	1,240 (19)	116 (31)	
Current drinker	4,445 (68)	230 (61)	
Episodes per week of moderate and strenuous physical activity, <i>n</i> (%)			<0.0001
None	1,146 (17)	95 (25)	
Some of limited duration	2,971 (45)	176 (46)	
2–3	1,061 (16)	61 (16)	

VARIABLE	BASELINE ANTIDEPRESSANT USE N = NUMBER (%)		P VALUE ^a
	NO N = 6,615 (95)	YES N = 383 (5)	
4+	1,429 (22)	51 (13)	
Body mass index, <i>n</i> (%)			0.0514
<25	1,930 (29)	97 (26)	
25–29	2,389 (36)	129 (34)	
30+	2,262 (34)	153 (40)	
Prior hormone therapy, <i>n</i> (%)			<0.0001
No	3,641 (55)	155 (40)	
Yes	2,972 (45)	228 (60)	
Hypertension, <i>n</i> (%)			<0.0001
None	3,376 (51)	156 (41)	
Current/controlled	1,047 (16)	87 (23)	
Current/uncontrolled	2,192 (33)	140 (37)	
History of diabetes, <i>n</i> (%)			<0.0001
No	6,092 (92)	326 (85)	
Yes	514 (8)	57 (15)	
High cholesterol requiring pills, <i>n</i> (%)			0.0007
No	5,366 (82)	285 (75)	
Yes	1,166 (18)	94 (25)	
History of cardiovascular disease ^c , <i>n</i> (%)			<0.0001
No	5,730 (87)	296 (77)	
Yes	885 (13)	87 (23)	
History of stroke or transient ischemic attack, <i>n</i> (%)			0.0125
No	6,381 (96)	360 (94)	
Yes	234 (4)	23 (6)	
Hormone therapy assignment, <i>n</i> (%)			0.5600
Active	3,262 (49)	183 (48)	
Placebo	3,353 (51)	200 (52)	
3MS (mean, standard deviation)	95.3, 4.2	94.6, 4.5	0.0021
Depression status, <i>n</i> (%)			<0.0001
No	6,159 (93)	291 (76)	
Yes	456 (7)	92 (24)	

^a P value for categorical variables is based on χ^2 test and for continuous variables, t test.

^b Based on collapsing to three categories (White, African American, and other).

^c Based on self-report of prior myocardial infarction, angina, coronary revascularization, cardiac arrest, congestive heart failure, cardiac catheterization, carotid endarterectomy, atrial fibrillation, or aortic aneurysm.

Table 2

Hazard ratio (95% CI) of developing adverse cognitive outcomes with antidepressant use versus none

COGNITIVE OUTCOME	BASELINE ANTIDEPRESSANT USE		UNADJUSTED HR (95% CI) p-VALUE	ADJUSTED HR (95% CI) p-VALUE*
	YES (N = 383)	NO (N = 6,615)		
Mild cognitive impairment			1.97 (1.36–2.85)	1.70 (1.14–2.54)
Number (%) of cases	31 (8)	300 (5)	0.0003	0.009
Probable dementia			1.55 (0.93–2.58)	1.24 (0.71–2.17)
Number (%) of cases	16 (4)	200 (3)	0.09	0.45
Mild cognitive impairment or probable dementia			1.69 (1.21–2.35)	1.55 (1.09–2.20)
Number (%) of cases	38 (10)	433 (7)	0.002	0.02

* Fully adjusted for age, ethnicity, education, family income, and marital status, smoking, alcohol use, baseline depressive symptoms, physical activity, body mass index, prior hormone therapy, high cholesterol requiring medication, hypertension, diabetes mellitus (treated or not), history of cardiovascular disease (based on self-report of prior myocardial infarction, angina, coronary revascularization, cardiac arrest, congestive heart failure, cardiac catheterization, carotid endarterectomy, atrial fibrillation, or aortic aneurysm), stroke or transient ischemic attack, hormone therapy assignment in Women's Health Initiative Memory Study, and baseline Modified Mini-Mental State Examination score.

Abbreviations: HR = hazard ratio; CI = confidence interval.

Table 3

Hazard ratio (95% CI) of developing adverse cognitive outcomes according to antidepressant classes versus no antidepressant

COGNITIVE OUTCOME	ANTIDEPRESSANT USE BY CLASS			
	SSRI (N = 170)	TCA (N = 160)	OTHER/MULTIPLE ANTIDEPRESSANTS (N = 53)	NO ANTIDEPRESSANTS (N = 6,615)
Mild cognitive impairment				
Number (%) of cases	15 (9)	13 (8)	3 (6)	300 (5)
Unadjusted HR (95% CI)/p-value	2.18 (1.30–3.66)/0.003	1.93 (1.11–3.37)/0.02	1.40 (0.45–4.36)/0.56	
Adjusted HR (95% CI)/p-value *	1.78 (1.01–3.13)/0.05	1.78 (0.99–3.21)/0.05	1.23 (0.39–3.90)/0.73	
Probable dementia				
Number (%) of cases	6 (4)	8 (5)	2 (4)	200 (3)
Unadjusted HR (95% CI)/p-value	1.32 (0.59–2.98)/0.50	1.82 (0.90–3.69)/0.10	1.43 (0.36–5.77)/0.61	
Adjusted HR (95% CI)/p-value *	0.96 (0.38–2.41)/0.93	1.77 (0.85–3.67)/0.13	0.75 (0.17–3.40)/0.71	
Mild cognitive impairment or probable dementia				
Number (%) of cases	17 (10)	17(11)	4(8)	433 (7)
Unadjusted HR (95% CI)/p-value	1.73 (1.06–2.80)/0.03	1.78 (1.09–2.88)/0.02		
Adjusted HR (95% CI)/p-value *	1.50 (0.89–2.53)/0.13	1.75 (1.05–2.91)/0.03	1.30 (0.49–3.48)/0.60	1.12 (0.41–3.05)/0.82

* Fully adjusted for age, ethnicity, education, family income, and marital status, smoking, alcohol use, baseline depressive symptoms, physical activity, body mass index, prior hormone therapy, high cholesterol requiring medication, hypertension, diabetes mellitus (treated or not), history of cardiovascular disease (based on self-report of prior myocardial infarction, angina, coronary revascularization, cardiac arrest, congestive heart failure, cardiac catheterization, carotid endarterectomy, atrial fibrillation, or aortic aneurysm), stroke or transient ischemic attack, hormone therapy assignment in Women's Health Initiative Memory Study, and baseline Modified Mini-Mental State Examination score.

Abbreviations: HR = hazard ratio; CI = confidence interval; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants.

Table 4

Hazard ratio (95% CI) of developing adverse cognitive outcomes according to baseline depression and antidepressant use versus neither

COGNITIVE OUTCOME	BASELINE DEPRESSION/ANTIDEPRESSANT USE			
	DEPRESSED/USER (N = 92)	DEPRESSED/NON-USER (N = 456)	NOT DEPRESSED/ USER (N = 291)	NOT DEPRESSED/ NON-USER (REFERENCE GROUP) (N = 6159)
Mild cognitive impairment				
Number (%) of cases	11 (12)	38 (8)	20 (7)	262 (4)
Unadjusted HR (95% CI)/p-value	2.98 (1.63–5.44)/0.0004	2.11 (1.50–2.96)/<0.0001	1.82 (1.15–2.86)/0.01	
Adjusted HR (95% CI)/p-value *	2.44 (1.24–4.80)/0.01	1.62 (1.13–2.32)/0.009	1.79 (1.13–2.85)/0.01	
Probable dementia				
Number (%) of cases	5 (5)	20 (4)	11 (4)	180 (3)
Unadjusted HR (95% CI)/p-value	1.92 (0.79–4.66)/0.15	1.62 (1.02–2.57)/0.04	1.50 (0.82–2.76)/0.19	
Adjusted HR (95% CI)/p-value *	1.21 (0.43–3.43)/0.72	1.50 (0.92–2.44)/0.10	1.45 (0.78–2.72)/0.24	
Mild cognitive impairment or probable dementia				
Number (%) of cases	13 (14)	48 (11)	25 (9)	385 (6)
Unadjusted HR (95% CI)/p-value	2.41 (1.39–4.19)/0.002	1.82 (1.35–2.46) /<0.0001	1.56 (1.04–2.34) /0.0306	
Adjusted HR (95% CI)/p-value *	2.34 (1.27–4.32)/0.006	1.65 (1.20–2.26)/0.002	1.60 (1.06–2.41)/0.03	

* Fully adjusted for age, ethnicity, education, family income, and marital status, smoking, alcohol use, physical activity, body mass index, prior hormone therapy, high cholesterol requiring medication, hypertension, diabetes mellitus (treated or not), history of cardiovascular disease (based on self-report of prior myocardial infarction, angina, coronary revascularization, cardiac arrest, congestive heart failure, cardiac catheterization, carotid endarterectomy, atrial fibrillation, or aortic aneurysm), stroke or transient ischemic attack, hormone therapy assignment in Women's Health Initiative Memory Study, and baseline Modified Mini-Mental State Examination score.

Abbreviations: HR = hazard ratio; CI = confidence interval.