

Antidepressant Treatment and Worsening White Matter on Serial Cranial Magnetic Resonance Imaging in the Elderly The Cardiovascular Health Study

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Background and Purpose—In some studies, late life depression is associated with white matter lesions on MRI. The effect of different classes of antidepressants on progression of white matter lesions is unknown. Selective serotonergic reuptake inhibitors (SSRIs) may decrease platelet aggregation. We hypothesized that Cardiovascular Health Study participants taking SSRIs would less often have worsening white matter on serial MRI than participants not on antidepressants.

Methods—Among 1826 participants who were not using an antidepressant at initial MRI scan, we examined the association of worsening in white matter grade from initial to follow-up MRI scans, 5 years apart on average, and antidepressant use between the scans. Logistic regression models were used, controlling for a variety of potential confounding variables.

Results—Use of any antidepressant during the period of study was associated with worsening white matter. In a multivariable model, risk was slightly increased, not reduced, with use of serotonergic agents (OR 1.36, 95% CI 0.87 to 2.12) and was significantly increased with the use of tricyclic antidepressants (OR 1.77, 95% CI 1.07 to 2.94).

Conclusions—The association between worsening white matter and use of tricyclic antidepressants was an unexpected finding that may relate to indications for use other than depression or to side effects such as hypotension. Protection against worsening was not seen with use of serotonergic agents. (*Stroke*. 2008;39:857-862.)

Key Words: antidepressant ■ depression ■ neuroimaging ■ serotonin ■ white matter

Late-life depression has been associated with vascular disease defined by brain MRI.¹⁻³ These findings have led to the development of the vascular depression hypothesis to explain etiology of depression in the elderly.^{4,5} In clinical samples, progression of MRI white matter lesions is related to lack of response to antidepressants or recurrence of depression.⁶ However, in these samples nearly all subjects received pharmacological treatment. The effect of antidepressant medications on progression of brain vascular disease defined by MRI is unclear. Selective serotonin reuptake inhibitors (SSRIs) are known to reduce platelet aggregation and may thus affect progression of brain vascular disease.⁷ A recent review of the influence of antidepressants on hemostasis notes that potent inhibitors of serotonin reuptake such as fluoxetine, paroxetine, and sertraline are associated with decreased platelet aggregability and activity and prolonged bleeding time.⁸ Non-SSRI antidepressants, including tricyclic antidepressants (TCAs), would be unlikely to positively affect progression, at least not through an antithrombotic mechanism. Indeed, in one study, risk of

myocardial infarction was increased with TCAs but not SSRIs.⁹ With the exception of clomipramine, TCAs have much lower serotonin transporter affinity compared with SSRIs,¹⁰ so much higher doses are needed, and such doses are uncommonly prescribed, especially in the elderly. TCAs may also have noradrenergic effects that could increase cardiovascular risk.¹⁰

The Cardiovascular Health Study (CHS) is a large multisite sample of individuals at risk for cardiovascular and cerebrovascular disease. A previous report found no association between depression score on the Centers for Epidemiological Studies Depression scale (CES-D) 10-item version and worsening white matter on serial MRIs.¹¹ In the present study, we examined the association between worsening white matter and antidepressant use in the CHS. In light of potential antithrombotic effects of SSRIs, we hypothesized that participants taking SSRIs and other serotonergic antidepressants in the period between the initial and follow-up MRI scans would be less likely to show worsening white matter compared with participants not taking antidepressants.

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Materials and Methods

The Population Sample

The CHS cohort of 5201 participants was enrolled from 1989 to 1990 with an additional 687 African Americans enrolled from 1992 to 1993. Details regarding the CHS study design and characteristics of the original CHS cohort have been published previously.^{12,13} All eligible participants had to be 65 years or older, able to give informed consent, and able to respond to questions without a proxy respondent. Among the eligible participants, 58% agreed to enroll in the study and underwent baseline evaluation. The present study included 1919 participants who agreed to have an initial MRI brain scan in 1991 to 1994 and a follow-up MRI brain scan in 1997 to 1999 (see MRI section below).

Classification of Antidepressants

As part of an annual clinical assessment, participants brought their prescription medication containers to the clinic, where interviewers transcribed the drug name, strength, and dosing instructions from the medication labels.¹⁴ The participants were then asked how many doses of each medication they actually took during the previous 2 weeks. Based on this information, we determined who used antidepressants in the interval between the scans and classified participants as using TCAs or serotonergic agents (SAs), which included SSRIs, trazodone, or nefazodone. In our study sample, 5 participants could not be classified in either group, 4 on bupropion (nontricyclic/nonserotonergic) and 1 on venlafaxine (mixed serotonergic/noradrenergic), and were excluded from analyses. In addition to these 5, 88 of the 1919 participants with 2 scans were taking an antidepressant at the time of the initial scan and were also excluded. Therefore, analyses included 1826 participants: 1663 having not used antidepressants between the scans, 88 having used only SAs, 60 having used only TCAs, and 15 having used both. In 103 participants having used SAs, only 11 participants had used non-SSRI serotonergic antidepressants.

Clinical Assessment

Functional impairment was assessed by participants' self-report of ability to perform tasks included in Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL). A modified version of the Health Interview Survey Supplement on Aging questionnaire was used to assess both ADL and IADL.¹⁵ The Modified Mini-Mental State examination (3MS)¹⁶ was used to measure cognitive status. Age at the time of the initial MRI was recorded. Educational level was obtained from participants at study entry. Hypertension, orthostatic hypotension, diabetes, smoking, and blood pressure were recorded as defined previously.¹¹ Depression was assessed using the shortened (10-item) version of the CES-D scale.¹⁷ Medical records were obtained and the information was evaluated by a physician panel using standard criteria to adjudicate cardiovascular disease events and stroke.^{18,19}

MRI Procedure

All members of the cohort were invited to have cranial MRI scans between January 1991 and May 1994, and of the 80% who agreed to do so, 95% successfully completed an MRI scan.^{20,21} A total of 3600 participants underwent the initial MRI scan. The CHS participants were again invited to have cranial MRI scans between May 1997 and December 1999, and 2317 participants completed a follow-up MRI scan. A total of 2116 participants underwent both scans, roughly 5 years apart.²²

The MRI scans were reviewed by trained readers blinded to clinical data. A white matter grade was estimated based on the total extent of white matter hyperintensity on the spin density images in the periventricular and subcortical white matter. Images were compared with 8 sets of reference images showing increasing total white matter hyperintensities. Grades were assigned based on these comparisons and ranged from 0 to 9, with a higher grade indicating more severe hyperintensities.^{23,24}

Pairs of initial and follow-up scans were reread in 2001 to 2002 in a side-by-side fashion to ascertain more precisely change in white matter grade. Raters were blinded as to the original grade and the order of the 2 MRI scans. Of the 2116 participants with 2 scans, a total of 1919 pairs of MRI scans were available with side-by-side readings of white matter grade.¹¹ Worsening white matter was defined as present if an increase by one or more white matter grades was evident between the initial and follow-up scans.

Statistical Approach

Our analyses focused on antidepressant use rather than on depression, as previous CHS studies have examined the effects of depression (using the 10-item CES-D) and white matter grade.^{11,25,26}

Characteristics of participants at the initial scan and longitudinal antidepressant use from initial to follow-up scans were summarized using either means or proportions.

Multivariate logistic regression was used to model worsening white matter (present or absent). Model covariates included SA use in the interval between the scans (yes/no), TCA use in the interval between scans (yes/no), MRI information (white matter grade at initial scan, time between scans), demographics (age, gender, race), 10-item CES-D score, cardiovascular risk factors at initial scan (diabetes, hypertension, systolic blood pressure, presence of orthostatic hypotension, prevalent transient ischemic attack, prevalent stroke, prevalent myocardial infarction), and functional and cognitive measurements (ADL, IADL, and 3MS). Unless noted otherwise, we presented results from the fully-adjusted model in this article.

The 15 participants who had used both SAs and TCAs were included in primary analyses, so the association of SA use was examined conditioning on TCA use and other confounders. Likewise, the association of TCA use was examined conditioning on SA use and other confounders. To explore the possibility that the associations of SA use and TCA use might be driven largely by these 15 participants, we performed a sensitivity analysis after excluding them. In this sensitivity analysis, the reference group for SA use and for TCA use was simply nonantidepressant users. Two additional sensitivity analyses were conducted. First, we noted that follow-up scans were available for only 2116 (70%) of 3105 participants who underwent the initial scan and who were alive at the time of the follow-up scan. Given the considerable missing data with respect to availability of the follow-up scan, we fitted a weighted logistic regression model to account for the missing data. The probabilities of completing a follow-up MRI scan, which were to be used for appropriate weights, were modeled as a function of age, gender, self-reported general health, and cardiovascular disease history (at the time of the follow-up MRI scan invitation) in the 3105 participants. This weighting approach is analogous to the use of sampling weights in survey data analysis. Second, duration of antidepressants between the 2 MRI scans was considered in an attempt to explore a dose-response relationship. We defined a relative duration variable as years of antidepressant use divided by years between scans, and we tested for significance of this duration variable.

Intercooled Stata (version 9.2; StataCorp LP, College Station, Texas) was used for analyses. All analyses were based on data available in the CHS database as of December 2005.

Results

Characteristics of the 1826 participants at the time of the initial MRI scan are shown in Table 1. The sample was about 59% female, 84% White, and had a mean age of 74. About 42% of the participants had hypertension, with fewer individuals reporting diabetes, prior myocardial infarction, transient ischemic attack, or stroke. About 8% of participants had any ADL difficulty, and about 19% had any IADL difficulty. Half of the participants had a white matter grade score of 2 or greater on the initial scan. Sample characteristics are also provided based on whether subjects used antidepressant medications in the interval between MRI scans.

Table 1. Descriptive Statistics of the Sample at Time of Initial MRI Scan

	Total	Worsening White Matter*		Antidepressant Use Between Scans	
		No	Yes	No	Yes
n	1826	1317	509	1663	163
Age, mean (\pm SD)	74.1 (\pm 4.4)	74.0 (\pm 4.5)	74.2 (\pm 4.2)	74.0 (\pm 4.5)	74.8 (\pm 4.3)
Women, %	58.8	58.8	58.7	57.7	69.3
White, %	83.6	83.4	84.1	83.3	86.5
CES-D score, mean (\pm SD)	4.5 (\pm 4.4)	4.4 (\pm 4.4)	4.5 (\pm 4.2)	4.2 (\pm 4.1)	6.9 (\pm 6.0)
Hypertension, %	41.8	41.7	42.2	41.7	42.9
Orthostatic hypotension, %	13.7	13.3	14.8	13.4	16.8
Diabetic, %	11.3	11.3	11.4	10.8	16.6
Current smoking, %	8.5	7.9	10.0	8.2	11.7
Prevalent myocardial infarction, %	7.8	8.0	7.1	7.5	11.0
Prevalent transient ischemic attack, %	2.0	2.0	2.2	1.8	4.3
Prevalent stroke, %	3.0	2.9	3.1	2.7	5.5
Any ADL difficulty, %	8.5	9.4	6.3	8.2	12.3
Any IADL difficulty, %	18.6	19.3	16.9	17.2	33.1
3MS score, mean (\pm SD)	92.6 (\pm 6.4)	92.7 (\pm 6.4)	92.4 (\pm 6.3)	92.7 (\pm 6.4)	92.1 (\pm 6.7)
WMG on initial scan, %					
0	16.7	17.7	14.2	17.3	11.0
1	32.9	35.6	25.9	32.8	34.4
2	24.3	23.2	27.1	24.2	24.5
3	13.8	12.7	16.7	13.8	14.1
4 to 9	12.3	10.9	16.1	12.0	16.0
Median WMG (Interquartile range)	2 (1, 3)	1 (1, 2)	2 (1, 3)	1 (1, 3)	2 (1, 3)

CES-D indicates Centers for Epidemiological Studies, depression scale 10-item version; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; 3MS, Modified Mini-Mental State; WMG, white matter grade.

*Worsening white matter was defined as present if an increase by 1 or more white matter grades was evident between the initial and follow-up MRI scans.

Worsening white matter was documented in 450 (27.1%) of 1663 participants who did not use antidepressants between the 2 scans, compared with 59 (36.2%) of 163 antidepressant users. Worsening occurred in 29 (33.0%) of 88 participants who only used SAs, in 21 (35.0%) of 60 who only used TCAs, and in 9 (60.0%) of 15 who used both.

Table 2 shows the results from a series of logistic regression models examining the association of SA use and TCA use with worsening white matter. In the fully adjusted logistic regression model, we found an insignificant (but positive) association with SA use (OR=1.36, 95% CI=0.87 to 2.12) and a significant association with TCA use (OR=1.77, 95% CI=1.07 to 2.94). Although the estimated association of TCA use was approximately twice as large as that of SA use, we noted widely overlapping confidence intervals for SA use and TCA use, and a postestimation test revealed no significant difference in the coefficients of SA use and TCA use ($P=0.46$).

The sensitivity analyses generally yielded similar results. In the weighted logistic regression model, the odds ratio for SA use was 1.36 (95% CI=0.86 to 2.16), and the odds ratio for TCA use was 1.68 (95% CI=1.001 to 2.82). When the duration variables were considered instead of binary indicators for TCA use and for SA use, we found a significant

association for TCA use ($P=0.004$) but not for SA use ($P=0.99$). When the 15 participants who had used both TCAs and SAs between the MRI scans were excluded, the odds ratio for SA use was 1.27 (95% CI=0.79 to 2.05) and for TCA use was 1.61 (95% CI=0.91 to 2.84).

When we repeated the analysis after excluding non-SSRI serotonergic agent users ($n=11$), the odds ratios for SSRI use was 1.30 (95% CI=0.81 to 2.08) and the odds ratio for TCA use was 1.84 (95% CI=1.11 to 3.06).

We performed two sets of post-hoc analyses to try to understand the finding for TCA use. First, we wanted to examine whether the effect of TCA use on worsening white matter might have been related to indication for the TCA use. For instance, TCAs may have been used for treatment of certain pain syndromes, eg, diabetic neuropathy. If painful neuropathy is a proxy for severity of diabetes and these individuals were on TCAs, severity of diabetes may in part explain the worsening white matter in this group. In the analysis in which 207 participants with prevalent diabetes at initial MRI scan were excluded, the odds ratio for TCA use reduced from 1.77 to 1.52 and was no longer significant ($P=0.16$). Second, we sought to determine whether the relationship with TCA and worsening white matter might be explained by orthostatic hypotension. In the analysis in which

Table 2. Results of Logistic Regression of Worsening White Matter

Model	OR (95% CI)	P Value
Model A (n=1826)		
SA use	1.35 (0.87, 2.08)	0.18
TCA use	1.78 (1.09, 2.91)	0.02
Model B (n=1801)*		
SA use	1.34 (0.87, 2.09)	0.19
TCA use	1.74 (1.06, 2.86)	0.03
Model C (n=1801)*		
SA use	1.36 (0.87, 2.12)	0.17
TCA use	1.77 (1.07, 2.94)	0.03

SA indicates serotonergic agent; TCA, tricyclic antidepressant; OR, odds ratio; CI, confidence interval.

Covariates in Model A: SA use (yes/no) between scans, TCA use (yes/no) between scans, MRI information (time between scans, white matter grade at initial scan), Demographics (age, gender, and race), and 10-item CES-D score.

Covariates in Model B: Covariates in Model A, cardiovascular risk factors (diabetes, hypertension, systolic blood pressure, orthostatic hypotension, smoking, prevalent cardiovascular diseases).

Covariates in Model C: Covariates in Model B, functional and cognitive measures (ADL difficulty, IADL difficulty, 3MS score).

*Smaller sample sizes for Models B and C attributable to 25 subjects missing data on the diabetes and orthostatic blood pressure variables.

248 participants with orthostatic hypotension at initial MRI scan were excluded, the odds ratio for TCA use was reduced from 1.77 to 1.65 and was no longer significant ($P=0.07$).

Discussion

In this study, we did not find less frequent worsening white matter among SA users compared with nonusers of antidepressants as we hypothesized. We in fact observed a statistically insignificant effect of SA use in a direction opposite to our hypothesis. However, we did find that TCA users were more likely to experience worsening white matter compared with non-users of antidepressants. We note that a previous CHS study found no link between depression score and worsening white matter.¹¹

Although one should be cautious about implying a causal link, the association between worsening white matter and TCA use may be in part a specific effect of this antidepressant drug class. A prior study found that TCAs but not SSRIs were associated with myocardial infarction.⁹ In one study of SSRIs and stroke, the investigators found no association between SSRI use and either hemorrhagic stroke (odds ratio=1.0) or ischemic stroke (odds ratio=1.1).²⁷ TCAs are associated with cardiovascular effects, including an increase in heart rate and orthostatic hypotension.²⁸ Repeated drops in blood pressure may cause damage to the white matter. In contrast, SSRIs do not appear to cause orthostatic hypotension.²⁸ In a post-hoc analysis, inclusion of orthostatic hypotension in models weakened our results for TCA users, as would be expected if the effect of TCAs on worsening white matter was mediated in part through orthostatic hypotension. However, the loss of significance in this instance may also have been due to loss of statistical power resulting from removal of 207 participants.

The presence of clinically significant depression itself may increase risk of cardiovascular events. For example, in the Women's Health Initiative Observational Study, among 93 676 women, those with depressive symptoms were at greater risk to experience cardiovascular disease events, and depression was an independent predictor of CVD death (relative risk, 1.50) and all-cause mortality (relative risk, 1.32) after adjustment for age, race, education, income, diabetes, hypertension, smoking, high cholesterol level requiring medication, body mass index, and physical activity.²⁹ In this study, the authors noted that taking antidepressant medications did not alter the depression-associated cardiovascular risks.

Another explanation for the association may relate to indication for TCA use. For example, when we removed 207 individuals with diabetes to account for the possibility that some may have used TCAs for treatment of painful diabetic neuropathy, the odds ratio for worsening white matter and TCA use was slightly reduced (from 1.77 to 1.52). Although we carried out this post-hoc analysis, our data are limited in that we did not have information about reasons for taking certain antidepressants. Another condition that future studies might address is migraine headaches, which are associated with both MRI hyperintensities³⁰ and with antidepressant use.³¹ As with TCAs, we are not clear on why participants would be using SAs. Certainly the SSRIs are likely to be used for depression, but they may also have been used for anxiety. Trazodone is commonly used for sleep, either by itself or in addition to another antidepressant in the context of depression. Removing participants taking trazodone from subsequent analyses did not appreciably alter our results. Future studies will be needed to examine more closely the issue of antidepressant use versus antidepressant indication and worsening white matter. Finally, participants may be prescribed TCAs if their depression is more severe, and such individuals may have more severe cerebrovascular disease.

Both TCAs and SSRIs have been used in patients with cerebrovascular disease. A recent study of randomly assigned stroke patients to a 12-week double-blind course of nortriptyline, fluoxetine, or placebo early in the recovery period after a stroke.³² The authors found that 50 of 104 patients (48.1%) had died by the time of the 9-year follow-up. Of 53 patients who were given a full dose of either antidepressant, 36 (67.9%) were alive at follow-up, compared with only 10 (35.7%) of 28 placebo-treated patients, a significant difference. A recent review has suggested use of SSRIs in post-stroke depression, and has cautioned against the use of some TCAs because of increased risk of orthostatic hypotension and cardiac arrhythmias.³³

The antithrombotic properties of SSRIs have come under greater scrutiny in the past few years. SSRIs have been implicated in bleeding disorders,³⁴ particularly in gastrointestinal bleeding among elderly patients.³⁵ A recent systematic literature review identified increased bleeding risk in patients treated with an SSRI.³⁶ SSRI use did not increase risk of intracerebral hemorrhage.³⁷ However, SSRI use was not found to decrease the risk of developing first-time acute myocardial infarction³⁸ or ischemic stroke.²⁷ The SSRI ser-

traline has been shown to be safe and effective in patients with recent myocardial infarction.³⁹

The large cohort of elderly people, the systematic brain imaging with MRI, and the medication ascertainment are all strengths of the present study, but it also has several limitations. These include the relatively small sample size of individuals on antidepressants, as well as the lack of data on why participants were taking them and for what duration. Another limitation relates to the time between data collection points and onset of worsening white matter. For example, with an interval of approximately 5 years between initial and follow-up MRI scan, we are unable to determine with any precision the time of change in the white matter grade. This fact in turn limits our ability to perform more sophisticated analyses, such as with time-dependent variables. We are also unable to capture interval development and course of depression during this time period.

A final concern is possible selection bias in reference to the cohort for this study. We focused on CHS participants who were able to undergo 2 MRI scans. As previously noted, participants in the CHS are healthier than the general population of elderly people.¹¹ Subjects who were alive at follow-up and able to undergo a follow-up MRI scan are likely to be healthier than the general elderly population. One cannot predict precisely the effect of selective survivorship and participation in this study that required survival through the time of the follow-up MRI. For example, those with the most dramatic worsening white matter may have been more likely to die over the 5 years or become disabled and not continue to participate. Future studies are needed to sort out these issues.

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Disclosures

Dr Steffens is on the Speaker's bureau and has received honoraria from Forest Pharmaceuticals and Wyeth Pharmaceuticals. Dr Krishnan serves as a consultant to the following companies: Amgen, Bristol-Myer Squibb, CeNeRx, Corcept, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, Organon, Pfizer, Sepracor, and Wyeth. Drs Burke, Carlson, Chung, and Longstreth do not report any potential conflicts.

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