Inhibition of Serotonin Reuptake by Antidepressants and Cerebral Microbleeds in the General Population

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Background and Purpose—Serotonin reuptake inhibiting antidepressants decrease platelet aggregation. This may cause an increased risk of intracerebral hemorrhage. However, the risk of subclinical microbleeds, which are highly prevalent in middle-aged and elderly people, is unknown. We studied whether serotonin reuptake inhibiting antidepressants increase the frequency of cerebral microbleeds and secondarily whether they lower the presence of ischemic vascular damage.

Methods—Within the population-based Rotterdam Study, information on antidepressant use was obtained from continuously monitored pharmacy records. Brain MRI was available in 4945 participants (55% women, mean age 64 years) between 2005 and 2011. We categorized antidepressants based on affinity for the serotonin transporter: high, intermediate, or low. Microbleeds (presence and location) and ischemic lesions (lacunes, white matter lesions) were rated on MRI. Logistic and linear regression, adjusted for age, sex, depressive symptoms, and cardiovascular risk were used to study the association of antidepressants with microbleeds and ischemic vascular lesions.

Results—Antidepressant use with strong serotonin reuptake inhibition was not associated with microbleed presence (odds ratio compared with nonuse, 1.03; confidence interval, 0.75–1.39) irrespective of microbleed location in the brain. Exclusion of antithrombotic users or persons with cortical infarcts did not change our results. Furthermore, serotonin reuptake inhibition was not related to ischemic vascular brain damage.

Conclusions—In the general population, use of serotonin reuptake inhibiting antidepressants is not related to presence of cerebral microbleeds. This strengthens the idea that the platelet inhibitor effects of antidepressant drugs with affinity for serotonin are minimal and further supports the safety of selective serotonin reuptake inhibitors for nongastrointestinal bleedings. (Stroke. 2014;45:1951-1957.)

Key Words: antidepressive agents ■ cerebral small vessel diseases ■ serotonin

See related article, p 1917.

The use of antidepressant medication in the general population has increased considerably in past decades, in particular the use of selective serotonin reuptake inhibitors (SSRIs).1,2 This increase in SSRI use may be explained by a broadened indication of SSRI, a different adverse effect profile, and a lower toxicity compared with classic tricyclic antidepressants.1-3

Yet, despite a more favorable adverse effect profile, the use of SSRIs is not entirely risk free.4-9 SSRIs block the reuptake of serotonin by platelets and decrease serotonin platelet concentration, which may lead to impaired aggregation and prolonged bleeding times.10-14 SSRIs have, therefore, extensively been studied in relation to intracerebral hemorrhages,15-22 and a recent meta-analysis of controlled observational studies showed an increased risk of intracerebral hemorrhages in SSRI users compared with nonusers.23

In addition, via the same pathophysiological pathway of reducing platelet aggregation, antidepressants with a high inhibition for serotonin reuptake may also reduce the risk of ischemic stroke, although to date this hypothesis is scarcely supported by literature.15,16,21-24,25

Apart from major cerebrovascular events, it has not yet been investigated whether SSRIs or strong inhibitors of serotonin reuptake are associated with subclinical cerebrovascular lesions and more particularly with subclinical bleedings. Cerebral microbleeds have increasingly been recognized on MRI in stroke patients and mostly in association with larger intracerebral hemorrhages.26-28 Yet, microbleeds are also highly prevalent in the general population, and microbleeds may...
similarly represent bleeding-prone vessels in these people. Support for this is provided in our previous studies in which we showed an association between antiplatelet drugs use and the presence of cerebral microbleeds in the general population.9,30

Given the association of microbleeds with symptomatic bleeds and antiplatelet drug use, we hypothesized that people who use antidepressants with a great inhibition of serotonin reuptake may have a higher prevalence of cerebral microbleeds than nonusers and users of antidepressant with a low serotonin affinity. Moreover, we secondarily investigated whether the use of these drugs is associated with the presence of ischemic vascular damage on MRI, in particular a lower frequency of lacunes of presumed vascular origin31 and lower white matter lesion (WML) volume.

Methods
Participants
The Rotterdam Study is a prospective population-based cohort study, within Ommoord, a suburb in Rotterdam, the Netherlands. The study comprises 14,926 participants and investigates the prevalence, incidence of, and risk factors for diseases in an aging population.32 The study started in 1990, and after baseline examination, follow-up assessments were conducted every 4 to 5 years including interviews and an extensive set of examinations. From 2005 onward, brain MRI was embedded within the core protocol of the Rotterdam Study to investigate age-related brain changes on imaging.33 The institutional review board approved the study. Between 2005 and 2011, 5735 participants visiting the study center in that period were eligible to undergo a brain MRI. After informed consent was signed, a total of 5074 nondemented people were scanned. After excluding participants in whom MRI was not completed (N=72) and scans with low quality (N=507), data on 4945 participants were available for analyses.

Assessment of Antidepressant Drug Use
We determined antidepressant drug use prior to brain MRI based on fully computerized pharmacy records from the 7 pharmacies in the Ommoord district. More than 99% of the participants have their drug prescriptions filled at these regional pharmacies. Medication records were continuously monitored from January 1, 1991, onward. Records included the date of prescribing, the total amount of drug units per prescription, the prescribed daily number of units, the product name of the drugs, and the anatomic therapeutic chemical code. The duration of treatment was calculated by counting the number of prescription days. The average prescribed daily dose was expressed in standardized defined daily doses calculated by summing up the total number of prescribed defined daily doses from all prescriptions divided by the total duration.

We classified antidepressants based on their degree of serotonin reuptake inhibition. The classification is based on the dissociation constant ($K_d$) for the serotonin transporter. A lower dissociation constant reflects a higher affinity for the serotonin transporter and, therefore, a higher inhibition of serotonin reuptake. Based on previous literature, we categorized antidepressants into high (paroxetine, clomipramine, sertraline, duloxetine, fluoxetine), intermediate (escitalopram, citalopram, imipramine, fluvoxamine, amitriptyline, venlafaxine), and low (desimipramine, opipramol, nor-triptiliny, doxepin, doxazosin, maprotiline, moclobemide, mianserin, trazodone, nefazodone, mirtazapine) degrees of serotonin reuptake inhibition.13,28-30 People who used multiple antidepressants from the different groups were excluded from the main analyses (n=268), to secure a pure exposure. These users were considered switchers and were analyzed in subsequent analyses.

Brain MRI and Assessments of MRI Markers
Brain MRI scans were performed on a 1.5-Tesla MRI scanner (GE Healthcare, Milwaukee, WI).31 Our multisquence MRI protocol included the following scans: T1-weighted, proton-density-weighted, T2-weighted, and fluid-attenuated inversion recovery.33 For microbleed detection, we used a custom-made accelerated 3-dimensional T2*-weighted gradient-recalled echo sequence with high spatial resolution and long echo-time to enhance the detection of microbleeds.39 Microbleeds were defined as focal areas of low signal intensity on T2*-weighted imaging. Their presence, location, and numbers were scored by 1 of 5 trained research physicians, with good intraobserver and interobserver agreement.40 We categorized microbleeds based on their presumed underlying cause into lobar microbleeds (presumably reflective of cerebral amyloid angiopathy) and deep or infratentorial microbleeds (presumably reflective of hypertensive arteriopathy).39 Lacunes and cortical infarcts were rated on fluid-attenuated inversion recovery, proton-density-weighted, and T1-weighted sequences by the same raters of microbleeds. Lacunes were defined as focal lesions between ≥3 and <15 mm in size.40 Infarcts showing involvement of gray matter were classified as cortical infarcts. Brain tissue was segmented into gray matter, white matter, and cerebrospinal fluid, using validated automated postprocessing steps that include conventional k-nearest-neighbor brain tissue classifier extended with WML segmentation.41,42

Assessment of Covariables
We addressed potential confounders by characterizing depressive symptoms, cardiovascular risk factors, and cardiovascular medication use in our study population. Antidepressant drugs are mainly prescribed for depressive disorders. Depression has a bidirectional association with cardiovascular disease, and cardiovascular disease is related to the presence of microbleeds.43,44 Presence of depressive symptoms was evaluated using the Center for Epidemiological Studies Depression Scale.45 A score of 16 or higher was indicative of participants with clinically relevant depressive symptoms. A high sensitivity for major depression for this score was reported in older adults in the Netherlands.46

Participants’ cardiovascular risk was assessed during the center visit preceding MRI, using interview, laboratory, and physical examinations.9 This included presence of diabetes mellitus, smoking status (ever versus never), serum total cholesterol levels, serum high-density lipoprotein cholesterol levels, and systolic and diastolic blood pressure. Finally, use of lipid-lowering drugs (C10), antihypertensive drugs (C02, C03, C07, C08, and C09), and antithrombotic drugs (B01AA, B01AB, B01AC, and B01AX) was assessed from pharmacy records during follow-up before MRI.

Statistical Analysis
We analyzed the association between use of antidepressants, their degree of serotonin reuptake inhibition (high, intermediate, low) with the presence of cerebral microbleeds (present versus absent) using multiple logistic regression, taking nonusers as reference category. Analyses were repeated for microbleeds at different locations in the brain, namely strictly lobar regions and deep or infratentorial regions (with or without lobar microbleeds). Furthermore, we repeated all analyses using low and intermediate serotonin reuptake inhibition antidepressant users as reference category. Switchers were excluded from the main analyses, and the subsequent analyses were repeated including switchers.

All analyses were adjusted for age and sex. We additionally adjusted for presence of depressive symptoms, diabetes mellitus, smoking, total and high-density lipoprotein cholesterol, systolic and diastolic blood pressure, use of lipid-lowering medication, antihypertensive medication, and antithrombotic agents. Sensitivity analyses were performed with exclusion of MRI-defined cortical infarcts or exclusion of antithrombotic drug users. Moreover, analyses were stratified for sex, the exposure was dichotomized based on the duration of treatment (cutoff was 90 days), and interaction tests with antithrombotic drug users were performed. The average prescribed daily dose, expressed in standardized defined daily dose, was also studied dichotomized on 1.00 defined daily dose as the cutoff to look at an effect of dose.
Furthermore, we studied the association between the degree of serotonin reuptake inhibition of antidepressants and the presence of lacunes and WML volume with, respectively, multiple logistic and linear regression. People with cortical infarcts were excluded from these analyses. Analyses were adjusted for the same factors as described above. Analyses of WML volume were additionally adjusted for intracranial volume. WML was log-transformed because of the skewed distribution.

We considered a P value <0.05 as statistically significant, and analyses were performed with a commercially available software program (IBM SPSS Statistics for Windows, Version 21.0).

**Results**

Characteristics of the study population are presented in Table 1 and Table I in the online-only Data Supplement. Mean age was 64.0 years (SD, 11.0), and 2724 (55.1%) were women. A total of 930 (18.8%) persons had a history of antidepressant use before MRI, and 311 (6.2%) had exclusively used antidepressants with a high degree of serotonin reuptake inhibition, 304 (6.1%) of an intermediate, and 47 (1.0%) antidepressants of a low degree. Among users, 268 (5.4%) switched between the different antidepressant drug categories. In the total study population, 957 (19.4%) had microbleeds, of whom 629 had strictly lobar and 328 deep or infratentorial microbleeds. In the group of antidepressant drug users (n=930), 18.9% had microbleeds, which did not significantly differ from the 19.5% in the population of nonusers. Of all participants in our study, lacunes were present in 370 (7.5%), and median WML volume was 3.0 mL.

Compared with nonuse, the use of antidepressants with a high serotonin reuptake inhibitory potential was not associated with cerebral microbleed presence (age, sex-adjusted odds ratio [OR], 1.03; 95% confidence interval [CI], 0.75–1.39). In addition, no association was found for low (OR, 0.76; 95% CI, 0.36–1.62) or intermediate (OR, 1.04; 95% CI, 0.77–1.39) serotonin affinity antidepressants. Compared with nonuse, the use of antidepressant medication with high, intermediate, or low affinity for serotonin was neither related to lobar nor to deep or infratentorial microbleeds (Table 2). Additionally, no association between antidepressant use and microbleeds was found for people who switched between different antidepressant drugs (OR, 0.95; 95% CI, 0.68–1.33). Additional adjustments for cardiovascular risk factors, cardiovascular medication, and depressive symptoms did not change any of the results significantly (Table 2). Excluding participants with MRI-defined cortical infarcts (n=158) and excluding ever antithrombotic drug users (n=1326) also did not significantly change our results (data not shown). Moreover, the exposure split by duration and average prescribed daily dose of antidepressant drug treatment and stratification by sex did not significantly change our results (data not shown). Effect modification of antidepressant drug exposure by antithrombotic drugs was not present (P=0.96).

We did not find a higher frequency of cerebral microbleeds, irrespective of their location in the brain, when comparing the high affinity group with the combined intermediate and low affinity group (OR, 1.03; 95% CI, 0.68–1.56; Table 3).

Finally, we did not find a lower frequency of lacunes (OR, 1.14; 95% CI, 0.67–1.94) nor a smaller WML volume (mean difference of WML volume: 0.06; 95% CI, −0.16–0.28) for use of antidepressants with a high serotonin reuptake inhibition potential compared with nonuse, neither did we find a relation when investigating the use of low and intermediate degree of serotonin reuptake inhibition (Table 4).

**Discussion**

In the general population, we did not find an association between antidepressant drug use with a greater inhibition of serotonin reuptake and the presence of cerebral microbleeds. In addition, the degree of serotonin reuptake inhibition was not associated with presence of lacunes or WML volume.

Microbleeds are thought to precede the onset of large symptomatic hemorrhages, and may thus reflect a clinically relevant preclinical imaging marker, although evidence from longitudinal studies is still limited.55,56,41 The novelty of our study lays in the fact that we investigated the use of SSRIs in relation to subclinical hemorrhagic brain lesions in the general population, in contrast to clinical studies investigating symptomatic hemorrhage. We did not observe an association between degree of serotonin reuptake inhibition and the presence of microbleeds. This is in line with the majority of previous
Intracellular serotonin is subsequently released into the blood and stimulates the production of gastric acid, which increases intestinal bleedings. Here, SSRI use increases serotonin levels associated with extracranial bleeds, in particular gastrointestinal bleedings. Nonetheless, for both mechanisms, we could argue that diminishing intraplatelet serotonin levels only affects hemostasis to a limited extent and thus that remaining platelet function is sufficient to halt significant bleeding. Depletion of serotonin levels in platelets may well be compensated for by other adequately working hemostatic mechanisms. This would partly explain why SSRI use was more consistently associated with extracranial bleeds, in particular gastrointestinal bleedings. Here, SSRI use increases serotonin levels and stimulates the production of gastric acid, which increases the risk of gastrointestinal bleedings. Bleeding complications may, therefore, be induced by a third mechanism, which does not necessarily involve platelet dysfunction.

No association was found for antidepressants with an affinity for serotonin with microbleeds in either lobar or deep or infratentorial regions of the brain. Although microbleeds at both locations are representative of bleeding-prone
vessels, their causes differ. Microbleeds in lobar regions are more likely to result from blood leaking from destructed vessel walls containing amyloid, whereas deep or infratentorial microbleeds most likely represent hemosiderin deposits as a consequence of hypertensive arteriopathy.\textsuperscript{28,40,43,51} Our findings suggest that regardless of the underlying pathology, the decrease of intracellular serotonin platelets caused by antidepressants with a strong serotonin reuptake potential is insufficient to increase the frequency of small, asymptomatic bleedings.

Finally, we did not find a protective effect of antidepressant drugs, with a high affinity for the serotonin transporter, on ischemic vascular brain lesions. This is in line with findings from previous studies in patients with ischemic stroke\textsuperscript{15,21} and strengthens the idea that the platelet inhibitor effects of antidepressant drug with affinity for serotonin are minimal. Two previous studies showed an increased risk of ischemic stroke in current SSRI users.\textsuperscript{16,24} This increased risk could be explained by a different biological mechanism, which postulates that serotonin induces vasoconstriction of large vessel, and may lead to thromboembolic ischemic stroke in the presence of atherosclerosis.\textsuperscript{35} However, in our study, we focused on silent ischemic vascular lesions, involving the small cerebral arteries, which are typically not caused by thromboembolic events.

The strengths of our study are the large sample size, population-based character of our study, and the prospectively gathered electronic pharmacy records that we used to determine antidepressant drug use. Based on a 19.5% prevalence of microbleeds in unexposed subjects, with a 2-sided significance of 0.05, we had sufficient power (80%) to detect an OR of 1.22 or greater. Less strong associations may not have been detected in our study, although based on the recent meta-analysis on SSRIs and symptomatic brain hemorrhages we would expect an estimate of at least this magnitude for subclinical bleedings.\textsuperscript{33} Some limitations of our study need to be considered. The cross-sectional design of our study limits our conclusions on a causal pathway. MRI does not provide information on the timing of when cerebral microbleeds occurred because cerebral microbleeds remain visible in the brain for an undefined period. Therefore, there is a possibility that cerebral microbleeds occurred before antidepressant use was initiated. This may have led to an underestimation of the true association presented because of nondifferential misclassification of SSRI users, and further longitudinal investigations are warranted.

Furthermore, confounding by indication and contraindication poses a problem in our observational study. Depression, the most important indication to prescribe antidepressants, has a bidirectional association with cardiovascular disease, and cardiovascular diseases are associated with an increased number of microbleeds. Moreover, tricyclic antidepressants are relatively contraindicated for patients with cardiovascular disease. We minimized these forms of confounding by adjusting for presence of depressive symptoms, cardiovascular risk factors, and cardiovascular medication. Also, we reclassified the antidepressant drugs based on their affinity to the serotonin reuptake transporter. Although we aimed to address all potential confounders in our study, residual confounding cannot be ruled out and may have affected our results to an extent that associations may have been overestimated.

In conclusion, this study adds important information to the previous reports on antidepressant drug use and bleeding risk. We report that, in the general population, the use of antidepressant drugs that inhibit serotonin reuptake is not related

### Table 4. Degree of Serotonin Reuptake Inhibition for Antidepressant Drugs and the Presence of Lacunes and White Matter Lesion Volume

<table>
<thead>
<tr>
<th>Degree of Serotonin Reuptake Inhibition</th>
<th>Lacunes</th>
<th>White Matter Lesion Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuse</td>
<td>260/3888</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Low</td>
<td>3/45</td>
<td>0.82 (0.25 to 2.74)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>23/288</td>
<td>1.20 (0.76 to 1.90)</td>
</tr>
<tr>
<td>High</td>
<td>16/298</td>
<td>1.14 (0.67 to 1.94)</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuse</td>
<td>247/3728</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Low</td>
<td>3/43</td>
<td>0.89 (0.26 to 3.02)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>22/275</td>
<td>1.13 (0.70 to 1.82)</td>
</tr>
<tr>
<td>High</td>
<td>15/285</td>
<td>1.05 (0.60 to 1.86)</td>
</tr>
</tbody>
</table>

Lacunes: values represent odds ratios for lacunes in antidepressant drug users with low, medium, and high affinity for serotonin compared with nonusers. White matter lesion volume: values represent differences in mean log-transformed white matter lesion volumes (mL) in antidepressant drug users with low, medium, and high affinity for serotonin compared with nonusers. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, depressive symptoms, diabetes mellitus, smoking, total and high-density lipoprotein cholesterol, systolic and diastolic blood pressure, use of lipid-lowering drugs, antihypertensive drugs, and antithrombotic drugs. Number of cases/total population deviate from model 1 because we performed a complete caseset analysis. White matter lesion volume analyses were additionally adjusted for intracranial volume and participants with unreliable white matter lesion segmentations were excluded from analyses. CI indicates confidence interval; n, number of cases; and N, total population within the exposure category.
to the presence of cerebral microbleeds. This further supports the safety of these antidepressants for nongastrointestinal bleedings. Because these results are cross-sectional, further longitudinal research on antidepressant drug use and the risk of microbleeds in relation to major intracerebral hemorrhage is of high interest.

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Disclosures
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<table>
<thead>
<tr>
<th></th>
<th>Degree of serotonin reuptake inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-users</td>
</tr>
<tr>
<td></td>
<td>N=4015</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.0 (11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>2100 (52.3)</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>194 (4.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>337 (8.5)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2777 (69.4)</td>
</tr>
<tr>
<td>Presence of cerebral microbleeds</td>
<td>781 (19.5)</td>
</tr>
<tr>
<td>Strictly lobar</td>
<td>511 (13.6)</td>
</tr>
<tr>
<td>Deep or infratentorial</td>
<td>270 (7.7)</td>
</tr>
<tr>
<td>White matter lesion volume, mL</td>
<td>2.9 (1.6 – 6.4)</td>
</tr>
<tr>
<td>Lacunes</td>
<td>297 (7.4)</td>
</tr>
<tr>
<td>Cortical infarcts</td>
<td>127 (3.2)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.5 (1.1)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>139.4 (21.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>82.3 (10.9)</td>
</tr>
<tr>
<td>History of lipid lowering drug use</td>
<td>927 (23.3)</td>
</tr>
<tr>
<td>History of antihypertensive drug use</td>
<td>1315 (32.8)</td>
</tr>
<tr>
<td>History of antithrombotic drug use</td>
<td>1110 (27.6)</td>
</tr>
</tbody>
</table>

Values represent mean (standard deviation) or number (percentage). White matter lesion volume is represented as median (interquartile range). * Degree of serotonin reuptake inhibition: High=paroxetine, clomipramine, sertraline, duloxetine, fluoxetine. Intermediate = escitalopram, citalopram, imipramine, fluvoxamine, amitriptyline, venlafaxine. Low = desipramine, opipramol, nortriptyline, doxepin, dosulepin, maprotiline, moclobemide, mianserin, trazodone, nefazodone, mirtazapine.