Selective Serotonin Reuptake Inhibitors and Risk of Hemorrhagic Stroke

Jordan Kharofa, BS; Padmini Sekar, MS; Mary Haverbusch, RN, BSN; Charles Moomaw, PhD; Matthew Flaherty, MD; Brett Kissela, MD; Joseph Broderick, MD; Daniel Woo, MD, MS

Background and Purpose—Selective serotonin reuptake inhibitors (SSRI) are widely prescribed. Several reports have observed an increased bleeding risk associated with SSRI use, which is hypothesized to be secondary to their antiplatelet effect.

Methods—We tested the hypothesis that SSRIs increase the risk for or potentiate the risk of hemorrhagic stroke associated with antiplatelet and anticoagulants.

Results—In multivariate analysis, we found no increased risk associated with SSRI use for intracerebral stroke (odds ratio = 1.1, 95% CI: 0.7 to 1.8; \( P = 0.63 \)) or subarachnoid hemorrhage (odds ratio = 0.6, 95% CI: 0.4 to 1.0; \( P = 0.054 \)). In addition, potentiation of risk with warfarin or antiplatelets was not observed.

Conclusions—Further studies with larger populations would be needed to exclude a small increase in intracranial hemorrhage risk with SSRI use. (Stroke. 2007;38:3049-3051.)

Key Words: hemorrhage ■ SSRI ■ stroke

A pproximately 99 000 hemorrhagic strokes occur each year in the United States, accounting for 10% to 15% of all strokes.\(^1\) Known risk factors for hemorrhagic stroke include increasing age, prior ischemic stroke, hypertension, smoking, and treatment with anticoagulant and antiplatelet medications. Between 1988 and 2002, 67.6 million new patients were started on the selective serotonin reuptake inhibitors (SSRI) fluoxetine, paroxetine, and sertraline.\(^2\) Thus, a potential effect of SSRIs on bleeding risk is of major significance.

Serotonin is released by platelets at the site of vascular injury to promote clot formation. When the endothelial layer is damaged, platelets come in contact with subendothelial collagen, which leads to release of intracellular serotonin granules that promote clot formation. Platelets contain a serotonin reuptake transporter that is similar to in the brain. It has been demonstrated that SSRIs inhibit this transporter in platelets.\(^3,4\) One study demonstrated an 83% decrease in platelet serotonin concentrations after 2 weeks of therapeutic paroxetine administration.\(^4\) We tested the hypothesis that SSRIs increase the risk for hemorrhagic stroke and potentiate the risk associated with antiplatelet and anticoagulant drugs.

Methods

As part of our Genetic and Environmental Risk Factors for Hemor-
 rhagic Stroke study (NS36695), cases of intracerebral (ICH) and
 subarachnoid hemorrhage (SAH) were identified in the Greater
 Cincinnati region from May 1997 to August 2001 and from July
 2002 to October 2005\(^5\) through retrospective screening of all area
 emergency rooms and discharge ICD-9 codes and prospective
 screening of neurosurgery admissions at the busiest hospitals.
 Patients were approached for enrollment in a genetic sampling and
 interview arm. Subjects who agreed were matched by age, race,
 and gender to population-based controls by random digit dialing.
 All medications taken 2 weeks before index date were recorded.
 The index date for cases was the date of onset; for controls it was 1 to 2
 weeks before the interview, to avoid recall bias. SSRIs used for the
current analysis included citalopram, escitalopram, fluoxetine, par-
oxetine, and sertraline. Classification of antiplatelet drugs included
 aspirin, clopidogrel, and dipyridamole. Because of the small number
 of subjects on both nonaspirin antiplatelet drugs and SSRIs (5
 patients), the analysis was limited to aspirin alone.

Statistical Analysis

The data were managed and analyzed using SAS version 9.1 (SAS
Institute). Univariate and multivariable analysis for the association of
independent variables with stroke was achieved using a conditional
logistic modeling approach (PROC LOGISTIC). The multivariable
analysis used a backward elimination procedure for risk factors with
significance levels of \( P < 0.10 \). Interaction terms of SSRI with and
without aspirin or warfarin use were included into secondary models.

Results

During the study period, 2441 patients with ICH and 894
patients with SAH were identified, of which 500 ICH (20%) and
416 SAH (46.5%) cases were enrolled in the case-control
study. Comparison of interviewed and noninterviewed pa-
tients found that interviewed patients were younger for both
SAH (50.9 versus 57.7 years) and ICH (65 versus 70.2 years).
After adjustment for age, there was no significant difference in
the prevalence of hypertension, diabetes, heavy alcohol

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use, race, gender, or SSRI use between interviewed and noninterviewed patients with ICH or SAH. There was a trend toward higher rates of current smoking among interviewed SAH patients compared with noninterviewed patients (50.4 versus 43.5%; P = 0.054).

Of the 916 hemorrhagic stroke patients enrolled, 71 (7.8%) were on an SSRI at the time of stroke, and of 1776 demographically matched controls, 158 (8.9%) were on an SSRI. The Table presents the univariate and multivariate analysis of SSRI risk for all hemorrhages. After controlling for multiple risk factors, SSRI use was not independently associated with increased risk for hemorrhagic stroke (odds ratio [OR] = 0.8, 95% CI: 0.5 to 1.2; P = 0.25).

Of ICH and SAH subtypes, 44 and 27, respectively, were using an SSRI. Multivariate analyses revealed no increased risk associated with SSRI for ICH (OR = 1.1, 95% CI: 0.7 to 1.8; P = 0.63) or SAH (OR = 0.6, 95% CI: 0.4 to 1.0; P = 0.054). In interaction analysis, the use of SSRIs and warfarin did not confer a significantly greater risk of hemorrhagic stroke (OR = 4.7, 95% CI: 1.2 to 18.4) than warfarin alone (OR = 3.0, 95% CI: 1.8 to 5.0). The use of SSRIs and aspirin did not confer a significantly greater risk (OR = 0.9, 95% CI: 0.5 to 1.5) than aspirin alone (OR = 1.1, 95% CI: 0.8 to 1.3). After stratification by subtype, SSRI potentiation of aspirin was not observed for ICH (OR = 1.1 95% CI: 0.5 to 2.5) or SAH (OR = 0.4, 95% CI: 0.1 to 1.7).

**Discussion**

We did not find an increased risk of hemorrhagic stroke or its subtypes with SSRI use, nor did we find evidence that SSRIs potentiate the bleeding risk conferred by warfarin or aspirin. These results are important given the widespread use of SSRIs, the prior reports of systemic bleeding complications, and the specific use of SSRI for poststroke depression.

A growing number of case reports attribute bleeding events to SSRI use. Sites of bleeding include genitourinary, respiratory, and gastrointestinal systems.6–8 Two population-based cohort studies found SSRI users were more likely to be hospitalized for gastrointestinal bleeding than nonusers.9,10 Both studies found that the bleeding risk of aspirin was potentiated by SSRI treatment.9,10

Our results are in accordance with 2 prior reports which assessed intracranial bleeding risk associated with SSRIs.11,12 A nested case-control study in a cohort of antidepressant users found no association between SSRI use and intracranial hemorrhage.10 Although no increased risk of hemorrhage was observed, the study identified only 65 cases of hemorrhage of which 7 were exposed to SSRIs. Another nested case-control study based on information from a patient registry concluded that SSRI exposure was not a risk factor for ICH.12 The study included 21 ICH cases exposed to SSRI. Hypertension, diabetes, atrial fibrillation, and ischemic heart disease were adjusted for using drug prescriptions as proxy measures.

The present study includes a larger number of SSRI-exposed cases of hemorrhagic stroke (n = 71) and controls and a more comprehensive list of relevant risk factors. Our results strengthen the argument that SSRI use does not lead to an increased risk of hemorrhagic stroke. After an ischemic stroke, many patients experience depression and are frequently placed on an SSRI along with antiplatelet or anticoagulant drugs, and our findings provide reassurance that no major increase in hemorrhage risk is expected.

A limitation is that our study had 81% power to detect an OR of 1.6 or greater and a smaller risk may not have been detected. Although our interviewed cases were similar to noninterviewed cases, they were slightly younger. Thus, our study may miss an increased risk of hemorrhagic stroke with SSRI use among an older population.

Further study is needed to determine whether SSRI use increases the risk of hemorrhage among patients with a prior ischemic stroke or has a small effect on risk.

### Table. All Hemorrhagic Strokes: Univariate and Multivariate Risks

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. Cases, n (%)</th>
<th>No. Controls, n (%)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>71 (7.8)</td>
<td>158 (8.9)</td>
<td>0.9 (0.6–1.2)</td>
<td>0.300</td>
<td>0.8 (0.5–1.2)</td>
<td>0.254</td>
</tr>
<tr>
<td>Frequent alcohol</td>
<td>84 (9.2)</td>
<td>95 (5.2)</td>
<td>1.9 (1.4–2.6)</td>
<td>&lt;0.001</td>
<td>1.7 (1.2–2.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Warfarin</td>
<td>77 (8.4)</td>
<td>43 (2.4)</td>
<td>4.1 (2.7–6.3)</td>
<td>&lt;0.001</td>
<td>3.2 (2.0–5.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart disease</td>
<td>208 (22.7)</td>
<td>270 (15.2)</td>
<td>1.6 (1.3–2.0)</td>
<td>&lt;0.001</td>
<td>1.4 (1.1–1.8)</td>
<td>0.011</td>
</tr>
<tr>
<td>History of ischemic stroke</td>
<td>60 (6.7)</td>
<td>30 (1.7)</td>
<td>4.5 (2.8–7.2)</td>
<td>&lt;0.001</td>
<td>3.7 (2.1–6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>275 (6.6)</td>
<td>285.6 (6.6)</td>
<td>0.98 (0.96–0.99)</td>
<td>&lt;0.001</td>
<td>0.97 (0.96–0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>326 (35.6)</td>
<td>363 (35.7)</td>
<td>1.3 (1.1–1.6)</td>
<td>0.004</td>
<td>1.4 (1.1–1.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Untreated hypertension</td>
<td>200 (21.8)</td>
<td>135 (7.6)</td>
<td>3.9 (3.0–5.0)</td>
<td>&lt;0.001</td>
<td>3.5 (2.6–4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia with statin</td>
<td>125 (13.7)</td>
<td>328 (18.5)</td>
<td>0.6 (0.5–0.8)</td>
<td>&lt;0.001</td>
<td>0.5 (0.4–0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia with nonstatin</td>
<td>10 (1.1)</td>
<td>25 (1.4)</td>
<td>0.6 (0.3–1.4)</td>
<td>0.234</td>
<td>0.4 (0.1–0.9)</td>
<td>0.036</td>
</tr>
<tr>
<td>Untreated hypercholesterolemia</td>
<td>125 (13.7)</td>
<td>320 (18.0)</td>
<td>0.7 (0.5–0.8)</td>
<td>&lt;0.001</td>
<td>0.7 (0.5–0.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>362 (39.5)</td>
<td>433 (24.4)</td>
<td>2.2 (1.8–2.7)</td>
<td>&lt;0.001</td>
<td>1.8 (1.4–2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Former smoker</td>
<td>249 (27.2)</td>
<td>627 (35.3)</td>
<td>0.9 (0.7–1.1)</td>
<td>0.224</td>
<td>0.9 (0.7–1.1)</td>
<td>0.240</td>
</tr>
<tr>
<td>Less than high school education</td>
<td>218 (23.8)</td>
<td>193 (10.9)</td>
<td>3.2 (2.5–4.1)</td>
<td>&lt;0.001</td>
<td>2.7 (2.1–3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High school education</td>
<td>352 (38.4)</td>
<td>612 (34.5)</td>
<td>1.7 (1.4–2.0)</td>
<td>&lt;0.001</td>
<td>1.5 (1.2–1.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Disclosures
None.

References
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