

## Selective Serotonin Reuptake Inhibitors and Risk of Hemorrhagic Stroke: A Population-Based Case-Control Study

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**Background:** Selective Serotonin Reuptake Inhibitors (SSRI) are among the most widely prescribed classes of drugs. Several reports have observed an increased bleeding risk (gastrointestinal, respiratory, vaginal, and cerebral) associated with SSRI use, which is suspected to be due to their antiplatelet effect. In addition to its effects in the brain, serotonin is also used by platelets as a signaling molecule in the promotion of clot formation. SSRIs have been shown to decrease serotonin receptor activity, serotonin levels, and uptake in platelets. We tested the hypothesis that SSRIs increase the risk for hemorrhagic stroke and potentiate the risk of hemorrhagic stroke associated with antiplatelets and anticoagulants.

**Methods:** Cases of intracerebral (ICH) and subarachnoid hemorrhage (SAH) in the Greater Cincinnati region from 5/97 to 10/05 were identified by screening all area hospital admissions, emergency room logs, and discharge ICD-9 codes. 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. Medical records were reviewed for risk factors and medication use, including SSRIs, antiplatelet agents, anticoagulants, and statins. Logistic regression was used to determine the risk of significant factors to hemorrhagic stroke and subtypes of hemorrhagic stroke.

**Results:** Total enrollment included 916 patients with hemorrhagic stroke of which 71 (7.7%) were on an SSRI at the time of stroke and 1,776 age-, race-, and gender-matched controls of which 158 (8.8%) were on an SSRI. After controlling for smoking, hypertension, frequent alcohol use, heart disease, prior ischemic stroke, BMI, hypercholesterolemia, statin use, and education level, SSRI use was not independently associated with increased risk for hemorrhagic stroke ( $p=0.25$ ). Analysis of ICH and SAH separately revealed no increased risk of SSRI use for ICH (OR= 1.1 CI: 0.7-1.8;  $p=0.63$ ) or SAH (OR= 0.6 CI: 0.4-1.0;  $p=0.054$ ). In multivariate analysis, the use of SSRIs concomitantly with warfarin was not associated with a significantly greater risk of hemorrhagic stroke (OR = 4.7 CI: 1.2-18.4) than warfarin alone (OR= 3.0 CI: 1.8-5.0). Similarly, the use of SSRIs concomitantly with antiplatelets was not significantly greater in risk of hemorrhagic stroke (OR=0.8 CI: 0.5-1.5) than antiplatelets alone (OR=1.1 CI: 0.9-1.3).

**Conclusion:** Despite reports that SSRI use increases the risk of bleeding complications, we did not find an independent association of SSRI use with hemorrhagic stroke, ICH, or SAH in a large population-based case-control study. In addition, potentiation of risk with aspirin or warfarin was not observed. SSRI use does not appear to lead to significant risk of hemorrhagic stroke.