Selective Serotonin Reuptake Inhibitors and Risk of Cerebral Bleeding

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The opinions expressed in this commentary are not necessarily those of the editors or of the American Heart Association.

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Selective serotonin reuptake inhibitors (SSRIs) are used commonly to treat poststroke depression.1,2 They are also being evaluated in clinical trials for their effectiveness in facilitating functional recovery after stroke.3,4

However, observational studies suggest that SSRIs are associated with several adverse outcomes in older people (aged >65 years), including an increased risk of all-cause mortality (10.61% per year with SSRI versus 7.04% per year with no antidepressant; hazard ratio [HR], 1.54, 95% confidence interval [CI], 1.48–1.59), stroke (2.61% versus 2.23%; HR, 1.17; 95% CI, 1.10–1.26), myocardial infarction (1.15% versus 1.00%; HR, 1.15; 95% CI, 1.04–1.27), epileptic seizures (0.38% versus 0.21%; HR, 1.83; 95% CI, 1.49–2.26), falls (5.67% versus 3.46%; HR, 1.66, 95% CI, 1.58–1.73), fractures (2.74% versus 1.76%; HR, 1.58; 95% CI, 1.48–1.68), hyponatremia (0.44% versus 0.29%; HR, 1.52; 95% CI, 1.33–1.75), and upper gastrointestinal bleeding (0.51% versus 0.42%; HR, 1.22; 95% CI, 1.07–1.40).5

Furthermore, a meta-analysis of 16 observational studies involving 506,411 participants reported that SSRIs are also associated with an increased risk of intracerebral hemorrhage (ICH; adjusted risk ratio, 1.42; 95% CI, 1.23–1.64; P=29%).6 Given an estimated global incidence of ICH of 24.6 per 100,000 person-years, these data suggested that SSRIs may realize 1 additional ICH per 100,000 persons (0.01%) treated for 1 year.7

The validity of these observational data is supported to some extent by known biological effects of SSRIs, which include inhibition of the serotonin reuptake transporter (5-HTT) in neurons and other cells, including platelets.8 Because SSRIs block reuptake of serotonin by platelets, the concentration of serotonin in platelets decreases, thus compromising hemostasis and predisposing to an increased risk of hemorrhagic events (but also a reduction in thromboembolic ischemic events).8

However, a causal relationship between exposure to SSRIs and increased risk of ICH is yet to be established. The above observational studies could not exclude potential confounding by indication, residual confounding by alcohol abuse, smoking, diabetes mellitus, intracranial small-vessel disease (each of which may be associated with exposure to SSRIs and ICH), and potential reverse causality bias (ie, cerebral microbleeds may be a risk factor for depression and fatigue).6,9-11

Moreover, a systematic review of 56 randomized controlled trials of SSRIs versus controls identified only 2 trials that recorded bleeding as an adverse effect and reported that there was a no significant increase in bleeding with exposure to SSRIs versus control among a total of 249 participants (risk ratio, 1.63; 95% CI, 0.20–13.05; P=0%; P for heterogeneity=0.59).3

In this issue of Stroke, Aarts et al12 extend our knowledge by exploring the hypotheses that potent SSRIs may increase the prevalence of subclinical (ie, neurologically asymptomatic) intracerebral hemorrhage (ie, cerebral microbleeds) and reduce the prevalence of subclinical ischemic brain lesions because of small-vessel disease (ie, lacunes and white matter lesion volume). They undertook a cross-sectional epidemiological study of 4945 individuals (mean age, 64 years; 55% women) who were enrolled in the population-based Rotterdam cohort study in 1990, were not demented, and underwent a brain MRI scan between 2005 and 2011. Usage of single antidepressants before the MRI was obtained from continuously monitored computerized pharmacy records (ascertainment >99%).12

Aarts et al12 found that 930 (18.8%) persons had a history of antidepressant use before MRI, of whom 311 (6.2%) exclusively used antidepressants with a high degree of serotonin reuptake inhibition (paroxetine, clomipramine, sertraline, duloxetine, fluoxetine). Cerebral microbleeds were detected in 957 individuals (19.4%), of whom 53 (5.5%) used antidepressants with a high degree of serotonin reuptake inhibition. Previous exposure to antidepressants with high affinity for the serotonin transporter and strong serotonin reuptake inhibition was not associated with an increased prevalence of previous cerebral microbleeds or a lower prevalence of previous ischemic brain lesions because of small-vessel disease, as hypothesized.12

The results of the study of Aarts et al12 are consistent with the null hypothesis that there is no significant causal relationship between exposure to SSRIs and risk of hemorrhagic and ischemic brain lesions in the general population. However, there are several methodological caveats to this study, as discussed by the authors. Notably, this study lacked statistical power to identify or exclude reliably a small but important absolute increase in risk of ICH of 0.01% per year with SSRIs, as suggested by the meta-analysis of Hackam and Mrkobrada.6

For the general population and patients with hemorrhagic and ischemic stroke, who develop depression and warrant...
treatment with an SSRI, there remains insufficient reliable data to make valid and accurate recommendations about any possible increased or decreased risk, or severity, of intracerebral bleeding and ischemic stroke with an SSRI, and with and without concurrent antiplatelet or anticoagulant medication.\textsuperscript{13}

At least 3 large randomized, placebo-controlled trials of the SSRI, fluoxetine, in patients with recent stroke (the United Kingdom Fluoxetine or Control Under Supervision [FOCUS] trial, the Australasian Assessment of Fluoxetine in Stroke Recovery [AFFINITY] trial, and the Swedish Effectiveness of Fluoxetine–A Randomized Controlled Trial in Stroke [EFFECTS] trial) promise to evaluate not only the effectiveness of fluoxetine in facilitating functional recovery after stroke but also the effects, if any, of fluoxetine on recurrent hemorrhagic and ischemic stroke and other safety and efficacy outcomes.\textsuperscript{4}

**Disclosures**

Dr Hankey is coprincipal investigator of the Assessment of Fluoxetine in Stroke Recovery (AFFINITY) trial, Australian New Zealand Clinical Trial Registry number ACTRN12611000774921.

**References**


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