Selective serotonin reuptake inhibitors and brain hemorrhage

A meta-analysis

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ABSTRACT

Objective: We synthesized the epidemiologic evidence concerning selective serotonin reuptake inhibitor (SSRI) exposure and the risk of CNS hemorrhage.

Methods: We searched for controlled observational studies comparing SSRI therapy with a control group not receiving SSRIs. We used DerSimonian and Laird fixed effect models to compute summary risk associations.

Results: Intracranial hemorrhage was related to SSRI exposure in both unadjusted (rate ratio [RR] 1.48, 95% confidence interval [CI] 1.22–1.78) and adjusted analyses (RR 1.51, 95% CI 1.26–1.81). Intracerebral hemorrhage was also associated with SSRI exposure in both unadjusted (RR 1.68, 95% CI 1.46–1.91) and adjusted (RR 1.42, 95% CI 1.23–1.65) analyses. In a subset of 5 studies (3 of intracranial hemorrhage and 1 each reporting hemorrhagic stroke and intracerebral hemorrhage), SSRI exposure in combination with oral anticoagulants was associated with an increased risk of bleeding compared with oral anticoagulants alone (RR 1.56, 95% CI 1.33–1.83). When all studies were analyzed together, increased risk was seen across cohort studies (1.61, 95% CI 1.04–2.51), case-control studies (odds ratio [OR] 1.34, 95% CI 1.20–1.49), and case-crossover studies (OR 4.24, 95% CI 1.95–9.24).

Conclusions: SSRI exposure is associated with an increased risk of intracerebral and intracranial hemorrhage, yet given the rarity of this event, absolute risks are likely to be very low. ***Neurology***® **2012;79:1862–1865**

GLOSSARY

CI = confidence interval; **OR** = odds ratio; **RR** = rate ratio; **SSRI** = selective serotonin reuptake inhibitor.

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used antidepressant medications today.[1] Because they inhibit platelet aggregation, these agents increase the risk of gastrointestinal bleeding; however, studies conflict on their association with brain hemorrhage.[2] We performed a systematic review and meta-analysis of observational studies reporting on the association of SSRIs with brain hemorrhage. Because definitions for this outcome vary considerably between studies, we pooled studies according to the subtype of hemorrhage reported.

METHODS We screened Medline, Web of Science (including conference proceedings), EMBASE, Scopus, ProQuest Dissertations, and article reference lists for controlled epidemiologic studies reporting risk estimates for the association of SSRIs with brain hemorrhage. Studies had to include a control group not receiving SSRI therapy; prospective cohorts, retrospective cohorts, case-crossover studies, and case-control designs were permitted. We focused on observational studies because clinical trials of antidepressant medications rarely report intracranial hemorrhagic events. Hemorrhage was categorized according to the definitions used in the original studies: 1) any intracranial hemorrhage; 2) hemorrhagic stroke (a composite of intracerebral and subarachnoid hemorrhage); 3) intracerebral hemorrhage alone; and 4) subarachnoid hemorrhage alone.

We extracted both unadjusted and multivariate-adjusted risk estimates which we then synthesized using DerSimonian-Laird fixed effect rate ratios (RRs) with 95% confidence interval (CI).[3] In a sensitivity analysis, we repeated our analyses using random effects models. Studies contributing only unadjusted results were analyzed only in unadjusted models. We quantified heterogeneity using the I^2 statistic.[4] We used Duval-and-Tweedie trim-and-fill analysis to quantify whether publication bias influenced the results. We also analyzed the additive risk of hemorrhage (of any type) in relation to SSRI exposure and oral anticoagulants vs oral anticoagulants alone. Finally, we used subgroup analysis to determine whether study design had an influence on the results.

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Supplemental data at www.neurology.org

Supplemental Data

From the Stroke Prevention and Atherosclerosis Research Centre (SPARC) (D.G.H.) and Clinical Trials Unit (M.M.), Robarts Research Institute, and Departments of Medicine (D.G.H., M.M.), Clinical Neurological Sciences (D.G.H.), and Epidemiology and Biostatistics (D.G.H.), Western University, London, Canada.

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Table 1 Characteristics of included studies

Study	No.	Setting	Design	Outcomes	Covariates controlled through matching or regression
e1	44,765	Denmark (population-based)	Case-control	Intracerebral hemorrhage, subarachnoid hemorrhage	Age, sex, index date, and use of diuretics, β-blockers, calcium channel blockers, ACE inhibitors, anti-arrhythmics, anti-anginal medication, SSRIs, warfarin, phenprocoumon, antidiabetics, lipid-lowering drugs, low-dose ASA, and other NSAIDs
e2	89,511	Germany (population-based)	Case-control	Intracerebral hemorrhage	Age, interaction between phenprocoumon exposure and age, sex, diabetes, hypertension, ischemic heart disease, ischemic cerebral infarction, cerebral amyloid angiopathy, cerebral aneurysm, brain tumor, epilepsy, liver diseases, renal failure, alcohol dependence, epistaxis, previous hospitalization for intracerebral hemorrhage or for other bleeding events, platelet aggregation inhibitors, heparins, diuretics, NSAIDs, ASA, SSRIs, diuretics, corticosteroids, statins
e3	7,601	United States (population-based)	Case-control	Intracranial hemorrhage	Age, sex, index date, history of depression, antidepressants, other medications that are known or proposed to affect risk of stroke (e.g., aspirin, anticoagulants, risperidone), other psychiatric comorbidities (e.g., anxiety, alcohol abuse, substance abuse), and medical comorbidities (e.g., hypertension, diabetes, dyslipidemia, ventricular hypertrophy, other cardiac diseases, obesity)
e4	644	United States (population-based)	Case-control	Intracranial hemorrhage	Age, sex, index date, history of depression, antidepressants, other medications that are known or proposed to affect risk of stroke (e.g., aspirin, anticoagulants, risperidone), other psychiatric comorbidities (e.g., anxiety, alcohol abuse, substance abuse), and medical comorbidities (e.g., hypertension, diabetes, dyslipidemia, ventricular hypertrophy, other cardiac diseases, obesity)
e5	319	United Kingdom (population-based)	Case-control	Intracranial hemorrhage, intracerebral hemorrhage, subarachnoid hemorrhage	Age, sex, calendar time, practice, SSRIs, hypertension, smoking, body mass index, asthma or COPD, migraines, NSAID use (including ASA)
e6	1,988	United Kingdom (population-based)	Case-control	Hemorrhagic stroke	Age, sex, registration date, practice, smoking, alcohol consumption, body mass index, prior history of stroke/TIA, hypertension, diabetes, NSAID use, aspirin use, clopidogrel or dipyridamole use, year of first prescription for SSRI or TCA, total observation time
e7	2,692	United States (hospital-based)	Case-control	Intracerebral hemorrhage, subarachnoid hemorrhage	Age, sex, race, SSRIs, antiplatelet drugs (ASA, clopidogrel, dipyridamole), frequent alcohol use, warfarin, heart disease, history of ischemic stroke, body mass index, treated and untreated hypertension, hypercholesterolemia, statin use, smoking, education
e8	6,772	Finland (hospital-based)	Cohort	Intracranial hemorrhage	Age, sex, PPIs, oral glucocorticoids, warfarin exposure, SSRIs, ward
e9	80,574	United States (population-based)	Cohort	Hemorrhagic stroke	Age, sex (all were women), marital status, ethnicity, parental history of myocardial infarction, physical activity level, body mass index, alcohol consumption, smoking status, menopausal status, postmenopausal hormone therapy, current aspirin use, current multivitamin use, Dietary Approaches to Stop Hypertension dietary score, history of hypertension, hypercholesterolemia, diabetes, cancer, and heart diseases (including myocardial infarction, angina, and revascularization)
e10	11,037	Holland (population-based)	Case-control	Subarachnoid hemorrhage	Age, sex, calendar date, SSRIs
e11	7,666	Holland (population-based)	Case-control	Intracranial hemorrhage	Age, sex, coumarin exposure, duration of coumarin exposure, geographic region, index date, NSAIDs, antiplatelet agents, glucocorticoids, inhibitors or inducers of coumarin metabolism, antibiotics, SSRIs, thyroid disorders, diabetes mellitus, cancers, and heart failure
e12	13,026	Denmark (population-based)	Case-control	Subarachnoid hemorrhage	Age, sex, SSRI exposure, index date
e13	136,293	United States (population-based)	Cohort	Intracranial hemorrhage	SSRIs, decile of propensity score (derived from 33 variables), hormonal therapy, depression screen score, body mass index, history of MI or stroke, systolic blood pressure, migraine or "bad" headaches, aspirin or NSAID use
e14	79,075	Holland (population-based)	Case-control	Intracranial hemorrhage	Age, sex, geographic area, index date, duration of exposure history, SSRIs, NSAIDs, oral glucocorticoids, platelet aggregation inhibitors, vitamin K antagonists, and past hospitalizations for various comorbidities
e15	234	Sweden (hospital-based)	Cohort	Intracranial hemorrhage	Age, sex, warfarin exposure, atrial fibrillation
e16	24,214	Taiwan (population-based)	Case-crossover	Intracranial hemorrhage	All between-subject factors such as age, sex, and comorbidity (case-crossover design) as well as time-variant factors such as antipsychotics, antidiabetic agents, diuretics, antithrombotic agents, antihypertensive agents, lipid-modifying agents, SSRIs, and number of outpatient visits

Abbreviations: ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

RESULTS Our search retrieved 2,493 citations for screening by titles, abstracts, and key words. Of these, 81 citations were potentially relevant and reviewed as full text (including 11 doctoral theses). Sixteen articles were eligible for the review, comprising 506,411 subjects (table 1 and table e-1 and e-References on the *Neurology*® Web site at www.neurology.org). All except 3 studies[e10,e12,e15] provided both univariate and multivariate risk estimates.

Table 2 Meta-analysis of brain hemorrhage and SSRI exposure

Outcome	Adjustment	Fixed effects model RR (95% CI)	Random effects model RR (95% CI)	I^2 (p value)[a]
Intracranial hemorrhage	Unadjusted	1.48 (1.22–1.78)	1.48 (1.22–1.78)	0% (0.70)
Intracranial hemorrhage	Adjusted	1.51 (1.26–1.81)	1.72 (1.16–2.55)	49% (0.08)
Hemorrhagic stroke[b]	Unadjusted	1.17 (0.97–1.41)	1.17 (0.95–1.43)	10% (0.34)
Hemorrhagic stroke[b]	Adjusted	1.05 (0.84–1.30)	1.05 (0.84–1.30)	0% (0.57)
Intracerebral hemorrhage	Unadjusted	1.68 (1.47–1.91)	1.49 (1.03–2.15)	71% (0.01)
Intracerebral hemorrhage	Adjusted	1.42 (1.23–1.65)	1.30 (1.02–1.67)	29% (0.24)
Subarachnoid hemorrhage	Unadjusted	0.93 (0.76–1.13)	0.93 (0.76–1.13)	0% (0.37)
Subarachnoid hemorrhage	Adjusted	0.62 (0.38–1.01)	0.62 (0.38–1.01)	0% (0.70)

Abbreviations: CI = confidence interval; RR = rate ratio; SSRI = selective serotonin reuptake inhibitor.
[a] Test of heterogeneity.
[b] Hemorrhagic stroke is the combination of intracerebral hemorrhage and subarachnoid hemorrhage.

Intracranial hemorrhage was related to SSRI exposure in both unadjusted (RR 1.48, 95% CI 1.22–1.78) and adjusted analyses (RR 1.51, 95% CI 1.26–1.81). Studies reporting hemorrhagic stroke as a composite of intracerebral hemorrhage and subarachnoid hemorrhage showed a trend toward higher risk with SSRI exposure in unadjusted (RR 1.17, 95% CI 0.97–1.41, $p = 0.108$) but not adjusted (RR 1.05, 95% CI 0.84–1.30) analyses. Intracerebral hemorrhage was strongly associated with SSRI exposure in both unadjusted (RR 1.68, 95% CI 1.46–1.91) and adjusted (RR 1.42, 95% CI 1.23–1.65) analyses. Subarachnoid hemorrhage was not increased in either unadjusted (RR 1.02, 95% CI 0.77–1.34) or adjusted (RR 0.62, 95% CI 0.38–1.01) analyses.

Heterogeneity was low for most analyses with the exception of unadjusted intracerebral hemorrhage ($I^2 = 71\%$, $p = 0.01$); however, random effects models gave materially similar results (table 2). In a subset of 5 studies reporting oral anticoagulant exposure (3 studies of intracranial hemorrhage and 1 each reporting hemorrhagic stroke and intracerebral hemorrhage), SSRI exposure in combination with oral anticoagulants was associated with an increased risk of bleeding compared with oral anticoagulants alone (RR 1.56, 95% CI 1.33–1.83). When all studies were analyzed together, increased risk was seen across cohort studies (1.61, 95% CI 1.04–2.51), case-control studies (odds ratio [OR] 1.34, 95% CI 1.20–1.49), and case-crossover studies (OR 4.24, 95% CI 1.95–9.24). Finally, Duval-and-Tweedie trim-and-fill analyses yielded concordant results, suggesting that publication bias was not operative.

Seven studies performed analyses by duration of exposure (table 3).[e1,e3,e5,6,e11,e14,e16] Six of the 7 suggested that short-term, recent exposure was more strongly associated with hemorrhagic events than long-term exposure, a finding in keeping with the reported diminution of platelet function following several weeks of exposure to SSRIs.[5] Platelet function may improve with prolonged exposure, or short-term

Table 3 Study-reported analyses of exposure duration

Study	Analytic results[a]
e1	No influence by treatment duration (<91 vs ≥91 days) on risk of intracerebral hemorrhage (numeric estimates not reported)
e3	Higher risk for intracranial hemorrhage with current exposure (HR 1.18, 95% CI 0.64–2.16) than past SSRI exposure (HR 0.71, 95% CI 0.09–6.51); both were compared with the group of remote users and nonusers
e5	Higher risk for intracranial hemorrhage with short-term exposure (1–2 prescriptions; OR 1.6, 95% CI 0.4–5.6) than long-term exposure (3 prescriptions; OR 0.6, 95% CI 0.2–2.2)
e6	Higher risk for hemorrhagic stroke with current/recent use (OR 1.15, 95% CI 0.85–1.54) than ever use (OR 1.03, 95% CI 0.77–1.37)
e11	Higher risk for intracranial hemorrhage with current use (OR 1.6, 95% CI 0.7–3.4) than recent or past use (estimates not provided but "immediate attenuation of the effect … with risk no longer increased"[b])
e14	Higher risk for intracranial hemorrhage in new users (OR 2.30, 95% CI 0.90–5.88) than prevalent users (OR 1.40, 95% CI 1.20–1.63)[c]
e16	Higher risk for short-term users (one prescription: OR 2.89, 95% CI 2.55–3.28; 2 prescriptions: OR 1.68, 95% CI 1.39–2.02) than long-term users (3 prescriptions: OR 0.91, 95% CI 0.77–1.09; 4 prescriptions: OR 0.62, 95% CI 0.53–0.72)[d]

Abbreviations: CI = confidence interval; HR = hazard ratio; OR = odds ratio; RR = rate ratio; SSRI = selective serotonin reuptake inhibitor.
[a] All analyses are multivariable-adjusted and refer to exposure to SSRIs, unless otherwise noted.
[b] Text for the latter refers to nongastrointestinal hemorrhage, of which intracranial hemorrhage was a dominant cause.
[c] Refers to users of serotoninergic antidepressants.
[d] Estimates here were provided for total stroke only, but overall risk estimates for total stroke, ischemic stroke, and hemorrhagic stroke in relation to SSRIs were nearly identical (ORs 4.22, 4.11, and 4.24, respectively).

exposure might deplete susceptible patients from the pool of patients at risk for hemorrhage.

DISCUSSION SSRI exposure is associated with an increased risk of brain hemorrhage (largely due to intracerebral bleeding). Given an estimated global incidence of 24.6 per 100,000 person-years, 1 additional intracerebral bleeding episode per 10,000 persons treated for 1 year could be expected.[6] Rates would likely be higher in patients with a past history of intracerebral hemorrhage, in particular lobar hemorrhage. No previous study has investigated the association of SSRIs with recurrent intracerebral hemorrhage; hence more data are needed in this setting.

Our data have a number of limitations. Although we found an increased risk of intracranial and intracerebral hemorrhage related to SSRI exposure in both unadjusted and adjusted models, only 1 study delimited subdural hemorrhage as a distinct entity (with only 1 case reported in that study).[e15] Therefore, it was not possible to analyze subdural hemorrhage in isolation. As well, no data were reported on subtype of intracerebral hemorrhage (e.g., lobar vs deep).

Given the large range of sample sizes between included reports, some studies had a greater likelihood of predominating in pooled analyses (for example, Behr et al.,[e2] which contributed more than half of the information to the adjusted analysis of intracerebral hemorrhage). This implies that further studies would be helpful, in particular those which precisely examine intracerebral hemorrhage as a distinct entity. A further limitation is that variables such as hypertension were defined somewhat differently between reports, with a lack of direct physiologic data for blood pressure, cholesterol, or renal function. Future reports should also consider providing SSRI-related risk data among patients with a history of coronary artery disease or cerebrovascular disease, since such individuals often receive antithrombotic medication for secondary prevention.

While the data we reviewed were not randomized, we believe clinicians might consider alternate classes of antidepressants in patients with intrinsic risk factors for intracerebral hemorrhage, such as those receiving long-term oral anticoagulation, individuals with previous intracranial bleeding, and patients with cerebral amyloid angiopathy or severe alcohol abuse.[7]

AUTHOR CONTRIBUTIONS

Drafting/revising the manuscript: Dr. Hackam, Dr. Mrkobrada. Study conception or design: Dr. Hackam, Dr. Mrkobrada. Analysis or interpretation of data: Dr. Hackam, Dr. Mrkobrada. Acquisition of data: Dr. Hackam, Dr. Mrkobrada. Statistical analysis: Dr. Hackam. Study supervision or coordination: Dr. Hackam.

DISCLOSURE

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