Cerebrovascular Effects of Selective Serotonin Reuptake Inhibitors: A Systematic Review

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Objectives: An understanding of cerebrovascular effects of selective serotonin reuptake inhibitors (SSRIs) is essential, since SSRIs are a widely used antidepressant, serotonin is a vasoactive and thrombostatic amine, and there is a bidirectional relationship between depression and cerebrovascular disease.

Data Sources: A MEDLINE search was performed to identify published reports over the period of 1966 through 2003, using the terms *SSRIs* and *antidepressants* matched with the terms *platelets, coagulation, anticoagulation, bleeding, fibrinolysis, thrombosis, embolism, cerebral ischemia, stroke, cerebrovascular accident, acute and chronic cerebrovascular disease, intracranial hemorrhage, cerebrovascular disorder,* and *cerebral circulation*. Adverse event reports collected from the World Health Organization (WHO), manufacturers, and the *Physicians' Desk Reference* (PDR) were also examined.

Data Synthesis: Two case-control studies failed to show an association between SSRI use and intracranial hemorrhage, and of these, 1 showed no association with ischemic stroke. Sixteen studies of SSRI treatment in poststroke patients found no significant cerebrovascular adverse reactions. The WHO data have shown several hundred cases of SSRI-associated cerebrovascular disease, but definitive causal relationships remain undetermined. Four cases of vasoconstrictive stroke related to drug interactions between SSRIs and other serotonergic drugs have been reported. PDR and manufacturer reference sources categorized cerebrovascular reaction as an infrequent or rare adverse event related to SSRI use.

Conclusions: Available evidence suggests that SSRI treatment has a very low rate of cerebrovascular adverse reaction. Pharmacovigilance is required in the use of SSRIs in high-risk populations for bleeding and vasoconstrictive stroke. More research is warranted to examine the variability of pharmacologic and genetic factors, depressive illness, and stroke on the antiplatelet and vasospastic effects of SSRIs and their significance to cerebrovascular protection or adverse reactions.

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The cerebrovascular effects of selective serotonin reuptake inhibitors (SSRIs) are important clinical concerns, since SSRIs are commonly used antidepressants in patients with cerebrovascular disease (CVD) and cardiovascular disease. The use of SSRI antidepressants in patients with CVD may be considerable, given that stroke is the third leading cause of morbidity and mortality among the elderly in North America[1] and approximately 30% to 50% of stroke patients may suffer from depression during the first 2 years after a stroke.[2] In addition, a significant proportion of late-onset geriatric depression is frequently associated with brain vascular lesions.[3,4]

The effects of SSRIs on cerebral circulation and vasculature have become a major concern after the observations that SSRIs may increase the risk of bleeding[5–8] and serotonergic activation may cause vasoconstriction in cerebral arteries.[9,10] Another related issue is that recent epidemiologic studies have shown that depression may be a long-standing risk factor for stroke morbidity.[11] Hence, it is imperative to examine whether SSRI treatment has a confounding or modifying effect on depression-related stroke outcomes, as any relationship may have major implications, particularly to depressed patients who are receiving long-term SSRI treatment. This article examines the evidence linking SSRI treatment to CVD and discusses the relevance to clinical practice and future research.

DATA SOURCES

All published articles investigating or citing SSRI-related cerebrovascular incidents over the period 1966 through 2003 were identified through a MEDLINE search

Table 1. Case-Control Studies of SSRI Use and Stroke Risk

Author (Year)	Type of Stroke	SSRI Use	Cases	Controls	Adjusted OR (95% CI)	Adjusted Variables
Bak et al (2002)[15]	Hemorrhagic	Never user	606	38,058	1 (reference)	Age, sex, calendar year, use of other medications
		Current user	21	742	1.0 (0.6 to 1.6)	
	Ischemic	Never user	2460	38,058	1.0 (reference)	
		Current user	100	742	1.1 (0.9 to 1.4)	
		Past user	149	1132	1.3 (1.0 to 1.5)*	
de Abajo et al (2000)[14]	Hemorrhagic	Nonuser	44	160	1 (reference)	Age, sex, calendar time, practice, hypertension, smoking, body mass index, asthma/COPD, migraine, and NSAID use
		Current user	7	24	0.8 (0.3 to 2.3)	

*p = .02.
Abbreviations: COPD = chronic obstructive pulmonary disease, NSAID = nonsteroidal anti-inflammatory drug, SSRI = selective serotonin reuptake inhibitor.

using the keywords *SSRIs* and *antidepressants* matched with the terms *platelets, coagulation, anticoagulation, bleeding, fibrinolysis, thrombosis, embolism, cerebral ischemia, stroke, cerebrovascular accident (CVA), acute and chronic cerebrovascular disease, intracranial hemorrhage (ICH), cerebrovascular disorder,* and *cerebral circulation.* An additional search was performed to identify the reports of cerebrovascular adverse reactions in SSRI treatment studies that include randomized controlled trials (RCTs), open trials, case reports involving 5 or more patients, case-control studies, and chart reviews. Case reports of cerebrovascular adverse events for the specific SSRI antidepressants were also searched using the keywords *adverse events* and *cerebrovascular accident* or *stroke* or *ischemia* for each specific SSRI antidepressant: citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Additional data were requested from respective drug manufacturers concerning cerebrovascular adverse events with each specific SSRI. The *Physicians' Desk Reference* (PDR)[12] was reviewed for adverse event data. Further, the number of cases of cerebrovascular adverse events associated with SSRI treatment reported in the World Health Organization (WHO) adverse reaction (ADR) database,[108] as of July 12, 2002, were included in this review. The WHO International Drug Monitoring Program maintains the ADR database, which currently contains over 2 million reports of ADR reported from 68 participating countries.[13]

DATA SYNTHESIS

Two case-control studies,[14,15] 3 case reports,[9,10,16] and 16 clinical trials[17–32] were extracted from the literature for this review. The details of case-control studies are presented in Table 1. De Abajo et al.[14] utilized the U.K.-based general practice research database (GPRD) to examine the association between SSRI use and increased risk of ICH. Subjects of both genders, aged 18 to 79 years, who received first-time antidepressant prescriptions from 1990 to 1997, were followed up until the occurrence of ICH (N = 65). The patients with a history of cerebrovascular and cardiovascular diseases and other conditions or treatments that could be associated with increased risk of ICH were excluded. The controls matched for age, sex, calendar time, and practice were randomly selected from the same cohort (N = 254). The results have shown that the current use of SSRIs (prescription lasted until or before 30 days prior to first admission for stroke, i.e., index date) was not associated with increased risk of ICH compared with nonuse (nonusers were defined as those who had no antidepressant supply for more than 60 days before the index date) (OR = 0.8; 95% CI = 0.3 to 2.3) after adjusting for covariates (see Table 1). However, authors acknowledged that smaller but clinically relevant increased risk could not be completely ruled out due to lack of statistical power.

The study by Bak et al.[15] was conducted in Funen County, Denmark. Subjects with first-ever stroke (hemorrhagic and ischemic stroke) during the period of 1994 to 1999 were the cases (N = 4765), and controls (N = 40,000) were randomly selected from the same population. As shown in Table 1, the current use of SSRIs was not associated with increased risk of ICH or decreased risk of ischemic stroke. Interestingly, previous users of SSRIs (if the prescription ended before 61 days prior to the index date) seemed to have an increased risk of ischemic stroke compared with never users (never users were defined as those who had no prescription of antidepressants before the index date), whereas the risk of ischemic stroke in current SSRI users was comparable to that of never users. There was a trend showing an increased risk of hemorrhagic stroke and decreased risk of ischemic stroke in persons with concurrent use of both SSRIs and nonsteroidal anti-inflammatory drugs (NSAIDs) compared with never users of SSRIs or NSAIDs (OR = 2.4; 95% CI = 0.9 to 6.2).

The data from 16 studies[17–32] of SSRI therapy in stroke patients are presented in Table 2. No incidence of stroke was reported in 12 studies.[19–23,25,26,28–32] The studies by the Robinson group[20,23] excluded hemorrhagic stroke from the fluoxetine treatment arm. Three studies reported stroke and/or transient ischemic attack with SSRI treat-

Table 2. Cerebrovascular Adverse Reactions During Clinical Trials of SSRIs[a] in Stroke Patients

Author (Year)	Study Design	Treatment (N)	New Stroke During Treatment	Other Relevant Findings	Comments
Treatment of poststroke depression					
Anderson et al (1994)[17]	Double-blind placebo-controlled RCT, 16-wk follow-up	Citalopram 10–40 mg/d (33) Placebo (33)	Citalopram stroke—3 TIA—2 Placebo stroke—1 TIA—1 Not significant	…	No comparison available on severity/types of CVD, vascular risk factors, anticoagulants between groups No causality assessment of SSRI-related stroke
González-Torrecillas et al (1995)[18]	Open, non–placebo-controlled comparative trial with randomized controls; 6-wk follow-up	Fluoxetine 20 mg/d (26) Nortriptyline 75 mg/d (11)	Stroke 1 (Drug group not reported)	…	…
Wiart et al (2000)[19]	Multicenter, double-blind placebo-controlled RCT; 6-wk follow-up	Fluoxetine 20 mg/d (16) Placebo (15)	None reported	…	…
Robinson et al (2000)[20]	Double-blind placebo-controlled RCT; 12-wk follow-up	Fluoxetine 10–40 mg/d (40) Nortriptyline 25–100 mg/d (31) Placebo (33)	None reported	Hemorrhagic stroke was excluded from fluoxetine group	High dropouts in fluoxetine group Details of 2 dropouts in fluoxetine group due to medical deterioration are not known
Turner-Stokes and Hassan (2002)[21]	Open-label prospective cohort study, 15-mo period	Sertraline 50–100 mg/d (27)	None reported	…	…
Spalletta et al (2003)[22]	Open-label comparative study, 8-wk period	Fluoxetine 20–40 mg/d (24) Sertraline 50–100 mg/d (21)	None reported	…	…
Prevention of poststroke depression					
Narushima et al (2002)[23]	Naturalistic follow-up, 21 mo	Fluoxetine 10–40 mg/d (17) Nortriptyline 25–100 mg/d (15) Placebo (16)	None reported	Hemorrhagic stroke was excluded from fluoxetine group	The cause of 3 deaths in fluoxetine group was not reported. Reasons for dropouts not given
Rasmussen et al (2003)[24]	Double-blind placebo-controlled RCT, 12-mo follow-up	Sertraline, mean dose, 62.9 mg/d (70) Placebo (67)	Sertraline stroke—2 Placebo stroke—5 Not significant	Sertraline group had fewer cardiovascular side effects	Type of stroke associated with sertraline and placebo groups not available
Treatment of poststroke emotional lability					
Anderson et al (1993)[25]	Double-blind placebo-controlled crossover, 3 wk each	Citalopram 10–20 mg/d (16)	None reported	Increase in transient dizziness and spasticity	…
Brown et al (1998)[26]	Double-blind placebo-controlled RCT, follow-up 10 d	Fluoxetine 20 mg/d (9) Placebo (10)	None reported	…	…
Burns et al (1999)[27]	Double-blind placebo-controlled RCT, 8-wk period	Sertraline 50 mg/d (14) Placebo (14)	Sertraline stroke—1 (fatal) Placebo stroke—1 (fatal)	…	Type of CVD between groups not available
Muller et al (1999)[28]	Open-label, non–placebo-controlled comparative trial, 6-wk follow-up	Paroxetine 10–40 mg/d (11) Citalopram 10–40 mg/d (11)	None reported	…	…
Seliger et al (1992)[29]	Open label (duration of study not known)	Fluoxetine 20 mg (8)	None reported	…	…
Stroke rehabilitation					
Dam et al (1996)[30]	Placebo-controlled, randomized trial; 3-mo treatment period	Fluoxetine 20 mg/d (16) Maprotiline 150 mg/d (14) Placebo (16)	None reported	…	…
Paolucci et al (2001)[31]	Case-control study, 64-mo period	Fluoxetine 10–40 mg/d (120) Paroxetine 10–20 mg/d (16) Amitriptyline or mianserin (9)	None reported	…	Duration of treatment and details of dropouts were not given
Whyte et al (2003)[32]	Chart review, 9-mo period	SSRIs (85) No SSRIs (62)	None reported	Higher incidence of gastrointestinal and other bleeding in SSRI treatment group	Dose and duration of treatment not mentioned No hemorrhagic conversion of ischemic stroke

[a]Clinical trials include randomized, controlled, open trials with ≥ 5 patients; chart review; and case-control studies.
Abbreviations: CVD = cerebrovascular disease, RCT = randomized controlled trial, SSRI = selective serotonin reuptake inhibitor, TIA = transient ischemic attack. Symbol: … = not applicable.

ment, but this was not statistically significant when compared with placebo treatment.[17,24,27] Whyte et al.[32] reported a higher incidence of gastrointestinal and cutaneous bleeding in the SSRI treatment group, but there was no occurrence of ICH in this group.

Three case reports describing 4 cases of SSRI-related vasoconstrictive stroke are presented in Table 3. Up to July 2002, approximately 400 cases of CVD related to SSRI treatment were included in the WHO International Drug Monitoring Program (Table 4). Finally, the frequency of SSRI-related CVD adverse reaction reported in the PDR for each SSRI is presented in Table 5.

DISCUSSION

To address the complex issues of SSRI use as a risk factor for stroke and SSRI treatment-related acute and chronic cerebrovascular adverse events, it is essential to examine and discuss (1) the potential pathophysiologic mechanisms of antiplatelet and vasospastic effects of SSRIs in the incidents of hemorrhagic, vasoconstrictive, and thrombotic stroke and (2) the evidence supporting the causal association between SSRI use and stroke, based on these pathogenic mechanisms.

However, prior to discussing the evidence, the limitations of the available data need to be addressed. Some are discussed in detail where appropriate in subsections. Only 2 case-control studies examined the association between SSRI use and the risk of stroke, therefore limiting the confidence with which firm conclusions can be drawn.[14,15] Despite the strengths of the case-control studies (minimal selection and recall biases), there are several methodological concerns (e.g., lack of control for potential confounders, exclusion of stroke patients, small sample of cases) that prevent clinical utilization of these findings. In WHO data, the limitations are related to underreporting, selective reporting, and differential reporting rates, with highest reporting from U.S. and U.K. centers.[13] Further, the author did not have access to WHO-ADR signal detection and drug usage data. Hence, the importance of the WHO data is weakened by the lack of information on causality assessment and reporting rates (the number of reports per million defined daily doses sold per year). In the absence of reporting rates, no inferences can be drawn regarding the differences between SSRIs with respect to the incidence and the type of cerebrovascular adverse reaction. The drawbacks of clinical trials data include small sample size, short-term follow up in RCT, lack of information about dropouts and drug-related worsening of physical or neurologic symptoms, absence of causality assessment, possible nonreporting due to misattribution of stroke incidence to progression of CVD (especially in chart reviews), exclusion of hemorrhagic stroke in RCT, lack of control for vascular risk factors, medication use, and severity and type of stroke between groups.[17–32] These limitations might have influenced the results of SSRI-related cerebrovascular adverse reactions. Nevertheless, despite these limitations, this article represents the most comprehensive review to date of available data on SSRIs and risk of stroke. Further, although the existing body of literature is small, the inferences drawn from the available data will allow us to understand and appreciate the mechanistic aspects and pharmacovigilance of SSRI treatment–related CVD.

Intracranial Hemorrhage and SSRI Use

Platelet functions play a fundamental role in thrombus formation and in the repair of vascular injury.[5,33] Serotonin concentration in platelets is crucial in maintaining the hemostatic function of platelets.[33,34] The major source of serotonin in blood is released from platelets. In platelets, serotonin is not synthesized and the serotonin transporter (5-HTT) carrier protein located on platelets is responsible for acquiring serotonin from extracellular space.[35] Thus, the maintenance of homeostasis of intraplatelet serotonin concentration and serotonin level in blood is the function of 5-HTT. SSRIs have been shown to inhibit 5-HTT and to block the reuptake of serotonin, leading to depletion of serotonin storage in platelets after several weeks of treatment.[36,37] This depletion may lead to attenuation of platelet activity, resulting in disrupted aggregation and adhesion and increased risk of bleeding. Consistent with this hypothesis, there were several reports documenting an association between SSRIs and bleeding disorders.[6–8]

In contrast, 2 population-based, case-control studies failed to show any significant association between the use of SSRIs and intracranial bleeding after adjusting for the confounding variables.[14,15] Methodological limitations need to be addressed prior to validating the negative results of these studies. Uncontrolled confounding of cerebrovascular risk factors is a major drawback in nested case-control studies. Smoking and alcohol intake could not be controlled in the study by Bak and colleagues.[15] If the incidence of ICH were high in SSRI never users, due to high prevalence of smoking and alcohol, the odds ratio of hemorrhagic stroke in SSRI users compared with never users may be underestimated. However, the authors have argued that since smoking and high alcohol intake are generally more common in SSRI users as evidenced in population-based surveys, the odds ratio of hemorrhagic stroke in SSRI users compared with never users may be overestimated. But taking into account the documented association of depression with smoking[38,39] and alcohol,[40] and the beneficial effects of SSRIs on depression[41] and alcohol intake,[42] it is possible that variations in treatment response (improved vs. not improved) between populations may differentially affect the risk of ICH. Hence, the observed correlation of SSRI use with high alcohol intake and smoking in one population survey may not be applicable to other populations in terms of stroke risk.

Table 3. Case Reports of SSRI-Related Vasoconstrictive Stroke

Study	Sex/Age, y	Medical History	SSRI Dosage and Duration	Concomitant Medications, Dosage	Onset of Symptoms	Nature of Symptoms	Investigatory Findings	Resolution of Symptoms
Singhal et al (2002)[9]								
Case 1	F/46	Migraine, depression, asthma	Sertraline 150 mg/d for 3 mo	Trazodone 50 mg Thioridazine Clonazepam Albuterol (dosage NA) Dextromethorphan hydrobromide	5 d after taking cold remedy	Worsening headaches, visual loss, dysarthria, Balint's syndrome	Diffuse intracranial vasoconstriction Left internal carotid aneurysm Left occipital parietal ischemic stroke	Symptoms improved within a week after discontinuation of sertraline and cold remedy Angiogram at 6 mo showed normal intracranial arteries
Case 2	F/45	Migraine, depression, obesity	Paroxetine 40 mg/d for 4 mo	Clonazepam 0.5 mg/d Cold remedy (dextromethorphan hydrobromide 10 mg, pseudoephedrine hydrochloride 30 mg, acetaminophen 250 mg)	1 h after taking cold remedy	Sudden headache, nausea; 3 wk later developed left-hand clumsiness, numbness	Bilateral vasoconstriction Multiple ischemic strokes Right ICA aneurysm Left bronchial carcinoid tumor	Resolution of symptoms, headache subsided a few days after paroxetine and cold remedy were discontinued Magnetic resonance angiography at 14 mo showed normal intracranial arteries
Molaie (1997)[10]								
Case 3	F/30	OCD, migraine	Fluoxetine 100 mg/d for several mo; switched abruptly to clomipramine 200 mg	…	48 h after switch	Convulsions, altered neural state	MRI Temporoparietal and cerebellar infarct CSF—normal EEG Focal slow activity in right temporal and occipital areas Cerebral/angiogram normal Cardiac status normal	Steady improvement of neurologic status over 5 y follow-up No OCD/antidepressant
Conde Lopez et al (1998)[16]								
Case 4	Adolescent girl, age NA	NA	Toxic doses of paroxetine, caffedrine, theodrenaline, and phlebotonic agent	…	Acute (exact time of onset NA)	Call-Fleming syndrome (nature of symptoms NA)	…	…

Abbreviations: CSF = cerebrospinal fluid, EEG = electroencephalogram, ICA = internal carotid artery, MRI = magnetic resonance imaging, NA = not available, OCD = obsessive-compulsive disorder, SSRI = selective serotonin reuptake inhibitor. Symbol: … = not applicable.

Table 4. Number of Cerebrovascular Adverse Reactions to SSRIs[a]

Type of Stroke	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Hemorrhagic					
Cerebral hemorrhage	7	16	3	8	6
Cerebellar hemorrhage	1	…	…	…	…
Intracranial hemorrhage	2	15	1	8	7
Subarachnoid hemorrhage	4	13	…	3	1
Brain stem hemorrhage	…	…	…	1	…
Ischemic					
Cerebral ischemia	5	3	…	3	…
Cerebral thrombosis/infarction	3	6	1	10	5
Cerebellar infarction	…	1	…	2	…
Transient ischemic attack	1	2	…	6	8
Cerebral embolism	…	1	…	1	…
Cerebrovascular disorder	13	122	7	51	47
Cerebral thrombophlebitis	1	…	…	…	…
Carotid thrombosis	…	…	…	…	1

[a]Data from World Health Organization.[108]
Abbreviation: SSRIs = selective serotonin reuptake inhibitors. Symbol: … = none reported.

Table 5. SSRI Treatment–Associated Cerebrovascular Adverse Reactions (CV ADRs)[a]

SSRI	CV ADR[b]	Frequency[c]
Citalopram	Cerebrovascular accident	Infrequent
	Transient ischemic attack	Rare
Paroxetine	Cerebral ischemia	Infrequent
	Cerebrovascular accident	Infrequent
Fluoxetine	Cerebral embolism	Rare
	Cerebral ischemia	Rare
	Cerebral accident	Rare
Sertraline	Cerebrovascular disorder	Rare
Fluvoxamine	Cerebrovascular disease	Infrequent
	Cerebrovascular accident	Rare

[a]Data from *Physicians' Desk Reference*.[12]
[b]Adverse reaction reported in MedDRA terminology.
[c]Frequent: occurring in at least 1/100 patients; infrequent: occurring in 1/1000 to 1/100 patients; rare: occurring in < 1/1000 patients.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, SSRI = selective serotonin reuptake inhibitor.

The proxy indicators of vascular risk factors, such as current or previous medication use, would not give a clear account of the illness status of vascular diseases. The severity and complications of diabetes mellitus and hypertension may influence the risk for stroke. Failure to control these factors would also bias the results. The exclusion of subjects with vascular risk factors (diabetes mellitus, hypertension) in the study by de Abajo et al.[14] and stroke patients in the study by Bak et al.[15] would prevent generalization of these findings to patients with vascular diseases or stroke. In both studies, there was no information available on primary indications for SSRI use. If depression was the primary indication for SSRI treatment, at least 20% to 30% might have persistent depressive symptoms despite antidepressant treatment. Then, depression-associated platelet activation and resulting increased risk for ischemic stroke could be counterbalanced by the antiplatelet effect of SSRIs,[43,44] thereby reducing the number of cases of ICH in SSRI users compared with nonusers.

In the de Abajo et al.[14] study, the small number of SSRI-exposed cases (N = 7) might have impeded its ability to find a meaningful effect of SSRIs on ICH. Further, among the 120 potential cases of ICH, 30 were excluded because the diagnosis could not be confirmed or medical records or death certificates were not available. This would have reduced the actual number of ICH cases. Similarly, the Bak et al.[15] study showed a trend suggesting increased risk for hemorrhagic stroke with concomitant exposure to SSRIs and NSAIDs, but failed to show statistical significance due to a small number of cases using both drugs.

The antiplatelet effect of SSRIs is considered to be dose-dependent. Since there is a linear relationship between antiplatelet effect and ICH,[45,46] the antiplatelet effect sufficient to induce ICH may occur only at high doses of SSRIs. However, in the 2 population-based studies, the daily doses of SSRIs used were within the average therapeutic range, suggesting a weak antiplatelet effect resulting in weak potentials for ICH.[14,15]

Further, taking into account the correlation of antiplatelet effect with affinity for 5-HTT,[7,36] SSRIs with moderate affinity for 5-HTT, such as citalopram, may have lower risk for ICH than SSRIs with high affinity for 5-HTT (paroxetine, fluoxetine, and sertraline).[47] In the Bak et al.[15] study, citalopram was the most commonly used SSRI in the cohort, which might have minimized the strength of the association. The reanalysis of the data using the classification of antidepressants based on their affinity for 5-HTT did not seem to show any difference from the original results, although the authors have not reported the reanalyzed data. Given the total number of 21 current SSRI users in cases with ICH, the number of patients with ICH who used high-affinity SSRIs might be too small to detect any statistical significance.

The adverse reaction data from WHO documented a few hundred cases of intracranial bleeding associated

with SSRI treatment (Table 4). However, considering the absence of information on causality relations in these reports, the rarity of cerebrovascular adverse reaction in the context of millions of SSRI prescriptions across the world,[13] and the negative results in case-control studies,[14,15] it is reasonable to conclude that at moderate therapeutic doses, SSRIs in monotherapy may not increase the risk of ICH in the general population. At the same time, it is not possible to rule out the risk of ICH in patients who are vulnerable for bleeding diathesis, with the use of high-affinity SSRIs at high therapeutic doses or in combined use of anticoagulants.

Vasoconstrictive Stroke and SSRI Use

Serotonergic innervation to cerebral vasculature functions as a neuronal link between perfusion and functional and metabolic events of the brain.[48] Serotonin is a potent vasoactive amine with complex actions on cerebral arteries. It induces vasoconstriction of larger cerebral arteries and vasodilatation of small vessels.[48,49] The vasoconstrictive effect of serotonin is probably mediated by 5-hydroxytryptamine-2 (5-HT_2) receptors on smooth muscle cells, as ketanserin, a 5-HT_2 receptor antagonist, prevents serotonin-mediated vasoconstriction.[50–53] Cerebral atherosclerosis potentiates the vasoconstrictor response of larger cerebral arteries and collateral vessels to serotonin.[51] In atherosclerosis, the damaged endothelium is unable to produce sufficient amounts of endothelium-derived relaxing factor (nitric oxide) to counteract the vasoconstrictive effects of serotonin.[54–56]

Serotonin has been implicated in the pathogenesis of cerebral vasospasm associated with migraine, subarachnoid hemorrhage, and vasoconstrictive stroke.[57] The cerebrovascular syndrome due to arterial vasoconstriction, called Call-Fleming syndrome, is an uncommon cause of stroke.[58] The characteristic features of this syndrome include sudden onset of severe headache, focal neurologic deficits, and seizures, most commonly in women aged 20 to 50 years. This reversible vasoconstrictive stroke is recognized to occur in migraine, postpartum angiopathy subarachnoid hemorrhage, sympathomimetic drug abuse, surgical manipulation, and closed head injury.[57,58]

Consistent with coronary vasoconstrictive effects of SSRIs,[59–63] 4 cases of Call-Fleming syndrome (vasoconstrictive stroke) associated with SSRI use have been documented in the literature (Table 3).[9,10,16] The analysis of these cases suggests that the occurrence of vasoconstrictive stroke in patients 2 and 4 might be due to drug interactions between SSRIs and sympathomimetic drugs (serotonergic-noradrenergic synergism),[9,16] and the stroke incidence in patients 1 and 3 might be due to serotonergic overstimulation (serotonin syndrome) resulting from the combined use of serotonergic drugs.[9,10]

A cause-effect relationship could be established on the basis of a temporal link between exposure to combined use of SSRIs with serotonin-enhancing drugs or sympathomimetic drugs and the onset of stroke (patients 1, 2, 3, and 4) and the quick resolution of symptoms following the discontinuation of these drugs (patients 1 and 2).[9,10,16] The pathophysiologic mechanism of serotonin-induced vasoconstriction for SSRI-related stroke was demonstrated by angiographic findings showing bilateral vasoconstriction involving anterior and posterior circulation originating in the Circle of Willis. Unlike vasoconstrictive stroke, ischemic or hemorrhagic stroke usually involves major territorial arteries. Thus, the angiographic findings of bilateral vasoconstriction might distinguish Call-Fleming syndrome from ischemic and hemorrhagic stroke.[57,58] Sometimes, vasoconstrictive stroke may resemble cerebral vasculitis, but evidence of inflammation would be absent and these patients would improve without immunosuppressive treatment. In patient 2, a serotonin-secreting bronchial carcinoid tumor would have also contributed to vasoconstriction.[9] However, the observed small unruptured aneurysms in patients 1 and 2 appeared to be coincidental.[9] Migraine and female gender could be considered as predisposing factors for serotonergic drug–induced vasoconstrictive stroke.

Besides these case reports, some proportion of cases with SSRI treatment–associated CVD (not otherwise specified) documented in the WHO program might be related to vasoconstrictive stroke (Table 4). A detailed assessment of these cases would help to determine the prevalence and characteristics of Call-Fleming syndrome in these patients. A better understanding of pathophysiology and pharmacologic risk factors of serotonergic drug–related vasoconstrictive stroke may be helpful in the prediction, prevention, and treatment of this serious adverse event. In summary, given the available evidence and biological plausibility of vasoconstrictive stroke secondary to serotonergic overstimulation, vasoconstrictive stroke may be a potential cerebrovascular adverse event due to higher doses of SSRIs, or combined use of SSRIs with either serotonergic drugs or sympathomimetic drugs, especially in subjects who are vulnerable for vasospasm.

Ischemic Stroke and SSRI Use

Two possibilities can be proposed to study the association between SSRI use and risk of ischemic stroke. The first possibility is that SSRI treatment may attenuate the risk of ischemic stroke through its antiplatelet and antidepressant effects.[36,43,44,64,65] The second possibility is that SSRI use may increase the risk of ischemic stroke by triggering thromboembolic phenomenon in patients with cerebral atherosclerosis through its vasoconstrictive effect on damaged endothelium in large cerebral arteries.[51,53–59] The pathophysiology of SSRI-induced vasospasm has been discussed in detail in the previous section. Another potential mechanism by which SSRI treatment may induce thrombus formation and ischemic stroke is by acti-

vating platelet 5-HT_{2A} receptors. Literature suggests that a hyperactive platelet 5-HT_{2A} receptor system may mediate platelet aggregation through increases in intraplatelet calcium mobilization.[66–70] However, there is no empirical support for SSRI treatment–related platelet 5-HT_2 activation or aggregation in depressed patients.[71,72] Although one in vitro study has shown augmented intracellular calcium in platelets in normal subjects following acute administration of SSRIs,[73] the effects of long-term SSRI treatment on platelets remain unknown. On balance, the thrombogenic effect of SSRIs is not considered a strong biological plausibility in the causal relation between SSRIs and stroke.

The main findings of the case-control study by Bak et al.[15] rejected both competing hypotheses linking SSRI use and ischemic stroke. However, the secondary findings, including the increased risk of ischemic stroke in previous users compared with nonusers and the comparable ischemic stroke risk between current users and nonusers, may indirectly support the possibility that SSRI use may have some protective effect against depression-related elevated ischemic stroke risk.[74] This possibility is based on the evidence that depression may increase the risk of ischemic stroke[11] and also on the assumption that depression is a common indication for SSRI treatment. The protective effect in current SSRI users might be related to the drugs' antidepressant effects (depression recovery) as well as to their antiplatelet effect.

A better understanding of the beneficial effects of SSRI use on ischemic vascular events comes from studies that examined the relationship between SSRI use and myocardial infarction (MI) risk.[75–78] These studies suggest that SSRIs, especially those that have a high affinity for 5-HTT (e.g., paroxetine), may decrease the risk of developing MI in both post-MI depressed patients[75] and smokers,[77] but not in subjects who were free of cardiovascular risk factors.[76] If these findings are translated to the association of SSRI use with ischemic stroke, it is possible that SSRIs may have a preventive effect on the recurrence of stroke in patients with poststroke depression or depression associated with multi-infarct dementia, which needs further evaluation. The exclusion of patients with stroke or recurrent stroke from the cohort might have contributed to the negative results of the study by Bak et al.[15] Evidence from the small sample showing decreased incidence of ischemic stroke with concomitant use of SSRIs and NSAIDs suggests that SSRIs and NSAIDs may have an additive effect in ischemic stroke prevention. The negative results with SSRIs alone might be due to their weak antiplatelet effect, which may be insufficient to prevent ischemic stroke.

Although cases of SSRI-related ischemic stroke have been documented in WHO data,[108] the lack of causality assessment precludes any definitive conclusions about whether or not SSRIs were etiologically related to ischemic stroke. In conclusion, the risk of thromboembolic stroke due to vasoconstrictive effects of SSRIs may be small and clinically irrelevant. The antiplatelet effect of SSRIs may have weak protective effects against ischemic events.

Clinical Implications

The limited evidence from case-control studies documents the cerebrovascular safety of SSRI treatment. However, the possibility of an increased stroke risk with SSRI use cannot be totally ruled out in high-risk patients who are vulnerable for hemorrhagic stroke, bleeding diathesis, or vasospasm. Further, despite the low probability, the serious consequences of SSRI-related stroke might be a major concern to patients and families. Furthermore, because of the increased utilization of SSRI antidepressants in recent years, even low-frequency adverse effects such as stroke may become more clinically relevant. Hence, until more information is available on this subject, it is important for practicing clinicians to know general guiding principles that would enable them to use SSRIs effectively and safely in stroke patients. In clinical practice, consideration should be given to the evaluation of the benefit-risk relationship while prescribing SSRIs to stroke patients. The issues related to prevention and management of SSRI-associated cerebrovascular adverse reaction and the evaluation of the cause-effect relationship between SSRI use and stroke in a given clinical situation also need attention.

In regard to risk-benefit assessment, SSRIs such as citalopram and fluoxetine have been shown to be effective in the treatment of poststroke depression in randomized, controlled trials.[17,20] In addition, sertraline was found to be effective in the prevention of depression in stroke patients,[24] and fluoxetine seems to facilitate stroke recovery, even in nondepressed stroke patients.[30] The neuronal recovery in stroke might be mediated through the effects of SSRIs on brain-derived neurotrophic factor and neurogenesis.[79] The documented protective effects of paroxetine on the incidence of myocardial infarction in post-MI depressed patients[75] may also suggest additional benefits in stroke patients with cardiac disease. Sertraline also seems to have antiplatelet effects in post-MI depressed patients,[78] and it reduces the risk of MI in stroke patients.[80] Hence, the use of SSRI antidepressant treatment in stroke patients has an additional advantage due to antiplatelet effects against ischemic events. Interestingly, treatment with fluoxetine for 12 weeks during the first 6 months after stroke seems to reduce the mortality rate in both depressed and nondepressed patients.[81] Further, SSRIs as a class are relatively safer in overdose and have fewer cardiotoxic effects than tricyclics.[82,83] Although clinical trials demonstrated safety and efficacy of nortriptyline in poststroke depression,[20,23,84] some recent studies have reported more cardiac side effects with nortriptyline treatment than with paroxetine in post-MI patients.[85] Further, the maintenance efficacy of

nortriptyline has not been demonstrated in geriatric depression.[86] In summary, the benefits of treating poststroke depression with SSRIs seem to outweigh the small risk of bleeding and vasospasm.

Since little is known about the prediction of SSRI-related risk of intracranial bleeding or vasospasm, some general principles can be followed to prevent these serious adverse events. Greater antiplatelet effects are generally associated with SSRIs, which have high affinity for 5-HTT (paroxetine, fluoxetine, and sertraline) and at higher doses.[75] The high-affinity SSRIs at higher doses may provide protection against ischemic events but increase the risk of bleeding or vasospasm due to antiplatelet effects or serotonergic overstimulation.

To minimize bleeding risk with SSRI use, it may be advisable to select an SSRI of low or moderate affinity with proven efficacy in poststroke depression, such as citalopram,[17] and to initiate it at low doses. The use of high-end therapeutic doses requires careful monitoring of platelet function if bleeding is a concern, especially in concomitant use with anticoagulants and in patients with intracranial bleeding. The recent availability of a new reliable platelet function analyzer (PFA 100) will enable clinicians to monitor medication-related platelet dysfunction accurately, which might prove useful to predict and prevent medication-induced bleeding.[87,88]

To reduce the bleeding risk due to combined use of SSRIs with anticoagulants or NSAIDs, the following steps can be taken. Citalopram and sertraline are known to have mild inhibition on P450 enzymes and, hence, the concomitant use of anticoagulants (e.g., warfarin) may have less potential for drug interactions and bleeding.[89] When the combination of an NSAID and an SSRI is clinically inevitable, cyclooxygenase-2 (COX-2)–selective NSAIDs may be preferred due to their weak effect on platelet aggregation.[90]

There is no credible evidence against the use of SSRIs in patients with intracranial bleeding. Hence, SSRIs are not contraindicated in hemorrhagic stroke. If another class of antidepressants is preferred, consideration should be given to non-SSRI antidepressants with low or no affinity for 5-HTT such as nortriptyline, mirtazapine, venlafaxine, or noradrenergic antidepressants.[47] However, the effectiveness and safety of mirtazapine, venlafaxine, and noradrenergic antidepressants in poststroke depression have not been evaluated in randomized, controlled trials.

The vasospastic effects of SSRIs can be minimized by preventing serotonergic overstimulation (serotonin syndrome) and serotonin-catecholamine drug interactions. To that effect, it is preferable to avoid maximal or higher therapeutic doses of SSRIs. Caution should be exercised in the concomitant use of SSRIs with other serotonergic or serotonin-enhancing drugs such as lithium, monoamine oxidase inhibitors, antimigraine drugs, and cold remedies,[91] especially in patients who are at risk of vasospastic diseases (migraine, subarachnoid hemorrhage postpartum).

The increase in aging population[92] and high utilization of antidepressants[93] may lead to spurious associations between SSRI use and stroke. Hence, it is inevitable that clinicians might be faced with the question of whether SSRI use has contributed to either the development or progression of stroke in a given patient. Liaison with neurologists is crucial in the causality assessment. Because cerebrovascular adverse events with SSRIs are rare and infrequent, it is pertinent to rule out all common causes of stroke and to look for alternative explanations, differential diagnosis, and preexisting CVD. Careful analysis of comorbid medical conditions (migraine, cerebral aneurysm, cerebrovascular atherosclerosis), concomitant medication use (anticoagulants, NSAIDs, antimigraine drugs, serotonergic or serotonin-enhancing drugs), prior reports of reaction with SSRIs (worsening of migraine; cutaneous, gastrointestinal, or other bleeding with previous SSRI use), and a temporal relationship between dose increases or higher dose titration and cerebrovascular reaction may help to determine a causality relationship. Specific findings such as high concentrations of SSRIs in plasma, impairment in platelet function and bleeding parameters, and bilateral vasoconstriction may also be helpful to justify the causal effect. The application of structured instruments (ADR probability scale or diagnostic instruments)[94,95] will be useful in classifying the causality outcomes into categories from doubtful to highly probable groups. The reporting of cerebrovascular adverse reaction to medical journals and/or adverse drug reaction databases is important.

Besides causality assessment, the management of the offending agent as well as reporting of ADRs to medical journals and/or adverse reaction databases are also considered to be the responsibilities of the treating physician. Discontinuation of the offending agent is a recommended treatment strategy for ADRs. Although abrupt discontinuation of SSRIs in serotonin syndrome usually will not lead to discontinuation syndrome, it may do so in other situations.[96] The manifest symptoms of discontinuation syndrome, including agitation, ataxia, and muscle weakness, may complicate the clinical picture of stroke.[97] Discontinuation syndrome can be prevented by switching from high-affinity SSRIs to low-affinity SSRIs or weaning the medication in 48 to 72 hours or substituting with another class of antidepressants.[96] The issue of rechallenge[98] with SSRIs may not be a practical option given the seriousness of stroke incident, and switching to non-SSRI medication will be more reassuring to the patient and the family.

CONCLUSIONS AND FUTURE DIRECTIONS

The weak antiplatelet and vasoconstrictive effects of SSRIs have no demonstrable significant cerebrovascular

protection or adverse reactions in the general population as evidenced in limited empirical data. More prospective case-control studies are needed to examine the class effect and specific drug effect of SSRIs, based on their affinity for 5-HTT for ischemic and hemorrhagic stroke. The role of SSRIs in the alteration of risk of ischemic stroke or increasing the risk of ICH in high-risk stroke patients needs to be examined. To date, there have been no in vivo or in vitro studies examining directly the effect of SSRIs on platelet function in stroke patients. Since both stroke[99] and depression are associated with platelet activation,[100,101] the antiplatelet effect of SSRIs may benefit patients with poststroke depression, an effect that needs further evaluation. Since 5-HTT promoter region polymorphism determines the transcriptional activity of 5-HTT[102] and the antiplatelet effect of SSRIs dependent on the affinity for 5-HTT,[7,36] the association between this polymorphism and the bleeding potentials or ischemic protective effects of SSRIs awaits further elucidation. More information is needed to fully understand the pathophysiology of vasospastic effects of SSRIs. The effects of SSRIs at 5-HT_2 receptor sites in the endothelium and atherosclerotic cerebral vessels as well as the effect of 5-HT_2 antagonism on the vasoconstrictive effect of SSRIs need further exploration through preclinical and clinical studies.

More studies are required to understand cellular mechanisms mediating the antiplatelet effect of SSRIs and other antidepressants. Antidepressants may exert antiplatelet activity through multiple mechanisms, such as inhibition of 5-HTT, reduction in intraplatelet calcium mobilization, down-regulation of noradrenergic receptors, and alteration in secondary messenger systems.[101] If the antiplatelet effect of SSRIs is related to multiple mechanisms, in addition to inhibition of 5-HTT, then the selection of SSRIs based on their affinity in the treatment of depression with vascular diseases needs revision. Mechanistic studies would also help to determine whether SSRIs are better than non-SSRI antidepressants in ischemic protection in patients with vascular disease and depression. Future studies are needed to investigate the effect of depression recovery versus nonrecovery in the association between SSRIs and the risk of ischemic stroke, since both depression recovery and SSRI peripheral action on platelet function may have independent and additive effects in the normalization of platelet activation associated with depression and acute stroke.

Because of the low rate of SSRI-related cerebrovascular adverse reactions in the general population, a large sample size will be needed, which could be achievable only with national or international data collection. Hence, voluntary adverse event reporting is crucial in understanding the infrequent, but serious, cerebrovascular adverse reaction. Implementation of mandatory reporting of any serious adverse event such as stroke needs consideration. In this context, the emphasis on postmarketing surveillance is also well placed.[103]

Causality assessment is an important step toward the recognition of true adverse reaction from spurious associations.[104–106] Identification of SSRI treatment–associated cerebrovascular ADRs will be a challenge if the occurrence of CVA is widely separated in time from the onset of SSRI treatments, which may be the case in most clinical situations. Further, this causality assessment will also be problematic in patients with preexisting stroke or stroke risk factors, since recurrence of stroke due to nondrug vascular causes is common in these populations. The evaluation of cause-effect relationship should be based on both clinical judgment (clinical, radiological, and biochemical parameters) and adverse reaction probability scales or adverse reaction diagnostic instrument (Bayesian Adverse Reaction Diagnostic Instrument).[94,95,104] The development of the Bayesian Confidence Propagation Neural Network (BCPNN), a method used for ADR signal detection, as a research tool for analysis of ADRs[107] is an important step toward unbiased recognition of causality, drug interaction, and other risk factors of ADRs documented in WHO data. In summary, more information is needed to improve our understanding of the contribution of SSRI treatment to the prevention or progression of cerebrovascular diseases.

Drug names: albuterol (Ventolin, Proventil, and others), amitriptyline (Elavil and others), citalopram (Celexa), clomipramine (Anafranil and others), clonazepam (Klonopin and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil and others), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor), warfarin (Coumadin, Jantoven, and others).

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