Serotonin Reuptake Inhibitors and Risk of Abnormal Bleeding

Chittaranjan Andrade, MD[a,*], Eesha Sharma, MD[b]

KEYWORDS

• Antidepressant • Serotonin reuptake inhibitor • Selective serotonin reuptake inhibitor
• Bleeding • Postpartum hemorrhage • Intracranial hemorrhage
• Nonsteroidal anti-inflammatory drugs • Antiplatelet drugs

KEY POINTS

- Antidepressants with potent serotonin reuptake inhibitor (SRI) activity increase the risk of bleeding through different mechanisms.
- The upper gastrointestinal (GI) tract is the commonest site of SRI-related abnormal bleeding.
- The risk of SRI-related upper GI bleeding is raised by concurrent treatment with nonsteroidal anti-inflammatory drugs, antiplatelet drugs, and anticoagulant drugs; the risk is lowered by acid-suppressing drugs.
- SRIs may also increase the risk of intracranial bleeding, perioperative bleeding, postpartum bleeding, and bleeding at various sites in patients with liver disease.
- Patients are at risk of SRI-related abnormal bleeding primarily during the period of actual use.

Serotonin reuptake inhibitor (SRI) drugs (**Box 1**), which include the selective serotonin reuptake inhibitors (SSRIs) and antidepressants such as clomipramine and venlafaxine, are extensively prescribed in psychiatry for short- and long-term use across a range of diagnoses. This article updates an earlier review[1] on bleeding as an adverse effect (AE) of SRI treatment.[1] Although most of the research addresses SSRI use, the findings are conceptually applicable to all potent SRIs.

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[a] Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore 560 029, India; [b] Department of Psychiatry, King George's Medical University, Lucknow 226 003, India
* Corresponding author.
E-mail address: andradec@gmail.com

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Box 1
Important serotonin-reuptake inhibitor drugs

Selective serotonin reuptake inhibitors:

Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram

Other potent serotonin reuptake inhibitors:

Clomipramine, venlafaxine, vilazodone

MECHANISMS OF ABNORMAL BLEEDING ASSOCIATED WITH SEROTONIN REUPTAKE INHIBITORS

Platelets release serotonin in response to vascular injury; this triggers vasoconstriction and platelet aggregation, resulting in hemostasis. SRIs inhibit uptake of serotonin into platelets much as they inhibit reuptake of serotonin into presynaptic neurons; because platelets do not synthesize serotonin, the SRI effect results in serotonin depletion in platelets, and hence, reduced efficiency of hemostasis.[1]

SSRIs also increase gastric acidity, which may explain why most of the literature on SSRI-related bleeding addresses upper gastrointestinal (GI) bleeds.[1] In this context, a population-based case-control study found that SSRI users (compared with nonusers) had odds of 1.5 (95% confidence interval [CI], 1.18–1.90) of uncomplicated peptic ulcers.[2]

SSRIs may reduce platelet/endothelial activation beyond that associated with concurrent antiplatelet drugs such as aspirin and clopidogrel.[3,4] Other indirect platelet-related mechanisms include interaction with the glycogen IIb/IIIa surface receptor involved in platelet activation.[5] Also, long-term treatment with sertraline upregulates the expression of glycogen synthase kinase 3-β(GSK3B) on platelets[6]; GSK3B acts as a negative regulator of platelet function and thrombosis and might contribute to bleeding risk with SRI use.

Cardiovascular and cerebrovascular benefits associated with these mechanisms are reviewed elsewhere.[7] The timelines for bleeding risks are presented in **Boxes 2** and **3**.[8]

SITES OF ABNORMAL BLEEDING

SRI-related bleeding has been reported at several important sites. These sites are listed in **Box 4**. Stray reports describe bleeding at other sites[9–17]; in this context, underreporting may be a problem because patients, caregivers, and physicians may not suspect a connection between the bleeding and the SRI. In support of such case reports, which by themselves do not constitute evidence, one study[18] reported that in patients taking SSRIs and coumarins, there was an increased risk of bleeding from non-GI sites such as the eye, nose, joints, skin, respiratory tract, uterus, or sites of surgical procedure (odds ratio [OR] = 1.7; 95% CI, 1.1 to 2.5).

EVIDENCE OF ABNORMAL BLEEDING: GENERAL ISSUES

Meta-analyses of observational studies have found ORs of 1.5 to 1.6 for risk of upper GI bleeding with SRIs[19,20] (**Box 5**). Meta-analysis also suggests SSRI-related increased risk of intracranial hemorrhage (relative risk [RR] = 1.51; 95% CI, 1.26–1.81) and intracerebral hemorrhage (RR = 1.42; 95% CI, 1.23–1.65),[21,22] and