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Which patients taking SSRIs are at greatest risk of bleeding?

It depends on degree of SSRI selectivity and concomitant use of other agents

Practice recommendations

- For patients at high risk of abnormal bleeding, consider prescribing an antidepressant with low serotonin reuptake inhibition, which may lower risk.
- For patients taking high–serotonin reuptake inhibition antidepressants, recommend avoidance or minimal use of nonsteroidal anti-inflammatory drugs and aspirin.

Patients taking selective serotonin reuptake inhibitors (SSRIs) seem to be at higher risk of bleeding episodes than those taking non-SSRI antidepressants. But risk also varies within the SSRI category.

What the literature tells us

We identified 7 retrospective studies, 1 pilot study, and several case reports that discuss the relationship between SSRIs and bleeding. We also identified 2 additional papers that addressed the issue from epidemiologic and pharmacologic perspectives. While many case reports also document this relationship, our focus is on studies with larger samples.

Degree of reuptake inhibition matters

The most recent study[1,2] examined SSRI use and the risk of abnormal bleeding associated with the degree of serotonin reuptake inhibition (SRI). Antidepressants were divided into 3 groups: *high SRI* (fluoxetine [Prozac], sertraline [Zoloft], paroxetine [Paxil]), *intermediate SRI* (venlafaxine [Effexor], amitriptyline [Limbitrol], fluvoxamine [Luvox]), and *low SRI* (mirtazapine [Remron], bupropion [Wellbutrin], nortriptyline [Aventyl, Pamelor]). The high-SRI group showed the greatest risk of hospitalization due to abnormal bleeding (odds ratio [OR]=2.6 compared with the low-SRI group), followed by the intermediate-SRI group (OR=1.9 compared with the low-SRI group).

Similarly, another study[3] found a 3.7-fold increased risk of blood transfusion among elderly users of SSRIs (paroxetine, fluoxetine, clomipramine [Anafranil]) who underwent orthopedic surgery.

A third study[4] showed patients taking high-SRI antidepressants (paroxetine, fluoxetine, sertraline, and clomipramine) had a higher risk of developing upper gastrointestinal (GI) bleeding compared with those taking low-SRI antidepressants (bupropion, nortriptyline, desipramine [Norpramin,

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Pertofrane]). This risk was even higher among patients with a history of GI bleeding.

NSAIDs, aspirin aggravate bleeding potential

A population-based case-control study[5] also found an increased incidence of upper GI bleeding with SSRIs, though this effect was not found to be modified by age, sex, dose, or treatment duration. The effect however, was enhanced by the concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs), with a relative risk (RR) of 15.6 (95% CI, 6.6–36.6), as well as with aspirin but to a lesser degree (RR=7.2; 95% CI, 3.1–17.1).

A large (N=26,005) cohort study[6] of all users of antidepressants in a Danish county found that the risk of upper GI bleeding was higher with SSRIs compared with non-SSRIs and other antidepressants. Concomitant use of aspirin and NSAIDs further increased the risk by 12.2 and 5.2 times, respectively.

Risk of bleeding not dependent on duration of therapy

A large observational cohort study[7] found rates of abnormal bleeding 1 month after initiating SSRI therapy (fluoxetine, fluvoxamine, sertraline, paroxetine) did not differ significantly from 2 to 6 months into treatment. Nonetheless a combined SSRI cohort was found to be at greater risk for a hemorrhagic event compared with a baseline cohort.

The remaining 2 retrospective studies found no evidence of increased intracranial hemorrhage in patients taking SSRIs.[8,9]

In terms of clotting and bleeding parameters, a pilot study (n=10) did not show any significant differences before and after a trial of fluoxetine.[10] One case report,[11] however, has suggested that antidepressants may influence these parameters as was seen by a prolonged bleeding time.

The retrospective studies examined the degree that SRI increased the risk of abnormal bleeding, and considered confounding factors such as body mass index, NSAID use, smoking status, sex, and age. However, these were not randomized controlled trials and most participants were women.

How SSRIs increase the risk of bleeding

Serotonin promotes platelet aggregation, and it is thought that SSRIs limit uptake of blood serotonin by platelets.[1] The decreased amount of serotonin in platelets may increase the risk of abnormal bleeding.[1,3,4,6] SSRIs also appear to modify the formation of platelet plugs, as well as the responsiveness of peptide-induced activation of platelets through stimulation of the thrombin receptor.[12]

Take-home messages

SSRI use increases risk of bleeds, admission for abnormal bleeding, and perioperative transfusion. Moreover, the higher the degree of SRI, the higher the risk of bleeding.

Concomitant use of NSAIDs or aspirin further increases this risk.

Antidepressants with low SRI, such as bupropion and mirtazapine, may be associated with a lower risk of abnormal bleeding, although data are insufficient to make a definitive conclusion. Further research is needed to determine if these antidepressants may be more appropriate for patients at high risk of abnormal bleeding.

More research is also needed to clarify conflicting results to date on whether antidepressants cause abnormalities in bleeding or clotting profiles.

FAST TRACK

Use of SSRIs increases the risk of bleeding; concomitant use of NSAIDs or aspirin increases this risk

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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