Serotonin Reuptake Inhibitor Antidepressants and Abnormal Bleeding: A Review for Clinicians and a Reconsideration of Mechanisms

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Background: It is generally believed that selective serotonin reuptake inhibitor (SSRI) drugs increase the risk of abnormal bleeding and decrease the risk of ischemic heart disease events by blocking the uptake of serotonin into platelets, leading to an impairment in the platelet hemostatic response.

Objective: To perform a detailed qualitative review of existing literature on the association of abnormal bleeding with the use of SSRIs.

Data Sources: We conducted a PubMed search during June 2009 using the search terms *antidepressants* and *SSRIs* (including the names of individual SSRIs: *fluoxetine*, *sertraline*, *paroxetine*, *fluvoxamine*, *citalopram*, and *escitalopram*) in association with *bleeding*, *platelets*, *hemostasis*, *nonsteroidal anti-inflammatory drugs* (*NSAIDs*), *aspirin*, *antiplatelet drugs*, *proton pump inhibitors*, *peptic ulcer*, *premenstrual dysphoric disorder*, *menstruation*, *pregnancy*, *postpartum hemorrhage*, *surgery*, *tooth extraction*, *dental bleeding*, *stroke*, *ischemic heart disease*, and other terms related to the field. We then searched the reference lists of identified studies.

Study Selection: We provide a qualitative discussion of all studies that would inform clinicians about the mechanisms of bleeding and bleeding risks associated with these drugs in different clinical contexts.

Results: Epidemiologic studies show that SSRI use is associated with roughly doubled odds of upper gastrointestinal (GI) bleeding; bleeding at other sites has been less commonly described, as has a possibly increased risk of bleeding associated with surgical procedures. The risk of SSRI-associated GI bleeding is increased with the concurrent use of NSAIDs, anticoagulants, and antiplatelet agents and is decreased by concurrent proton pump inhibitors. The risk of bleeding is increased in patients with cirrhosis of the liver or liver failure. There is, curiously, little literature on use of SSRIs and menstrual or postpartum blood loss. Selective serotonin reuptake inhibitors appear protective against ischemic heart disease events. The data are too limited to allow interpretations about influences on ischemic and hemorrhagic stroke.

Conclusions: On the basis of the findings of our literature search, we suggest that SSRI-induced increase in gastric acid secretion may explain the GI bleeding risk and that SSRI-related effects on platelet reactivity, endothelial reactivity, and inflammatory markers may explain the ischemic heart disease protective effect. Because the absolute risk of GI bleeds with SSRIs is low, precautions are probably necessary only in high-risk patients, such as those with acid-peptic disease and those with a history of bleeds. We discuss management issues and areas for future research.

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Selective serotonin reuptake inhibitor (SSRI) drugs are used in the treatment of diverse disorders in psychiatry, including depression, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and other conditions.[1] During the past decade, much literature has been published on the risk of abnormal gastrointestinal (GI) bleeding as an infrequent adverse effect of SSRI treatment. During the past decade, studies have also indicated that SSRIs may protect against ischemic heart disease events. Both effects have been suggested to arise from impaired hemostasis because serotonin weakly potentiates platelet aggregation and because SSRIs inhibit the uptake of serotonin into platelets.

As bleeding disturbances with SSRIs can be life-threatening, it is necessary to understand the magnitude of the risk and to identify factors that may magnify or diminish the risk so that treatment decisions can be rationally made. Protection against ischemic heart disease events is of major public health significance. This article therefore presents a qualitative and clinically relevant review of the field and challenges certain currently held views on the mechanisms involved in the findings.

An advance note is made here that most of the clinical data have been obtained within the context of SSRI drugs (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram); however, as will be apparent from the section on mechanisms (as well as the section on the drugs that increase the risks of bleeds), some of the conclusions that apply to SSRIs could also apply to nonselective serotonin reuptake inhibitor (SRI) drugs such as venlafaxine.

METHOD

Data Sources

A PubMed search was conducted during June 2009 using the search terms *antidepressants* and *SSRIs* (including the names of individual SSRIs: *fluoxetine*, *sertraline*, *paroxetine*, *fluvoxamine*, *citalopram*, and *escitalopram*) in association with *bleeding*, *platelets*, *hemostasis*, *nonsteroidal anti-inflammatory drugs* (*NSAIDs*), *aspirin*, *antiplatelet drugs*, *proton pump inhibitors*, *peptic ulcer*, *premenstrual dysphoric disorder*, *menstruation*, *pregnancy*, *postpartum hemorrhage*,

For Clinical Use

- Patients at risk for abnormal bleeding with serotonin reuptake inhibitor (SRI) drugs include those with acid-peptic or liver disease, those undergoing surgical or dental procedures, and those receiving concurrent anticoagulant, antiplatelet, or nonsteroidal anti-inflammatory drugs. Whereas the absolute risk appears low, non-SRI drugs may be preferable in such patients.
- Proton pump inhibitors may decrease the risk of SRI-related gastrointestinal (GI) bleeds. SRIs should be withdrawn, if feasible, before elective major or minor surgical procedures.
- Whenever relevant, the risk of SRI-related bleeding should be monitored, such as through testing for occult blood in stools in patients at risk of GI bleeds.

surgery, *tooth extraction*, *dental bleeding*, *stroke*, *ischemic heart disease*, and terms related to the field as evident from the subsections that follow. Snowball searches were also conducted of the reference lists of identified articles to find additional studies.

Study Selection

The literature identified was qualitatively evaluated for clinical leads that could provide scholarly answers to questions such as the following:

- What is the evidence for SSRI-associated bleeding?
- Which are the antidepressants associated with an increased risk of bleeds?
- How serious is the risk?
- What are the mechanisms proposed to explain bleeding with SSRIs?
- Which concurrently administered medications increase or decrease the risk?
- Which concurrent medical and physiologic conditions increase the risk?
- What are the bleeding risks associated with SSRI use by patients who undergo surgical procedures?
- Do SSRIs increase the risk of menstrual or postpartum bleeding in women?
- What are the (other) sites at which SSRIs increase the risk of bleeding?
- What are the hemostatic benefits and risks of SSRIs in patients with ischemic heart disease and stroke?

We present our findings with a predominantly clinical slant; whereas we do critically evaluate selected studies, a general discussion on the limitations of epidemiologic and case-control studies has been well presented by Ramasubbu[2] and will not be detailed in this review.

RESULTS AND DISCUSSION

What Is the Evidence for Abnormal Bleeding With Selective Serotonin Reuptake Inhibitors?

A large number of case reports, case series, and epidemiologic studies suggest that SRIs but not other antidepressant drugs are associated with an increased risk of bleeding, especially from the upper GI tract. Drugs with stronger inhibition of serotonin reuptake may carry higher risks. Older patients may be at greater risk. The risk is present only for as long as the drugs are taken. The risk is increased by the concurrent use of drugs such as aspirin and NSAIDs. In Table 1, we summarize the findings of large studies on the subject, published during the past 10 years.[3–16]

Which Antidepressants Increase the Risk of Abnormal Bleeding?

As we discuss under mechanisms, antidepressants that inhibit serotonin reuptake are specifically associated with the risk of abnormal bleeding. Therefore, the risk could be greatest with the designated SSRIs—but also evident with newer dual-action drugs, such as venlafaxine, that also potently inhibit serotonin reuptake. Several studies have shown that the risk is specific to SRIs and that non-SRI antidepressants do not increase the risk.[3,5,6,12,15] Some studies have also shown that the risk increases with increased potency of serotonin reuptake inhibition.[4]

Some studies examined risks associated with individual drugs. In one study,[6] only amitriptyline, fluoxetine, clomipramine, and paroxetine significantly increased the risk of GI bleeds. Such results must be viewed with caution because sample sizes may not have been adequate to identify risks with exonerated drugs.

How Serious Is the Risk of Abnormal Bleeding With Use of Selective Serotonin Reuptake Inhibitors?

Not all studies indicate an increased risk of GI bleeding with SRI drugs (Table 1). In studies that do indicate a risk, distortion in risk estimation may arise from samples comprising patients hospitalized for bleeds; data are unavailable for patients with bleeds who are not diagnosed or admitted.

Overall, the risk of abnormal bleeds with SSRIs appears low. For example, de Abajo et al[3] obtained a crude incidence of 1 upper GI bleed per 8,000 SSRI prescriptions. Van Walraven et al[4] found that, during a median observation period of 1 to 2 months, the number needed to harm was 85 for new bleeding with SSRIs in elderly patients with a history of previous bleeds; in octogenarians, the corresponding number needed to harm was 244. Dalton et al[5] observed that the use of SSRIs increased the risk of bleeding by only 3.1 patients per 1,000 treatment years. Meijer et al[6] found that the crude risk of bleeding with antidepressant drugs was 4.9 per 1,000 patient-years. In a meta-analysis of 4 observational

Table 1. Bleeding With Use of Selective Serotonin Reuptake Inhibitors (SSRIs): Evidence[a,b]

Study	Sample	Findings
de Abajo et al[3] (1999)	1,651 patients with upper GI bleeding; 248 patients with ulcer perforation; 10,000 matched controls from the population	Risk of upper GI bleeding was increased in patients receiving SSRIs (RR = 3.0; 95% CI, 2.1–4.4) and nonselective SRIs (RR = 1.4; 95% CI, 1.1–1.9) but not in those receiving antidepressants that do not inhibit serotonin reuptake (RR = 0.8; 95% CI, 0.1–2.4) Use of SSRIs with NSAIDs increased the risk of upper GI bleeding beyond the sum of their independent effects (RR = 15.6; 95% CI, 6.6–36.6) Antidepressants were not associated with the risk of ulcer perforation (SSRIs: RR = 1.3; 95% CI, 0.4–3.7; non-SSRIs: RR = 0.4; 95% CI, 0.2–1.1; other antidepressants: RR = 1.3; 95% CI, 0.2–10.1)
van Walraven et al[4] (2001)	317,824 elderly subjects in a patient database, observed for > 130,000 person-years	Drugs with stronger inhibition of serotonin reuptake were more likely to be associated with GI bleeds than drugs with weaker inhibition of serotonin reuptake (RR = 1.10; 95% CI, 1.02–1.19) The risk was most apparent in older subjects and in those with previous GI bleeding
Dalton et al[5] (2003)	Hospitalization for upper GI bleeding compared between 26,005 users of antidepressant drugs and population-based controls who did not receive an antidepressant prescription	Use of an SSRI more than tripled the risk of hospitalization for upper GI bleeding (O/E = 3.6; 95% CI, 2.7–4.7). The risk returned to unity when SSRI use was terminated The risk was much increased when low-dose aspirin (O/E = 5.2; 95% CI, 3.2–8.0) or an NSAID was concurrently used (O/E = 12.2; 95% CI, 7.1–19.5) Other antidepressant drugs that (less potently) inhibit serotonin reuptake also increased the risk (O/E = 2.3; 95% CI, 1.5–3.4), but antidepressants without effect on serotonin reuptake did not increase the risk (O/E = 1.7; 95% CI, 0.8–3.1)
Meijer et al[6] (2004)	64,647 new antidepressant users followed up for an average of 229 days; 972 matched controls	Risk of hospitalization for abnormal bleeding was significantly greater for antidepressants with intermediate (OR = 1.9; 95% CI, 1.1–3.5) and high (OR = 2.6; 95% CI, 1.4–4.8) degrees of serotonin reuptake inhibition relative to antidepressants with low affinity for the serotonin transporter
Tata et al[7] (2005)	11,261 patients with upper GI bleeding; 53,156 database-matched controls	SSRI (OR = 2.38; 95% CI, 2.08–2.72) and NSAID (OR = 2.15; 95% CI, 2.02–2.28) use was associated with an increased risk of bleeding. The risk was only marginally higher when SSRIs and NSAIDs were concurrently used (OR = 2.93; 95% CI, 2.25–3.82)
Wessinger et al[8] (2006)	579 inpatients with GI bleeding; 1,000 matched inpatient controls without GI bleeding	SSRI use was more common in patients than in controls (OR = 1.5; 95% CI, 1.2–2.0) SSRI use was significantly associated with lower (OR = 1.8; 95% CI, 1.2–2.8) but not upper (OR = 1.3; 95% CI, 0.8–1.9) GI bleeds Risk of bleeding with SSRIs was increased in patients who concurrently used NSAIDs (OR = 12.2; 95% CI, 1.5–99.7) or aspirin (OR = 2.1; 95% CI, 1.3–3.3) but not in those who used COX-2 inhibitors (OR = 0.6; 95% CI, 0.3–1.4)
Helin-Salmivaara et al[9] (2007)	9,191 inpatients with serious upper GI events; 41,780 population-based matched controls	Risk of serious upper GI events was elevated with SSRI use (OR = 1.30; 95% CI, 1.13–1.50) and with concurrent SSRI and NSAID use (OR = 4.19; 95% CI, 3.30–5.31) relative to the nonuse of either drug. Risk was elevated with concurrent SSRI and NSAID use relative to NSAID-only use (OR = 1.57; 95% CI, 1.24–1.99)
Ziegelstein et al[10] (2007)	158 acute coronary syndrome inpatients who received SSRIs; propensity-matched controls	SSRI-treated patients were significantly more likely to experience abnormal in-hospital bleeding (OR = 1.65; 95% CI, 1.02–2.66). Non-SSRIs did not affect bleeding events
de Abajo et al[11] (2008)	1,321 patients with upper GI bleeding; 10,000 matched population-based controls	Significantly more patients than controls were currently using SSRIs (5.3% vs 3.0%; OR = 1.6; 95% CI, 1.2–2.1) or venlafaxine (1.1% vs 0.3%; OR = 2.9; 95% CI, 1.5–5.6) Association between SSRIs and bleeding was further enhanced by the concurrent use of NSAIDs (OR = 4.8; 95% CI, 2.8–8.3). In particular, risk was more in nonusers of acid-suppressing agents (OR = 9.1; 95% CI, 4.8–17.3) compared with users of these drugs (OR = 1.3; 95% CI, 0.5–3.3)
Opatrny et al[12] (2008)	4,028 patients with GI bleeding; 40,171 population-based matched controls	SSRIs (OR = 1.3; 95% CI, 1.1–1.6) and venlafaxine (OR = 1.9; 95% CI, 1.3–2.6) but not TCAs (OR = 1.0; 95% CI, 0.8–1.3) were associated with the risk of bleeding
Vidal et al[13] (2008)	2,813 patients with upper GI bleeding; 7,193 population-based matched controls.	The odds ratio for upper GI bleeding in users of SSRIs and NSAIDs (OR = 8.32; 95% CI, 4.69–14.76) did not differ from that in users of NSAIDs only (OR = 7.82; 95% CI, 6.79–9.00) SSRIs did not increase bleeding risk, either by their degree of affinity for the serotonin transporter (OR = 1.23; 95% CI, 0.90–1.68) or by their dose
Targownik et al[14] (2009)	1,552 inpatients with acute upper GI bleeding; 68,590 matched outpatients without upper GI bleeding	SSRI use increased the risk of bleeds (OR = 1.43; 95% CI, 1.09–1.89). Combined use of SSRIs and NSAIDs did not increase the risk of bleeds (OR = 1.20; 95% CI, 0.78–1.92) beyond that associated with NSAIDs alone. Proton pump inhibitor use reduced the risk of SSRI-related bleeds (OR = 0.39; 95% CI, 0.16–0.94)
Dall et al[15] (2009)	3,652 patients with a first discharge diagnosis of serious upper GI bleeding; 36,502 matched controls selected by risk-set sampling; data sourced from prescription database and county patient register	Risk of upper GI bleeds was significant for all categories of SSRI users; the adjusted ORs among current, recent, and past users were 1.67 (95% CI, 1.46–1.92), 1.88 (95% CI, 1.42–2.50), and 1.22 (95% CI, 1.07–1.39), respectively The risk with SSRIs was not dose- or gender-dependent. It was higher with more recent initiation of treatment. It was significantly elevated only at > 55 years of age The risk was not higher in TCA users (OR = 1.15; 95% CI, 0.89–1.47). The risk was significantly elevated with fluoxetine, sertraline, and citalopram but not with other SSRIs or venlafaxine The ORs were elevated from 1.70 (95% CI, 1.49–1.95) in current SSRI users to 8.00 (95% CI, 4.80–13.00) with concurrent SSRI and NSAID use, and to 28.00 (95% CI, 7.60–103.00) in concurrent users of SSRIs, NSAIDs, and aspirin
Barbui et al[16] (2009)	11,025 inpatients with bleeding abnormalities and 21,846 matched inpatient controls; 1,008 inpatients with GI bleeding and 1,990 matched inpatient controls	Antidepressants as a group did not increase the risk of any bleeding abnormalities (OR = 0.99; 95% CI, 0.90–1.08) but increased the risk of GI bleeding (OR = 1.34; 95% CI, 1.01–1.80) Risk of GI bleeding was not increased by SSRIs (OR = 1.31; 95% CI, 0.91–1.88) or TCAs, whereas it was significant with non-SSRI, nontricyclic antidepressants (OR = 1.74; 95% CI, 1.04–2.93)

[a]In some of the articles, it was not clear what the reference groups were or how the risk was calculated. Whenever we were in doubt, we used the authors' own words or numbers. [b]As a general rule, reported ORs were adjusted for confounders.

Abbreviations: COX-2 = cyclooxygenase-2, GI = gastrointestinal, NSAID = nonsteroidal anti-inflammatory drug, O/E = observed-expected risk ratio, OR = odds ratio, RR = relative risk, SRI = serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

studies with a pooled sample size of about 153,000 patients, Loke et al[17] found that 411 patients would need to receive an SSRI for a year for 1 extra patient to experience a GI bleed. A comparison of patients during SSRI-exposed and SSRI-unexposed periods showed that the number needed to harm was 718 (95% CI, 529–1,026) person-years.[15] It must be appreciated that the risk, although small, is not insignificant, especially as GI bleeding is potentially life-threatening.

What Mechanisms Underlie the Bleeding Risk?

Several mechanisms may explain bleeding with SSRI use. These are briefly considered.

Inhibition of serotonin uptake into platelets. Serotonin reuptake inhibitors inhibit the serotonin transporter protein and thereby block the uptake of synaptic serotonin into the presynaptic neuron; they similarly inhibit the entry of serotonin from blood into platelets. As platelets do not synthesize serotonin, and as serotonin release from platelets in response to vascular injury triggers vasoconstriction and platelet aggregation, the use of SRIs could decrease intraplatelet serotonin stores, thereby decreasing the efficiency of platelet-mediated hemostasis. Through this mechanism, SRIs could predispose to bleeding disturbances.[18] The most common resultant hemostatic abnormalities are decreased platelet aggregability and activity and bleeding time prolongation.[19] There is, however, no interaction between serotonin transporter polymorphisms and SSRIs in the modulation of platelet function as assessed by platelet function analyzer closure time and other parameters[20]; alternately, the platelet function analyzer may not be a suitable measure of SSRI-related platelet function impairment.[21]

Increase in gastric acid secretion. Importantly, SSRIs have been shown to directly increase gastric acidity; this increase could have an ulcerogenic effect, resulting in GI bleeding. In a rodent model, fluoxetine and sertraline both increased gastric acid secretion; this effect was abolished by vagotomy.[22] Again, in a rodent model, paroxetine dose-dependently increased gastric acid secretion; this effect was synergistic with coadministered low-dose aspirin.[23] In this context, de Jong et al[24] found that the incidence rate ratio (IRR) for the first prescription of peptic ulcer drugs was not significantly elevated with the combination of an NSAID and a nonselective antidepressant drug (N = 74; IRR = 2.5; 95% CI, 0.3–20.3) but was markedly elevated with the NSAID-SSRI combination (N = 86; IRR = 12.4; 95% CI, 3.2–48.0). Findings that proton pump inhibitors reduce the risk of SSRI-related GI bleeds will be presented in a later section.

Surprisingly, whereas the serotonin uptake mechanism for bleeding risk has been widely referenced in literature, the gastric acidity mechanism has received almost no attention. We believe that the gastric acidity mechanism may be more important if only because, as will be evident from the sections that follow, SRI-related bleeding has most commonly been described at upper GI sites. Curiously, GI adverse effects with SSRIs are very well known, but the prescribing information for the SSRIs includes gastritis and peptic ulcer only as infrequent or rare adverse effects.

Other mechanisms. Fluoxetine, fluvoxamine, and paroxetine potently inhibit cytochrome P450 (CYP) enzymes such as CYP 1A2, 2D6, 3A4, and 2C9. Thereby, they may inhibit the metabolism and raise the blood levels of NSAIDs, antiplatelet drugs, and other drugs that are metabolized by these enzymes and that are themselves associated with bleeding risk; thereby, the risk of bleeding with such drugs could increase.[25] Such a mechanism may not contribute much to the interaction between (for example) SSRIs and NSAIDs in potentiating the bleeding risk because most NSAIDs are metabolized by CYP 2C9, an enzyme that is inhibited only by fluvoxamine.[26] Of note, SSRIs have also been described to act on other metabolic pathways that may theoretically impact hemostasis.[27]

Paroxetine inhibits nitric oxide synthase[28]; as nitric oxide inhibits platelet aggregation and adhesion,[29] decreased nitric oxide production associated with paroxetine may actually improve platelet functioning.

Concurrent Nonsteroidal Anti-inflammatory Drug Use as an Aggravating Factor

Nonsteroidal anti-inflammatory drugs increase the risk of upper GI bleeds. Does the combined use of SSRIs and NSAIDs magnify the risk? Many studies suggest so[3,5,8,11,15] (Table 1). For example, Dall et al[15] found that the odds of GI bleeding were elevated from 1.70 (95% CI, 1.49–1.95) in current SSRI users to 8.00 (95% CI, 4.80–13.00) with concurrent use of SSRIs and NSAIDs, and to 28.00 (95% CI, 7.60–103.00) with concurrent use of SSRIs, NSAIDs, and aspirin.

Mort et al[30] examined 4 retrospective studies on GI adverse effects associated with the SSRI-NSAID combination. The risk of an upper GI bleed was increased in persons receiving this drug combination relative to persons not receiving either drug; the relative risk (RR) ranged from 3.3 to 15.6. Two of the studies reviewed by Mort et al[30] found that the risk of bleeding with the combination was greater than the additive risk of the individual drugs. The RR of an upper GI bleed with the SSRI-aspirin combination was 1.9 to 7.2. The number needed to harm for a GI bleed with the SSRI-NSAID combination ranged from 62 to 75 patient-years.

Loke et al[17] described a systematic review and meta-analysis of studies on the risk of GI bleeding with SSRIs and NSAIDs. There were 4 observational studies with a pooled sample of about 153,000 patients. Selective serotonin reuptake inhibitors more than doubled the risk of upper GI bleeding (OR = 2.36; 95% CI, 1.44–3.85). The risk was increased 6-fold when SSRIs and NSAIDs were administered together (OR = 6.33; 95% CI, 3.40–11.80). The absolute risk was nonetheless low. For example, in patients aged > 50 years with no other upper GI bleeding risk factors, the number needed to harm across a year of treatment was 411 for SSRIs alone and 106 for SSRIs with concomitant NSAIDs.

Two recent population-based case-control studies,[13,14] however, reported no increased risk associated with the SSRI-NSAID combination (Table 1). These results and the large number-needed-to-harm values in the pooled analyses suggest that the absolute risk of GI bleeding, although significant, is low when SSRI and NSAID drugs are combined.

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Table 2. Risks of Bleeding Associated With Use of Selective Serotonin Reuptake Inhibitors (SSRIs) Combined With Aspirin, Other Antiplatelet Drugs, and Anticoagulants[a,b]

Study	Sample	Findings
de Abajo et al[3] (1999)	1,651 patients with upper GI bleeding; 10,000 population-based matched controls	Concurrent use of aspirin with SSRIs increased the risk of upper GI bleeding; the OR for the interaction was 7.2 (95% CI, 3.1–17.1), representing an excess risk of 3.5
van Walraven et al[4] (2001)	317,824 elderly subjects observed for >130,000 person-years. Data obtained from patient database	The risk of GI bleeding associated with SSRIs (RR = 1.4; 95% CI, 1.1–1.7) was approximately doubled with concurrent aspirin (RR = 1.7; 95% CI, 1.4–2.0) or anticoagulant use (RR = 2.2; 95% CI, 1.7–2.8)
Dalton et al[5] (2003)	Hospitalization for upper GI bleeding compared between 26,005 users of antidepressant drugs and population-based controls who did not receive an antidepressant prescription	The risk of upper GI bleeding associated with combined use of SSRIs and low-dose aspirin (RR = 5.2; 95% CI, 3.2–8.0) was greater than that with SSRIs alone (RR = 3.6; 95% CI, 2.7–4.7)
Wessinger et al[8] (2006)	579 inpatients with GI bleeding; 1,000 matched inpatient controls without GI bleeding	Logistic regression showed a significant interaction between SSRIs and aspirin for the risk of GI hemorrhage (OR = 2.1; 95% CI, 1.3–3.3)
de Abajo et al[11] (2008)	1,321 patients with upper GI bleeding; 10,000 population-based matched controls	There was no interaction with combined use of SRIs and antiplatelet drugs (primarily low-dose aspirin) (antiplatelet drugs only: OR = 2.4; 95% CI, 1.7–3.3; SRIs only: OR = 2.2; 95% CI, 1.9–2.6; concomitant use: OR = 2.6; 95% CI, 1.6–4.2; RERI = −1.0) or oral anticoagulants (oral anticoagulants only: OR = 2.4; 95% CI, 1.7–3.3; SRIs only: OR = 1.9; 95% CI, 1.5–2.5; concomitant use: OR = 2.9; 95% CI, 1.0–8.9; RERI = −0.4) An interaction between SSRIs and antiplatelet drugs was found in nonusers (OR = 4.7; 95% CI, 2.6–8.3) but not in users of acid-suppressing drugs (OR = 0.8; 95% CI, 0.3–2.5)
Opatrny et al[12] (2008)	4,028 patients with GI bleeding; 40,171 population-based matched controls	No interaction was found with concurrent use of SSRI and warfarin ($P = .43$), SSRI and clopidogrel ($P = .30$), TCA and warfarin ($P = .88$), and TCA and clopidogrel ($P = .79$)
Schalekamp et al[33] (2008)	1,848 patients with abnormal major bleeding with coumarin; 5,818 matched controls selected by risk-set sampling	The SSRI-coumarin combination was associated with an increased risk of hospitalization for non-GI bleeding (OR = 1.7; 95% CI, 1.1–2.5) but not for GI bleeding (OR = 0.8; 95% CI, 0.4–1.5)
Wallerstedt et al[34] (2009)	117 warfarin-treated atrial fibrillation patients who received SSRIs; 117 matched controls who did not receive SSRIs	Clinically relevant bleeding with use of SSRIs occurred at the rate of 51 (95% CI, 26–92) events per 1,000 treatment-years relative to 24 (95% CI, 13–40) events per 1,000 treatment-years in controls. The adjusted hazard ratio for first bleeds with warfarin plus SSRI versus warfarin alone was 3.5 (95% CI, 1.4–8.9)
Hauta-Aho et al[35] (2009)	6,772 warfarin-treated inpatients; 48% were exposed to interacting comedication	Increased risk of bleeding was associated with combined use of warfarin with CYP2C9 inhibitors (eg, fluvoxamine) (OR = 3.6; 95% CI, 2.4–5.6) and SSRIs (OR = 2.6; 95% CI, 1.5–4.3); the use of warfarin with non-SSRI drugs was not associated with increased risk of bleeding (OR = 1.2; 95% CI, 0.3–4.3)
Dall et al[15] (2009)	3,652 patients with a first discharge diagnosis of serious upper GI bleeding; 36,502 matched controls selected by risk-set sampling; data retrieved from a prescription database and county patient register	There was no increase in bleeding risk associated with concurrent use of aspirin and SSRIs (but the analysis may have been underpowered)
Kim et al[36] (2009)	1,076 coronary artery bypass graft patients who received SSRIs compared with propensity-matched controls	There was no increase in bleeding events associated with SSRI use, even in patients who concurrently used antiplatelet or anticoagulant drugs (OR = 1.03; 95% CI, 0.40–2.61) compared to SSRI use alone (OR = 0.93; 95% CI, 0.50–1.76)

[a]In some of the articles, it was not clear what the reference groups were or how the risk was calculated. In 1 article, only probability values were presented. Whenever we were in doubt, we used the authors' own words or numbers. [b]As a general rule, reported ORs were adjusted for confounders.
Abbreviations: GI = gastrointestinal, OR = odds ratio, RERI = relative excess risk due to interaction, RR = relative risk, SRI = serotonin reuptake inhibitor.

Concurrent Antiplatelet and Anticoagulant Drug Use as an Aggravating Factor

Selective serotonin reuptake inhibitors are dose-dependently associated with reduced platelet activation over and above that associated with drugs such as aspirin and clopidogrel.[31,32] So, do SSRIs increase the risk of abnormal bleeding that is associated with the use of antiplatelet or anticoagulant medication? Several studies have examined this question with positive[3–5,8,11,33,34] and negative[12,15,36] results (Table 2).

In a randomized, placebo-controlled, crossover study, Kotzailias et al[37] examined the effects of paroxetine and aspirin on platelet function as assessed by the platelet function analyzer and by flow cytometry. Paroxetine (20 mg/d) was administered to 20 male smokers for 18 days, and aspirin (100 mg/d) was added during the last 4 days. Paroxetine prolonged the epinephrine-dependent predictive index within 14 days; aspirin further enhanced the predictive index. Paroxetine nonsignificantly decreased thrombin receptor–activating, peptide-induced P-selectin (CD62P) expression, and aspirin significantly enhanced this effect. The combination of paroxetine and aspirin did not further inhibit platelet plug formation under high shear stress.

Overall, the data suggest that SSRIs probably do increase the risk of abnormal bleeding associated with antiplatelet and anticoagulant medications, especially aspirin.

Concurrent Proton Pump Inhibitor Use as a Mitigating Factor

Proton pump inhibitors decrease the risk of GI bleeding with NSAIDs. Might these drugs similarly attenuate risks associated with SSRIs? In a case-control study of 1,321 patients with upper GI bleeding and 10,000 matched controls, de Abajo et al[11] found that the synergistic effect of SSRIs and NSAIDs on bleeding risk was magnified among those not using acid-suppressing agents (OR = 9.1; 95% CI, 4.8–17.3)

but was not significant among users of acid-suppressing agents (OR = 1.3; 95% CI, 0.5–3.3). Similarly, the association between SSRIs and bleeding was enhanced by the concurrent use of antiplatelet agents in nonusers of acid-suppressing agents (OR = 4.7; 95% CI, 2.6–8.3) but was not significant among users of acid-suppressing agents (OR = 0.8; 95% CI, 0.3–2.5).

In a population-based case-control study, Targownik et al[14] matched hospitalized patients with upper GI bleeding with nonbleeding controls. Selective serotonin reuptake inhibitor use was associated with a 43% increased risk of bleeds, and concurrent treatment with a proton pump inhibitor significantly reduced this risk (OR = 0.39; 95% CI, 0.16–0.94). In a similar study,[15] elevated bleeding risk in current SSRI users (OR = 1.67; 95% CI, 1.46–1.92) was rendered nonsignificant in those who concurrently used proton pump inhibitors (OR = 0.96; 95% CI, 0.50–1.92).

Timelines

The risk of bleeding with an SSRI is likely to begin from the time that the drug increases gastric acidity and from when serotonin reuptake inhibition becomes clinically significant—such as by the time the drug reaches steady state levels after dose initiation, or even earlier. A caveat here is that platelet serotonin depletion may need to cross a certain threshold for platelet impairment to become clinically significant, in which case the onset of risk may be delayed for several weeks.

The risk is likely to end after increased gastric acidity and serotonin reuptake inhibition are no longer clinically significant, such as when the drug is washed out of the body after treatment discontinuation. As an example, Dalton et al[5] found that the risk of abnormal bleeding was increased in patients only during the period that the SSRIs were taken.

One study[15] found the risk of SSRI-related GI bleeds to be highest during the early weeks of treatment; perhaps patients who experience GI discomfort with SSRIs (ie, those who might be vulnerable to GI bleeds as an adverse effect) may self-select themselves out of longer-term treatment.

In this context, it must be understood that a primary pathology, such as a gastric mucosal lesion, must exist for bleeding to occur. Peptic ulceration and bleeding will not develop immediately upon the initiation of SSRI therapy even if SSRIs do increase gastric acidity. Therefore, bleeding may not occur until the primary pathology develops for whatever reason. Time to bleeding can consequently be very variable. In an analysis of 101 spontaneous reports, Loke et al[17] found that upper GI bleeding occurred after a median of 25 weeks of SSRI treatment. About 67% of these patients were also receiving NSAIDs. The ability of a study to detect SSRI-related upper GI bleeding therefore depends not only on sample size but also on duration of observation.

Abnormal Bleeding From Nongastrointestinal Sites

If inhibited platelet aggregation is a mechanism of SSRI-related bleeds, then bleeds should also be reported from non-GI sites. Such reports, however, are infrequent. Shen et al[38] described bleeding from the gums with sertraline 50 mg/d. Lake et al[39] described 5 children, aged 8–15 years, who developed bruising or epistaxis 1 week to 3 months after starting SSRI treatment. Duijvestijn et al[40] reported a possible association between maternal use of paroxetine and neonatal intraventricular hemorrhage. Sharma[41] described subconjunctival bleeding with escitalopram. Case reports of this nature are few and far between; however, underreporting may be a confound because patients, caregivers, and clinicians who experience or observe such bleeding may not even suspect a possible connection between the bleeding and concurrent SSRI treatment. It must be remembered that case reports provide weak evidence, at best, for an association between SSRI use and abnormal bleeding. Regrettably, little information from clinical samples is available on SSRI-associated abnormal bleeding from non-GI sites.

In patients taking SSRIs and coumarins, Schalekamp et al[33] reported an increased risk of bleeding from non-GI sites such as the eye, nose, joints, skin, respiratory tract, uterus, or surgical procedure sites (OR = 1.7; 95% CI, 1.1–2.5).

Intracranial bleeding. In a systematic review of the literature from 1966 to 2003, Ramasubbu[2] noted that 2 case-control studies failed to show an association between SSRI use and intracranial hemorrhage; one of these also found no association with ischemic stroke. None of 16 studies of SSRI treatment in poststroke patients recorded significant cerebrovascular adverse reactions.

In a very small study of 65 cases of idiopathic intracranial hemorrhage and 254 matched controls, de Abajo et al[42] observed current exposure to SSRIs in 7 cases (10.8%) and 24 controls (9.7%). There was no significant association between SSRI use and the risk of intracranial bleeding. In a larger study, Kharofa et al[43] examined 500 patients with intracerebral hemorrhage and 416 patients with subarachnoid hemorrhage along with population-based controls matched 1:2 for age, sex, and race. About 8% of cases and 9% of controls were receiving SSRIs during the 2 weeks preceding the index event. Kharofa et al[43] found that SSRI use was not associated with an increased risk of intracerebral (OR = 1.1; 95% CI, 0.7–1.8) or subarachnoid (OR = 0.6; 95% CI, 0.4–1.0) hemorrhage, nor did SSRIs potentiate the risk of these events associated with the use of warfarin or antiplatelets agents. The study, however, was not adequately powered to identify a < 60% elevation of risk.

Other notes. The risk of SSRI-related abnormal bleeding in surgical and gynecologic contexts is considered in later sections. In general, it appears that SSRI-related abnormal bleeding may be clinically significant primarily in the context of GI bleeds; perhaps the primacy of SSRI-stimulated gastric acidity is responsible. However, we do not as yet know for certain whether the limited literature on the risk of non-GI bleeds with use of SSRIs is due to a rarity of such bleeds or a lack of attribution of causality to SSRIs when such bleeds occur. Abnormal GI bleeding that results in hospitalization readily reaches the researcher's attention. It is less likely that milder bleeding and bleeding from other sites will be reported or recorded—and hence rendered retrievable in research.

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Abnormal Bleeding Associated With Surgical Procedures

If SSRIs predispose to abnormal bleeding by inhibiting platelet aggregation, they should increase blood loss during or after surgery. In a retrospective study of 520 patients who underwent orthopedic surgery, Movig et al[44] found that blood transfusion was nearly 4 times as frequent in SRI (SSRIs, clomipramine, and venlafaxine; N = 26) users relative to antidepressant nonusers (OR = 3.71; 95% CI, 1.35–10.18). In contrast, non-SRI antidepressant users (N = 14) had no increase in transfusions (OR = 0.74; 95% CI, 0.10–5.95). Mean perioperative blood loss was slightly over a liter in the SRI patients; this quantity was nearly double the quantity in the other patients. A limitation of this study is that the number of patients receiving selective and nonselective SRIs was small.

Selective serotonin reuptake inhibitors are commonly used to treat depression in patients with ischemic heart disease and may even protect against ischemic events in such populations.[31] Might SSRIs increase surgical risks in these patients? Andreasen et al[45] identified 3,454 patients who underwent coronary artery bypass grafting (CABG) during a 6-year period. Of these, 3.5% had used SSRIs during the previous 90 days. The RR for transfusion of blood products was examined after adjustment for confounders such as age, sex, and use of NSAIDs, anticoagulants, or platelet inhibitors. In comparison with patients who had never used any antidepressant drug, there was no increase in the risk of transfusion in current users of SSRIs (RR = 1.1; 95% CI, 0.9–1.3), current users of nonselective SRIs (RR = 0.9; 95% CI, 0.6–1.3), current users of other antidepressants (RR = 1.0; 95% CI, 0.7–1.5), and former users of SSRIs (RR = 1.0; 95% CI, 0.7–1.4). The risk of reexploration for bleeding and the risk of mortality within 30 days also did not differ across drug and exposure categories. A limitation of the study is that there is no assurance that the so-defined current users had actually used their SSRIs perioperatively.

Kim et al[36] described another retrospective analysis of adults (N = 1,380) who received antidepressant medication (78% SSRIs) before CABG surgery. The analysis controlled for the propensity for receiving SSRIs relative to non-SSRIs. In the SSRI versus non-SSRI groups, bleeding events characterized 6.5% vs 7.2% of subjects, respectively, and in-hospital mortality characterized 3.1% versus 2.3%, respectively. The differences were not significant. Selective serotonin reuptake inhibitors did not increase risks even when the analysis was restricted to patients who received antiplatelet and anticoagulant therapy for acute coronary syndromes (OR = 1.03; 95% CI, 0.40–2.61) and when the data were examined by age, gender, NSAID use, and type of CABG (on-pump or off-pump).

Tooth extraction is a minor surgical procedure that may carry a special risk for SSRI-related bleeding because the extraction socket is open and a boggy mass of raw tissue is left exposed, unlike surgical wounds that are closed.[46] However, with the exception of the report of Van Cann and Koole,[46] a PubMed search identified no literature on an association between SSRI treatment and bleeding associated with tooth extraction.

Considering the quantity of literature on abnormal GI bleeding with SSRIs, it is surprising that there is so little literature on risks in surgical and dental contexts. There are many possible explanations. Nonessential medications are usually stopped before elective surgery. Blood loss during and after surgery is difficult to accurately quantify and compare between at-risk groups. In the absence of awareness of the effects of SSRIs on hemostasis, excessive dental bleeding may be attributed to idiosyncrasy. The absence of risk in CABG patients may have been masked by the risks related to concurrent antiplatelet agents.

Abnormal Bleeding in Women

Women compose about half of the population, and a substantial number of these are of childbearing age. Women are also overrepresented in depressed populations, and SSRIs are first-line treatments for depression. The uterus is an important site from which bleeding occurs during menstruation and delivery. Therefore, if SRIs impair hemostasis, abnormal bleeding may manifest in women, especially those of childbearing age.

Case reports and small studies. A 67-year-old woman developed vaginal bleeding after receiving sertraline 25 mg/d for 3 days; the bleeding stopped within 2 days of drug discontinuation.[47] A 41-year-old woman developed vaginal bleeding with venlafaxine 75 mg/d; the bleeding stopped within a day of venlafaxine withdrawal and recurred after venlafaxine rechallenge.[48] Other reports of vaginal bleeding with sertraline have also appeared.[49] The rarity of such reports suggests that the risk could be low. In a subgroup analysis[6] of 93 women with menorrhagia, metorrhagia, or postmenopausal bleeding, an increased although nonsignificant risk of bleeding was observed in women using antidepressants with intermediate (OR = 1.7; 95% CI, 0.7–4.1) or high (OR = 3.0; 95% CI, 0.8–4.9) potency for inhibition of serotonin reuptake relative to antidepressants with a low potency of inhibition.[6]

Menstruation. Selective serotonin reuptake inhibitors such as fluoxetine, sertraline, and paroxetine have been approved for the treatment of premenstrual dysphoric disorder. No literature is available on whether or not menstrual blood loss is increased as a result of treatment. Treatment-emergent adverse effect tables in published studies of SSRIs for this indication do not list increased menstrual blood loss as an adverse event.

Pregnancy. Selective serotonin reuptake inhibitor use during pregnancy has been suggested to predispose to bleeding complications.[50] However, in a large, retrospective, population-based, nested case-control study of 2,460 women with postpartum hemorrhage and 23,943 matched controls, neither SSRIs (OR = 1.30; 95% CI, 0.98–1.72) nor non-SSRIs (OR = 1.12; 95% CI, 0.62–2.01), used 90 days before delivery, increased the risk of postpartum hemorrhage.[51] In another study,[52] indices of platelet function were normal in 27 SSRI-treated mother-neonate pairs relative to 27 SSRI-unexposed pairs; there were no abnormal bleeding events in either group.

Considering the number of studies published on abnormal bleeding with SSRIs, it is surprising that there is so little literature on risks associated with menstrual and postpartum bleeding. Perhaps it is difficult to quantify blood loss of this nature, or to observe increased blood loss when there is much variation within and across subjects, especially when the increase may not necessarily be large. It is tempting to speculate that the absence of literature suggests relative safety; after all, millions of women would have received SSRIs during the past decades, and, if concerns had been valid, adverse events would have been reported by now. Whereas it seems reasonable to conclude that the use of SSRIs in women should be governed by indication and not by the fear of abnormal bleeding, the subject merits formal study.

We add 2 explanations for why SSRIs may not increase the risk of postpartum hemorrhage. The sinuses in the uterine wall are blood spaces that lie between muscle bundles. Hemorrhage after delivery is prevented by uterine retraction and contraction and by thrombosis in the sinuses. As the uterus is emptied, the muscular layers slide over each other and the blood sinuses twist and bend on themselves. This checks the blood flow through the sinuses. Such a mechanism of hemostasis is unlikely to be susceptible to SSRI-induced platelet dysfunction. Additionally, SSRIs elevate plasma serotonin levels[53]; this may prevent postpartum hemorrhage by increasing the uterine tonicity.[54]

Selective Serotonin Reuptake Inhibitors and Bleeding in Patients With Liver Disease

Patients with liver disease are at known risk of abnormal bleeding events. Weinrieb et al[55] examined whether SSRIs increase the risk of abnormal bleeding in hepatitis C patients suffering from cirrhosis with portal hypertension and/or hepatic failure. In a systematic review, they identified 6 retrospective studies and 18 case reports of bleeding in 37 patients. They described a possible association between SSRI treatment and fatal GI bleeding in an additional patient. They observed that bleeding events in 19 of 24 patients were closely associated with the use of SSRIs. They concluded that aspirin or NSAIDs combined with SSRIs (prescribed for interferon-induced depression) could have increased the risk of bleeding.

A retrospective analysis[56] of 303 consecutive hepatitis C patients found no increase in the risk of bleeding associated with SSRIs and interferon. However, the sample was small by epidemiologic standards, and the patients may not have been especially vulnerable with regard to the presence of cirrhosis or the concurrent use of aspirin or NSAIDs.

Might the "Risks" Carry Benefits in Other Contexts?

Platelet reactivity is heightened in depression,[57,58] and depressed patients are at increased risk of ischemic heart disease events.[59] Selective serotonin reuptake inhibitors reduce platelet/endothelial activation over and above that associated with concurrent antiplatelet drugs.[31,32] Selective serotonin reuptake inhibitors also reduce C-reactive protein and interleukin-6 levels and improve flow-dependent endothelium-mediated dilation.[60] Selective serotonin reuptake inhibitors may therefore reduce ischemic cardiovascular and cerebrovascular events. The limited clinical data available appear to confirm this view for ischemic heart disease events[10,61–63]; however, negative data have also been published.[64] The limited data available on stroke suggest that SSRIs neither increase nor decrease the risk of ischemic or hemorrhagic stroke.[2,65,66] A more detailed discussion on this subject is out of the scope of this review.

Management

SRI-related bleeding is infrequent. There is therefore no reason to absolutely contraindicate SRI use in any subpopulation of patients. However, clinicians should be aware of the risk of SRI-related bleeds at GI and non-GI sites. Whereas alertness is warranted in all patients, it is particularly necessary in patients at heightened risk of bleeds. Such patients include those with acid-peptic disease or liver disease, those undergoing surgical or dental procedures, and those receiving concurrent NSAIDs, anticoagulant drugs, or antiplatelet drugs. Although there are no data indicating cause for concern, it may be prudent to advise SRI-treated women to watch for consistent, clinically significant increase in menstrual flow.

It may be desirable to prefer non-SRI antidepressants in patients with a history of bleeding disorders or serious acid-peptic disease. Non-SRI antidepressants may also be considered in hepatically compromised patients; unfortunately, many antidepressants have long half-lives, inhibit liver enzymes, cause sedation, or exert anticholinergic effects, all of which are undesirable in patients with liver disease.

The risk of SRI-related bleeds may be decreased by prescribing proton pump inhibitors to patients at particular risk of GI bleeds. Serotonin reuptake inhibitors should be withdrawn, if feasible, to decrease clinically significant risks, such as before elective major or minor surgical procedures.

Whenever relevant, the risk of SRI-related bleeding should be monitored, such as through testing for occult blood in stools in patients at risk of GI bleeds. Hemostatic abnormalities with SRI therapy may be difficult to detect[19]; therefore, monitoring of hematologic or hemostatic parameters may not be useful.

Should unexplained, abnormal bleeding arise during the course of SRI treatment, investigations should be conducted to determine the seriousness of the situation, preferably in collaboration with specialists from the relevant medical discipline(s). No intervention may be deemed necessary, as in the case of a woman who suspects mildly increased menstrual flow after commencing SRI medication. In more serious cases, such as GI bleeding, SRI withdrawal may be prudent because GI bleeding may predispose to more serious morbidity and even mortality; specific interventions to address the pathology may also need to be instituted. A non-SRI antidepressant should be preferred should antidepressant continuation be deemed necessary.

Drugs likely to be safe in patients at risk of abnormal bleeding include mirtazapine, bupropion, and reboxetine,

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that is, drugs that do not inhibit serotonin reuptake. Interestingly, animal data suggest that mirtazapine may have antiulcer properties.[67] Animal data also suggest that fluvoxamine has dose-dependent antiulcer properties[68]; however, there are no adequately powered studies that examine the differential risk of bleeding among different SRI drugs, and so recommendations regarding fluvoxamine cannot be made at the present time.

In the final reckoning, decision-making should be based on the risks likely with a specific drug in the context of a specific patient. When choosing between SRIs and other antidepressants, clinicians should weigh the adverse effects associated with conventional or predominantly noradrenergic antidepressants against the small risk of bleeding with SRIs offset by a possible protection against ischemic heart disease events.[10,61,62]

Directions for Future Research

The data at present are insufficient to definitively conclude whether the risk of bleeding with SRI drug use plateaus beyond a certain point or continues to increase, such as with increasing dose or increasing potency of serotonin reuptake inhibition. Confirmatory data are required to determine whether different clinical and demographic subgroups are especially at risk, either independently or as a function of their greater propensity to receive antiplatelet, anticoagulant, or NSAID group drugs. The magnitude of the risk needs to be quantified for different drugs, doses, and subgroups of patients. Whether the experience of GI adverse effects predicts the risk of GI bleeding requires study.

Research should examine subgroups that do not appear to have been adequately studied; these include women who are menstruating or in labor, alcoholic subjects, patients who undergo major or minor dental or surgical procedures, patients with liver disease, patients with preexisting bleeding disorders, and patients with preexisting bleeding (eg, hematuria) due to other pathologies. The risks associated with SRI drugs (eg, venlafaxine) as distinct from SSRI drugs must be examined. Clomipramine, in particular, merits attention because, since it is anticholinergic, it may not increase gastric acidity as much as the SSRIs.

Research should examine whether testing stools for occult blood is a viable screening measure for the risk of SSRI-related GI bleeds. Studies are necessary to determine whether (besides proton pump inhibitors) H2 receptor blockers such as ranitidine and famotidine protect against SSRI-related GI bleeds. Finally, research is necessary to determine whether SRIs are protective in patients at risk of ischemic heart disease or ischemic stroke and whether they increase the likelihood of bleeding in patients at risk of hemorrhagic stroke.

The effects of SSRIs on platelet serotonin and hence on platelet aggregation have been widely offered as an explanation for the increased risk of bleeding and the decreased risk of ischemic heart disease events with these drugs. However, we believe that the offered explanation is inadequate in both contexts. Increased gastric acidity could explain the increased risk of upper GI bleeding with SSRIs if only because this is the only site from which bleeding with SSRIs has consistently been demonstrated. The effect of SSRIs on endothelial activation and inflammatory markers[31,32,59,60,69] may explain reduced ischemic heart disease event risks if only because platelet serotonin levels are already low in depressed patients,[70–72] whereas platelet reactivity is heightened.[57] These views need further study.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clopidogrel (Plavix), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), mirtazapine (Remeron and others) paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), warfarin (Coumadin, Jantoven, and others).
Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.
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