Review Article

Clinical Management of Bleeding Risk With Antidepressants

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Abstract

Objective: This nonsystematic review describes risk of bleeding in treatment with serotonin reuptake inhibitors (SRIs) and provide recommendations for the management of patients at risk of bleeding. **Data Sources:** Articles were identified by English-language MEDLINE search published prior to June 2018 using the terms *SRI, serotonin and noradrenaline reuptake inhibitors*, OR *antidepressive agents*, AND *hemorrhage* OR *stroke*. **Study Selection and Data Extraction**: Meta-analyses were utilized to identify information regarding risk of bleeding with antidepressants. Individual studies were included if they had information regarding bleeding risk with specific SRIs, timing of risk, or risk with medications of interest. **Data Synthesis:** SRIs increase risk of bleeding by 1.16- to 2.36-fold. The risk is synergistic between SRIs and nonsteroidal anti-inflammatory drugs (NSAIDs; odds ratio [OR] range between studies 3.17-10.9). Acid-reducing medications may mitigate risk of gastrointestinal bleeds in chronic NSAIDs and SRI users (OR range between studies 0.98-1.1). Antidepressants with low or no affinity for the serotonin transporter, such as bupropion or mirtazapine, may be appropriate alternatives for patients at risk of bleeding. **Relevance to Patient Care and Clinical Practice:** This review includes data regarding bleeding risk for specific antidepressants, concomitant medications, and risk related to duration of SRI use. Considerations and evidence-based recommendations are provided for management of SRI users at high bleeding risk. **Conclusions**: Clinicians must be aware of the risk of bleeding with SRI use, especially for patients taking NSAIDs. Patient education is prudent for those prescribed NSAIDs and SRIs concurrently.

Keywords

serotonin, antidepressants, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, anticoagulation, antiplatelets

Introduction

In the United States, the lifetime prevalence of depression is 16.6%, and antidepressants are the third most commonly prescribed medication class.[1,2] Antidepressants, in particular serotonin reuptake inhibitors (SRIs), are used for a variety of indications such as depression, anxiety, premenstrual dysphoric disorder, pain disorders, and vasomotor symptom relief. Recently, more attention has been given to SRIs surrounding the risk of bleeding. Serotonin is taken up by the platelets via serotonin transporter and released following vascular injury. Serotonin then binds to the platelet 5-HT_{2A} receptor, accelerating platelet aggregation and leading to thrombus formation.[3,4] Bleeding associated with SRI use is hypothesized to be a result of inhibition of the serotonin transporter on platelets, leading to reduced platelet aggregation. Based on the mechanism, any medication that involves inhibition of serotonin reuptake would put patients at an increased risk of abnormal bleeding. Additionally, selective serotonin reuptake inhibitors (SSRIs) increase gastric acidity, which can increase the risk of ulcer formation and gastrointestinal bleeds (GIBs).[5] It has also been hypothesized that SRIs with high serotonin transporter binding affinity (eg, clomipramine, duloxetine, fluoxetine, paroxetine, sertraline, vilazodone, and vortioxetine) place patients at a higher bleeding risk than intermediate (eg, amitriptyline, citalopram, escitalopram, imipramine, and venlafaxine) and low (eg, bupropion, doxepin, mirtazapine, nortriptyline, phenelzine, tranylcypromine, and trazodone) binding affinity SRIs.[5-7]

Furthermore, cytochrome-P450 (CYP)-mediated drug interactions may pose a risk of bleeding when medications

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with additive bleeding risk are combined.[8,9] Duloxetine (moderate CYP2D6 inhibition), fluvoxamine (strong CYP1A2, 2C9, 2C19, moderate CYP3A4, and weak CYP2D6 inhibition), fluoxetine (strong CYP2D6, 2C9, moderate CYP3A4, 2C19, and weak CYP1A2 inhibition), and paroxetine (strong CYP2D6 and weak CYP1A2, 3A4, 2C9, 2C19 inhibition) are the most notable CYP inhibitors among the SRIs.[8] Citalopram, escitalopram, sertraline, and venlafaxine are weak CYP2D6 inhibitors only. Drug-drug interactions are crucial to consider when determining the risk of bleeding with SRIs.[8]

Laporte et al[3] summarized observational studies reporting an increased risk of bleeding associated with SRI use. Outcomes highlighted in these studies include abnormal bleeding in the GI tract, postpartum hemorrhage (PPH), intracranial hemorrhage (ICH), and various other sites of bleeding, such as female genital tract bleeding, epistaxis, and hematoma.

Despite the observed risk of bleeding with SRI use, there is little guidance on strategies to overcome this risk. The purpose of this article is to review the risk of bleeding associated with SRI use illustrated in meta-analyses, examine the impact of concomitant medications, and discuss strategies to mitigate this risk.

Data Sources

For this nonsystematic review, primary articles in the English-language were identified by MEDLINE search for meta-analyses published prior to May 2018 using the following search terms: ("Stroke"[Mesh] OR "Hemorrhage"[Mesh]) AND ((("Antidepressive Agents"[Mesh] OR "Serotonin Uptake Inhibitors"[Mesh]) OR "Serotonin Uptake Inhibitors"[Pharmacological Action]) OR "Serotonin and Noradrenaline Reuptake Inhibitors"[Mesh]).

Study Selection and Data Extraction

A total of 35 meta-analyses were screened, and 25 were excluded because they were not designed to examine the risk of bleeding with antidepressants. Nine relevant meta-analyses were identified regarding the risk of bleeding with SRIs (Table 1),[3,10-17] and 1 meta-analysis was identified concerning risk for bleeding with mirtazapine and bupropion.

Original research studies were discussed in terms of whether they had information to answer questions regarding bleeding risk with specific SRIs, the timing of risk, or bleeding risk between SRIs and medications of interest. To determine the impact of additional medications on bleeding risk among antidepressant users, the following search terms were added to the above criteria: *platelet aggregation inhibitors, anti-inflammatory agents non-steroidal*, and *anticoagulants*. Original research articles were considered if they examined the risk of bleeding among one of the above agents in addition to antidepressants. Bleeding risk for specific antidepressants was analyzed by identifying studies that discussed "affinity" for the serotonin transporter. Timing that bleeding risk is highest was determined by review of the 10 meta-analyses. Bibliographies of relevant articles were reviewed to identify additional applicable information.

Data Synthesis

Overall Incidence of Bleeding With SRIs

SRIs have been associated with a variety of bleeds, including GIB, ICH, PPH, and operative bleeding, but the inclusion of patients with differing sites and severities of bleeding vary by the article, leading to significant heterogeneity.[3] A meta-analysis of observational studies examining bleeding risk with SSRIs in 1 443 042 patients found a significant increase in any bleeding type of 41% (odds ratio [OR] 1.41; 95% CI = 1.27-1.57; $P < 0.001$).[3] This risk was high especially in relation to GIBs, with an increased risk of 55% (OR = 1.55; 95% CI = 1.32-1.82), and lower for ICH, with an increased risk of 16% (OR = 1.16; 95% CI = 1.01-1.33). Most case-control studies explicitly focused on GIBs. In contrast, 8 of 11 cohorts included in the meta-analysis examined bleeding risk in the postsurgical population, and 2 of 11 studies included warfarin-treated patients, which contributed to heterogeneity ($P < 0.001$). Despite differences among these studies, most of the published literature examining the effect of SRIs on bleeding risk focuses on the risk of GIB, making it difficult to determine the absolute risk of bleeding at other sites.

The impact of SRIs on bleeding at other sites, such as brain hemorrhage, PPH, and operative-related bleeds, is difficult to demonstrate given the low incidence of events. In a meta-analysis, Hackam and Mrkobrada[15] examined SSRI exposure associated with brain hemorrhage and found that that there was an increased risk of 61% (OR = 1.61; 95% CI = 1.04-2.51). Similarly, women taking antidepressants during pregnancy have a 32% increase in the odds for developing PPH than those who do not use antidepressants (OR = 1.32; 95% CI = 1.17-1.48; $P < 0.001$).[16] The highest risk of PPH was for patients with antidepressant use within 30 days of delivery, those taking SNRIs, and for women who underwent cesarean deliveries. The bleeding risk from preoperative use of serotonergic antidepressants remains difficult to ascertain. In a meta-analysis of cohort studies, there was no significant difference in reoperation caused by bleeding among antidepressant users (OR = 1.48; 95% CI = 0.84-2.62).[17] Failure to account for antiplatelet medications and

Table 1. Risk of Bleeding Associated With SSRI Use.[3,10-17]

Study	Number of Studies	n	OR	95% CI	*P* Value	Type of Bleed	Control Group	Intervention Group
Laporte et al,[3] 2017	42	1 443 029	1.41	1.27-1.57	<0.0001	Any	Non–SSRI users	SSRI
Laporte et al,[3] 2017	NP	NP	1.55	1.32-1.83	NP	GIB	Non–SSRI users	SSRI
Loke et al,[10] 2008	4	153 000	2.36	1.44-3.85	0.0006	GIB	Non–SSRI users	SSRI
Jiang et al,[11] 2015	22	1 073 000	1.55	1.35-1.78	<0.001	UGIB	Non–SSRI users	SSRI users (included duloxetine and venlafaxine)
Anglin et al,[12] 2014	15	393 268	1.66	1.44-1.92	NP	UGIB	No treatment	SSRI
Oka et al,[13] 2014	6	223 947	1.73	0.65-2.82	NP	UGIB	Non–SSRI users	SSRI
Laporte et al,[3] 2017	NP	NP	1.16	1.01-1.33	NP	ICH	Non–SSRI users	SSRI
Shin et al,[14] 2014	13	964 252	1.32	1.02-1.71	NP	Hemorrhagic stroke	Non–SSRI users	SSRI
Hackam and Mrkobrada,[15] 2012	4	223 873	1.61	1.04-2.51	NP	Brain hemorrhage	Non–SSRI users	SSRI
Jiang et al,[16] 2016	8	572 686	1.32 (RR)	1.17-1.48	<0.001	PPH	Non–antidepressant users	Antidepressant users
Singh et al,[17] 2015	8	565 312	1.48	0.84-2.62	NP	Reoperation bleeding event	Non–antidepressant users	Serotonergic antidepressants

Abbreviations: GIB, gastrointestinal bleed; ICH, intracerebral hemorrhage; NP, not provided; OR, odds ratio; PPH, postpartum hemorrhage; RR, risk ratio; SSRI, selective serotonin reuptake inhibitors; UGIB, upper gastrointestinal bleed.

potential CYP enzyme inhibition may confound these results. More studies are necessary to determine how bleeding risk with SRI use can be correlated with brain hemorrhage, PPH, and surgical interventions.

Gastrointestinal Bleeding Associated With SRI Use

Although significant bleeding is rare, with a baseline incidence of upper GIB of 23 per 10 000 patients per year, GIB-associated mortality is between 3% and 14%.[16,18,19] Thus, it is essential to recognize that SRIs can increase this risk. In an observational study by Kim et al[18] examining risk factors for GIBs in patients in South Korea, unspecified SSRI exposure was associated with a 0.44% annual prevalence of GIB. Risk of bleeding increased with the number of risk factors present (eg, comorbid conditions, concomitant drugs, and personal habits, such as smoking and alcohol consumption) and consistently increased with age. In fact, 1.2% to 1.9% of SSRI users older than 70 years developed a GIB. In a meta-analysis examining the risk of upper GIB with SSRI use, the risk was increased by 55% (OR = 1.55; 95% CI = 1.35-1.78; $P < 0.001$) with SSRIs.[16] Based on these results, the number needed to harm (NNH) was 791 patients. Other meta-analyses have reported similar findings, ranging from a 1.55- to 2.36-fold increased risk of GIB among SRI users (Table 1).[3,11-13] These results solidify the association between SRI use and risk of GIBs.

Concomitant Medications That Affect SRIs' Impact on Bleeding

In addition to SRIs increasing the risk of bleeding, it is vital to consider concomitant medications that may additively increase the risk, such as antiplatelet medications and nonsteroidal anti-inflammatory drugs (NSAIDs). A population-based retrospective study examined the risk of GIBs associated with SSRIs (ie, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) and antiplatelet therapy (eg, aspirin and clopidogrel) following acute myocardial infarction.[9] Compared with aspirin alone, use of SSRIs with aspirin was associated with an increased risk of bleeding (hazard ratio [HR] = 1.42; 95% CI = 1.08-1.87). Similarly, compared with dual antiplatelet therapy alone (aspirin and clopidogrel), SSRI use in combination with dual antiplatelet therapy increased the risk of bleeding (HR = 1.57; 95% CI = 1.07-2.32). Supporting these findings, a nationwide population-based study of clopidogrel users found that SSRI use in addition to clopidogrel increases the risk of lower but not upper GIB (HR = 2.22, 95% CI = 1.91-4.58, $P = 0.048$ and HR = 1.27, 95% CI = 0.56-2.89, $P = 0.565$, respectively).[20] In contrast, an analysis of the French Spontaneous Reporting Database examining bleeding adverse drug reactions among those exposed to antiplatelet agents failed to show a significant association between bleeding events and SRI use (adjusted reporting OR = 0.8; 95% CI = 0.5-1.2; $P = 0.3$). However, there were only 62 cases (4.7%)

Table 2. Additive Risk of Gastrointestinal Bleed With Concomitant SSRIs, NSAIDs, and Acid-Suppressing Agents.[10-13,27-29]

Study	SSRI[a]	SSRI + PPI[a]	NSAIDs[a]	SSRI + NSAIDs[a]	SSRI + NSAID + PPI[a]
Anglin et al,[12] 2014	1.66 (1.44-1.92)	NR	2.8 (2.2-3.56)	4.25 (2.82-6.42)	NR
Loke et al,[10] 2008	2.36 (1.44-3.85)	NR	3.16 (2.40-4.18)	6.33 (3.40-11.8)	NR
Oka et al,[13] 2014	1.73 (0.65-2.82)	NR	2.55 (1.51-2.59)	4.02 (2.89-5.15)	NR
Dall et al,[27] 2009	1.67 (1.46-1.92)	0.96 (0.5-1.82)	NR	8.0 (4.8-13)	NR
Targownik et al,[28] 2009	1.43 (1.09-1.89)	0.56 (0.24-1.3)	NR	3.17 (2.01-5.0)	0.93 (0.29-3.03)
de Abajo and García-Rodríguez,[29] 2008	1.8 (1.1-2.9)	1.3 (0.5-3.3)	NR	9.1 (4.8-17.3)	1.1 (0.3-3.4)[b]
Jiang et al,[11] 2015	1.55 (1.35-1.78)	0.81 (0.43-1.53)	NR	10.9 (7.3-16.2)	0.98 (0.51-1.88)[b]

Abbreviations: NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Reported as OR (95% CI).
[b]PPIs were grouped with other acid-suppressing medications.

of combined SRI and antiplatelet users.[21] Because aspirin, clopidogrel, and SRIs each inhibit platelet function, providers must be aware that concomitant use can increase the risk of bleeding and monitor patients appropriately.

In addition to antiplatelet agents, anticoagulants are associated with a risk of abnormal bleeding events. The risk of bleeding associated with anticoagulants and SRIs has been examined throughout the literature. In a retrospective cohort of patients treated with low-molecular-weight heparin for venous thromboembolism, SSRI use (n = 92/575) was not associated with an increased incidence of major bleeding when compared with patients without SSRI treatment (n = 483/575): 19.6% versus 17%; $P = 0.548$.[22] However, significantly more patients in the SSRI group were also on acid suppressive therapy, which was shown to significantly reduce major bleeding (OR = 0.24; 95% CI = 0.07-0.90; $P = 0.014$). Interestingly, 42.6% (n = 6/13) of patients on escitalopram experienced a major bleeding event, which warrants further investigation. In addition, warfarin was associated with an increased rate of hemorrhage among SSRI users in the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study (adjusted relative risk [RR] = 1.41; 95% CI = 1.04-1.92; $P = 0.03$).[23] Similar studies have found an increased risk of clinically relevant bleeding with or without an increased risk of hospitalization among SSRI and warfarin users.[24-26] Based on these studies, concomitant warfarin and SRI use should be done cautiously.

NSAIDs increase the risk of GIBs through a variety of mechanisms; therefore, their use with SRIs is of particular interest. Consistently throughout the literature, the risk of GIB is increased when SSRIs and NSAIDs are used simultaneously (Table 2).[10,12,13] In a meta-analysis of observational studies looking at SSRI use and GIBs, concomitant use of NSAIDs was associated with an increased risk of bleeding (OR = 6.33; 95% CI = 3.40-11.8; $P < 0.00001$), with a NNH of 82 per year.[10] This effect is synergistic because concurrent use of SSRIs and NSAIDs was associated with a higher risk than either medication alone. Additionally, of the 101 postmarketing reports included in this meta-analysis, 80% had concomitant exposure to NSAIDs, antiplatelets, or anticoagulants. A similar meta-analysis was published to obtain a more precise estimate of upper GIB risk with SSRIs with or without NSAIDs.[12] Risk of upper GIB was additive for the combination of SSRIs and NSAIDs. Unfortunately, the authors did not describe NSAID agent, dose, and duration of use, a significant limitation of the published literature. Given the substantial increase in GIB rates for patients taking NSAIDs in combination with SSRIs, providers must consider strategies to mitigate this risk.

Because one proposed mechanism of increased GIB rates is an increase in gastric acidity, one strategy to reduce the risk of GIB for patients on SSRIs is to utilize acid-suppressing agents.[14,27-29] There is no single study strictly examining the use of proton-pump inhibitors (PPIs) with SSRIs to determine bleeding risk. However, a few studies assess the combination of these medications in subgroup analyses (Table 2).[14,27-29] This evidence suggests that PPI use diminishes the risk of SSRI-associated GIBs, especially when patients are taking NSAIDs concomitantly. Although PPIs may reduce the risk of GIBs among SRI users, there are several adverse effects with long-term use (eg, fracture, hypomagnesemia, vitamin B12 deficiency, dementia, kidney damage, *Clostridium difficile* infection, and pneumonia).[30] Recent data suggest that PPI use increases the probability of depression among the elderly population (adjusted OR = 2.38; 95% CI = 0.49-4.38; $P = 0.045$).[31] However, only 9% of participants in the PPI group and 3% in the non-PPI group were taking SSRIs at baseline. Therefore, this study does not provide evidence that PPI use would worsen preexisting depression. As with the initiation of any medication, the risks and benefits must be deliberated to make the best decision for an individual patient.

Risks for Specific Antidepressants

Beyond the use of acid-suppressive agents, another strategy for prescribers to reduce bleeding episodes in high-risk patients is to consider an antidepressant agent with lower binding affinity to the serotonin transporter. Several studies have included subgroup analyses examining SRI by affinity and suggest that agents with high and even intermediate-affinity for the serotonin transporter are associated with an increased risk of bleeding.[32-37] However, some subgroup analyses indicate no significant association between SSRI affinity and bleeding.[38,39] In a case-control study (n = 359) examining GI bleeds among SSRI users, high-affinity SSRIs, defined as having a dissociation constant (K_D) less than 1.0 (clomipramine, fluoxetine, paroxetine, and sertraline), and intermediate-affinity SSRIs, with K_D 1.0 to 10.0 (amitriptyline, citalopram, escitalopram, imipramine, and venlafaxine), were associated with an increased risk of upper GIB (OR = 2.1, 95% CI = 1.3-3.3, OR = 2.0, 95% CI = 1.1-3.6, respectively).[40] In contrast, low-affinity or non-SSRI antidepressants, with K_D greater than 10.0 (amoxapine, bupropion, desipramine, doxepin, maprotiline, mirtazapine, nefazodone, nortriptyline, phenelzine, protriptyline, tranylcypromine, trazodone, and trimipramine) were not associated with significantly increased risk of GIB (OR = 1.0; 95% CI = 0.4-2.3). In a cohort study by Castro et al,[41] risk of bleeding was compared between high-affinity (duloxetine, escitalopram, fluoxetine, paroxetine, and sertraline) and low- to intermediate-affinity SRIs (bupropion, mirtazapine, and nefazodone); a higher risk of GIB (adjusted RR = 1.17; 95% CI = 1.02-1.34) and stroke (adjusted RR = 1.18; 95% CI = 1.06-1.32) was found in the high-affinity group.

Despite these studies, a consensus was still lacking on the risk of bleeding associated with agents with low or no affinity for the serotonin transporter. To bridge this gap, Na et al[42] conducted a meta-analysis of 7 studies to classify the bleeding risk with mirtazapine and bupropion. Neither agent significantly decreased the risk of bleeding when compared with SSRIs (OR = 1.0, 95% CI = 0.87-1.14, and OR = 0.90, 95% CI = 0.69-1.18, respectively). Mirtazapine was associated with a significant risk of GIB when compared with no antidepressants (OR = 1.18, 95% CI = 1.01-1.38), but there was no significant difference between all types of bleeding (OR = 1.12, 95% CI = 0.97-1.27). Information comparing the bupropion group with a control group free from antidepressant use was not available. This meta-analysis was limited by the small number of studies, the limited number of patients taking mirtazapine or bupropion compared with SSRIs, and the inability to control for confounding bleeding risk factors.[42]

Based on the mechanism of bleeding associated with SRIs, any antidepressant that inhibits the reuptake of serotonin, such as tricyclic antidepressants, would carry a risk of bleeding. The study by Lewis et al[40] classifies tricyclic antidepressants appropriately by their affinity for the serotonin transporter. Additionally, the above literature does not include newer antidepressants such as vortioxetine and vilazodone. However, these agents inhibit the reuptake of serotonin with high affinity for the serotonin transporter: Ki = 2.6 and 0.1 nM, respectively.[6,7] Theoretically, vortioxetine and vilazodone would have a risk of bleeding similar to that of other high-affinity SSRIs. Despite the lack of literature regarding bleeding risk with these agents, the prescribing information includes caution that these serotonergic antidepressants may increase the risk of abnormal bleeding, which may be increased if administered with other medications that affect coagulation.[6,7] More evidence is needed examining the bleeding risk associated with low-affinity and non–serotonin transporter antidepressants. However, available data support that there is a lower risk of bleeding associated with these agents.

Bleeding Risk Timeline

In conjunction with concomitant medications and antidepressant selection, the impact of exposure time on bleeding risk should be considered. SRIs can increase gastric acidity almost immediately, whereas it may take a week to deplete platelets of serotonin.[5] In a meta-analysis by Loke et al,[10] the median time to upper GIB was 25 weeks. In contrast, Dall et al[27] and Targownik et al[28] found the risk of bleeding to be highest in the first 28 days of SRI use, making it difficult to determine how duration of SRI use affects bleeding risk.

Because, mechanistically, GIBs have a slightly different pathophysiological mechanism, and other bleed types have different confounding variables, it may be difficult to compare the timing of risk of these bleed types. When looking at the timing of first-onset stroke among SSRI users, a survival analysis found cumulative incidence ratios for ischemic and hemorrhagic stroke to be higher during the first 3 years of SSRI exposure, with 20% of strokes occurring in the first 6 months.[43] However, in the meta-analysis by Hackam and Mrkobrada,[15] 6 of the 7 studies that correlated time of SSRI exposure to brain hemorrhage demonstrated that risk was highest with short-term recent exposure than long-term exposure. Risk of PPH increased among those with antidepressant use within 30 days before the delivery date; however, total exposure time was not studied.[16] Overall, bleeding risk with SSRI use appears to be highest early in the course of therapy, likely within the first 30 days, but more studies are needed to validate this conclusion.

Relevance to Patient Care and Clinical Practice

Because GIB is the most common type of bleed associated with SRI use, providers should consider preventive strategies for GIBs in high-risk patients. When clinicians

Table 3. Summary of Risk Factors for Abnormal Bleeding.[3,10-17]

Risk Factors
• Gastrointestinal bleed
○ Medications
▪ NSAIDs
▪ Antiplatelet agents
▪ Anticoagulants
○ Current use of SRIs
▪ SSRIs
▪ SNRIs
○ Increased age
○ Comorbid conditions
▪ Peptic ulcer disease
▪ Diabetes
▪ Chronic liver disease
▪ Chronic renal failure
▪ Gastroesophageal reflux disease
○ Personal habits
▪ Smoking
▪ Alcohol consumption
• Brain hemorrhage
○ Current use of SSRIs
○ New and short-term use of SSRIs
○ Depression
• Postpartum hemorrhage
○ Cesarean delivery
○ Multiple pregnancies
○ Prolonged labor
○ Previous postpartum hemorrhage
○ Hypertension
○ Diabetes
○ Coagulation disorders
○ Anticoagulant use
○ Maternal age
○ SRI use within 30 days of delivery

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SNRI, serotonin and norepinephrine reuptake inhibitor; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

stratify a patient's risk factors for GIB, they must also include SRIs as one of these factors (Table 3). In a patient at high risk for bleeding or with a history of bleeding, a medication with little to no effect on the serotonin transporter may be considered. Mirtazapine, bupropion, and trazodone theoretically have little effect on the serotonin transporter and would not have the same risk of bleeding as SRIs. On the other hand, trazodone and mirtazapine are antagonists of 5-HT_{2A}, which theoretically would reduce platelet response and aggregation.[44] More studies are needed to establish the role of 5-HT_{2A} antagonism in platelet response. Additionally, prescribers should consider patient history and response to prior antidepressants when deciding between agents. Because bupropion has a mechanism of action independent of serotonin, it provides a suitable alternative for patients at increased risk of bleeding until further studies are conducted.

Whereas most studies included PPIs, acid-reducing medications may reduce the risk of SRI-associated GIB. However, risk versus benefit of adding a PPI must be considered because long-term PPI use is not without risk. The elderly population presents a unique challenge because advanced age is a risk factor for GIB and GIB-associated mortality as well as adverse effects of PPIs.[30]

At this time, SSRI-induced bleeding risk among the surgical population remains of unknown significance. Although antiplatelet agents are often held before surgery, there is no evidence to support stopping or tapering SRIs.[17] Therefore, SRI treatment should continue in patients undergoing surgical procedures because abruptly stopping these medications may lead to serotonin withdrawal symptoms or negatively affect management of target psychiatric symptoms.

Providers must inquire about all over-the-counter medications, especially NSAID and aspirin use. For patients

Table 4. Medication Prescribing and Patient Education Considerations.

- Educate the patient about the increased risk of bleeding associated with SRIs before initiating therapy
- Educate the patient on how to identify signs and symptoms associated with abnormal bleeding and when to seek medical treatment
- Weigh the risks and benefits of antidepressant use against the risk of abnormal bleeding
- Avoid discontinuing antidepressants in patients with an active indication for use based on bleeding risk alone
- If a patient develops a GIB, the risks and benefits must be weighed before discontinuing antidepressant therapy, and an acid-suppressing agent may be added to reduce the risk of developing additional bleeds
- Avoid unnecessary NSAID use
- When prescribers must use high doses of NSAIDs with SSRIs, they should consider acid-suppression therapy to reduce the risk of GIBs

Abbreviations: GIB, gastrointestinal bleed; NSAIDs, nonsteroidal anti-inflammatory drugs; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

who routinely use these or other medications that increase bleeding risk, patient education among new SRI users should include explaining that GIB is a rare but serious adverse effect of SRIs and how to recognize symptoms of a GIB (Table 4).

Pharmacists may have a positive impact on patients treated with SRIs at high risk of bleeding. Pharmacist interventions have been shown to increase medication adherence and reduce side effects of antidepressants.[45,46] Additionally, high-risk medications, such as anticoagulants, are followed by pharmacists in many inpatient hospitals and outpatient clinics. Among patients starting warfarin, daily consultation by a pharmacist has been shown to significantly decrease hospital stay, number of days the patient received excessive anticoagulation, and number of significantly interacting drugs with warfarin.[47] However, it is unclear if the increased risk of bleeding between warfarin and SRIs was highlighted in these study patients. Pharmacists must be proactive about intervening in patients who are at high risk of bleeding, such as those on anticoagulants and SRIs. Additionally, providers should consult their pharmacist regarding any questions related to drug-drug interactions.

Conclusion

SRI use is associated with an increased risk of bleeding, which is more notable early in the course of treatment. Concomitant NSAID use substantially increases the risk of experiencing GIBs. Acid-suppressing agents or use of a no or low-affinity serotonin transporter antidepressant should be considered for patients at high risk of bleeding, especially those on NSAIDs or of advanced age. Although prospective, randomized controlled trials would be an ideal method to fully evaluate the risk of bleeding with antidepressants, differential risk among agents, and the impact of acid-suppressing medications, a prospective study of this magnitude is not practically feasible. In the absence of this level of evidence, it remains crucial to include SRIs in bleeding risk assessments, especially in high-risk patients.

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