

Selective Serotonin Reuptake Inhibitor Use and Risk of Gastrointestinal and Intracranial Bleeding

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Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed medications in the United States. Although SSRIs are highly tolerable relative to other antidepressants, they are associated with a number of adverse effects, including increased gastrointestinal tract bleeding and intracranial bleeding. Mechanisms include increased gastric acid secretion and inhibition of serotonin entrance into platelets. Patients with other bleeding risk factors, such as warfarin, clopidogrel, or aspirin use, may be at heightened risk of these adverse effects. The purpose of this article is to review the incidence of gastrointestinal tract bleeding or intracranial bleeding associated with concomitant SSRI use, the proposed mechanisms of, and the potential pharmacokinetic/pharmacodynamic interactions with anticoagulants and antiplatelets. Given the prevalence of SSRI use in the ambulatory setting, osteopathic physicians should be aware of potential drug-drug interactions and the clinical implications of SSRI-associated bleeding risk.

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The use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) in the United States markedly increased from 7.7% in 1999 to 12.7% in 2014.¹ From 2011 to 2014, approximately 1 in 8 persons aged 12 years or older reported taking an antidepressant in the previous month.¹ According to the 2015 National Ambulatory Medical Care Survey, antidepressants are the third most frequently mentioned medications during physician office visits.² A significant portion of these prescriptions are written by primary care physicians. These trends may be influenced by the shift in beliefs about depression, the wide range of indications, and the variety of available medications.^{3,4}

Selective serotonin reuptake inhibitors are proven to be cost-effective and have a tolerable adverse effect profile. US Food and Drug Administration–approved indications for SSRIs include major depression, anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder. Although the adverse effect profile of SSRIs is favorable compared with other antidepressants, SSRIs are associated with a number of potential drug-drug interactions and severe adverse effects. They are known inhibitors of cytochrome-P450 isoforms. Isoform inhibition and the extent of inhibition vary depending on the specific SSRI. Fluoxetine and paroxetine are strong CYP2D6 inhibitors, whereas fluvoxamine is a strong CYP1A2 and CYP2C19 inhibitor.⁵ Citalopram has

minimal effects on the major CYP isoforms. The co-administration of select SSRIs with other CYP-mediated medications may result in clinically significant pharmacokinetic/pharmacodynamic (PK/PD) changes. Notable examples of medications that interact with SSRIs include warfarin and clopidogrel. This drug-drug interaction results in increased bleeding risk, such as minor bruising and bleeding.⁵

Abnormal bleeding is listed as a warning in the US Food and Drug Administration–approved package labeling for SSRIs. Patients taking concomitant nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants, or antiplatelets have an increased risk of bleeding through several mechanisms, which are discussed in the Proposed Mechanisms for SSRIs and Bleeding section. Examples of severe clinical bleeding include gastrointestinal tract (GI) bleeding and spontaneous intracranial bleeding. Both observational and interventional studies have noted an increased risk of GI bleeding and intracranial bleeding associated with SSRIs independent of other bleeding risk factors. Reported excess GI bleeding attributed to SSRIs in patients without a history of GI bleeding is approximately 3.1 per 1000 patient years.⁶ Intracranial bleeding is relatively rare but poses a serious consequence, especially among patients in whom SSRIs may be initiated for poststroke depression.

Considering the wide use of SSRIs and severe clinical adverse events such as GI bleeding and intracranial bleeding, it is important for health care professionals to be informed of potential interactions with other medications known to increase bleeding risk. The objective of this narrative review is to describe the proposed mechanisms, incidence, and PK/PD interactions between SSRIs and medications that may put patients at risk for GI bleeding and intracranial bleeding if co-administered with SSRIs. The scope of this review is limited to outpatient management.

Literature Search

A search of the MEDLINE and PubMed databases was performed to identify articles describing

SSRI-associated bleeding and PK/PD changes when co-administered with anticoagulants and antiplatelets. Combinations of the following Medical Subject Headings and terms were searched: *gastrointestinal bleeding, intracranial bleeding, serotonin reuptake inhibitors, warfarin, anticoagulants, clopidogrel, aspirin, platelet aggregation inhibitor, pharmacokinetics, and pharmacodynamics*. The search was restricted to abstracts and articles on human studies in English with no date limits. References cited in the articles identified by the search were also evaluated and included if relevant. Fourteen observational studies related to risk of GI bleeding or intracranial bleeding associated with SSRI use were included. Descriptive statistics are reported as mean (SD) unless otherwise specified.

Proposed Mechanisms for SSRIs and Bleeding

Several pharmacologic mechanisms may provide an explanation for the actions of SSRI antidepressants to increase the risk of bleeding. Selective serotonin reuptake inhibitors are known to downregulate serotonin (5-hydroxytryptamine [5HT]) receptors not only in the brain but also in blood platelets.⁷ Only neurons and platelets express 5HT receptors in a nonactivated state. The majority of 5HT is synthesized in the GI tract by enterochromaffin cells.⁸ 5HT is then taken up by platelets and metabolized by the liver or pulmonary vascular endothelium. Approximately 99% of the whole 5HT is stored in platelets.⁹ Another mechanism of action for SSRI-induced bleeding is increased gastric acidity leading to potential ulcerogenic effects.¹⁰

Inhibition of 5HT Entrance Into Platelets

Selective serotonin reuptake inhibitors inhibit the 5HT transporter protein that blocks the uptake of synaptic 5HT into the presynaptic neuron and, similarly, the entrance of 5HT into the platelet.^{11,12} The mechanism of this blockade in the presynaptic neuron is demonstrated by paroxetine and (S)-citalopram, which lock 5HT by lodging into the 5HT transporter.¹³ Based on

in vitro and in vivo studies, the 5HT transporter blockade results in a wide spectrum of antiplatelet activity.^{11,12} Various mechanisms include the blockade of intraplatelet calcium mobilization in the coagulation cascade; inhibition of nitric oxide synthase; depletion of intracellular 5HT stores; decreased platelet secretion in response to collagen; decreased secretion of platelet factors in response to a chemical or traumatic stimulation; and decreased expression of membrane receptors involved with platelet activation and blood vessel vasoconstriction or vasodilation.^{8,11,12,14} Nitric oxide (NO) synthase is required for NO production from the NO donor L-arginine.¹⁵ Nitric oxide activates cyclic guanosine monophosphate, which acts to relax smooth vascular muscle and regulate platelet aggregation.¹⁵

Meijer et al¹⁶ proposed a significant correlation between antidepressant potency for 5HT reuptake inhibition and bleeding. Antidepressant potency was divided into 3 groups based on dissociation constant for the 5HT transporter: high (0-1 nmol/L); intermediate (1-10 nmol/L); and low (≥ 10 nmol/L). The high degree of 5HT reuptake noted for fluoxetine, sertraline, clomipramine, and paroxetine was associated with most of the case reports of abnormal bleeding (53.1%) compared with 15 other antidepressants. The adjusted odds ratio (OR) for bleeding risk for patients who took these high-potency antidepressants was 2.6 (95% CI, 1.4-4.8) compared with patients using the other agents.

Several SSRIs undergo biotransformation to metabolites that may also influence bleeding and platelet aggregation. Fluoxetine is converted to norfluoxetine, which has an elimination half-life of 7 to 15 days.¹⁷ Physicians should be aware of this factor when prescribing fluoxetine because norfluoxetine is as potent as fluoxetine for inhibiting 5HT reuptake.¹⁸ Sertraline's metabolite *N*-desmethylsertraline is 5 to 10 times less potent for 5HT reuptake, with lower concentrations detected in patients.¹⁹⁻²¹ Both compounds were reported to significantly ($P < .05$) inhibit platelet aggregation induced by adenosine diphosphate, collagen, and thrombin.²² Paroxetine metabolites possess very weak 5HT inhibition compared with the parent drug.²³

The effects of SSRIs to inhibit platelet aggregation may be dose-dependent, as shown by in vitro studies and clinical case reports.^{23,24}

Increased Gastric Acid Secretion

Although not commonly recognized by physicians, SSRIs have been shown to increase gastric acid secretion directly. This action can potentially enhance the likelihood of ulcerogenic effects leading to GI bleeding.¹⁰ The role of 5HT in gastric acid secretion was investigated by a series of animal studies. One of the studies²⁵ examined the use of a fluoxetine pretreatment that potentiated a metabolically stable thyrotropin analogue RX77368. Thyrotropin-releasing hormone and RX77368 act in the brain to stimulate gastric function and enhance gastric acid and pepsin secretion, motility, gastric emptying, mucosal blood flow, and, therefore, the formation of gastric erosions.²⁵⁻²⁷

The 5HT pathways are known to innervate a number of brain areas, including the dorsal vagal complex.²⁸ Vagal stimulation releases 5HT into the GI tract, where specific 5HT receptor subtypes will modulate gastric acid secretion. Gastric acid inhibition modulated by 5HT occurs with 5HT1 receptor agonists but not 5HT1A receptor agonists.²⁹ Other 5HT receptor agonists (eg, 5HT2, 5HT3) are not involved with gastric acid inhibition.²⁹ Vagal stimulation can increase the basal rate of 5HT release into the gastric lumen and portal circulation by 600% and 265%, respectively.³⁰ Osteopathic manipulative treatment directed to areas of vagus nerve irritation could potentially attenuate gastric acid secretion because of the parasympathetic component of this mechanism. Balancing this treatment with the treatment of somatic areas related to sympathetic tone—originating from the thoracic spine and traveling through the celiac ganglion—is an important consideration as well.

Both fluoxetine and sertraline may have a dose-dependent effect on gastric acid secretion, possibly attenuated by vagotomy.³¹ Fluoxetine has also been shown to potentiate RX77368-induced gastric acid secretion, which suggests an interaction between 5HT and thyrotropin-releasing hormone to promote gastric acid

secretion.²⁵ The concomitant use of paroxetine and aspirin may produce a dose-dependent increase in gastric acid secretion greater than either agent alone.³² This pharmacologic mechanism may account for the increased likelihood of upper GI bleeding when SSRIs and NSAIDs are used together.

GI Bleeding

The association between SSRIs and an increased risk of GI bleeding is well described in the literature but yields inconsistent results. A systematic review and meta-analysis by Jiang et al³³ of 22 cohort and case-controlled studies involving more than 1 million people reported 1.55-fold higher odds of upper GI bleeding in SSRI users compared with nonusers (95% CI, 1.35-1.78). In subgroup analyses, the risk was found to be greatest among participants taking concurrent NSAIDs or antiplatelet medications. There was considerable heterogeneity among the included studies ($I^2=88.9\%$; $P<.001$). A meta-analysis of observational studies in 2017 by Laporte et al³⁴ included 42 studies accounting for greater than 1 million people who experienced severe bleeding with SSRI use. A 41% increased risk of severe bleeding was noted for SSRI users (95% CI, 1.27-1.57), which was mostly attributed to GI bleeding (22 studies: OR, 1.55; 95% CI, 1.32-1.81).

The first epidemiologic study to support this association was conducted by de Abajo et al³⁵ in 2009. Using the United Kingdom-based General Practice Research Database, patients aged 40 to 79 years between April 1993 and September 1997 were matched to 10,000 controls for age, sex, and time based on the source population. Use of SSRIs was present in 52 participants (3.1%) among 1651 incident cases of upper GI bleeding compared with 95 of 10,000 participants (1%) among the control group (adjusted OR, 3.0; 95% CI, 2.1-4.4). Relevant factors included non-SSRI antidepressants (relative risk [RR], 1.4; 95% CI, 1.1-1.9) and concurrent NSAID (adjusted RR, 15.6; 95% CI, 6.6-36.6) or low-dose aspirin (adjusted RR, 7.2; 95% CI, 3.1-17.1) use. No differ-

ences were found among individual SSRIs, and use was not associated with the 248 cases of ulcer perforation. The conclusions of de Abajo et al³⁵ are supported by findings in recent observational studies presented in [Table 1](#).^{6,36-41}

Dall et al³⁹ reported a more modest association of SSRI use and GI bleeding. Using 3 databases from Denmark, this case-controlled study identified 3652 cases of serious upper GI bleeding from 1995 to 2006. Use of SSRIs was associated with increased risk of upper GI bleeding in current users (adjusted OR, 1.67; 95% CI, 1.46-1.92), recent users (adjusted OR 1.88; 95% CI, 1.42-2.5), and past users (adjusted OR, 1.22; 95% CI, 1.07-1.39). Concurrent users of NSAIDs and SSRIs had an elevated risk of much greater magnitude, contrary to proton-pump inhibitor (PPI) use, which was associated with a decreased risk.

There is controversy among SSRI-specific factors that may contribute to elevated GI bleeding risk, such as potency of serotonin reuptake or receptor affinity. In a 2012 cohort study, Castro et al⁴¹ identified 36,389 antidepressant users from an electronic medical record database in Massachusetts. The relative affinity of serotonin reuptake of each antidepressant was stratified by low-, moderate-, or high-affinity. The authors observed GI bleeding in 333 (n=14,927) in the low-affinity group vs GI bleeding in 601 (n=21,462) in the high-affinity group (adjusted RR, 1.17; 95% CI, 1.02-1.34). Similar findings were noted among patients who had a stroke. Additionally, a case-control study by Lewis et al³⁸ found increased odds of GI bleeding due to moderate- or high-affinity serotonin reuptake inhibitor use among 359 case participants and 1889 control participants (adjusted OR, 2.0; 95% CI, 1.4-3.0), but a dose-response relationship was not observed ($P=.17$).

The association between SSRIs and GI bleeding has been identified by numerous studies and summarized by 3 large meta-analyses.^{33,34,42} Inconsistencies may be attributed to enrollment criteria, potential confounders, and exposure definition. Selective serotonin reuptake inhibitors with a moderate to high affinity of serotonin reuptake could increase a person's risk for

Table 1.
Selective Serotonin Reuptake Inhibitors (SSRIs) and Risk for Gastrointestinal Tract (GI) Bleeding

Study (N)	Population	Methods	Results
de Abajo et al ³⁵ (11,899)	Antidepressant users 1993-1997	1651 cases of upper GI bleeding; 248 cases of ulcer perforation matched to 10,000 controls by age, sex, and time	Increased risk of upper GI bleeding with SSRIs (RR, 2.9; 95% CI, 2.0-4.2)
Van Walraven ³⁶ (317,824)	Antidepressant users aged ≥65 y 1992-1998	Observation for the duration of the prescription or until patients were admitted for upper GI bleeding	Overall bleeding rate of 7.3 per 1000 person-years; highest rates with older age, high inhibition of serotonin, and previous GI bleeding
Tata et al ³⁷ (64,417)	Upper GI bleeding 1990-2003	11,261 cases and 53,156 controls matched for age and sex	Increased risk of GI bleeding with SSRIs (OR 2.38; 95% CI, 2.08-2.72); higher risk with concurrent NSAIDs
Dalton et al ⁶ (26,005)	Antidepressant users 1991-1995	Observation from first prescription to first hospital admission for GI bleeding	Rate of GI bleeding for SSRI users is 3.1 per 1000 treatment y; increased risk with concomitant NSAID or aspirin
Lewis et al ³⁸ (2248)	Upper GI bleeding	359 cases matched to 1889 controls	Moderate - or high-affinity SSRI increased odds of hospitalization (OR, 2.0; 95% CI, 1.4-3.0); higher odds with concomitant high-dose NSAIDs (OR, 3.5; 95% CI, 1.9-6.6)
Dall et al ³⁹ (40,154)	Peptic ulcer diagnosis 1995-2006	3652 cases of GI bleeding and 36,502 controls matched for age and sex	Adjusted OR, 1.67 (95% CI, 1.46-1.92) for current SSRI users; adjusted OR, 0.96 (95% CI, 0.50-1.82) among PPI users
Schelleman et al ⁴⁰ (666,235)	Warfarin users 1999-2005	13,026 cases of GI bleeding and 653,209 controls matched for index date and state	Increased OR upon initiation of citalopram, fluoxetine, paroxetine, amitriptyline, and mirtazapine
Castro et al ⁴¹ (36,389)	Antidepressant users 1990-2009	Exposure period of initial prescription to end of a continuous documented period of exposure	Adjusted RR, 1.17 (95% CI, 1.02-1.34) for antidepressants with high affinity for serotonin transporters

Abbreviations: HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; RR, relative risk.

GI bleeding. However, there is limited evidence on whether this risk is dose-responsive. Concomitant use of NSAIDs, anticoagulants, or antiplatelet medications with SSRIs is associated with a significantly elevated risk of GI bleeding. Concomitant PPI use may be protective, but more evidence is needed.

Intracranial Bleeding

Observational studies⁴³⁻⁴⁸ of intracranial bleeding are presented in [Table 2](#). A 2000 study examined the United Kingdom-based General Practice Research Database with participants aged 18 to 79 years who received a first-time prescription for antidepressants from January 1, 1990, to October 31, 1997.⁴³

Antidepressants were classified by SSRIs or tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors were excluded. From the database, 65 confirmed intracranial bleeding cases were identified and matched to 247 controls. This study reported an OR of 0.8 (95% CI, 0.3-2.3) for SSRIs, which implied no increased intracranial bleeding risk. Age, sex, antidepressant dose, and treatment duration were not significantly related to increased intracranial bleeding risk. However, smoking was found to be significantly related (OR, 3.7; 95% CI, 1.7-8.1).

Smoller et al⁴⁵ described the risk of incident cardiovascular morbidity and mortality among community-dwelling postmenopausal women taking antidepressants. A higher RR of all-cause mortality (hazard ratio [HR],

Table 2.
Selective Serotonin Reuptake Inhibitors (SSRIs) and Risk for Intracranial Bleeding

Study (N)	Population	Methods	Results
de Abajo et al ⁴³ (319)	Antidepressant users 1990-1997	65 cases and 254 controls matched for age, sex, and time	Incident intracranial bleeding (OR, 0.8; 95% CI, 0.3-2.3) with current SSRI; no effect related to dose or treatment duration
Chen et al ⁴⁴ (644)	Antidepressant users with hemorrhagic stroke 1998-2002	92 cases and 552 controls matched by age, sex, and index date of depression diagnosis	Risk of hemorrhagic stroke did not significantly differ among antidepressants based on degree of serotonin inhibition
Smoller et al ⁴⁵ (5496)	Postmenopausal women from WHI study with new antidepressant use 1993-1998	Observation from baseline to end of study period if patient had at least 1 follow-up visit	HR, 1.45 (95% CI, 1.08-1.97) for stroke; HR, 1.32 (95% CI, 1.10-1.59) for all-cause mortality with SSRIs; not associated with CHD
Douglas et al ⁴⁶ (1996)	Antidepressant users 1998-2006	365 cases of intracranial bleeding matched to 1631 controls	No evidence of hemorrhagic stroke with SSRI or TCA
Verdel et al ⁴⁷ (15,149)	Hospital admissions for intracranial bleeding 1998-2007	5651 cases matched to 9498 controls	Increased risk with SSRI (OR, 1.39; 95% CI, 1.13-1.70) and TCA (OR, 1.35; 95% CI, 1.03-1.78)
Renoux et al ⁴⁸ (92,738)	New antidepressant users 1995-2014	3036 cases of intracranial bleeding matched to 89,702 controls	Increased risk with SSRI (RR, 1.17; 95% CI, 1.02-1.35), especially within 30 d; concomitant anticoagulant use further increased risk (RR, 1.73; 95% CI, 0.89-3.39)

Abbreviations: CHD, coronary heart disease; GI, gastrointestinal; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; RR, relative risk; TCA, tricyclic antidepressant; WHI, Women's Health Initiative.

1.32; 95% CI, 1.10-1.50) and increased stroke risk (HR, 1.45; 95% CI, 1.08-1.97) were associated with SSRIs. Increased all-cause mortality (HR, 1.67; 95% CI, 1.33-2.09) was associated with TCAs. Differences between SSRIs and TCAs were not found. A commentary⁴⁹ was later published stating that depression is an important and underrecognized risk factor for cardiovascular mortality, with a known lower quality of life, unhealthy life choices, and poor adherence to treatment regimens.⁴⁵ These factors can contribute to poor outcomes and leave physicians to make their own clinical judgements and monitor patients carefully.

The latest population-based cohort study used the Clinical Practice Research Datalink that spanned over 650 general practices.⁴⁸ The number of intracranial bleeding cases found was 3036, which yielded an overall incidence rate of 3.8 per 10,000 persons per year. Use of SSRIs was associated with an increased

intracranial bleeding risk (RR, 1.17; 95% CI, 1.02-1.35) relative to the TCAs; the highest risk was during the first 30 days of treatment (RR, 1.44; 95% CI, 1.04-1.99). Selective serotonin reuptake inhibitors classified as potent or strong 5HT inhibitors were also associated with an increased intracranial bleeding risk (RR, 1.25; 95% CI, 1.01-1.54). Use of SSRIs can place a small number of patients at increased intracranial bleeding risk, especially with higher 5HT potency agents during the first 30 days of therapy.

Antiplatelet or anticoagulant medications are often prescribed for patients with stroke, and their concomitant use with SSRIs may further increase intracranial bleeding risk. In a study by Renoux et al,⁴⁸ concurrent anticoagulants were found to increase intracranial bleeding incidence (RR, 1.73; 95% CI, 0.89-3.39), but the increase was not statistically significant. The concurrent use of antiplatelet agents, however, did not

increase intracranial bleeding risk (RR, 1.08; 95% CI, 0.65-1.34). The small number of patients with intracranial bleeding who used SSRIs and agents typically associated with bleeding (anticoagulants [n=291], antiplatelets [n=852], NSAIDs [n=708]) was acknowledged as a potential study limitation. Another study⁵⁰ reported an increased intracranial bleeding incidence when SSRIs were prescribed with anticoagulants compared with anticoagulants alone (RR, 1.56; 95% CI, 1.33-1.83). Patients should be carefully assessed when SSRIs and TCAs are used with anticoagulants, and prudent judgment should be used because of the routine prescription of antiplatelets and NSAIDs.

Studies published from 1995 to 2005 reported a lack of association between SSRIs and intracranial bleeding, but later studies⁴³⁻⁴⁸ reported a slight increase in likelihood (Table 2). A large population-based cohort study reported the incidence to be 3.8 per 10,000 persons per year (0.038%).⁴⁸ One feature that may influence study results is the number of controls used per case; Renoux et al⁴⁸ used a strict approach, with up to 30 controls matched to each case and a varying number of covariate factors. An association between 5HT potency and intracranial bleeding has been inconclusive. The concurrent use of SSRIs and anticoagulants or antiplatelets may increase intracranial bleeding risk, but the reported incidence is low, which makes definitive answers challenging. Overall, physicians should be cognizant of intracranial bleeding symptoms especially within the first 30 days of treatment. Patients should be evaluated emergently if the clinical presentation of intracranial bleeding is suspected.

SSRI PK/PD Interactions

Warfarin

The combination of warfarin and SSRIs has been shown to increase bleeding risk. Proposed mechanisms behind this drug-drug interaction include altered platelet aggregation and CYP isoenzyme inhibition by SSRIs. Potency of CYP inhibition varies among SSRIs, though the effect of potency on bleeding risk is unclear. S-warfarin is the more potent isomer of warfarin

that is primarily metabolized by CYP2C9. Priskorn et al⁵¹ evaluated the interactions between warfarin and a weak CYP2C9 inhibitor, citalopram. Participants (N=12) either received a single 25-mg dose of warfarin alone or on day 15 of a 21-day regimen of citalopram 40 mg/d. Blood samples were then analyzed during a 168-hour period after warfarin dosing. Citalopram did not result in any pharmacokinetic changes in warfarin. However, compared with warfarin alone, the addition of citalopram increased the maximum mean (SD) prothrombin time (PTT) from 25.1 (3.7) seconds to 26.7 (5.1) seconds, which represents an increase of 1.6 (3.0) seconds (90% CI, 1.01-1.10). Additionally, the area under the PTT-time curve (AUC_{PT}) increased by a mean (SD) of 5.0% (5.7%) after the addition of citalopram to warfarin (90% CI, 1.03-1.07). This study was powered to detect a 3% difference in AUC_{PT} using a 90% CI. Given the lack of pharmacokinetic changes, the authors suggested that citalopram affects anticoagulation by a mechanism outside the CYP isoenzyme system. The interaction resulting in a small change in PTT may not be clinically significant.

Quinn et al⁵² evaluated 9186 participants from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) trial who were exposed to warfarin during the median 6-year study period. Compared with warfarin users who did not use SSRIs, concomitant SSRI users (n=1743) spent a greater proportion of time at a supratherapeutic international normalized ratio (12.3%, $P<.001$) and had a higher mean bleeding risk score (2.99 for SSRI users vs 2.45 for nonusers; $P<.001$). A multivariable model adjustment for the bleeding risk score showed an elevated risk of major bleeding for warfarin patients taking SSRIs compared with nonusers. Warfarin users taking concomitant SSRIs may necessitate closer monitoring with regard to increased international normalized ratio levels and elevated risk for bleeding.

Clopidogrel

Certain SSRIs may affect clopidogrel concentrations, resulting in decreased clopidogrel efficacy. Clopidogrel is a prodrug that undergoes a 2-stage activation process

mediated by CYP450 enzymes, most notably CYP2C19. The SSRIs fluoxetine and fluvoxamine are potent inhibitors of CYP2C19. In a PK/PD study of rats, pretreatment with high-dose fluvoxamine (27 mg/kg) resulted in significant increases in AUC₀ and half-life of clopidogrel carboxylic acid ($P < .05$ for both).⁵³ The difference in mean (SD) platelet aggregation percentage before and after fluvoxamine (21.63% [6.05%] vs 45.98% [5.11%], respectively, $P < .01$) administration suggested a significant inhibition of clopidogrel's effects.⁵³ In a large population-based cohort study of CYP2C19-inhibiting SSRI use ($n=9284$) vs non-CYP2C19-inhibiting SSRI use ($n=45,073$), researchers found an increased risk of ischemic events (HR, 1.12; 95% CI, 1.01-1.24) in patients taking CYP2C19-inhibiting SSRIs.⁵⁴ The difference was more pronounced in older adults. This finding suggests that the co-administration of CYP2C19-inhibiting SSRIs such as fluoxetine and fluvoxamine may result in clinically significant reductions in clopidogrel efficacy.

Aspirin

Both aspirin and SSRIs are associated with an independent increased risk of bleeding. The PK/PD interactions between SSRIs and aspirin are not well described. Serotonin was added to the platelets of 12 healthy participants in an ex vivo pharmacometabolomics study⁵⁵ of collagen-induced platelet aggregation. Before aspirin use, collagen-stimulated platelet aggregation was inhibited to a lesser extent among participants with higher serotonin levels compared with participants with lower serotonin levels (mean [SD], 61% [11%] vs 72% [8%], respectively, $P = .02$).⁵⁵ This study suggested that aspirin may further enhance serotonin's effects on platelets. Inhibition of serotonin reuptake into neurons and platelets is known to reduce platelet aggregation. Each patient's level of serotonin could potentially mediate the already additive effects of SSRIs and aspirin.

Limitations

Limitations inherent to this narrative review include limited data sources, possible selection bias, and no

measures of heterogeneity among included studies. Although references cited by identified studies were evaluated if relevant, we did not use hand searching or include gray literature in this review.

Conclusion

This review describes the rare but serious adverse effects associated with SSRI use: GI bleeding and intracranial bleeding. Mechanisms of SSRI-associated bleeding risk include increased gastric acid secretion and the inhibition of serotonin entrance into platelets. Concomitant use of warfarin, clopidogrel, and aspirin may further elevate a patient's risk of bleeding through various PK/PD interactions. Some studies suggest PPI use in patients taking these concomitant medications to mitigate GI bleeding risk. The application of OMT to associated areas of somatic dysfunction may also attenuate gastric acid secretion via modulation of the autonomic nervous system. However, more evidence is needed in this area. Regarding the risk of intracranial bleeding, prudent monitoring is highly recommended for patients taking anticoagulants or antiplatelets with or without SSRI use.

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