General

Selective Serotonin Reuptake Inhibitors and Associated Bleeding Risks: A Narrative and Clinical Review

Amber N. Edinoff[1],[a], Keerthiga Raveendran[2], Marc A. Colon[2], Bennett H. Thomas[3], Katie A. Trettin[3], Grace W. Hunt[3], Adam M. Kaye[4], Elyse M. Cornett[5], Alan D. Kaye[5]

[1] Department of Psychiatry, Harvard Medical School, Massachusetts General Hospital, [2] Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Science Center Shreveport, [3] School of Medicine, Louisiana State University Health Science Center Shreveport, [4] Department of Pharmacy Practice, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, [5] Department of Anesthesiology, Louisiana State University Health Science Center Shreveport

Health Psychology Research

Major Depressive Disorder (MDD) is a major cause of disability worldwide and is associated with serious lasting impairment. A leading hypothesis of the pathophysiology of MDD is the monoamine deficiency hypothesis which suggests that depression is caused by depletion of serotonin, norepinephrine, or dopamine in the central nervous system. Serotonin is the most widely studied neurotransmitter in the pathophysiology of depression, with studies showing that reduced central serotonin synthesis leads to depressive symptoms in individuals at risk for depression. Selective Serotonin Reuptake Inhibitors (SSRI) inhibit serotonin reuptake and subsequently increase the amount of serotonin available in synapses. Common side effects of SSRIs include increased suicidality of patients under the age of 25, sexual dysfunction, anxiety, dizziness, weight gain, gastrointestinal distress, and headache. Other side effects include prolonging the QT interval, coagulopathy, and the risk of serotonin syndrome, as well as SSRI discontinuation syndrome. Sites of increased bleeding related to SSRI use have been reported to occur in the upper gastrointestinal tract, as well as intracranially. Based on the current literature, three studies have found that SSRIs are not associated with increased bleeding and/or increased perioperative risk, while others have demonstrated that SSRIs are associated with an increased risk in perioperative use. The inhibition of serotonin reuptake can affect platelet aggregation since platelets also express the serotonin transporter. SSRIs can result in decreased storage of serotonin in platelet dense granules. Increased serotonin can also increase gastric acid secretion, which increases the risk for ulceration. SSRIs in combination with NSAIDs also show a significantly increased risk of upper GI bleeding. Some studies show an increased bleeding risk from 30% to 70% when taking a combination of vitamin K antagonists and SSRIs in hospitalized patients. Related to the high prevalence of conditions that are treated with SSRIs, the bleeding risk associated with this class of medication merits further study.

INTRODUCTION

Major Depressive Disorder (MDD) is defined in *The Diagnostic and Statistical Manual of Mental Disorders-5* (DSM-5) as greater than or equal to two weeks wherein, nearly every day, a patient has five out of the following nine symptoms: depressed mood, anhedonia, change in weight or appetite, insomnia or hypersomnia, psychomotor retardation, loss of energy or fatigue, worthlessness or guilt, impaired concentration or indecisiveness, and thoughts of death or suicide or a suicide attempt. MDD can be further quantified into fourteen subcategories, such as "with mixed features," "with atypical features," and "with melancholic features."

a **Corresponding author:**
Dr. Amber N. Edinoff, MD
Massachusetts General Hospital
55 Fruit Street
Boston, MA, 02114
Phone: (617) 855-3808
aedinoff@mgh.harvard.edu

An MDD diagnosis is also specified with regard to severity (mild, moderate, or severe), with or without psychotic features, and whether the condition is in full, partial, or unspecified remission.[1]

A common treatment for MDD is selective serotonin reuptake inhibitors (SSRI). SSRIs are a class of medications that act in accordance with their name; this class inhibits serotonin reuptake and subsequently increases the amount of serotonin available in synapses. This mechanism of action is efficacious in treating depressive episodes and is why the medication has been used for years. However, SSRIs' effects are not region-specific and can cause serotonergic effects in various regions of the central and peripheral nervous systems.[2] SSRIs are commonly selective for the serotonin transporter (SERT). However, 80% of patients taking SSRIs will experience at least one side effect, and over half of patients will experience more than one adverse effect. This frequency of side effects can affect patients' medication compliance and, in turn, the treatment's efficacy. Negative side effects include nausea, dopaminergic effects such as extrapyramidal symptoms, and sexual effects such as decreased libido and anorgasmia.[3]

While the individual medications in the SSRI class have well-documented individual profiles, both in regard to positive and negative effects, the goal of this manuscript is to determine the bleeding risk of SSRIs.[2]

MAJOR DEPRESSIVE DISORDER

MDD is one of the most commonly presenting psychiatric disorders today and has been described in medical texts dating back to ancient Greece.[4] MDD is a major cause of disability worldwide and is associated with serious lasting impairment. In most cases, MDD is a chronic illness, with many patients relapsing at some point in life. MDD is associated with many negative consequences, including severe work impairment, with some studies suggesting more impairment than asthma, heart disease, and chronic obstructive pulmonary disease.[5] However, it has been difficult in the past to quantify the extent of MDD prevalence in the general population. Large-scale population studies (namely the National Comorbidity Survey) have been able to estimate the lifetime prevalence of MDD by the American Psychiatric Association's DSM-IV criteria at about 11%. This same study found that 5% of the population reported meeting criteria for diagnosis of MDD in the last 30 days.[4] The best prediction of the population risk has not been established yet, with some studies reporting much lower and some much higher rates of depression. There is a need for more recent studies with regards to the prevalence of major depressive disorder since the replacement of DSM-IV with DSM-5 and the added specifiers of diagnosis. The National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III) conducted a survey that included the adult prevalence of MDD in 2012. The study found that out of the 36,309 adult participants, the 12 month and lifetime prevalence's were 13.4% and 26.1%.[6] The likelihood of having an MDD episode was found to be highest in young adults under the age of 30 years.[5]

PATHOPHYSIOLOGY

There are many theories behind the pathophysiology of major depression for several reasons, one being that along the course of the illness, the disease may involve different depressive pathophysiology.[7] Strong evidence has led to the notion that MDD has a genetic basis. Evidence from family, twin, and adoption studies show that genetic factors are involved in the development of MDD, with some studies showing a 30-40% influence.[7] The regulation of the stress hormone cortisol has been suggested to be involved in the development of depression. Although women and men have similar sensitivities to depressogenic effects, women generally have higher stress responsiveness than men and show greater cortisol responses to social rejection, which could be why women have higher rates of MDD.[7] In addition, the hyper cortisol state seen in some depressed subjects may lead to the long-term consequences seen in MDD, such as cardiovascular disease, osteoporosis, and type 2 diabetes.[7]

There has been no specific gene identified as being associated with depression; however, studies have indicated that multiple genes with small effects could be linked to MDD. The monoamine deficiency hypothesis is the most relevant theory to the treatment of depression because it suggests that depression is caused by depletion of serotonin, norepinephrine, or dopamine in the central nervous system.[7] Serotonin is the most widely studied neurotransmitter in the pathophysiology of depression, with studies showing that reduced central serotonin synthesis leads to depressive symptoms in individuals at risk for depression.[7] In addition, mutations in the serotonin- 1A receptor, which decreases the availability of the receptor, have been found in patients with MDD.[7] These receptor changes lead to decreased serotonin action and symptoms of depression.

CURRENT TREATMENT OF MDD AND OTHER USES OF SEROTONIN REUPTAKE INHIBITORS

There is extensive literature describing the use of antidepressants to treat moderate to severe depression. SSRIs are a second-generation antidepressant; but are now considered a first-line treatment related to a positive safety and risk profile as compared to first-generation antidepressants, the tricyclic antidepressants. SSRIs have some variation in side effects, but the most common class side effects include gastrointestinal upset, headache, vivid dreaming, dry mouth, agitation or jitteriness, and sexual dysfunction.[8]

SSRIs are considered first-line therapy for depression, as they are efficacious and have a more favorable side effect profile as compared with the previous first-line agents, monoamine oxidase inhibitors, and tricyclic antidepressants. SSRIs are considered heterogeneous, meaning that if one of the SSRIs is not effective in a patient's management, another SSRI may be effective.[9] Of note, an antidepressant choice between tricyclic antidepressants and SSRIs does not influence utilization or expenditure of inpatient services and, though SSRI use reduces outpatient

visits and prescriptions for patients overall, their use was found to increase outpatient utilization for depressive conditions specifically.[10]

In addition to the treatment of depression, SSRIs are also indicated as a treatment for anorexia nervosa, bulimia nervosa, and post-traumatic stress disorder.[11] SSRIs can also treat anxiety. Citalopram reduces patients' level of anxiety as well as their number of panic attacks as compared to the patients' baseline.[9] A similar benefit has been seen in patients taking citalopram for obsessive-compulsive disorder. The majority of patients with obsessive-compulsive disorder had a 50% reduction in symptoms compared to their baseline in multiple studies. Citalopram has also been used to treat social phobia; after 12 weeks of treatment with citalopram, 86% of patients reported their symptoms being much improved.[9]

Secondary to the favorable side effect profile as compared to tricyclic antidepressants, SSRIs are an option to consider when prescribing medications to treat geriatric depression. Tricyclic antidepressants can be associated with falls and confusion associated with their antihistamine effects. Citalopram treatment was found to be effective in an open trial, with patients reporting a significant change in anxiety, depressed mood, irritability, fear, panic, and restlessness. A similar study comparing citalopram to placebo found that improved cognition occurred in the group receiving citalopram in patient groups both with and without dementia following six weeks of treatment. Another study found that doses of citalopram between 10 mg and 40 mg were significant in the reduction of depression symptoms as compared with placebo.[9] Side effects were seen in the elderly population, with the most common across multiple studies being orgasmic and ejaculatory dysfunction.[9]

Major depressive disorder in adolescents is a major health problem, wherein teens with persistent depressive symptoms are more likely to attempt suicide and undergo psychiatric hospitalization. Adolescents with depression are more likely to have impaired social relationships as well as diminished academic achievement. SSRIs are used to treat major depressive disorder in adolescent-aged patients. However, two out of five teenagers with depression will be resistant to their initial treatment and may not tolerate it well. Paroxetine is associated with higher levels of suicidality, while citalopram and fluoxetine were both found to be good choices when considering joint efficacy and tolerability in analysis. Overall, treatment of adolescents with depressive disorders should be considered critical; response to SSRI treatment and overall remission from depressive disorders is increased when pharmacotherapy is augmented with psychotherapy.[12]

Fluoxetine is an SSRI that has been evaluated as a possible mainstay of nociceptive pain management. Fluoxetine was found to be effective in patients with inflammatory pain, as well as in patients with nociceptive pain that were either opioid-tolerant or opioid-dependent. Fluoxetine could be useful in this regard because it is better-tolerated long term as compared with the other mainstays of inflammatory and nociceptive pain, such as corticosteroids and non-steroidal anti-inflammatory drugs.[11]

Perinatal depression includes both major and minor depressive episodes either during the patient's pregnancy or during the first postpartum year and occurs in one out of seven women.[8] The standard of care in these patients includes mental health services along with antidepressant pharmacotherapy. Untreated depression results in increased morbidity for mothers and babies, with an increased risk of suicide and substance abuse in mothers and an increased risk of preterm birth, fetal growth restriction, and low birth weight for the babies. SSRIs are first-line in treating pregnant and breastfeeding women and are noted to improve mood, with clinical benefit beginning to show at an average length of two week's treatment.[8] Each SSRI has its own recommended starting and titrated dose for pregnant and breastfeeding mothers with depression, as well as its unique side effect profile. While SSRIs can cross the placenta, and the fetus can be exposed to the medication, there has been no definitive cause-and-effect relationship between antidepressants and maternal-fetal outcomes in regard to fetal malformation and spontaneous abortion. SSRIs increase the risk of postpartum hemorrhage and severe postpartum hemorrhage in the mother, while babies exposed to SSRIs in the third trimester of fetal development are at increased risk of post- or neonatal adaptation syndrome. This adaptation syndrome includes respiratory distress and cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying.[8] Paroxetine is directly contraindicated in pregnant mothers due to an increased risk for cardiac malformations. However, other SSRIs may be substituted during gestation for the treatment of depression. Patient education is crucial in deciding whether to treat a pregnant or breastfeeding woman with an SSRI.[8]

MECHANISM OF ACTION

SSRIs currently approved for use in the United States include fluvoxamine, fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and vilazodone. These medications are indicated in the treatment of MDD, generalized anxiety disorder, bulimia nervosa, bipolar depression, obsessive-compulsive disorder, panic disorder, premenstrual dysphoric disorder, post-traumatic stress disorder, and social anxiety disorder. Fluvoxamine, however, is only approved for the treatment of obsessive-compulsive disorder in the US. SSRIs increase the deficiency of serotonin seen in many of the conditions they treat by inhibiting the serotonin transporter (SERT) that is responsible for the reuptake of serotonin from the synapse. By inhibiting SERT, the amount of serotonin is increased in the synaptic cleft, which in terms allows serotonin to stimulate post-synaptic serotonin receptors for a longer period of time. SSRIs also cause downregulation of specific serotonin receptors.[13] One such receptor is the 5-HT$_2$ receptor, more specifically the 5-HT$_{2A/2C}$, which are known to be anxiogenic as well. Postmortem quantification of 5-HT2 receptors in the

frontal cortex of patients with MDD indicated that untreated patients had increased receptor binding compared to normal controls.[13]

SSRIs are metabolized by the cytochrome p450 system and are administered in oral formulations, including liquids, tablets, and capsules; no other forms of SSRI exist at this time, e.g., intramuscular, subcutaneous.[14] Excluding Vilazodone, meals are not required to take SSRIs. Common side effects of SSRIs include increased suicidality of patients under the age of 25, sexual dysfunction, anxiety, dizziness, weight gain, gastrointestinal distress, and headache. Other side effects include prolonging the QT interval, creating a coagulopathy, and the risk of serotonin syndrome, as well as SSRI discontinuation syndrome.[14] Patients who take SSRIs should have weight, and vital signs monitored, as well as their levels of anxiety, insomnia, and sexual dysfunction due to the side effect profile of the class as a whole[14]

Fluvoxamine's effects are likely due to its high-affinity σ1 receptors, the highest in the SSRI class. σ1 receptor activity modulates the NMDA-glutamate receptor activity, which can have effects on dopamine and substance P. By modulating these receptors, Fluvoxamine has been shown to improve memory impairment, depression, anxiety, and depression with psychotic features. Fluvoxamine is most often associated with a negative profile, including nausea, headache, and somnolence.[2]

Paroxetine has a high negative side effect profile, including dry mouth, fatigue, weight gain, and cognitive impairment, which secondary to its high cholinergic muscarinic receptor affinity.[2] Paroxetine is also a teratogen, causing cardiac malformations in the fetus if it is taken in the first trimester.[14]

Fluoxetine inhibits 5-HT2c receptors more than other receptors, resulting in modulated norepinephrine and dopamine activities that can cause activation of the central nervous system as well as weight loss. These effects can also cause negative effects, including insomnia and agitation.[2]

Citalopram is an SSRI that has little activating or sedating properties secondary to its high selectivity for the serotonin (5-HT) receptor. It is associated with food cravings and subsequent weight gain, as well as difficulty concentrating and sexual dysfunction. Escitalopram is a citalopram enantiomer that has a faster onset of action than citalopram while having similar effects and side effects as citalopram.[2]

PHARMACOKINETICS/ PHARMACODYNAMICS

SSRIs have become some of the most widely prescribed antidepressant medications due to their overall safety, lack of life-threatening side effects, and general ease of use. The varying pharmacokinetics and pharmacodynamics of each SSRI help guide clinicians to determine the most appropriate drug for each individual patient with MDD. All SSRIs reversibly block the reuptake of serotonin in the synaptic cleft to a certain degree and have a similar antidepressant efficacy and side effect profile.[15] The five SSRIs, fluvoxamine,

fluoxetine, sertraline, paroxetine, and citalopram, differ in their pharmacokinetic profiles, especially in drug-drug interactions.

One of the major pharmacokinetic differences between these antidepressant drugs is their half-life. Fluoxetine has a much longer half-life (1-4 days) than the other four drugs (21-36 hours).[15] This means fluoxetine tends to have a longer washout period after discontinuation of the drug than the other SSRIs. The long half-life of fluoxetine can be advantageous for patients who are poorly compliant with taking medications because forgetting a dose only slightly decreases drug concentration.[15] However, it can also be disadvantageous because of the time it takes to reach steady-state concentration and cause any effect, which is four weeks. Fluoxetine also exhibits nonlinear kinetics, resulting in disproportionately high blood concentrations after dose increases.[15]

The metabolism of each individual SSRI is variable and affected by cytochrome P450 isoenzymes, which leads to differing blood concentrations in patients and subsequent drug-drug interactions. Generally, SSRIs are absorbed via the gastrointestinal system very well, reaching peak plasma concentrations after about 4-6 hours.[16] Combining one of these SSRIs with a drug that is a substrate for one of the inhibited CYP enzymes can be very harmful to the patient if it is not recognized as it can increase the drug's serum concentration.[15] Fluvoxamine is the only SSRI that has been shown to interact with a certain isoenzyme, CYP1A2, different from CYP2D6, which has interactions with the other SSRIs.[15] The most potent SSRI available is paroxetine, although, in addition to blocking serotonin receptors, it also blocks muscarinic acetylcholine receptors.[15] This extra mechanism of paroxetine surprisingly shows little to no extra side effects. Sertraline is the only SSRI that binds to dopamine transporters. Citalopram is the most selective of the five SSRIs in inhibiting serotonin reuptake over noradrenaline reuptake.

SEROTONIN AND PLATELETS

Platelets contain and release a significant amount of whole blood serotonin that is known to be vital to hemostasis at sites of vascular injury. In fact, most of the serotonin found in the body is found stored in platelets and released once they are activated.[17] The first step in the process of hemostasis, called primary hemostasis, involves the formation of a platelet plug at the site of vascular injury within the vessel. Primary hemostasis can be broken down into the following steps: platelet initiation, adhesion, activation, and aggregation.[18] Vascular endothelial injury leads to transient vasoconstriction and then subsequent binding of von Willebrand factor (vWF) to exposed collagen. The adhesion step involves the adhesion of the platelet to the injured endothelium via its GpIIb receptor, effectively activating the platelet. Once a platelet is activated, ADP and serotonin are secreted from the platelet's dense granules and are involved in the aggregation of subsequent platelets to the site of injury. Serotonin is a known vasoconstrictor, and it also promotes cellular activation of surrounding platelets and

other immune cells via 5-HT receptors.[19] SSRIs block the reuptake of serotonin in the brain pre-synaptic terminals and therefore increase the amount and availability of serotonin in the synaptic cleft. This occurs by blocking SERT. SERT transports serotonin back into the brain nerve terminal, removing it from the synaptic cleft.[17] Platelets also express the serotonin transporter. Therefore, when SSRIs are used, they result in decreased storage of serotonin in platelet dense granules. Platelet serotonin depletion leads to decreased platelet aggregation amplification and can potentially lead to increased bleeding in patients on SSRIs or other antidepressants.[18] There have been several longitudinal studies suggesting that depression may be a risk factor for cardiovascular disease, and this increased risk may be related to platelet function abnormalities. Thus, this is suggestive of the effect of selective serotonin reuptake inhibitors on depression and the prevention of acute myocardial infarction.

SSRIS AND BLEEDING RISKS

Abnormal sites of increased bleeding due to SSRI use have been reported to occur in the upper gastrointestinal tract, as well as intracranially. The most common of these sites is gastrointestinal (GI). There seems to be a higher association in postpartum, perioperative, and liver disease patients. Other less common forms of bleeding include the gums, epistaxis, subconjunctival hemorrhage, vaginal bleeding, epidural hematoma, hemorrhagic patellar bursitis, retrobulbar hematoma, and bleeding into joints.[20]

There are two proposed mechanisms for SSRIs and bleeding. The first is the inhibition of serotonin into platelets, as previously introduced. This occurs by inhibition of the serotonin transport protein that blocks the uptake of synaptic serotonin into the presynaptic neuron.[21] Platelets normally release serotonin in response to vascular injury, which triggers vasoconstriction and platelet aggregation. This resulting hemostasis is inhibited by SSRIs.[20] The second proposed mechanism is through increased gastric acid secretion. Vagal stimulation releases serotonin into the gastrointestinal tract, where serotonin receptors modulate the release of serotonin. Vagal stimulation can increase the basal rate of serotonin into the gastric lumen and portal circulation.[21] Other proposed mechanisms include indirect platelet-related mechanisms such as interaction with the glycogen IIb/IIIa surface receptor involved in platelet activation.[20]

The timeline of the onset of bleeding with the use of SSRIs varies, but there are two central timelines that are suggested. The first mechanism suggests that bleeding occurs at the time it takes for serotonin reuptake inhibition to become clinically significant. This is when the drug reaches steady-state levels after dose initiation. This may take weeks, but conditions that impair platelet inhibition may speed up this process. The second mechanism suggests that bleeding onset occurs once the drug increases gastric acidity. This does not arise in all cases since mucosal ulceration is also needed. This bleeding may not occur immediately after administration of the SSRI, even if the gastric acidity is

increased by the drug.[20] SSRIs can increase gastric acidity almost immediately, making this timeline show a quicker onset.[22] Some patients may already have bleeding risk factors at the time of initiation, increasing the chance of early bleeds.

SSRIs were found to increase the risk of an upper gastrointestinal bleed (UGIB) by 55%.[21] An increased risk was especially found in patients who concomitantly used NSAIDs or antiplatelet drugs. Some studies show that SSRIs modify the risk of UGIB due to platelets not synthesizing serotonin. These inhibitors decrease the levels of serotonin in platelets, which inhibits the platelet's homeostatic ability. Extended treatment of SSRIs has shown to decrease serotonin uptake, leading to the depletion of serotonin after a few weeks. This risk, however, can be eliminated by used acid-suppressing drugs.[23] A problem with this effect of the combined drugs is that there is little evidence to show how much each drug contributes overall. There was a study that showed no evidence that bleeding risk was associated with the strength of SSRI inhibition of cytochrome P45. However, so this may effect may hold little value.[24]

While data about SSRIs alone has shown modest increases in risk for bleeding, SSRIs in combination with non-steroidal anti-inflammatory drugs (NSAIDs) show a significantly increased risk of upper GI bleeding.[25] Physicians that treat older patients with a history of GI bleeds or with increased risk factors for upper GI bleeds should consider these risk factors when deciding to prescribe an SSRI. Also, medication history in a patient who presents with a GI bleed should be reviewed. In these patients, the benefits of continuing the SSRI should be weighed against the negative effects of the GI bleed, as well as avoiding the combination of NSAIDs and SSRIs whenever possible. If both medications are thought to be essential, a medication such as a proton pump inhibitor should be considered to reduce the risk of bleeding.[25]

A recent study measured the hazard risk of taking an SSRI in a patient receiving treatment of atrial fibrillation. The combination tested was warfarin, a vitamin K antagonist, and rivaroxaban, a non-vitamin K antagonist. Results revealed that there was a slight, non-significant increase in danger while using rivaroxaban compared to standard warfarin treatment. There was also a small, non-significant increase in the rate of efficacy in patients taking SSRIs with anticoagulants, although the study was limited by a low population.[24] In another study, SSRIs were shown to increase the risk of exceptionally high INR values, which may be due to inhibition of the cytochrome P450 metabolism of warfarin. Another study, however, displayed that there was no evidence that bleeding risk was associated with SSRI inhibition of cytochrome P450 2C9. Some studies show an increased risk of bleeding when taking a combination of vitamin K antagonists and SSRIs in hospitalized patients from 30% to 70%.[24]

The presence of depression is increased in pregnancy, producing a higher rate of the use of SSRIs. There has been a reported prescribing rate of >2% of SSRIs to pregnant patients.[26] Postpartum bleeding is another potential concern when prescribing SSRIs to pregnant patients. There

have been studies that show an associated increase in post-partum hemorrhage when using SSRIs. This risk is higher with the use of Serotonin and norepinephrine reuptake inhibitors (SNRIs), especially in the last month of pregnancy. The later usage of SSRIs did not show an increase in post-partum hemorrhage like the SNRIs did.[26] It is important to note that the definition of postpartum hemorrhage in the data collection may skew the results of these studies as the definitions varied in terms of amount.

Another population that showed an increased bleeding risk is post-breast augmentation surgery. Hematomas typically present within a week of surgery and can be severe enough to need surgical drainage and medical treatment. The most common complication is hematomas from drugs such as platelet inhibitors, vitamin K antagonists, oral anticoagulants, estrogen, and NSAIDs. However, SSRIs are still considered a player in hematoma formation. The global incidence of post breast augmentation surgery hematomas is reported to be 1.44%, while patients who were taking SSRIs had an incidence of 4.59%.[27] A limitation outlined in this study is that patients who use antidepressants may have a less healthy lifestyle compared to patients that do not use antidepressants. Those with depression are more likely to partake in smoking, poor diet, and alcohol use when compared to those without depression. These are all potential confounders to the previously mentioned risks.[27] Table 1 summarizes the studies of SSRIs and associated bleeding risk.

SSRIs have been associated with adverse outcomes in the operating room and in interventional pain procedures. In this regard, SSRIs alone have been considered relatively safe in anesthesia and interventional pain practice in terms of increased bleeding risk. However, when combined with other agents that mediate or modulate interference of the coagulation cascade, such as nonsteroidals or selective herbals, increased intraoperative bleeding has been identified as well as potential increased risk of epidural/spinal hematoma.[28] Langerkranser et al.. performed a meta-analysis looking at medications and spinal hematomas and reported one patient on SSRIs of 160 cases.[29] Based on the current literature, three studies have found that SSRIs are not associated with increase bleeding and/or increased perioperative risk, while others have demonstrated that SSRIs are associated with an increased risk in perioperative use.[30–34] Auerbach et al. found that there is an increased risk with perioperative SSRI use; however, they did not account for NSAID use.[33] The other study that deemed a risk associated with perioperative SSRI use also noted that those patients receiving SSRIs are also more likely to have obesity and cardiovascular disease, which also affect perioperative risks.[32] Antithrombic guidelines, as put forth by the American Society of Interventional Pain Physicians (ASIPP), highlight the importance of taking a complete medication history to fully assess the patient's risk for bad perioperative adverse effects.[35] It is important to fully assess all risks as adverse events can affect the course of the rest of the patient's life, such as hematoma formations and spinal cord compression.

CONCLUSION

SSRIs are utilized as first-line treatment in many psychiatric conditions, including MDD. MDD is one of the most prevalent psychiatric disorders and may have serious adverse effects if left untreated. MDD causes these effects via a deficiency of monoamines, notably serotonin. SSRIs treat MDD by reversibly inhibiting the reuptake of serotonin from the synaptic cleft by the transporter SERT and is considered first-line treatment. This increases the bioavailability of serotonin and decreases a patient's symptoms of depression; however, these effects are only seen after an average of 4 to 6 weeks of patients being compliant with treatment.

As with any medication, SSRIs are documented to have many side effects, included but not limited to sexual dysfunction, weight gain, headache, et cetera. Related to the fact that serotonin can be stored in platelets, as well as its role in primary hemostasis, it is reasonable to investigate the role that SSRI class medications may play in creating a bleeding risk for patients taking these medications, with a possible increased risk in platelet function abnormalities and increased risk of cardiovascular disease.

Increased bleeding secondary to SSRI use has been noted in postpartum, perioperative, and liver disease patients. SSRIs most commonly are associated with upper GI bleeding and intracranial bleeding. There are a few studies that also suggest that there an increased risk of spinal cord compression secondary to an epidural hematoma in a routine pain intervention procedure; however, studies thus far have not taken into consideration the co-administration of NSAIDs. The mechanism of SSRI-mediated bleeding is hypothesized to be either related to inhibition of SERT transport of serotonin molecules into platelets, thus inhibiting primary hemostasis, or increased systemic serotonin creating a response that increases gastric acid secretion, which leads to erosion and ulceration, and subsequent gastrointestinal bleeding. For these reasons, it is important to counsel patients of bleeding risk, particularly those who are in the previously noted higher-risk demographics, prior to being placed on SSRI. In addition, the clinician should instruct patients who are prescribed SSRIs to avoid other medications that are associated with gastric ulceration and bleeding, most notably NSAIDs. Related to the high prevalence of conditions that are treated with SSRIs, the bleeding risk associated with this class of medication merits further study.

Table 1. Studies of SSRIs and bleeding risks

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Study 1: Andrade, et al. (2016)	Meta-analysis on use of SSRIs and risk of gastrointestinal bleeding. Studies included: 6 cohort and 16 case-control studies with >1,073,000 individuals.	Major findings: i. The odds of developing UGIB were 1.55-fold higher (95% CI, 1.35–1.78) in SSRI users. ii. A higher risk of UGIB was found with concurrent use of SSRIs and NSAIDs (OR 5 10.90; 95% CI, 7.33–16.21) or antiplatelet drugs (OR 5 5.00; 95% CI, 3.49–7.17). iii. The risk was increased with concurrent use of all 3 drugs (OR 5 9.13; 95% CI, 1.12–74.77). iv. The risk was eliminated by use of acid-suppressing drugs (OR 5 0.81; 95% CI, 0.43–1.53)	There is an especially increased risk of the use of both NSAIDs as well as SSRIs.
Study 2: Ruan, et al. (2015)	A total of 22 studies (6 cohort and 16 case-control studies) involving more than1,073,000 individuals were included in the meta-analysis.	In comparing SSRI users with patients who had not taken SSRIs, the odds fordevelopingUGIBwere1.55-foldhigher (odds ratio, 1.55; 95%confidence interval, 1.35–1.78). In subgroup analyses, the association was greatest for patients who received concurrent therapy with nonsteroidal anti-inflammatory or antiplatelet drugs; we found no significant increase in the risk of developing UGIB among patients receiving concurrent acid-suppressing drugs. SSRI	SSRI use was associated with an almost 2-fold increase in the risk of developing UGIB, especially among patients at high risk for GI bleeding (concurrent use of nonsteroidal anti-inflammatory or antiplatelet drugs). This risk might be reduced significantly by concomitant use of acid-suppressing drugs
Study 3: Quinn, et al. (2018)	Studied 737 patients taking SSRIs in the ROCKET AF trial of rivaroxaban compared with warfarin for the prevention of stroke/ systemic embolism in patients with atrial fibrillation. These patients were propensity score matched 1:1 to 737 patients not taking SSRIs.	Over a mean 1.6 years of follow-up, the rate of major/nonmajor clinically relevant bleeding was 18.57 events/100 patient-years for SSRI users versus 16.84 events/100 patient-years for matched comparators, adjusted hazard ratio (aHR) of 1.16 (95% confidence interval [CI], 0.95– 1.43). The aHRs were similar in patients taking rivaroxaban (aHR 1.11 [95% CI, 0.82–1.51]) and those taking warfarin (aHR 1.21 [95% CI, 0.91–1.60]). For the rarer outcome of major bleeding, the aHR for SSRI users versus those not taking SSRIs was 1.13 (95% CI, 0.62–2.06) for rivaroxaban; for warfarin, the aHR was higher, at 1.58 (95% CI, 0.96–2.60) but not statistically significantly elevated.	Found no significant increase in bleeding risk when SSRIs were combined with anticoagulant therapy, although there was a suggestion of increased bleeding risk with SSRIs added to warfarin. While physicians should be vigilant regarding bleeding risk, our results provide reassurance that SSRIs can be safely added to anticoagulants in patients with atrial fibrillation.
Study 4: Anglin, et al. (2014)	Fifteen case – control studies (including 393,268 participants) and four cohort studies were included in the analysis. There	There was an increased risk of upper GI bleeding with SSRI medications in the case-control studies (OR = 1.66, 95 % CI = 1.44,1.92) and cohort studies (OR = 1.68, 95 % CI = 1.13,2.50). The number needed to harm for upper GI bleeding with SSRI treatment in a low-risk population was 3,177, and in a high-risk population it was 881. The risk of upper GI bleeding was further increased with the use of both SSRI and NSAID medications (OR = 4.25, 95 % CI = 2.82,6.42)	SSRI medications are associated with a modest increase in the risk of upper GI bleeding, which is lower than has previously been estimated. This risk is significantly elevated when SSRI medications are used in combination with NSAIDs, and physicians prescribing these medications together should exercise caution and discuss this risk with patients.
Study 5: Perrota, et al. (2019)	This observational study was carried out between 2011 and 2017 to assess in a descriptive way the relationship, if any, between postpartum bleeding and consumption of an SSRI/SNRI during pregnancy. Pregnant women were recruited from the Psychopharmacological	In the FAERS database, 657 cases were related to PPH, of which 43 ICSRs reported at least one SSRIs or venlafaxine as suspect drug. The overall ROR of all antidepressant drugs included in our analysis was 3.56 (95% CI, 2.61e4.85), the highest values were observed with fluoxetine (ROR ¼ 6.42; 95% CI, 3.05e13.53), escitalopram (ROR ¼ 4.38; 95% CI, 2.18e8.80), and sertraline (ROR ¼ 3.25, 95% CI. 1.84e5.76) (Table II). Moreover, we performed data mining of the FAERS in order to identify similar Cases of postpartum	This study has to be considered descriptive of a condition that needs to be examined through more extensive clinical trials. While a potential protective effect of SSRIs/SNRIs on PPH cannot be established by our study, this study nonetheless corroborates their use during pregnancy. Moreover, this study

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
	and Pregnant Outpatients Department at Depressive Treatment Center; or from the Antenatal Clinic, ASST Fatebenefratelli-Sacco University Hospital.	bleeding related to the use of bupropion a non-serotonergic antidepressant. However, no cases were detected in the same period of observation (2004-2018). Study	highlights the importance of TDM in avoiding underdosing and subtherapeutic drug concentrations in special populations such as pregnant women.
Study 6: Basile, et al. (2013)	All patients with complete charts who underwent breast cosmetic plastic surgery procedures (breast augmentation, breast reduction, or mastopexy) in a single group practice at our hospital between January of 2001 and December of 2011 were reviewed. All the surgeries had been performed by one of two board-certified plastic surgeons working as part of an integrated multidisciplinary team. Data collected was computerized.	During the study period, 2,285 patients underwent breast cosmetic surgery, with 33 of these patients (1.44 %) experiencing a bleeding event (hematoma requiring surgical draining). Of the 196 patients (8.58 %) in the active-use group, 9 (4.59 %) experienced a bleeding event. Of the 2,089 patients in the no-use group, 24 (1.15 %) presented with hematoma requiring surgical draining. These data are shown in Table 1. The patients using SSRIs had a 4.14-fold greater risk of a breast hematoma needing intervention than the patients who were not SSRI users (OR, 4; 95 % CI, 1.90–9.04).	The use of SSRIs is associated with a fourfold increase in risk of bleeding after breast cosmetic surgery (from 1.44 to 4.59 %). Logistic regression showed that SSRIs increase the risk of bleeding regardless of weight, age, or type of procedure (breast reduction, mastopexy, or breast augmentation). The decision to stop SSRIs before surgery for psychologically vulnerable patients should not be made without a complete discussion of the risks and benefits.

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