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COMPLEX MEDICAL-PSYCHIATRIC ISSUES (MB RIBA, SECTION EDITOR)

Selective Serotonin Reuptake Inhibitor (SSRI) Bleeding Risk: Considerations for the Consult-Liaison Psychiatrist

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Abstract

Purpose of Review To present a clinically oriented review of selective serotonin reuptake inhibitor (SSRI)-related bleeding issues commonly addressed by consult-liaison psychiatrists.

Recent Findings Concomitant medical, surgical, or hospital-based conditions exacerbate the risk of SSRI-related bleeding even though a review of the literature suggests it is only marginally elevated. Psychiatrists and other clinicians need to consider these conditions along with antidepressant benefits when answering the question: to start, hold, continue, or change the antidepressant?

Summary Where an evidence base is limited, mechanistic understanding may help consult-liaison psychiatrists navigate this terrain and collaborate with other medical specialties on responsible antidepressant management. Most often, the risk is cumulative; data are not directly applicable to complex clinical situations. This review incorporates a hematologic perspective and approach to bleeding risk assessment along with extant data on SSRI-induced bleeding risk ad specific medical conditions.

Keywords Antidepressant side effects · Serotonin reuptake inhibitor · Bleeding risk · Medically complex patients · Hemorrhage · Thrombocytopenia

Introduction

Consultation-liaison psychiatrists are frequently asked whether a selective serotonin reuptake inhibitor (SSRI) should be discontinued, changed, or not started in patients with an elevated risk of bleeding. The answer should incorporate several key components such as the following: (1) the bleeding risk of SSRIs, (2) the bleeding risk of the individual patient, and (3) the affective symptom severity or trajectory for which the SSRI is prescribed. Naturally, questions arise about the utility of a proposed SSRI for a given patient and whether an adequate trial has been obtained, for example. SSRI bleeding-related questions are most frequently raised in an interdisciplinary setting by colleagues who are concerned about bleeding from gastrointestinal abnormalities, surgical procedures, thrombocytopenia and platelet function abnormalities, hemorrhagic strokes, and any other conditions related to the risk of bleeding. Most often, these consultations are relevant for patients with concomitant medical illnesses who are taking medications that also incur a risk of bleeding.

The consultant psychiatrist is often tasked with portraying the risk of bleeding stemming from the initiation or continuation of antidepressant therapy while weighing the need to treat anxiety or depression pharmacologically in various medically or surgically complex settings. This task is accomplished by not only understanding the relationship between SSRIs and bleeding but also the risk of bleeding posed by co-occurring medical/surgical scenarios. In addition, non-psychiatric clinicians and patients tend to have strong feelings about psychotropic medications further complicating the question. They may want to quickly rid themselves of an SSRI when it does not pose a significant bleeding risk (or without an adequate trial) or the opposite, they may feel an attachment to the SSRI when the risk of

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bleeding is significant and its efficacy uncertain. That is, consulting clinicians may wish to discontinue an antidepressant unnecessarily or wish to continue the medication despite an uncomfortably high risk of bleeding. A paucity of applicable data and the intersectionality of myriad clinical factors leave little high-quality data to drive these decisions, directly.

The next best step is to gain an understanding of the influential issues that the consultant psychiatrist should factor into her decision to stop, continue, or initiate SSRI therapy in the face of elevated bleeding risk. This review will address (1) background factors (i.e., overall SSRI-induced bleeding risk and the mechanism of SSRI-induced bleeding), (2) the assessment of bleeding risk (e.g., taking a bleeding history) and comorbid clinical scenarios with risk of bleeding, and (3) considerations for the consultant psychiatrist in providing SSRI management recommendations.

Background

How Great Is the Risk?

Numerous case reports and observational studies examine the risk of bleeding in people taking SSRIs. Many suggest an increased risk of bleeding but not uniformly. Results are also complicated by not only SSRI type and dose but the site of bleeding. Meta-analytic data assist in interpreting these data, especially where they are equivocal. In a meta-analysis of 42 observational studies (31 case–control, comprising 1,255,073 subjects and 11 cohort studies with 187,956 subjects), the risk of bleeding at any site was increased for patients on SSRIs versus controls (OR 1.41, 95% CI 1.27–1.57) [1•].

Bleeding into the gastrointestinal (GI) tract is the most frequently reported site of bleeding for patients on SSRIs. Epidemiologic studies have shown that although SSRI use is associated with roughly doubled odds of GI bleeding, for example, the absolute risk remains low [2••]. Fifteen case-controlled studies including 393,268 participants and four cohort studies demonstrated that the number needed to harm (NNH) for upper GI bleeding with SSRI treatment in a low-risk population was 3,177, and in a high-risk population, the NNH was 881 [3]. But, the risk of bleeding increases substantially when patients are taking other medications known to impact platelets and other hemostatic mechanisms. For individuals on SSRIs and anticoagulant or antiplatelet agents, major bleeding was also increased (OR 1.39, 95% CI 1.23–1.58) in a meta-analysis of 32 cohort or case–control studies including 1,848,285 individuals [4]. A similar meta-analysis verified these results showing patients on SSRIs demonstrated an increased risk of upper GI bleeding (OR 1.55, 95% CI 1.35–1.78) compared to controls in a meta-analysis of six cohort and 16 case–control studies involving more than a million individuals. The association was greatest in patients also taking nonsteroidal anti-inflammatory or antiplatelet drugs. Interestingly, there was no significant increase in upper GI bleeding in individuals who were also taking acid-suppressing medications, suggesting that these may mitigate gastrointestinal bleeding risk [5•].

Stroke risk was found to be increased (OR 1.40, 95% CI 1.09–1.80) in individuals on SSRIs in a meta-analysis of 13 studies [6]. An increased risk was seen for both ischemic and hemorrhagic stroke. But the authors noted that they could not completely exclude the confounding effect of depression.

In the surgical setting, pre-operative use of serotonergic antidepressants was not associated with a higher risk of re-operation for a bleeding event (OR 1.48, 95% CI 0.84–2.62) in a meta-analysis of eight cohort studies with 79,976 subjects compared to 485,335 controls. However, SSRI use was associated with an increased risk of needing transfusion (OR 1.19, 95% CI 1.09–1.30) [7]. Post-partum hemorrhage was increased (RR 1.32, 95% CI 1.17–1.48) in a meta-analysis of eight studies comprising 40,000 cases. An association was seen in subgroup analyses not only with SSRIs, but also with non-SSRI antidepressants [8].

A meta-analysis of non-SSRI antidepressants found that patients on mirtazapine were at greater risk of GI bleeding compared to patients not on antidepressants (OR 1.17, 95% CI 1.01–1.38). But no differences in bleeding were found between patients on mirtazapine and SSRIs or on bupropion versus SSRIs [9]. Of note, only seven studies met inclusion criteria, and the authors concluded that data were insufficient to conclude that non-SSRI antidepressants bupropion and mirtazapine were acceptable alternatives to mitigate SSRI-associated bleeding risk.

These meta-analyses provide evidence of an increased risk of bleeding in people on SSRIs based on large epidemiologic data sets that are observational rather than randomized and therefore are limited by confounding, particularly for the effects of depression itself, which remains an especially relevant issue. Further studies are needed to elucidate SSRI-related bleeding risk in pertinent clinical scenarios.

The Role of Serotonin in Clot formation

Clot formation happens in response to endothelial tissue damage and other physiological signals or stressors and is meant to propagate exponentially to stop bleeding [10]. Greater endothelial damage leads to more extensive clot propagation. Clotting is a dynamic process of formation and destruction that is usually in balance. Clot formation and destruction are the basis of hemostasis and address both physiological needs (i.e., to stop bleeding without creating excessive thromboses). It restores endothelial tissue and stops bleeding, and the opposite process keeps the vasculature patent. Clot formation is composed of two basic stages:

(1) primary hemostasis resulting in the formation of a platelet plug, and (2) secondary hemostasis stabilizing the newly formed platelet plug by overlaying a network of fibrin and other cohesive proteins [11]. Clot disintegration results from antithrombotic control mechanisms and the removal of clot by fibrinolysis (i.e., lysis of fibrinogen, which can be measured by its degradation product the d-dimer) [10]. Platelets and endothelial proteins (e.g., von Willebrand factor) are the principal components of primary hemostasis (i.e., formation of platelet plug). This process is accompanied by vasoconstriction (bringing platelets and proteins closer together) and several specific platelet activities (e.g., adhesion, activation, and aggregation).

In nature, there can be a distinct advantage to redundancy, especially for the life-saving process of hemostasis. In addition to making many more platelets than needed for hemostasis, there are also additional hemostatic elements that help platelets aggregate and adhere to the endothelial lining (e.g., adenosine diphosphate (ADP), thromboxane A2, and Gp IIb/IIIa). Secondary hemostasis secures the primary platelet plug and involves the intrinsic and extrinsic coagulation cascade pathways. The end result of the coagulation cascade is the development of thrombin (factor II), which overlays fibrin and secures the primary platelet plug.

Not only is serotonin (5-HT) the paragon neurotransmitter of mood regulation and stability, but it also plays a key role in coagulation [11–13]. Serotonin (5-HT) was first described in the early 1930s by the Italian pharmacologist and chemist Vittorio Erspamer who isolated it from the enterochromaffin cells of the gut [14]. A large quantity of this serotonin produced in the gut is taken up from the plasma and stored in the dense granulates of platelets [15]. Once released upon platelet activation, serotonin acts as a mild aggregator of platelets working with other proteins like adenosine diphosphate (ADP) in a dose-dependent manner [10]. Although serotonin can act as a vasodilator, it also potentiates vasoconstriction in areas of endothelial compromise [16].

It is not completely understood how depression may lead to either greater uptake of platelet serotonin or its release. But this physiological state is influenced by depression leading to cardiac and other complications from thrombotic processes. The serotonin receptor, 5-HTT located on the platelet cell membrane, facilitates serotonin amine uptake from plasma. SSRIs impair uptake and the platelet secretory response leading to less robust platelet aggregation, which is therapeutic for patients who are at enhanced physiological risk of clotting. SSRIs deplete platelet serotonin content and subsequently inhibit primary platelet plug formation. This is particularly beneficial in patients with depression and medical illnesses with a propensity to clot. At the same time, this activity is the basis for SSRI-induced bleeding risk.

What Is the Mechanism of SSRI-Related Bleeding?

Serotonin is a platelet aggregator and mild vessel constrictor. SSRI-induced restriction of serotonin activity contributes to a propensity to bleed as demonstrated in vivo and in vitro [17]. SSRI bleeding risk is balanced with the reduced risk of clotting in patients who are predisposed to clotting. Clinical decision-making regarding the contribution of SSRI to bleeding risk should be informed by understanding the role of serotonin and hemostatic mechanisms.

A relationship between depressive symptoms and increased platelet activity is established in otherwise healthy individuals, but this relationship is even more profound in patients with coronary artery disease [18]. Any condition that disrupts the endothelial lining will be associated with clotting since those exposed proteins start the coagulation cascade and clotting. In addition, increased serotonin and platelet activation underly this relationship and help explain the salutary antithrombotic effects of SSRIs in patients with CAD by mitigating the thrombotic damage following a myocardial infarction [11, 19]. SSRIs limit serotonin storage in platelets and overall platelet function in hemostasis [20]. In summary, SSRIs reduce pathological clotting, which is helpful in procoagulant settings such as after an MI but also contributes to prolonged hemostasis, especially when combined with other bleeding risk factors.

Assessing General Bleeding Risk and Comorbid Medical Conditions

Taking a "Bleeding History"

A "bleeding history" is helpful in assessing the risk of bleeding and the positive predictive value of coagulation testing and a hemophilic workup. While the signs and symptoms of moderate to severe bleeding dyscrasias are overt, milder bleeding dyscrasias are discrete and only become a major problem after a physiological stressor (e.g., surgery, pregnancy, trauma, polypharmacy). Diseases associated with bleeding are either congenital or acquired. Almost all congenital bleeding occurs early in life. A patient's ability to maintain hemostasis into adulthood essentially rules out congenital causes of bleeding. Nonetheless, clinicians need to still consider bleeding risk in adults starting SSRIs especially in the presence of new or worsening illness.

Adults have usually had their hemostatic systems challenged at one time or another through some sort of physiologic stress (i.e., trauma) and will recall episodes of what they will have determined as unusual bleeding. Easy bruising, taking a long time to heal or stop bleeding, or other signs and symptoms of abnormal bleeding may be recalled. Patients will provide their own conclusions of what is

normal or abnormal based on the patient's surroundings (i.e., family members' bleeding propensities). They may normalize bleeding if it is a known condition within their family so the clinician may hear, "everyone in my family bruises (or bleeds) easily." Congenital bleeding diatheses are genetic and cluster in familial settings. If they are mild, patients may make it to adulthood without being discovered. A covert susceptibility to bleeding may be unmasked by the presence of additional physiological stressors (i.e., medical illness, poor nutrition) polypharmacy, and especially the addition of antiplatelet agents or anticoagulants. This change in bleeding propensity may be reflected in laboratory testing (e.g., coagulation indices, thrombocytopenia). Even if the patient has no underlying susceptibility to bleeding, the risk may evolve in the setting of an autoimmune phenomenon or the presence of a newly created anti-platelet antibody (i.e., an inhibitor), for example, providing a diversion from previously "normal" hemostasis. Underlying and contemporaneous risk of bleeding should be considered alongside the administration of an SSRI.

Of note, there are two primary types of bleeding: (1) mucosal (e.g., gingival from brushing teeth, menstruation) and (2) deep tissue/joint bleeding, in addition to direct trauma. Understanding these two important mechanisms underscores key questions in obtaining a bleeding history. Mucosal bleeding is related to platelet and fibrin issues while deep tissue/joint bleeding is often secondary to factor deficiency (e.g., congenital or acquired hemophilia). Patients with congenital clotting issues have abnormal bleeding from childhood which may include prolonged bleeding, poor wound healing, easy bruising, heavy menstruation, or pain from bleeding into deep tissue (after trauma) or joints.

If there are any episodes of bleeding in the patient's past, the clinician should review the four W's: who, when, what, and where (see text box). Answers will direct the clinician to underlying bleeding mechanisms [21]. Mild bleeding disorders manifested under physiological stress (e.g., minor or major surgery, blunt trauma and abrasions, menstruation, brushing teeth too hard, childbirth) stem from graded bleeding disorders such as von Willebrand, mild factor deficiencies, and liver disorders (e.g., dysfibrinogenemia). The "who" provides a demographic description of the patient. The "when," "what," and "where" provide a history of the present illness and a way to describe the bleeding.

Four W's:
(1) Who: who is the patient, sex, age, race and family history?
(2) When: when did the bleeding occur, i.e., onset of bleeding? Is it related to drug ingestion or any underlying disorder? Did it develop after surgery or trauma?
(3) Where: sites of bleeding, skin, muscle etc
(4) What: description of the type of bleeding

Adult patients with an unremarkable bleeding history may present with new onset history of notable bleeds, which may be mucosal (e.g., gingiva or any mucosal membrane, fatigue from anemia, and bleeding into GI tract), deep tissue (e.g., bleeding into joints), and petechial. Especially in adults, a clear and detailed account of any new or recently administered medications is crucial as bleeding may result from an "inhibitor" antibody formed in reaction to starting a new medication. In younger patients, family history is crucial as abnormal bleeding histories are passed down through families. That is, many families with a bleeding diathesis will pass down these histories ("our family has always been easy to bruise) as noted above.

Menstrual histories provide invaluable historical information on the ability to control bleeding. One caveat is that women often compare their menstruation cycles to other members of their family, which again may fall outside of a normal range of acceptable bleeding. Nonetheless, menstruation is an easily identified indicator of bleeding propensity and clotting formation. Petechia, which are small pinpoint erythematous non-blanching rashes, are almost always a cause for concern arising most frequently from idiopathic thrombocytopenic purpura (ITP). In adults, it may be a sign of the development of an antiplatelet antibody inhibitor, which is rare but increases with age. Also, they may correspond to acute hematologic disorders such as malignancy (e.g., leukemia and myelodysplastic syndromes) or non-malignant serious conditions like thrombotic thrombocytopenic purpura (TTP) or disseminated intravascular coagulopathy (DIC).

History of Present Illness (HPI) and SSRI Bleeding Risk

Bleeding risk may be incorporated into a standard psychiatric assessment for the sake of the organization.

Bleeding HPI: the bleeding history including the four W's should be recorded here.
Psychiatric HPI: a summary of the patient's ongoing symptoms and psychiatric treatments (e.g., medication and therapies) and their efficacy.
Psychiatric history: this section provides an overview of lifetime illness occurrence.
Medical history: this section incorporates medical history with attention to those illnesses that may contribute to bleeding risk.
Surgical history: reviews previous surgeries and complications (i.e., hemostatic stressors)
Medication: review for polypharmacy, drug-drug interactions, and other high-risk medications
Physical exam: assess for sites of bleeding (mucosal, joints), petechiae, and signs of anemia (e.g., pallor)

Liver Disease

The synthetic function of the liver supports hemostasis and consists of making proteins such as prothrombin (conversion to thrombin is measured by prothrombin time [PT]), all the coagulation cascade factors except for factor VIII, protein C and S, fibrinogen, and antiplasmin-proteins. Coagulation testing PT/INR (international normalized ratio) and partial thromboplastin time (PTT) measures hepatic synthetic function. In addition to poor synthetic function, liver disease also demonstrates hepatocellular and cholestasis laboratory testing patterns measured by liver function testing. Coagulation cascade proteins needed for primary hemostasis are produced in the liver along with proteins C and S, fibrinogen, and antiplasmin-proteins involved in both clot formation and dissolution. When the synthetic function of the liver is reduced, these proteins are made inconsistently. In addition, cirrhotic livers trap platelets leading to thrombocytopenia and dilation of blood vessels (e.g., varices) both of which put patients at risk of bleeding. The synthetic function is measured by coagulation testing (PT/PTT/INR) clearly indicates an increased risk of bleeding and possibly lowered hepatic metabolic potential and so antidepressants, especially in the setting of polypharmacy, should be used judiciously.

In patients with liver disease like hepatitis C but without cirrhosis, data are mixed regarding the risk of bleeding secondary to SSRI use in this setting. In an observational series of 303 patients receiving interferon and ribavirin for hepatitis C, only one patient bled and was later found to have hemophilia [22]. This series followed a previous report of increased bleeding in patients with hepatitis C infection who were taking NSAIDs concomitantly [23]. But the combination of SSRIs and NSAIDs couples the risk of bleeding beyond using either agent alone and therefore bleeding likely stems from the basic mechanisms of each drug rather than underlying liver dysfunction especially when laboratory abnormalities are not present [24, 25].

Cancer and Bleeding Risk

While most solid tumor malignancies are associated with thrombotic states due to coagulopathy, renal cell carcinoma, melanoma, and choriocarcinoma are specifically known for their associations with hemorrhage. In addition to qualitative and quantitative platelet dysfunction and coagulopathy from cancer treatments, patients with cancer frequently undergo invasive procedures and are therefore at risk of bleeding from instrumentation [26]. Of course, hematologic malignancies create the highest malignancy-associated risk of bleeding, and they are also associated with thrombosis requiring anticoagulation [27]. Chemotherapy causes hypercoagulability but may precipitate bleeding through thrombocytopenia. Drugs that target the blood vessels directly (e.g., bevacizumab) are associated with bleeding, but the risk does not appear to be increased when combined with anticoagulants [28]. For patients with cancer taking an SSRI, drug-drug interactions may increase the risk of bleeding, especially for patients on anticoagulants, antiplatelet medications, or other medications associated with bleeding. Chemotherapeutics that are metabolized through CYP3A4 may interact with SSRIs and could potentiate therapeutic dosing.

Solid Organ/Hematopoietic Stem Cell Transplant and Bleeding Risk

All transplant procedures carry an acute and chronic risk of bleeding derived from several interrelated reasons. Once stem cells or a solid organ are transplanted, rejection is prevented with various immunosuppressant agents that can lead to bleeding from direct toxicity or indirectly (e.g., gastric ulcers). Depending on the organ type, antithrombotic and antiplatelet drug administration may be co-administered along with immunosuppressants. The use of additional immunosuppressant medications (steroidal, non-steroidal, and steroid-sparing) also confers a risk of bleeding [29]. Renal graft recipients have an increased risk of bleeding due to platelet dysfunction in the setting of renal impairment [30]. In liver transplant, bleeding during the procedure is associated with worse survival. In fact, it is a stronger predictor of survival than the MELD (model for end-stage liver disease) score. Patients with INR > 1.6 had the highest risk of bleeding [31]. Acute bleeding post-stem cell transplant is a common complication but is also considered a poor prognostic factor [32]. Bleeding is mostly correlated with thrombocytopenia in this setting. Hemorrhages in this situation have mostly occurred with a platelet count between 10 and 20 $*10^9$/L (normal range is 150–450 $*10^9$/L [32]. Delaying SSRI prescribing until the resolution of bleeding and platelet counts have started to rebound (i.e., rising above $20*10^9$/L) is a prudent clinical decision that would need to be considered among other risk factors for bleeding. For example, the CL psychiatrist would also need to consider SSRI-related drug-drug interactions and the prolonged periods of thrombocytopenia in the setting of a hematopoietic stem cell transplant. Sertraline and escitalopram have the lowest risk of drug-drug interactions in this situation [33]. Interestingly, there is evidence suggesting that the immunosuppressive effects of SSRIs may be helpful in decreasing graft versus host disease in patients who have undergone an allogeneic stem cell transplant [34].

Cerebrovascular Accident (Stroke) and Bleeding Risk

There is mixed evidence for the impact of SSRIs on stroke. While some studies show that SSRIs are associated with

abnormal bleeding, especially in the gastrointestinal tract, other studies have shown the potential benefits of SSRIs in the recovery following abnormal bleeding such as a stroke. Serotonin reuptake inhibition's association with platelet dysfunction is a likely mechanism for observed abnormal bleeding with SSRIs. Several factors influence the risk of bleeding from the use of SSRIs [2]. For example, stronger serotonin reuptake drugs and older patients pose a higher risk for bleeding from SSRIs [2]. A combination of SSRIs with other anticoagulants also elevates the risk of bleeding. Also, risk and benefit depend on the type of stroke, hemorrhage, or ischemic. In a study of 1252 hemorrhagic strokes, the 626 patients who were on SSRIs prior to the stroke were more likely to have a hemorrhagic stroke in the severe category (OR 1.41; confidence interval, 1.08–1.84) and have an increased risk of death within 30 days (OR, 1.60; confidence interval, 1.17–2.18). But for the 8956 patients who had ischemic strokes, which are more common, there was no difference in severity or mortality for those who were taking an SSRI prior to the stroke event [35]. The risks for hemorrhagic stroke have to be weighed against the benefits that patients with ischemic strokes have if they are taking an SSRI. Evidence suggests that SSRIs improve stroke-recovery outcomes. Also, a number of studies, with heterogeneous study designs, have suggested that SSRIs improve clinical outcomes (e.g., disability, neurological impairment, mood) after a stroke [36–38]. For example, Mead and colleagues used a systematic review and meta-analysis to show that Fluoxetine improved motor recovery and decreased dependency after a stroke even among patients without depression [39]. However, the biological mechanisms implicated in SSRI-induced stroke recovery remain unknown [36–38]. In addition, depression has been associated with poor clinical outcomes in patients with stroke and should be further considered in starting or continuing an SSRI in the setting of a recent stroke. Overall, the bleeding risk from SSRIs is low but more robust prospective studies with large sample sizes are needed to clarify the association between SSRIs and stroke incidence by stroke type (hemorrhagic versus ischemic). For patients with ischemic strokes, more research is needed to determine the best time to initiate an SSRI post-ischemic stroke.

Hemophilic Diseases

These rare congenital states include missing a coagulation factor (i.e., factor VIII in hemophilia A and factor IX in hemophilia B, and others) but may also result from an autoimmune type of condition following drug administration (e.g., development of an "inhibitor"). These states exist on a spectrum, which is why the bleeding history is important as well as a quantitative factor analysis. Of interest, von Willebrand Disease (vWD) is a spectrum of predominately milder forms that only become relevant in childbirth or other high-risk procedures for bleeding. The presence of these mild coagulopathies that become apparent under stress emphasizes the importance of the bleeding history. A retrospective cohort study looking at different blood clotting disorders including vWD, hemophilia A/B, as well as other intrinsic clotting disorders found no significant increased risk of bleeding over a 6-month period with the use of SSRI or SNRIs [40]. But these were patients whose hemophilias were treated and well controlled and were not undergoing other factors that would increase bleeding risk.

When a Patient Is on an Antiplatelet Drug or Anticoagulant

Patients on antithrombic or antiplatelet therapy may be at higher risk for bleeding with concomitant SSRI use [4]. Among antithrombic therapies, coumarin, the vitamin k antagonist, is most commonly studied and is associated with more risk of bleeding in patients on SSRIs [41]. The newer direct oral anticoagulants (DOAC) also have an increased risk of bleeding when taken alongside SSRIs [42]. The therapeutic window of coumarin depends on vitamin K storage, which is related to diet and therefore may become easily altered. Coagulation parameters must be monitored for patients taking coumarin but not for patients on DOACs. But a retrospective cohort study found a 1.74 times risk of bleeding for those patients taking either type of oral anticoagulants alongside antidepressants versus taking an oral anticoagulants alone [43]. But a large database study found that antithrombotics were unlikely to have a major impact on detecting bleeding risk from antidepressant medications [44]. Types of bleeding for patients on oral anticoagulants (coumarin or DOACS) and SSRIs include gastrointestinal bleeding (GIB), epistaxis, post-surgical bleeding, and subdural or intracranial bleeds [42, 45–47]. Intracranial bleeding was more commonly seen in patients on SSRIs and DOACS rather than NSAIDs. In contrast, the combination of SSRI with NSAIDs in patients on DOACs was no worse for upper GIBs than when patients taking a single drug (SSRI or NSAID) [42]. Importantly, other essential medications also confer bleeding risk in addition to SSRs, anticoagulants, and antiplatelet drugs. These include loop diuretics, certain chemotherapy agents (fluorouracil, capecitabine, and crizotinib), and certain antimicrobials (sulfanomides, cephalosporins, macrolides, penicillins, quinolones) when combined with oral anticoagulants [41, 48, 49]. Other physiological risk factors for severe bleeding include elderly (> 80 years), any prior serious bleeding episode, alcohol dependency, and comorbidities like renal failure, hypertension, diabetes, peripheral vascular disease, congestive heart failure, COPD, stroke or transient ischemic attack, and cancer [48].

Additional Caution for Patients on Warfarin

Citalopram, fluoxetine, and paroxetine appear to carry the greatest risk of bleeding when combined with warfarin [45, 50]. Of note, non-SSRI antidepressants mirtazapine and amitriptyline also confer an elevated risk of bleeding when combined with warfarin [41, 45]. Antidepressants that do not have a statistically significant risk of bleeding when combined with warfarin include venlafaxine, sertraline, and escitalopram [45].

Management Considerations and Options

Summarizing Risk Versus Antidepressant Benefit

For the treatment of anxiety, depression, and other psychiatric disorders, SSRIs are first-line therapy and are proven to be an essential component of psychiatric care, especially considering their exceptional tolerability [51, 52]; however, certain clinical situations require caution, limit, or preclude their use. As discussed above, these situations are diverse and require an individualized lens to assess the risk. At the same time, the benefit should be addressed before asking a consulting physician, and most importantly, the patient, to undergo the risk. Of note, SSRIs with higher serotonin reuptake inhibition (fluoxetine, paroxetine, sertraline, clomipramine, vilazodone, and vortioxetine) are associated with a higher risk for bleeding compared with those with lower to no serotonin binding affinities (mirtazapine, bupropion, reboxetine, trazodone, doxepin, nortriptyline) [53•, 54]. Citalopram, escitalopram, amitriptyline, imipramine, and venlafaxine are treated as intermediate-risk groups. Furthermore, pharmacodynamic interactions are important to consider. Antidepressants with stronger cytochrome-P450 (CYP) inhibitions (duloxetine, fluoxetine, paroxetine, fluvoxamine) may pose harm when joined with medications metabolized through the same enzyme that correspondingly elevate bleeding potentials. For instance, fluvoxamine, as a strong CYP-1A2 inhibitor, can elevate the anticoagulant effects of coumarin hence further increasing the potential for bleeding [55].

Factors such as previous and current antidepressant responses, patient preference, and other comorbidities and side effects should also be considered [51, 52]. Also, the consulting psychiatrist should consider the literature and any reported case series for their risk of bleeding from SSRIs versus other antidepressants such as the noradrenergic antidepressants (e.g., duloxetine, venlafaxine) highlighting the ways in which the clinical scenario of interest for which the psychiatrist was consulted varies from the reported clinical situation [56–58]. Clinicians may want to consider additional beneficial effects of the SSRI beyond mood regulation. In addition to the reduction of GVHD in patients undergoing hematopoietic stem cell transplant, the SSRI, fluoxetine was found to confer a survival benefit for patients with glioblastoma multiforme, for example [29, 59].

Figure 1 provides a framework for considering SSRI-related bleeding risk and managing questions that pertain to the risk of bleeding. In addition to personal and familial histories of abnormal bleeding, the clinician should consider the gamut of additional risk factors for various forms of bleeding. In addition to the general risk factors and acute medical situation, Fig. 1 asks the CL psychiatrist to consider antithrombotic or anticoagulant agents highlighting warfarin given its issues with dosing and drug-drug interactions. Attention should be given to any significant bleeding history, the presence of liver dysfunction, and cancers that are particularly susceptible to bleeding (e.g., renal cell carcinoma, choriocarcinoma, melanoma, and hematological). All active cancer is thrombogenic, which may require concurrent anticoagulant administration. The setting of a solid organ or hematological stem cell transplant or the presence of an ischemic versus hemorrhage stroke should also be considered. Figure 1 highlights specific SSRI recommendations in clinical situations that carry a high risk of bleeding.

Consideration of Drug Change

The current evidence base does not clearly establish absolute contraindications to SSRI use with respect to bleeding risk. Generally, the quality of the evidence is low owing to a lack of prospective studies or randomized controlled trials which would be logistically and ethically challenging to undertake. Retrospective analysis and expert consensus suggest that in most cases, the continuation of preexisting SSRI therapy is appropriate in many scenarios but with the caveat that modifying circumstances (e.g., severe thrombocytopenia, co-administration of anti-thrombotics, other risk factors for GI bleeding) must be considered on a case-by-case basis [60–62]. In especially high-risk situations, such as neurosurgical procedures with high intraoperative or postoperative bleeding risk, platelet function testing prior to operation has been suggested as a way to assess risk on an individual basis given the grave risks of bleeding in these circumstances [63]. Platelet function testing evaluates the responsiveness of primary hemostasis and could be considered in especially high-risk situations.

When Holding or Stopping the SSRI Is the Appropriate Option

Discontinuation of an SSRI should be considered on a case-by-case basis. Patients who demonstrate life-threatening, problematic bleeding, or coagulopathy generally discontinue

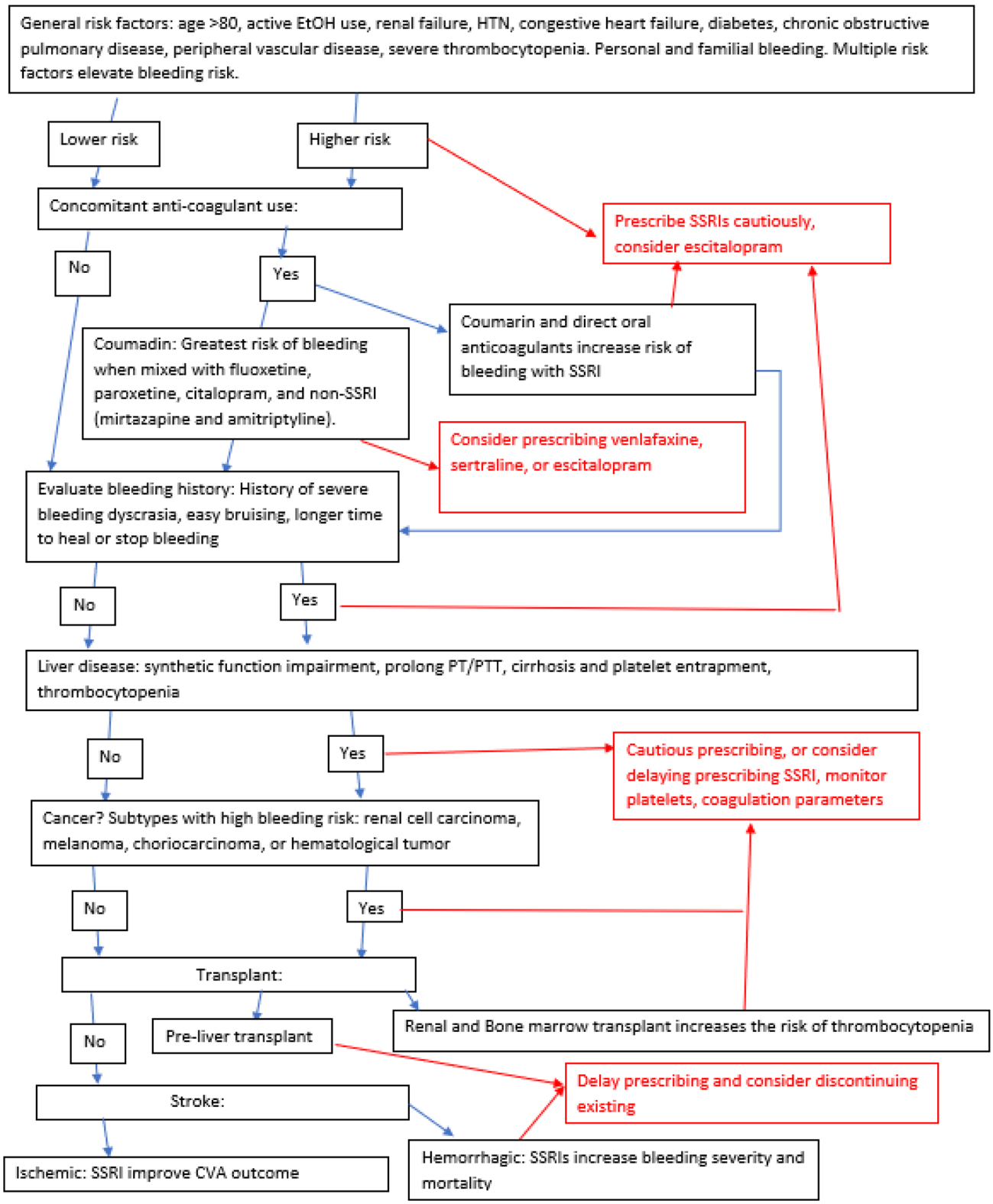

Fig. 1 Selective serotonin reuptake inhibitors (SSRIs) and bleeding risk: to start, continue, or discontinue in patients who are medically ill

any agent that induces bleeding such as aspirin, NSAIDs, and anticoagulants. The list of drugs that cause bleeding is extensive. While there does not appear to be a difference in bleeding risk based on specific SSRI agents, it is also not clear to what extent there is a dose effect. Drugs like aspirin and warfarin clearly demonstrate a dose effect with respect to bleeding. Clearly, conditions of life-threatening bleeding warrant the discontinuation of all drugs with a risk of bleeding. After a bleeding incident or in a patient with a high risk of bleeding, at-risk agents are usually added back one at a time and slowly so that the culprit drug would be discoverable and stopped. Interestingly, drugs are often prioritized based on clinical need when patients are on multiple drugs with bleeding risk.

Timing is key in the setting of acute medical illness and the administration of an SSRI. The length of time from cessation of bleeding or resolution of an acute coagulopathy should be strongly considered along with the laboratory trajectory of coagulopathy indices. Clinical judgment is needed to determine the ongoing and predicted risk of bleeding. Insights from medical and surgical colleagues are invaluable and should be readily sought when these questions arise.

Consideration of Primary Team Expectations Regarding Antidepressant Risk and Benefit

The consultant psychiatrist, by virtue of the consultation-liaison relationship, forms a triadic relationship with patients and their primary caregiving clinicians [38]. Therefore, they must consider patient and primary team expectations regarding the use and risk of the antidepressant. The decision to start, stop, or continue antidepressants in the setting of bleeding risk is strongly based on clinical judgment. In addition, the consult psychiatrist confronts various levels of understanding in terms of psychiatric illness and its treatment from both patients and caregiving teams. Clinical judgment is used in deciding how to navigate these potentially difficult situations. However, this clinical judgment is ultimately borne from liaison or ongoing dialogue between the consultant psychiatrist and the primary team. Assessment and management of the primary team's understanding of the patient's psychiatric state, as well as their understanding of antidepressants' role for the patient, will be critical in negotiating whether to start, stop, or continue pharmacotherapy in the context of bleeding risk.

The consultant psychiatrist should elicit the inpatient team or referring physician's understanding of the patient's psychiatric state and clarify the diagnosis (or lack thereof) as part of the liaison aspect of consultant psychiatry. The ability of non-psychiatrist physicians to diagnose depression is low [39, 40]. Thusly, the consultant psychiatrist provides an expert opinion regarding the immediate utility of an SSRI for a patient at risk of bleeding. In other words, they can determine if the patient's condition warrants psychopharmacologic intervention in the first place, the implication of partial treatment, or when foregoing an SSRI may be reasonable given the risk. If the primary team is underestimating a formal mood disorder or over ascribing symptoms to general medical causes, discussion around the risks of an untreated mood disorder on treatment adherence and general medical outcomes may be helpful. If the primary team is overestimating a formal mood disorder, it may be appropriate to recontextualize the patient's symptoms as secondary to the general medical condition or even a normal emotional reaction to their medical status. In addition, primary teams and referring physicians may either undervalue [39] or overvalue the efficacy of SSRIs. The consultant psychiatrist manages the primary team's expectations around SSRI treatment. If the primary team undervalues the benefit of SSRIs, either as non-essential or only providing quality-of-life benefit, it may be helpful to elicit and relay the patient's own perceived benefit, as well as general data surrounding SSRI efficacy including in medically complex populations. If the team is overvaluing the efficacy of SSRIs, particularly with regard to speed of response, consider discussing the expected time to response and the likelihood of limited benefit, for example.

Given the multidimensional nature of antidepressant bleeding risk and the role of clinical judgment around these decisions lacking relevant data or guidelines to support the decision, the consultant psychiatrist should reframe their role and perspective stemming from a single decision point to an ongoing dialogue. Despite the pressures of logistic issues on a consultation service, managing bleeding risk from SSRI use in a medically complex patient is probably best done using a longitudinal perspective corroborating medical disease trajectory with SSRI need and efficacy. This clinical scenario provides many opportunities for cross-collaboration across various disciplines involved in this decision. The evaluation of multiple perspectives ensures that important factors are considered as patients benefit from multidisciplinary communication [64]. It is also an opportunity to inform teams of the necessary use of psychiatric knowledge in caring for medically ill patients. This provides further opportunity for an in-depth discussion on both the psychiatric and general medical aspects of care, as well as managing primary team expectations around the risks and benefits of antidepressants.

Conclusion

Antidepressants provide an invaluable benefit to patients who are medically ill. Their risk of bleeding should be considered along a risk continuum and against the potential benefit of psychopharmacologic interventions. While various patient and medical situation characteristics should

be considered for their cumulative bleeding risk potential, every decision to start, continue, or discontinue an SSRI should be tailor-made for a given patient. Communicating with relevant subspecialists is essential for comprehensively appreciating the patient's risk of bleeding. CL psychiatrists confronted with this question should carry an appreciation of myriad aspects of bleeding risk, which will enable the CL psychiatrist to provide a well-informed opinion regarding the contributory nature of SSRIs to bleeding risk. Given the psychiatric and medical expertise inherent to training in consultation-liaison psychiatry, the CL psychiatrist is in an excellent position to delineate the contributory risk of bleeding from an SSRI and the extent to which the patient has or may be expected to benefit from the SSRI. The recommendation should be nuanced and well-coordinated with the patient's medical situation and psychiatric needs. The information herein should help the CL psychiatrist elicit key information and provide valuable feedback and care management for consulting clinicians, patients, and families.

Abbreviations CVA: Cerebrovascular accident (stroke); EtOH: Ethanol or alcohol; HTN: Hypertension; PT: Prothrombin time; PTT: Partial thromboplatin time; SSRI: Selective serotonin reuptake inhibitor

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Data Availability Data are available upon request.

Declarations

Ethics Approval Additionally, each author met each of the authorship requirements as stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

Conflict of Interest Daniel McFarland, Dale Merchant, Abhisek Khandai, Mona Mojtahedzadeh, Omar Ghosn, Jeremy Hirst, Depti Chopra, Shehzad Niazi, Jennifer Brandstetter, Andrew Gleason, Garrett Key, and Barbara Lubrano di Cicconeeach declare no potential conflicts of interest. Hermioni Amonoo has received a grant from the National Cancer Institute.

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- • Of importance
- •• Of major importance

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