Published in final edited form as:

J Clin Psychopharmacol. 2016 December ; 36(6): 704–709. doi:10.1097/JCP.0000000000000575.

Selective Serotonin Reuptake Inhibitors and Operative Bleeding Risk: A Review of the Literature

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Abstract

Objective—To review the data on the effect of selective serotonin reuptake inhibitors (SSRIs) on bleeding during or after operative procedures and to offer guidelines for clinical management.

Data Sources—Search of PUBMED and Medline for all articles in English from 1990–2016 with key words depression, antidepressants, bleeding, platelets, and operation. Study Selection: Studies were included if they reported information on bleeding complications during operative or childbirth procedures in patients taking antidepressants.

Data Extraction—Due to the limited number and heterogeneity of studies with respect to the range of operative procedures and definition of bleeding complications, a qualitative approach was taken to summarize results rather than abstracting and aggregating data.

Results—The weight of the evidence is that SSRI use increases the risk of bleeding complications during and immediately after surgery. However, given the limited data we cannot estimate the risk for a given patient having a given procedure.

Conclusions—Clinicians must consider the risk to benefit ratio of discontinuing an SSRI before an elective operative procedure. Discontinuing SSRI medications may result in discontinuation syndrome, symptom recrudescence, or relapse of depression, while continuing an SSRI during surgery exposes patients to significant bleeding risks. Antidepressant prescribers must be cognizant of and take responsibility for discussing this potential problem and considering different options. This issue must also be the responsibility of the doctor performing the procedure, but frequently it will be the prescribing physician who alerts the surgeon to the potential bleeding risk associated with SSRIs.

SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) are prescribed in 11% of people over age 12 in the United States, approximately 28–30 million people (1). It has

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Disclosures: Dr. Roose has no disclosures to report.

This paper has not been previously presented.

long been established that SSRIs and SNRIs, medications that block the reuptake of serotonin, significantly decrease the serotonin content of platelets and consequently reduce normal platelet function. For the sake of simplicity, we will only refer to SSRIs, though it is reasonable on the basis of available data to assume that the following discussion can be extended to the use of the SNRIs and the tertiary tricyclic antidepressants (imipramine, amitriptyline, and clomipramine) that also block serotonin reuptake (2,3). This effect results in an increase in bleeding time, and there are many clinical case reports that associate SSRI use with manifestations of abnormal bleeding such as ecchymosis, menorrhagia, and hemoptysis (4–8).

Systematic, replicated research documents that SSRI treatment is associated with an increased risk of upper gastrointestinal (UGI) bleeding, particularly in the elderly, and intracerebral hemorrhage (9). Patients who take SSRIs have a higher rate of UGI bleeding compared to matched control subjects (10). Fifteen studies have examined the association between upper gastrointestinal bleeding and the use of SSRIs or SNRIs (11). All showed an increased relative risk (RR) for UGI bleed associated with medication use compared with non-use, with patients treated with SSRI medication were 1.7 times more likely to experience UGI bleeding (95% CI 1.4–2.0) compared with non-SSRI users.

In the clinical setting, a frequent issue is the management of medications that are known to increase bleeding, such as acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs), prior to an invasive elective procedure. Should the SSRIs be included in this discussion? This paper will review the data on the effect of the SSRIs on operative procedures and offer guidelines for clinical management. A search of PUBMED and Medline was done for all articles in English from 1990–2016 with key words depression, antidepressants, bleeding, platelets, and operation.

Platelets and Serotonin

Platelets take up and store in dense granules the serotonin synthesized by enterochromaffin cells in the gut via the serotonin transporter located in the membrane (12). Serotonin is essential to normal platelet function. A critical component of platelet activation is serotonin secretion, which has a number of different effects, including: 1) strong vasoactive properties through direct action on serotonin receptors and nitric oxide production, 2) the potentiation of the aggregation induced by adenosine diphosphate, epinephrine and collagen, and 3) the enhancement of fibrin formation (12–15).

Platelet Function in Depression Patients with depression are at increased risk to develop both coronary and cerebral vascular disease (16,17). Platelets are a major determinant of the extent of thrombus formation following plaque rupture within a coronary artery, and in patients with coronary artery disease increased platelet reactivity is a risk factor for subsequent ischemic cardiac events. Multiple lines of evidence suggest that patients with depression have increased platelet activity compared to controls. In depressed patients, pro-coagulatory peptides secreted by platelets are increased, platelets aggregate more strongly to a given stimulus, platelet reactivity to mild stress is increased, and there is a greater density of α_2 -receptors (18,19). The “hyper-coagulable” state secondary to increased platelet

activation in depressed patients is postulated to be one of the mechanisms that accounts for the increased risk of ischemic vascular disease associated with the diagnosis of major depression (20,21).

SSRI Effects on Platelets

Selective serotonin reuptake inhibitors block the serotonin transporter resulting in the inhibition of serotonin uptake into platelets (22,23). Studies of SSRI treatment show that after weeks of SSRI administration there is a consistent and significant reduction in platelet serotonin content, which is in the range of 65–90% compared to controls (24,25). Studying the consequences of this serotonin reduction for platelet activation, bleeding time, and clotting time is a complex undertaking that is highly sensitive to methodological factors. Perhaps as a result, the data reported from such studies are mixed, but in general it appears that reducing the serotonin content in platelets significantly decreases both platelet secretory response and platelet aggregation, leading to decrements in platelet plug formation (26,27). As a rough approximation, the SSRIs can be considered to have an “anti-platelet” effect similar in magnitude to aspirin (28,29).

The anti-platelet effect of the SSRIs appears unconnected to the antidepressant effect and occurs in both responders and non-responders to the medication. In a study that compared paroxetine (an SSRI) to nortriptyline (a TCA that is a relatively weak reuptake inhibitor of serotonin), baseline indices of platelet activity, specifically platelet factor 4 and beta-thyroglobulin, were elevated in patients with depression and ischemic heart disease (IHD) compared with non-depressed patients with IHD or normal controls (30). Treatment with paroxetine normalized platelet activity. This effect occurred at low doses of paroxetine and before any discernable antidepressant effect of the medication. Though nortriptyline was a very effective antidepressant in this study, there was no reduction in platelet activity in the nortriptyline treated patients.

SSRIs in Depressed Patients with Ischemic Heart Disease

Platelets play a major role in the pathogenesis of acute ischemic disease by contributing to thrombus formation after plaque rupture within a coronary artery. After a myocardial infarction (MI) or an invasive coronary intervention, increased platelet reactivity is a risk factor for subsequent cardiac events (31). Antiplatelet interventions are a fundamental component of the treatment of acute and chronic coronary disease.

The “anti-platelet” effect of the SSRIs may be one of the mechanisms by which SSRI treatment reduces cardiac risk in depressed patients (20,22). It is well established that depressed patients post MI have a significantly higher cardiac mortality rate than comparably ill post MI patients who are not depressed (32). In two studies of the treatment of depression post MI, patients treated with an SSRI had a decreased number of ischemic related events and decreased cardiac mortality rate compared to patients who did not receive an SSRI (33,34). Furthermore, the antiplatelet effect of SSRIs may reduce the risk of a first ischemic cardiovascular event. SSRI-treated high-risk patients have a significantly lower rate of MI than the non-SSRI-treated patients. This lower MI rate appears not to be the result of

reduced psychiatric symptoms; for example, patients whose anxiety is reduced by anxiolytic medications do not have a reduced rate of MI (35).

SSRIs, Bleeding and Surgery

The question explored in this review is whether the data are sufficient that the SSRIs should be considered an “anti-platelet” medication and, if possible, be stopped before an elective procedure that will produce bleeding. As described above, review of the literature indicates that the effect of SSRIs on platelet function is well-established and the data are robust. The data with respect to increased risk of bleeding associated with surgery comes from 19 studies of post-operative complications. While these studies are neither randomized nor can control for many other potentially significant variables, on the basis of the effect of SSRIs on platelet function alone the question deserves consideration.

SSRIs and Peri-Operative or Post-partum Bleeding

To date there have been 19 studies that addressed the issue of whether SSRI treatment is associated with an increased risk of bleeding during or after a surgical procedure or childbirth (Table 1). The studies, which vary in terms of methodology and types of surgery, include: seven orthopedic (36–42), four coronary artery bypass grafting (CABG) (43–46), one breast cancer (47), one breast cosmetic (48), one facelift (49), two postpartum (50,51), one dental, (52) one percutaneous endoscopic biopsy (53), and one large study of all in-hospital operative procedures (3).

With respect to methodology, none of the studies are prospective, and of course none are randomized. Primarily, the studies use retrospective chart review and a case control comparison group to determine the rate of operative complications after assigning the patient to the SSRI user group or non-user group based on self-report or pharmacy records. The severity threshold of complication also varies across studies going from intra-operative blood loss to the need for reoperation because of bleeding.

The studies are listed in Table 1 including author, type of surgery, N of the SSRIs and comparison group, primary outcome measure and statistical result. The following salient characteristics are noted:

1. Of the seven studies of orthopedic surgeries – five for hips (36,39,40,41,42), one for all orthopedic procedures (37) and one for spinal fusion (38) – 6 of 7 report significantly higher rates of either intra-operative blood loss or need for transfusions in SSRI users compared with non-users.
2. Of the four studies of CABG, three reported no increased bleeding issues with SSRI users (43,44,45) and one reported an increased need for transfusion in the SSRI user but no increased rate of reoperation due to bleeding (46). Of note both the SSRI and non-groups received anti-platelet agents during the perioperative period. In addition, one of the studies compared SSRI users to patients on other anti-depressants, primarily

TCAs and found no difference in bleeding risk. However TCAs such as amitriptyline and imipramine also block the reuptake of serotonin and so one would not expect to see a difference between the SSRI and comparison group. Finally one study that reported no SSRI effect on bleeding defined SSRI use as taking the medication within 90 days of the surgery. As discussed previously once an SSRI is stopped it takes only 10–14 days to generate new, effective platelets.

3. Both breast surgery studies (47,48) reported a significant increase in the rate of reoperation because of bleeding in the SSRI users, up to a fourfold increase. The one face-lift study (49) used as complication of interest an increased rate of hematoma and there was no increase in the SSRI users.
4. One study of postpartum bleeding complications reported no increase in SSRI users (50), but in this study patients were categorized as taking an SSRI medication if they had received the medication anytime within 90 days of delivery. In a second study there was an increased risk of postpartum bleeding hemorrhage in current SSI users but not in past users (51).
5. The study of dental procedures (52), primarily extractions, did not report a higher rate of bleeding complications in SSRI users.
6. The study of percutaneous endoscopic biopsy (53) did report an increased rate of UGI bleeding in SSRI users.

Perhaps the most important study to date is by Auerbach et al. (3), who studied all patients over 18 who had major surgery between Jan 1, 2006 and Dec 31, 2008 at 375 US hospitals. The study identified 530,416 patients of whom 72,450 received an SSRI in the perioperative period as documented by the hospital pharmacy records. Patients receiving an SSRI had a greater risk for bleeding (OR 1.9, 95% CI 1.04–1.15; number needed to harm is 424) and higher mortality rate (adjusted OR 1.20, 95% CI 1.07–1.36, number needed to harm is 839) than patients who were not receiving a SSRI. There were also 23,395 patients taking SNRI medication and as expected they appeared to have the same outcomes as the SSRI treated patients. The numbers needed to harm, though seemingly large, are clinically significant given the number of patients who have surgery each year and the prescription rate of SSRI and SNRI medications in adults.

Thus, the weight of the evidence supports the conclusion that SSRI use increases the risk of bleeding complications during and immediately after surgery. However because of the heterogeneity of the studies with respect to the criteria used to define a bleeding complication, from the need for a transfusion to the need for reoperation to control bleeding, and the range of operative procedures, it is difficult to quantify the clinical magnitude of the increased risk. There is a risk but given the limited data we cannot estimate the risk for a given patient having a given procedure.

Clinical Recommendations Regarding SSRI Use Before Elective Surgical Procedures

The critical question with respect to clinical management is what is the risk - benefit ratio of discontinuing an SSRI before an elective operative procedure? The risks of stopping the SSRI are 1) discontinuation syndrome, and 2) symptom recrudescence and relapse of MDD.

The symptoms of the discontinuation syndrome include irritability, anxiety, agitation, nausea, sleep disruption and flu-like muscle aches and decreased energy, and may occur in up to 20% of people who abruptly discontinue SSRI treatment although many may have only mild or moderate symptoms (54,55). However, a non-emergency intervention allows for tapering the SSRI and this may reduce the risk and severity of discontinuation syndrome. The slower the taper presumably the less risk of discontinuation syndrome but a slow taper extends the time the patient will be off a therapeutic dose of medication. In addition to the time necessary for a tapered discontinuation and depending on the dose, assuming a 24 hour half-life and minimal active metabolites, an SSRI medication should be stopped at least two weeks before the operative procedure to allow for the generation of new platelets (56–59). Thus, in some cases a patient may be off a therapeutic maintenance dose of SSRI for as long as 6 weeks prior to the operative procedure. If the patient is taking a drug such as fluoxetine that has a long half-life (72 hours) as does the active metabolite nor-fluoxetine, that time may be significantly longer.

How soon after the operation can the SSRI be restarted will depend on the nature of the procedure and the course of recovery. The length of time off medication increases the risk of symptom recrudescence and relapse of MDD. An analysis of 27 double blind studies in which patients were either continued on medication or switched to placebo after at least one year of maintenance treatment reported that the relapse rate per month was 1.8% for patients continued on medication vs. 6.2% for patients switched to placebo (44). Thus the risks of discontinuing an SSRI with respect to discontinuation syndrome or relapse can be quantified.

Perhaps the most important data to estimate the risk of discontinuing medication is the history, severity and treatment response of the patient's illness. To facilitate the task of risk evaluation it may be helpful to categorize patients: (though the examples used are for depression comparable, categories could be developed for anxiety disorders, PTSD etc.)

1. Patients with severe illness or who have been difficult to treat. This group would include patients with recurrent depression who have had suicide attempts and/or required hospitalization or patients that required many medication trials and many months to achieve a therapeutic response.
2. Patients with recurrent but less severe and more treatment responsive illness.
3. Patients after at least 4 months of continuation treatment for a first episode

4. Patient for whom the SSRI treatment has been continued without a clear indication. In this case the impending surgery may serve as the impetus for an overdue medication discontinuation.

For many patients in category 1, the risk of SSRI discontinuation may outweigh the risks of peri-operative bleeding, whereas the risk of bleeding may be more pertinent for individuals in categories 3 and 4. Patients in category 2 fall somewhere in between. In all cases a discussion between psychiatrist, patient, and surgeon is necessary to determine the optimal balance between risks and benefits of SSRI discontinuation. Another important variable to consider when estimating the risk of relapse is the depth of the therapeutic relationship between doctor and patient and the patient's social support system.

The prescribing physician has to weigh these risks against the benefit of reducing post-operative bleeding. As discussed the problem is that an evidence based quantification of benefit is not yet possible given the limited data estimating the risk and consequences of bleeding across different kind of procedures. The transfusion of 1 more unit of blood may be a minimal risk, but reoperation because of bleed is obviously a serious adverse event. There is a compelling need for systematic studies of patients taking an SSRI within 1 week of operation that document a range of bleeding associated outcomes over a range of operative procedures while co-varying for variables such as age, other medications etc.

Nonetheless, both primary care doctors and psychiatrists, the most frequent prescribers of antidepressants, should be cognizant of and take responsibility for making sure that this potential problem is discussed and options considered. This issue must also be the responsibility of the doctor performing the procedure, but frequently it will be the prescribing physician who alerts the surgeon to the potential bleeding risk associated with SSRIs. If the procedure is elective, there is time for a discussion between the prescribing doctor and the surgeon to weigh the risks and benefits and come to a joint and reasoned recommendation to the patient. Most of all, the patient needs to be part of the decision making process starting with informing the patient of the problem when medication is first prescribed so that they alert the prescribing doctor if an elective procedure is being considered. The patient, prescribing doctor and surgeon must collaborate to make a decision informed by data and sometimes the decision-making process will be facilitated by the inclusion of the people who are at the core of the patient's social support system.

Acknowledgments

Work on this paper was supported by R01 MH102293 (Rutherford) and T32 MH015144 (SPR). Dr. Rutherford reports receiving consulting fees from Pfizer.

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Table 1

List of included case studies.

Author	Surgery	N	Outcome	Comment
Dall et al. 2014 (36)	Total hip	SSRI=83 Control=1202	Increase blood loss in patients on SSRI, mean = 93 ml (95% CI 38–147 ml)	
Movig et al 2003 (37)	Any orthopedic surgery	SSRI=26 Control=474	Risk of transfusion increased in SSRI patients (OR 21.71, 95% CI 1.35–10.18)	No increase in risk for patients on non-SSRI antidepressants
Sayadipour et al 2012 (38)	Spinal fusion	SSRI or SNRI=144 Control=352	23% increased blood loss in SSRI or SNRI patients (p < .0001)	
Schutte et al 2014 (39)	Hip repair replacement	SSRI=114 Control=352	Increased risk of transfusion in SSRI patients (OR 1.7, 95% CI 1.1–2.5)	
Seitz et al 2013 (40)	Hip fracture	SSRI=6668 Control=1900 (former SSRI users)	Increased Risk of transfusions in current SSRI patients (OR 1.28, 95% CI 1.14–1.43)	
Tavakoli et al 2012 (41)	Hip and knee replacement	SSRI=71 Control=123 Non-SSRI=29	No increased risk of bleeding or transfusions	
Van Haelst et al 2010 (42)	Hip Orthoplasty	SSRI=66 Non SSRI or SNRI=29 Control=285	Increased blood loss in SSRIs patients only (p< .01)	
Andreassen et al 2006 (43)	CABG	SSRI=124 Control=3320	No increase in transfusions (OR 1.1, 95% CI .9–1.5)	SSRI use defined as medication within 90 days before surgery
Kim et al 2009 (44)	CABG	SSRI=1076 Non-SSRI =304 antidepressant=304	No increase in bleeding events SSRIs compared to non SSRI antidepressants (OR 1.03, 95% CI .6–1.78)	Non SSRI group includes serotonin reuptake inhibitors, e.g. Amitriptyline
Tully et al 2012 (45)	CABG	SSRI=105 Control=4031	No increase in bleeding events (p< .2)	
Xiong et al 2010 (46)	CABG	SSRI=246 Control=4542	No Difference in reoperation rate secondary to bleeding (OR 1.14, 95% CI .52–2.47) Volume of RBC units transfused greater in SSRI group (p < .001)	
Gartner et al 2010 (47)	Breast cancer	SSRI user=201 SSRI former user=1391 Control=12872	Increase risk for reoperation secondary to post-op bleeding in current SSRI users (OR. 2.3, 95% CI 1.4–2.4) No increases risk in former SSRI users	

Author	Surgery	N	Outcome	Comment
Basile et al 2013 (48)	Cosmetic breast	SSRI=196 Control=2084	Increased risk in SSRI patients for breast hematoma needing intervention (OR 4.14, 95% CI 1.90–9.04)	
Harirchian et al 2012 (49)	Face lift	SSRI=60 Control=203	No difference in rate of post-operative hematomas	
Salkeld et al 2008 (50)	Postpartum Hemorrhage	Post-partum Hemorrhage =2460 Control=23,943	No increase in post-partum hemorrhage for SSRI users (OR 1.30, 95% CI .98–1.72)	SSRI use defined as medication taken within 90 days of delivery
Palmsten et al 2013 (51)	Postpartum Hemorrhage	Current SSRI=1495 Control=105,500	increased post-partum hemorrhage for current SSRI users (OR 1.47, 95% CI 1.33–1.62)	No increase risk for past users of SSRIs
Napenas et al 2011 (52)	Invasive dental treatment	SSRI=92 No control	2 bleeding events	
Richter et al 2011 (53)	Percutaneous endoscopic gastrostomy	SSRI=99 Control=891	Increased risk of UGI bleeding in SSRI patients (OR 4.1, 95% CI 1.1–13.4)	