Psychosomatics 2012:53:559–565 Published by Elsevier Inc. on behalf of The Academy of Psychosomatic Medicine.

Original Research Reports

Serotonin Reuptake Inhibitors and Bleeding Risks in Major Orthopedic Procedures

Hamid R. Tavakoli, M.D., Marlene DeMaio, M.D., Capt, M.C., U.S.N., Nathaniel C. Wingert, M.D., Thomas S. Rieg, Ph.D., Julie A. Cohn, M.D., Lt, M.C., U.S.N., Russell P. Balmer, M.D., Lt, M.C., U.S.N., Marie A. Dillard, B.S.

Background: *Risk of abnormal bleeding in surgery patients prescribed serotonin reuptake inhibitors (SRIs) is unclear. Considering the quantity of literature on abnormal gastrointestinal (GI) bleeding with SRIs, relatively little exists on SRI bleeding risks in surgical procedures. We investigated whether SRIs increase the risk of surgical bleeding in patients undergoing knee and hip total joint replacement.* **Methods:** *RA retrospective case-control study was conducted among subjects undergoing primary total hip and knee replacement surgeries from January 2005 to March 2011 at a single institution. The experimental group was defined by utilization of SRIs at the time of surgery (the independent variable). The control group was matched for age, sex, ethnicity, and type of surgery (hip or knee). Any case with preoperative hematocrit <30, platelets <100,000; abnormal prothrombin time, partial-prothrombin time, and international normalized ratio (INR), primary bleeding disorder, medical conditions, or medications associated with increased bleeding was excluded. All cases were randomly selected.* **Results:** *RA total of 194 subjects (hip 104, knee 90) were included. Statistical analysis was performed on the SRI group (n = 71) and the control, non-SRI group (n = 123). No difference was found between the groups in estimated blood loss, hemoglobin, hematocrit, platelets, PT, PTT, and INR from preoperative to postoperative day 1, 2, and 3. Furthermore, no subjects in either group required blood transfusions.* **Conclusion:** *SRIs were not associated with increased risk of bleeding in primary knee or hip replacement surgeries in this study. The hypothesis that SRIs increase the risk of bleeding based on presumptions about their action on platelet aggregation is uncertain and warrants further study.*

(Psychosomatics 2012; 53:559–565)

Serotonergic antidepressants are the most widely prescribed class of antidepressant medications.[1] The development of selective serotonin reuptake inhibitors (SSRIs) has led to an approximate 3-fold increase in antidepressant use for the treatment of primary care patients with depression.[2] In addition to SSRIs, dual acting serotonin and norepinephrine reuptake inhibitors such as venlafaxine and duloxetine are also widely used for treatment of depression. Collectively, these two classes of serotonergic antidepressants will be referred to as serotonin reuptake inhibitors (SRIs). The popularity of SRIs stems not only from their efficacy but also from a significantly less serious side-effect profile compared with older antidepressants (e.g., tricyclics and MAOIs).[3] Nonetheless, SRIs have their own profile of adverse effects. These

Received February 23, 2012; revised April 25, 2012; accepted April 26, 2012. From Dept. of Psychiatry and Dept. of Orthopedics, Naval Medical Center Portsmouth, Portsmouth, VA (HRT, MDM, TSR, JAC, MAD); Department of Orthopedics, Geisinger Medical Center, Danville, PA (NCW); Dept. of Psychiatry, Naval Hospital Camp Lejeune, Camp Lejeune, NC (RPB). Send correspondence to Hamid R. Tavakoli, M.D., Department of Psychiatry, Naval Medical Center Portsmouth, 620 John Paul Jones Circle, Portsmouth, VA 23708; e-mail: hamid.avakoli@med.navy.mil

Published by Elsevier Inc. on behalf of The Academy of Psychosomatic Medicine.

include the syndrome of inappropriate antidiuretic hormone secretion (SIADH), serotonin syndrome, serotonin-discontinuation syndrome, adverse neonatal/pregnancy effects, and bleeding. The complication, bleeding, is the focus of this article.

Bleeding complications of surgery constitute a substantial source of financial burden, patient morbidity, and mortality. Significant intraoperative bleeding may require blood transfusion and all of the inherent risks thereof. Even with meticulous surgical technique, certain operative procedures have a well-documented associated blood loss. Major orthopedic operations, such as total hip or knee replacement, result in some of the higher volumes of blood loss.[4–8]

Drugs that cause prolonged bleeding, such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), are routinely stopped well ahead of surgery. However, SRIs are rarely, if ever, stopped prior to surgery due to concerns about bleeding. In an article by Movig et al.,[9] it was determined that the risk of transfusion nearly quadrupled (adjusted OR 3.71, 95% CI 1.35–10.18) in the group taking serotonergic antidepressants. They also found that patients on serotonergic antidepressants had double the volume of intraoperative blood loss (1019 mL vs. 582 mL, $p = 0.001$). The main pharmacologic explanation for this finding has been the effect of serotonergic drugs on platelet aggregation. The limitations of the study were lack of control for significant confounding variables including concurrent use of medications and comorbid medical conditions that affect bleeding and homeostasis.

Numerous published studies and case reports suggest that SRIs may increase bleeding, but none excluded confounding variables that could affect bleeding, other than concurrent use of serotonergic medications. We know that patients on NSAIDs, steroids, and other anticoagulants have higher risk of bleeding. Therefore, we used extensive and strict criteria that excluded patients with these confounding variables to include any comorbid medical conditions and medications that could affect bleeding. Our study attempts to address an inconsistency between the literature and actual medical practice. That is, the medical literature reports increased risk of bleeding with SRIs (Movig et al. demonstrated four times the risk of bleeding and need for transfusions); however, in clinical practice, it is accepted that the risk of bleeding and need for additional transfusion is low.

The risk of abnormal bleeding in patients who take SRIs and undergo surgical procedures remains unclear. Considering the quantity of literature on abnormal gastrointestinal bleeding with SRIs,[10–24] little exists on SRI bleeding risks in surgical procedures.[8,9,25–28] Previous publications have investigated and reviewed possible mechanisms by which SRI medications may exert their pharmacologic effect.[29–37] Our study's purpose was to test the hypothesis that SRIs increase the risk of bleeding during hip and knee replacement surgeries.

METHODS

The study was approved by the Naval Medical Center Portsmouth (NMCP) institutional review board (IRB) and was conducted in a 326-bed, multi-specialty tertiary care military and teaching hospital (NMCP). A retrospective chart review was conducted for subjects who underwent total knee and/or hip replacement surgeries at NMCP between January 2005 and June 2011. The subjects were military health beneficiaries over 18 years of age who had hip or knee replacement during the period from January 2005 to March 2011. All subjects were selected at random via the hospital's computerized database. Procedure codes for all orthopedic operations performed during the study period were used. The experimental group consisted of subjects who were on SRIs at the time of surgery.

This retrospective case-control study investigated subjects who underwent a primary total hip or knee replacement surgery during the specified period. The SRI subjects were all on either SSRIs or SNRIs (Table 1). The non-SRI control subjects were matched to the SRI experimental subjects by age, sex, ethnicity, and type of surgery (hip or knee). Any case with pre-morbid hematocrit <30, platelets $<100{,}000$, abnormal PT/PTT/INR, primary bleeding disorders, medical conditions, or medications associated with increased bleeding were excluded (Table 2).

Estimated blood loss (EBL) was obtained from the anesthesia report. EBL was based on weighing of laps,

TABLE 1. Inclusion Criteria: Serotonergic Antidepressant Medications

Serotonin Reuptake Inhibitors (SRIs)	Number of Cases (*n*)
Sertraline (Zoloft)	23
Venlafaxine (Effexor)	14
Duloxetine (Cymbalta)	10
Escitalopram (Lexapro)	9
Paroxetine (Paxil)	6
Citalopram (Celexa)	3
Trazodone (Desyrel)	3
Fluoxetine (Prozac)	2
Mirtazapine (Remeron)	1
TOTAL	71

TABLE 2. Exclusion Criteria

Abnormal Laboratory Tests	Primary Bleeding and Blood Disorders	Medical Conditions Associated With Increased Bleeding
• Thrombocytopenia defined as platelet count <100,000 • Preoperative hematocrit <30 • Abnormal coags: ○ PT (normal 10–13) ○ PTT (normal 28–38) ○ INR (0.9–1.2)	• Hemophilia A (Factor VIII deficiency) • Hemophilia B (Factor IX deficiency) • Von Willebrand disease • Sickle cell anemia • Sickle cell trait • Thalassemia, major and minor • Hereditary spherocytosis • Anemia, unspecified	• Hepatic failure • Renal failure • Chronic immunosuppression • Organ transplant recipient • Rheumatoid arthritis • Systemic lupus erythematosus (SLE) • Bone marrow transplant

Medications Associated With Increased Bleeding		
Antiplatelets	**Anticoagulants**	**NSAID (Ingestion Within 14 Days)**
• Aspirin (acetylsalicylic acid) 81 mg/d or greater • Clopidogrel (Plavix) • Ticlopidine (Ticlid) • Abciximab (Reopro) • Dipyrimadone (Persantine) • Eptifibatide (Integrilin) • Tirofiban (Aggrastat)	• Heparin • Enoxaparin (Lovenox) • Fondaparinux (Arixtra) • Dalteparin (Fragmin) • Tinzaparin (Innohep) • Bivalirudin (Angiomax) • Lepirudin (Refludan) • Vitamin K Inhibitor ○ arfarin (Coumadin) ○ cenocoumarol (Sintrom, Sinthrome) ○ icoumarol	• Ibuprofen (Advil, Motrin) • Sulindac (Clinoril) • Naproxen (Miranax, Naprosyn) • Ketoprofen (Orudis, Oruvail • Indomethacin (Indocin, Indocid) • Dexibuprofen • Ketorolac (Toradol, Acular) • Diclofenac • Lornoxicam • Meloxicam (Mobic) • Piroxicam (Feldene)
Other Drug Classes • Calcium channel blockers • Corticosteriods • Iron supplements • Methotrexate	• Phenprocoumon (Marcoumar)	• Nabumetone (Relafen, Relifex) • Flurbiprofen (Ansaid) • Mefenamic Acid (Ponstel) • Oxaprozin (Daypro) • Tolmetin (Tolectin) • COX-2 Inhibitor ○ Celecoxib (Celebrex, Celebra)

patient response, and surgeon's input to the anesthesia. EBL is understood in the surgical community to have inherent errors and is not absolute. For this reason, other indicators to assess the amount of blood loss were evaluated. Laboratory data on hemoglobin, hematocrit, platelets, PT, PTT, and INR from preoperative to postoperative days 1, 2, and 3 were collected. (Patients were usually sent home by post-op day 3 and that is the last point at which lab data was available for most patients).

In order to provide an adequate level of protection to guard sensitive information, all patient records were de-identified and then coded by research assistants.

RESULTS

The orthopedic procedures included bilateral as well as unilateral knee and hip surgeries. One hundred ninety-four subjects (knee 90; hip 104) were included in the analyses below. Statistical analysis focused on SRI users ($n = 71$) and non-SRI users ($n = 123$).

The two groups' demographic variables were matched and found to be equivalent. There was no difference in age between the two groups [$p = 0.610$; *SRI* $M = 55.41$ (*SEM* $= 1.29$), non-*SRI* $M = 56.24$ (*SEM* $= 0.99$)]. There was no difference between the groups in terms of subject gender ($p = 0.195$). Females comprised 70% of the sample population. Finally, there were no differences in ethnic background among the subjects ($p = 0.209$). There was a difference in the number of bilateral vs. unilateral surgeries ($p < 0.002$); there were fewer bilateral surgeries (Table 3).

According to anesthesia reports, there was no difference in estimated blood loss between the two groups ($p = 0.436$) (Figure 1) using a repeated measures analysis of variance (ANOVA). In addition, both groups received equivalent amounts and types of fluid during surgery ($p = 0.055$). Repeated measures ANOVA analyses were used for measures of hemoglobin (HGB), hematocrit (HCT), platelets (PLTS), prothrombin time

TABLE 3. Types of Surgeries in SRI and Non-SRI Groups

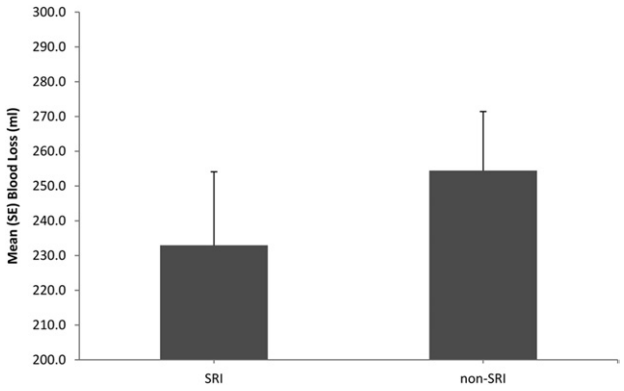
Count	Bilateral Total Knee	Left Total Hip	Left Total Knee	Right Total Hip	Right Total Knee	Total
SRI	3	18	15	16	19	71
% of Total	1.50%	9.30%	7.70%	8.20%	9.80%	36.60%
non-SRI	4	46	20	24	29	123
% of Total	2.10%	23.70%	10.30%	12.40%	14.90%	63.40%
Total	7	64	35	40	48	194
% of Total	3.60%	33.00%	18.00%	20.60%	24.70%	100.00%

(PT), partial thromboplastin time (PTT), and international normalized ratio (INR), from preoperative surgery (pre-op) to postoperative surgery (post-op) days 1, 2 and 3 (Table 4). For each of the measures, there were no differences between the groups [HGB $p = 0.168$; HCT $p = 0.762$; PLTS $p = 0.163$; PT $p = 0.271$; PTT $p = 0.546$; INR $p = 0.915$]. There was a decrease in hemoglobin from preoperation to postoperation days 1, 2, and 3 ($p < 0.001$; see Figure 2), however, this decrease was equivalent between the two groups ($p = 0.300$). In addition, no blood transfusions were required in any of the subjects in either group. Hematomas were not a major consequence given that no patient required surgical decompression postoperatively.

DISCUSSION

We found no statistically significant difference in the change in hemoglobin, hematocrit, platelet counts, PT, PTT, and INR from preoperation to postoperation days 1, 2, and 3 in patients who underwent total hip or knee replacement surgeries while on SRIs compared with those not on SRIs. Moreover, no difference in estimated blood loss was observed in the two groups. In short, taking SRIs was not associated with an increased risk of bleeding in this retrospective case controlled study. This negates our hypothesis and those of previous studies. It also contradicts the presumed SRI action on platelet aggregation that suggests an increased risk of bleeding in orthopedic surgeries.

FIGURE 1. Estimated Blood Loss Between SRI and Non-SRI Group.



Our findings lead to questions regarding the theoretical mechanism of SRIs' effect on bleeding. The current theory states that SRIs in the nervous system inhibit serotonin transport protein and block the uptake of synaptic serotonin into presynaptic neurons. Similarly, SRIs inhibit the entry of serotonin from blood into platelets.[31,32] During vascular injury, serotonin is released from platelets into the bloodstream and is involved in platelet aggregation.[32] Since platelets do not synthesize serotonin, SRIs could deplete intraplatelet serotonin stores and, therefore, decrease the efficacy of platelet mediated hemostasis.[31] This is the proposed mechanism by which SRI could predispose a patient to bleeding disturbance. Even though not directly studied here, our findings did not show any increase risk in bleeding and, therefore, this presumed pharmacologic mechanism.

Numerous studies suggest an association between SRIs and increased risk in bleeding from the upper GI tract.[10–24] A meta-analysis on GI bleeds and SRIs suggests that the only consistent finding in the literature is that this phenomenon is specific to gastric mucosa (a target tissue for SRIs) and not an intrinsic property of platelets.[16] Routinely, drugs that cause prolonged bleeding like aspirin, NSAIDS, or other antiplatelets are stopped well ahead of surgery. However, serotonergic antidepressants are rarely, if ever, stopped prior to surgery because of concerns about bleeding.

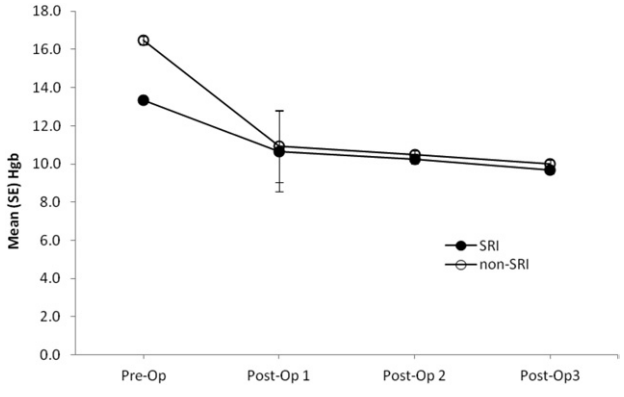
The strengths of our study are strict inclusion and exclusion criteria, case-matched design, and a large number of cases done at a single facility by surgeons using similar technique and medical management. Ex-

TABLE 4. Descriptive Statistics for HGB, HCT, PT, PLTS, PTT, and INR

	SRI		non-SRI	
	Mean	**SE**	**Mean**	**SE**
HGB				
Pre-op	13.33	2.11	16.46	1.88
Post-op day 1	10.66	0.24	10.93	0.22
Post-op day 2	10.24	0.19	10.48	0.17
Post-op day 3	9.66	0.24	10.02	0.21
HCT				
Pre-op	50.29	7.53	40.97	6.61
Post-op day 1	31.11	0.7	31.88	0.61
Post-op day 2	29.8	5.63	36.96	4.94
Post-op day 3	28.1	3.83	33.73	3.36
PLTS				
Pre-op	287.5	12.38	262.06	11.26
Post-op day 1	214.21	10.34	194.02	8.71
Post-op day 2	194.12	9.62	178.98	8.09
Post-op day 3	202.24	10.19	186.15	8.58
PT				
Pre-op	13.45	0.28	13.33	0.38
Post-op day 1	14.83	0.14	14.87	0.2
Post-op day 2	16.8	0.36	17.87	0.49
Post-op day 3	18.58	0.92	22.08	1.25
PTT				
Pre-op	28.94	1.1	30.76	0.98
Post-op day 1	31.51	4.86	35.87	4.3
Post-op day 2	35.69	1.19	36.24	1.06
Post-op day 3	42.61	1.17	40.33	1.92
INR				
Pre-op	0.99	0.04	1.04	0.04
Post-op day 1	1.15	0.02	1.143	0.02
Post-op day 2	1.39	0.05	1.38	0.05
Post-op day 3	1.65	0.09	1.58	0.1

tensive exclusion criteria were required to avoid confounding factors leading to increased bleeding. Although this study only involves military beneficiaries at a single medical center, this sample is most likely generalizable for adults of a similar demographic. It should be noted that there were significantly more female subjects in the experimental group. The control group was matched to reproduce this gender difference, which is reflective of the prescribing patterns of antidepressants in the general population (woman are two to three times more likely to take antidepressants).

FIGURE 2. Mean and Standard Error of Hemoglobin Levels at Preop, and Days 1 to 3 Post-Surgery.



Estimated blood loss reported by surgeons and documented by anesthesiologists may have some variability, but because it is an 'estimate' we doubt any significant variance would have been neglected (e.g., 200 mL vs. 400 mL is a notable difference).

Increased research regarding the effects of serotonergic antidepressants on hemostasis and bleeding risk is needed. This information would be essential not only for psychiatrists and surgeons, but also internists and other specialists who perform medical clearances for surgical procedures. To close, the hypothesis that SRIs increase the risk of bleeding based on present belief about their action on platelet aggregation is uncertain and warrants further study.

Special thanks to Elizabeth C. Clark "Cameron", Cynthia A. Quesenberry, David Whiddon, M.D., and staff at NMCP Clinical Investigation Department for their help.

Disclosure: The authors disclosed no proprietary or commercial interest in any product mentioned or concept discussed in this article.

The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government. Some authors are military service members. Others are employees of the U.S. Government. This work was prepared as part of their official duties. Title 17 U.S.C. 105 provides that 'Copyright protection under this title is not available for any work of the United States Government.' Title 17 U.S.C. 101 defines a United States Government work as a work prepared by a military service member or employee of the United States Government as part of that person's official duties.

Reprints are not available from the authors.

References

1. Looper KJ: Potential medical and surgical complications of serotonergic antidepressant medications. Psychosomatics 2007; 48(1):1–9
2. Pirraglia PA, Stafford RS, Singer DE: Trends in prescribing of selective serotonin reuptake Inhibitors and other newer antidepressant agents in adult primary care. Prim Care Companion J Clin Psychiatry 2003; 5(4):153–157
3. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT: Cyclic antidepressants and the risk of sudden cardiac death. Clin Pharmacol Ther 2004; 75(3):234–241
4. Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB: An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am 1999; 81(1):2–10
5. Lemos MJ, Healy WL: Blood transfusion in orthopaedic operations. J Bone Joint Surg Am 1996; 78(8):1260–1270
6. Mylod AG Jr., France MP, Muser DE, Parsons JR: Perioperative blood loss associated with total knee arthroplasty. A comparison of procedures performed with and without cementing. J Bone Joint Surg Am 1990; 72(7):1010–1012
7. Toy PT, Kaplan EB, McVay PA, Lee SJ, Strauss RG, Stehling LC: Blood loss and replacement in total hip arthroplasty: a multicenter study. The Preoperative Autologous Blood Donation Study Group. Transfusion 1992; 32(1):63–67
8. van Haelst IM, Egberts TC, Doodeman HJ, Traast HS, Burger BJ, Kalkman CJ, et al: Use of serotonergic antidepressants and bleeding risk in orthopedic patients. Anesthesiology 2010; 112(3):631–636
9. Movig KL, Janssen MW, de Waal Malefijt J, Kabel PJ, Leufkens HG, Egberts AC: Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. Arch Intern Med 2003; 163(19):2354–2358
10. Barbui C, Andretta M, De Vitis G, Rossi E, D'Arienzo F, Mezzalira L, et al: Antidepressant drug prescription and risk of abnormal bleeding: a case-control study. J Clin Psychopharmacol 2009; 29(1):33–38
11. Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J: An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. Clin Gastroenterol Hepatol 2009; 7(12):1314–1321
12. Dalton SO, Johansen C, Mellemkjaer L, Norgard B, Sorensen HT, Olsen JH: Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Arch Intern Med 2003; 163(1):59–64
13. de Abajo FJ, Garcia-Rodriguez LA: Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. Arch Gen Psychiatry 2008; 65(7):795–803
14. de Abajo FJ, Rodriguez LA, Montero D: Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. BMJ 1999; 319(7217):1106–1109
15. Helin-Salmivaara A, Huttunen T, Gronroos JM, Klaukka T, Huupponen R: Risk of serious upper gastrointestinal events with concurrent use of NSAIDs and SSRIs: a case-control study in the general population. Eur J Clin Pharmacol 2007; 63(4):403–408
16. Loke YK, Trivedi AN, Singh S: Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and nonsteroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2008; 27(1):31–40
17. Meijer WE, Heerdink ER, Nolen WA, Herings RM, Leufkens HG, Egberts AC: Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. Arch Intern Med 2004; 164(21):2367–2370
18. Opatrny L, Delaney JA, Suissa S: Gastrointestinal haemorrhage risks of selective serotonin receptor antagonist therapy: a new look. Br J Clin Pharmacol 2008; 66(1):76–81
19. Targownik LE, Bolton JM, Metge CJ, Leung S, Sareen J: Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. Am J Gastroenterol 2009; 104(6):1475–1482
20. Tata LJ, Fortun PJ, Hubbard RB, Smeeth L, Hawkey CJ, Smith CJ, et al: Does concurrent prescription of selective serotonin reuptake inhibitors and nonsteroidal anti-inflammatory drugs substantially increase the risk of upper gastrointestinal bleeding? Aliment Pharmacol Ther 2005; 22(3):175–181
21. van Walraven C, Mamdani MM, Wells PS, Williams JI: Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. BMJ 2001; 323(7314):655–658
22. Vidal X, Ibanez L, Vendrell L, Conforti A, Laporte JR: Risk of upper gastrointestinal bleeding and the degree of serotonin reuptake inhibition by antidepressants: a case-control study. Drug Saf 2008; 31(2):159–168
23. Wessinger S, Kaplan M, Choi L, Williams M, Lau C, Sharp L, et al: Increased use of selective serotonin reuptake inhibitors in

patients admitted with gastrointestinal haemorrhage: a multicentre retrospective analysis. Aliment Pharmacol Ther 2006; 23(7):937–944
24. Ziegelstein RC, Meuchel J, Kim TJ, Latif M, Alvarez W, Dasgupta N, et al: Selective serotonin reuptake inhibitor use by patients with acute coronary syndromes. Am J Med 2007; 120(6):525–530
25. Andreasen JJ, Riis A, Hjortdal VE, Jorgensen J, Sorensen HT, Johnsen SP: Effect of selective serotonin reuptake inhibitors on requirement for allogeneic red blood cell transfusion following coronary artery bypass surgery. Am J Cardiovasc Drugs 2006; 6(4):243–250
26. Kim DH, Daskalakis C, Whellan DJ, Whitman IR, Hohmann S, Medvedev S, et al: Safety of selective serotonin reuptake inhibitor in adults undergoing coronary artery bypass grafting. Am J Cardiol. May 15 2009; 103(10):1391–1395
27. Van Cann EM, Koole R: Abnormal bleeding after an oral surgical procedure leading to airway compromise in a patient taking a selective serotonin reuptake inhibitor and a nonsteroidal anti-inflammatory drug. Anesthesiology 2008; 109(3):568–569
28. Salkeld E, Ferris LE, Juurlink DN: The risk of postpartum hemorrhage with selective serotonin reuptake inhibitors and other antidepressants. J Clin Psychopharmacol 2008; 28(2):230–234
29. Andrade C, Sandarsh S, Chethan KB, Nagesh KS: Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. J Clin Psychiatry 2010; 71(12):1565–1575
30. Halperin D, Reber G: Influence of antidepressants on hemostasis. Dialogues Clin Neurosci 2007; 9(1):47–59
31. Hergovich N, Aigner M, Eichler HG, Entlicher J, Drucker C, Jilma B: Paroxetine decreases platelet serotonin storage and platelet function in human beings. Clin Pharmacol Ther 2000; 68(4):435–442
32. Lesch KP, Wolozin BL, Murphy DL, Reiderer P: Primary structure of the human platelet serotonin uptake site: identity with the brain serotonin transporter. J Neurochem 1993; 60(6):2319–2322
33. Li N, Wallen NH, Ladjevardi M, Hjemdahl P: Effects of serotonin on platelet activation in whole blood. Blood Coagul Fibrinolysis 1997; 8(8):517–523
34. Sauer WH, Berlin JA, Kimmel SE: Effect of antidepressants and their relative affinity for the serotonin transporter on the risk of myocardial infarction. Circulation 2003; 108(1): 32–36
35. Serebruany VL: Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? Am J Med 2006; 119(2):113–116
36. Serebruany VL, O'Connor CM, Gurbel PA: Effect of selective serotonin reuptake inhibitors on platelets in patients with coronary artery disease. Am J Cardiol 2001; 87(12):1398–1400
37. Skop BP, Brown TM: Potential vascular and bleeding complications of treatment with selective serotonin reuptake inhibitors. Psychosomatics 1996; 37(1):12–16