(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 4 , Page No: 01-09
July-August 2022

IJMSCR

Concurrent Use Of Antidepressants Serotonin Reuptake Inhibitors And Nonsteroidal Anti-Inflammatory Drugs Increase The Risk Of Intracranial Hemorrhage

Suttikarn Somboonsakdikul
Triamudomsuksa pattanakarn, Suan Luang, Bangkok, Thailand 10250

***Corresponding Author:**
Suttikarn Somboonsakdikul
Triamudomsuksa pattanakarn, Suan Luang, Bangkok, Thailand 10250

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Depression is a complex disease that many people suffered from. It can be caused by various reasons. Depression can be serious. It is, however, treatable in the meanwhile. It can be treated by selective serotonin reuptake inhibitors (SSRIs), selective serotonin, and norepinephrine inhibitors (SNRIs). The concurrent use of antidepressants with Nonsteroidal Anti-inflammatory Drugs (NSAIDs) raises the risk of Intracranial hemorrhage (ICH). In addition, Serotonin transporter and platelets both transport serotonin up to release vascular damage and then interact with the platelet 5-HT2A receptor to accelerate platelet aggregation and result in thrombus formation. Bleeding with SRI is caused by the inhibition of the serotonin transporter on platelets, which involves reducing the platelet aggregation. In conclusion, the mechanism related to or associated with serotonin reuptake inhibition would raise the risk of abnormal bleeding in patients.

Keywords: Depression; antidepressants; serotonin reuptake inhibitors; nonsteroidal anti-inflammatory drugs; intracranial hemorrhage

Introduction

Depression is a common illness that most people suffer. Approximately 280 million people in the world have experienced depression. The growth of prevalence of depression has been growing consistently (1). It poses a higher risk of chronic pain and arthritis. These physical comorbidities require treatment with Nonsteroidal Anti-inflammatory Drugs (NSAIDs) (2). Previous studies have discovered that using antidepressants and NSAIDs may increase the risks of gastrointestinal bleeding (GIB), but no evidence concluded that using these drugs one at a time going to poses more risk of intracranial hemorrhage (3). The prior study reported that using antidepressants with NSAIDs concomitantly suggests a potential drug-drug interaction (4). Depression is the most unhealthy condition that produces a huge decrement in our health (5). Using antidepressants can help the patients effectively but it may interact unfavorably with NSAIDs (2). The increase of abnormal bleeding may due to selective serotonin reuptake inhibitors (SSRIs) and NSAIDs (6, 7). This review aims to explain that antidepressants and NSAIDs are involved and related to increasing the risk of intracranial hemorrhage (ICH).

Depression and drugs used for treating depressive disorder

There is a correlation between depression and hemorrhagic stroke (8). Depression increased the risk of hemorrhagic stroke by not depending on the therapy (1). Most of the SSRIs prescriptions are for depression (9). Previous observational studies of the incidence of ICH with SSRI use have demonstrated and shown us a conflicting outcome, this may be due to a potential indication bias to the diagnosis of depression (10). The lifetime prevalence of depression in the United States is about 16.6% (11). Antidepressants can be counted as the third most

commonly prescribed medication class (10). Serotonin reuptake inhibitors (SRIs), specified antidepressants, can be used for a variety of indications (12). For example, anxiety, depression, vasomotor symptom relief, and pain disorder (12). In particular, people are giving more attention to SRIs surrounding the risk of bleeding (13, 14). Serotonin transporter and platelets take the serotonin up to release the vascular injury then bind with the platelet 5-HT_{2A} receptor to accelerate platelet aggregation and lead to thrombus formation (15). In order to reduce platelet aggregation, it was hypothesized that bleeding with SRI is a result of inhibition of the serotonin transporter on platelets (16, 17). Furthermore, the increased gastric acidity by selective serotonin reuptake inhibitors (SSRIs) will increase the risk of ulcer formation and GIBs (6, 18). It is hypothesized that patients may bleeds when SRIs is related to high serotonin transporter binding affinity (19). It places patients in a higher binding affinity SRIs bleeding risk than intermediate and low (20). It has been hypothesized that the SRIs related to the high serotonin transporter binding affinity (eg, clomipramine, duloxetine, fluoxetine, paroxetine, sertraline, vilazodone, and vortioxetine) places patients in a higher bleeding risk than intermediate (eg, clomipramine, duloxetine, fluoxetine, paroxetine, sertraline, vilazodone, and vortioxetine) and low (eg, bupropion, doxepin, mirtazapine, nortriptyline, phenelzine, tranylcypromine, and trazodone) binding affinity SRIs (6, 21). Moreover, when cytochrome-P450 (CYP)-mediated drug interactions are combined with medications with additive bleeding risks, it may poses a risk of bleeding. Duloxetine (moderate CYP2D6 inhibition), fluvoxamine (strong CYP1A2, 2C9, 2C19, moderate CYP3A4, and weak CYP2D6 inhibition), fluoxetine (strong CYP2D6, 2C9, moderate CYP3A4, 2C19, and weak CYP1A2 inhibition), and paroxetine (strong CYP2D6 and weak CYP1A2, 3A4, 2C9, 2C19 inhibition) are the most remarkable CYP inhibitors among the SRIs (22, 23). Weak CYP2D6 inhibitors can be classified as Citalopram, escitalopram, sertraline, and venlafaxine (24). When determine the risk of bleeding with SRIs, considering drug-drug interactions are crucial (6).

Incidence of Bleeding With SRIs

There's a correlation between SRIs with various type of bleeding such as GIB, ICH, PPH, and operative bleeding (6). Varieties of bleeding with inclusion of patients led to the significance of heterogeneity (25). It is difficult to demonstrate SRIs impact on bleeding at other sites such as PPH, brain hemorrhage, or operative-related bleeds due to the low incidents of the event (13, 26). A meta-analysis stated that there was an increase of 61% on the SSRIs exposure associated with brain hemorrhage (27). Likewise, the chance of developing PPH raises an increase of 32% in women who are taking antidepressants during pregnancy than those who do not (10). However, the highest risk of PPH was for those patients who take SNRIs, use antidepressants for 30 days, and for women who underwent cesarean deliveries (6, 27). It is still difficult to ascertain the bleeding risk from preoperative use of serotonergic antidepressants (25). According to a meta-analysis of the studies, there is no significant difference in reoperation caused by bleeding among users that use antidepressants. These results may be confounded because of the failure to account for potential CYP enzyme inhibition and antiplatelet medications. It is necessary to have more studies so that we can identify how bleeding risk with SRI use can be correlated with brain hemorrhage, PPH, and surgical interventions (27).

SSRIs Associated with the Risk of Intracranial Hemorrhage

Contemporary use of SSRIs, compared with TCAs, was related to an elevated risk of ICH, peculiarly during the first 30 days of treatment, in a large population-based cohort of new antidepressant users (28). These observations were supported by a marginally increased risk when antidepressants were categorised according to their degree of serotonin reuptake inhibition (8). However, this relative rise resulted in a minimal number of new incidents. Concurrent usage of oral anticoagulants significantly raised the risk of ICH (29, 30). Numerous observational studies have examined the link between ICH and SSRIs, with mixed findings (31). Possible explanations include insufficient statistical power, a varied comparator group, the inclusion of frequent users, inconsistent exposure definitions, and significant residual confounding (1, 32). All trials included a nonuser comparator group, and several investigations focused exclusively on intracerebral haemorrhage or hemorrhagic stroke (33, 34). According to the Women's Health Initiative cohort study, the exposure to SSRIs in the year preceding cohort enrollment was linked with a twofold

Volume 5, Issue 4; July-August 2022; Page No 01-09

increased risk of ICH compared to nonuse (35). Eventually, a meta-analysis of the significant observational studies comparing patients exposed to SSRIs to those who were not exposed to antidepressants revealed an elevated risk of ICH linked with SSRI usage (33). Comparing SSRI users to nonusers may add indication bias, as the condition being treated may be associated with an increased risk of bleeding (36). For example, it has been proposed that depression is associated with an increased risk of hemorrhagic stroke (37). This scenario limits disentangling the risk associated with antidepressants from the risk associated with the illness being treated, thereby inflating the risk estimate artificially (38, 39). However, we cannot rule out that some of this higher risk is due to residual confounding. On the other hand, our findings are consistent with a higher risk, given the biological plausibility and well-established increased risk of bleeding in other body systems (38, 40). Serotonin contained in platelets accounts for almost 99% of the serotonin in the human body (32). Serotonin is released into the bloodstream upon vascular damage and platelet activation and binds to specific receptors to enhance vasoconstriction and platelet aggregation, ultimately promoting hemostasis. Serotonin reuptake into platelets is mediated by a serotonin transporter that SSRIs inhibit serotonin reuptake into platelets (19). This inhibits platelet aggregation and thus platelet thrombus formation, resulting in an increased risk of bleeding (41, 42). SSRIs' antiplatelet mechanisms of action have been demonstrated in animal and human trials as early as 1 or 2 weeks following therapy initiation (42, 43). Antidepressants with the highest degree of serotonin reuptake inhibition have been connected with an increased frequency of abnormal bleeding and hemostasis marker changes (44, 45).

A few studies evaluated the risk of ICH about the degree to which antidepressants impede serotonin reuptake (33). The exposure criteria in one study (antidepressants used at least once during follow-up vs no usage) may have diluted any possible benefit (46). The second trial found a 13% greater risk, although it was not statistically significant (47). Another study reported an elevated risk with all antidepressant classes and any degree of serotonin inhibition, suggesting residual confounding (48). Although the evidence for an association between solid serotonin transporter inhibitors and gastrointestinal tract haemorrhage, abnormal bleeding, and the need for transfusion following surgery has been challenging to demonstrate and somewhat contradictory (probably because these events are rare), an association was discovered between potent serotonin transporter inhibitors and gastrointestinal tract haemorrhage, abnormal bleeding, and the need for transfusion following surgery (42, 49). Previously, an increased risk of ICH has been suggested in individuals treated concurrently with anticoagulants and SSRIs (48). In a cohort of new coumarin users, the risk of non–gastrointestinal tract bleeding rose when SSRI users were compared to nonusers, with a nonsignificant rise in ICH risk (37). In a case-control study, the use of SSRIs in combination with warfarin was associated with a numerically increased risk of hemorrhagic stroke compared to warfarin alone, but neither aspirin alone nor SSRIs combined with aspirin increased the risk (10). Two further studies discovered no statistically significant interaction between the use of SSRIs and aspirin and the risk of ICH, consistent with our findings (4). However, we cannot rule out the possibility that an enhanced risk occurs with concurrent use of SSRIs and antiplatelets and that we were unable to capture it precisely (31). Additionally, current antiplatelet use was defined broadly as exposure during the month before the index date (50).

Concomitant Medications That Affect SRIs' Impact on Bleeding

Apart from the fact that SRIs increase the risk of bleeding, it is critical to consider concurrent medications that may increase the risk additively, such as antiplatelet agents and nonsteroidal anti-inflammatory drugs (NSAIDs) (6, 51). People who had an acute myocardial infarction and received SSRIs and antiplatelet therapy were studied to see if they had an increased risk of gastroesophageal reflux disease (GIB) after taking these medications (52). In comparison to aspirin alone, the combination of SSRIs and aspirin increased the risk of bleeding (13). Similarly, when used in combination with dual antiplatelet therapy (aspirin and clopidogrel), SSRI use increased the risk of bleeding (43). To corroborate these findings, a nationwide population-based study of clopidogrel users discovered that using an SSRI in addition to clopidogrel increases the

Volume 5, Issue 4; July-August 2022; Page No 01-09

risk of lower GI bleeding but not upper GI bleeding (53).

On the other hand, a study of the French Spontaneous Reporting Database, which examined bleeding adverse drug reactions among those exposed to antiplatelet agents, failed to find a statistically significant link between SRI use and bleeding events (54). However, only 62 cases (4.7%) of SRI and antiplatelet users used both. Given that aspirin, clopidogrel, and selective receptor antagonists (SRIs) all inhibit platelet function, healthcare providers must be aware that concomitant use can increase the risk of bleeding and ensure that patients are monitored appropriately (55). Since NSAIDs increase the risk of GIBs via a variety of mechanisms, their use in combination with SRIs is of particular interest (55). Consistently across the literature, concurrent use of SSRIs and NSAIDs increases the risk of GIB (56). Concurrent use of NSAIDs was associated with an increased risk of bleeding in a meta-analysis of observational studies examining SSRI use and GIBs (56). SSRIs and NSAIDs were found to have a synergistic effect on the risk of cardiovascular disease because they were taken together (56, 57). Furthermore, 80% of the 101 postmarketing reports included in this meta-analysis involved concurrent exposure to NSAIDs, antiplatelets, or anticoagulants (3). SSRIs and NSAIDs were studied together in a similar meta-analysis to determine the upper GIB risk better (58). The results of this study were similar to those of the first (6). The risk of upper GI bleeding was additive when SSRIs and NSAIDs were combined (59). Cost-effectiveness and a tolerable adverse effect profile have been established for selective serotonin reuptake inhibitors. SSRIs are approved by the US Food and Drug Administration to treat major depression, anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder (34). The adverse effect profile of selective serotonin reuptake inhibitors (SSRIs) is favourable compared to that of other antidepressants, but they are associated with a range of potential drug-drug interactions and severe adverse effects (30). They are well-characterized inhibitors of various cytochrome-P450 isoforms. The isoforms are inhibited, and the extent to which they are inhibited varies according to the SSRI. Fluoxetine and paroxetine are potent inhibitors of CYP2D6, whereas fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19 (29). Citalopram exerts only a negligible effect on the major CYP isoforms (46). Changes may occur when certain SSRIs are combined with other CYP-mediated medications, clinically significant pharmacokinetic/pharmacodynamic (PK/PD) (60). Warfarin and clopidogrel are two medicines that interact with SSRIs (60). This drug-drug interaction increases the risk of bleeding, including minor bruising and bleeding (29, 60).

The FDA-approved labelling for SSRIs includes a warning about abnormal bleeding as one of the possible side effects (34). Several possible mechanisms have been proposed to explain the increased risk of bleeding in patients taking SSRIs and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants, or antiplatelets at the same time (34). GI bleeding and spontaneous intracranial bleeding are two examples of severe clinical bleeding (35). SSRIs have been associated with an increased risk of gastrointestinal and intracranial bleeding in observational and interventional studies, regardless of other bleeding risk factors (61). In patients without a history of GI bleeding, SSRIs are reported to cause an excess of GI bleeding at a rate of approximately 3.1 per 1000 patient-years (4). Intracranial bleeding is uncommon but can have serious consequences, particularly in patients receiving SSRIs for poststroke depression (42). Given the widespread use of SSRIs and the clinical severe adverse events associated with them, such as gastrointestinal bleeding and intracranial bleeding, health care professionals must be aware of potential interactions with other medications known to increase the risk of bleeding (19).

Clinical impact of selective serotonin reuptake inhibitors therapy with bleeding risks

SSRI medication may increase the risk of hemorrhagic episodes (62). SSRIs have been related to an increased risk of upper gastrointestinal bleeding, postoperative transfusions, and antiulcer prescription (4). Additionally, in numerous studies, it is critical to highlight that concomitant aspirin or NSAID therapy increased the risk of bleeding above the risk associated with SSRI therapy alone (9). In other cases, the risk exceeded the additive impact of either agent alone (28). As a result, the effects of SSRIs and aspirin/NSAIDS on bleeding risks may be cumulative, and caution should be given when more

Volume 5, Issue 4; July-August 2022; Page No 01-09

than one of these drug types is used in combination (59). Patient education regarding these side effects is critical. Additionally, considerable variance in the degree of risk linked with SSRI therapy was discovered (8, 39). This may be explained by changes in patient demographics across studies and SRIs (63). It is unknown whether the degree of serotonin reuptake inhibition impacts the outcome of hazardous bleeding events (64). It has been shown that antidepressants with a tremendous SRI concentration increase the risk of bleeding more than those with a lower SRI concentration (65). When examining bleeding linked with various degrees of SRI, one study found no statistically significant difference but did observe a trend toward more bleeding events with increasing SRI dosage, but serum concentrations were not evaluated (66). The same study discovered that patients with a history of gastrointestinal bleeding or who are >80 years of age are likewise more susceptible to the bleeding risk-reducing benefits of higher SRI medicines (6). Consideration should be made to these patient categories at increased risk (13). Additionally, the study discovered that the risk of bleeding during the first month of SSRI administration is quantitatively more significant than the risk in succeeding months (14, 67). Future research should integrate a temporal component into their design to better assess this risk (34, 68).

Conclusion

Concurrent use of antidepressants and NSAIDs may raise the risk of developing ICH, with nonselective NSAIDs and serotonergic antidepressants being the primary culprits. Within 30 days of initiating the combination, antidepressant and NSAID use was related to an increased risk of a cerebral haemorrhage. As a result of this analysis, doctors should exercise caution when administering these medicines in combination and closely monitor side effects. Additionally, because SSRI usage is prevalent in the ambulatory setting, osteopathic practitioners should be aware of potential drug-drug interactions and the clinical implications of SSRI-associated bleeding risk.

References

1. Kubiszewski P, Sugita L, Kourkoulis C, DiPucchio Z, Schwab K, Anderson CD, et al. Association of selective serotonin reuptake inhibitor use after intracerebral hemorrhage with hemorrhage recurrence and depression severity. JAMA neurology. 2021;78(1):61-7.
2. Lehrer S, Rheinstein PH. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce suicidal ideation and depression. Discovery Medicine. 2019;28(154):205-12.
3. Gu Z-C, Wei A-H, Zhang C, Wang X-H, Zhang L, Shen L, et al. Risk of major gastrointestinal bleeding with new vs conventional oral anticoagulants: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology. 2020;18(4):792-9.
4. Lee M-T, Park K-Y, Kim M-S, You S-H, Kang Y-J, Jung S-Y. Concomitant use of NSAIDs or SSRIs with NOACs requires monitoring for bleeding. Yonsei medical journal. 2020;61(9):741.
5. Chávez-Castillo M, Ortega Á, Nava M, Fuenmayor J, Lameda V, Velasco M, et al. Metabolic risk in depression and treatment with selective serotonin reuptake inhibitors: are the metabolic syndrome and an increase in cardiovascular risk unavoidable? Vessel Plus. 2018;2:6.
6. Bixby AL, VandenBerg A, Bostwick JR. Clinical management of bleeding risk with antidepressants. Annals of Pharmacotherapy. 2019;53(2):186-94.
7. Jeong HE, Oh I-S, Kim WJ, Shin J-Y. Risk of major adverse cardiovascular events associated with concomitant use of antidepressants and non-steroidal anti-inflammatory drugs: a retrospective cohort study. CNS drugs. 2020;34(10):1063-74.
8. Mortensen JK, Andersen G. Pharmacological management of post-stroke depression: an update of the evidence and clinical guidance. Expert Opinion on Pharmacotherapy. 2021;22(9):1157-66.
9. Syed MJ, Farooq S, Siddiqui S, Awan S, Wasay M. Depression and the use of selective serotonin reuptake inhibitors in patients with acute intracerebral hemorrhage. Cureus. 2019;11(10).
10. Trajkova S, d'Errico A, Soffietti R, Sacerdote C, Ricceri F. Use of antidepressants and risk of incident stroke: a systematic review and meta-

Volume 5, Issue 4; July-August 2022; Page No 01-09

analysis. Neuroepidemiology. 2019;53(3-4):142-51.
11. Fereidouni A, Jafarzadeh S, Ghanavati M. The Prevalence of Depression and Its Relationship with Demographic Variables in the Employees of Fasa University of Medical Sciences. Journal of Fasa University of Medical Sciences. 2021;11(1):3757-63.
12. Kang S, Han M, Park CI, Jung I, Kim EH, Boo YJ, et al. Use of serotonin reuptake inhibitors and risk of subsequent bone loss in a nationwide population-based cohort study. Scientific Reports. 2021;11(1):1-9.
13. Nochaiwong S, Ruengorn C, Awiphan R, Chai-Adisaksopha C, Tantraworasin A, Phosuya C, et al. Use of serotonin reuptake inhibitor antidepressants and the risk of bleeding complications in patients on anticoagulant or antiplatelet agents: a systematic review and meta-analysis. Annals of medicine. 2022;54(1):80-97.
14. Auschra B, Wilhelm MJ, Husung C, Jenewein J, Flammer AJ, Jellestad L. The use of serotonin reuptake inhibitors increases the risk of bleeding in patients with assist devices. BMC Cardiovascular Disorders. 2022;22(1):1-9.
15. Marcinkowska M, Kubacka M, Zagorska A, Jaromin A, Fajkis-Zajaczkowska N, Kolaczkowski M. Exploring the antiplatelet activity of serotonin 5-HT2A receptor antagonists bearing 6-fluorobenzo [d] isoxazol-3-yl) propyl) motif–as potential therapeutic agents in the prevention of cardiovascular diseases. Biomedicine & Pharmacotherapy. 2022;145:112424.
16. Peters MAM, van Faassen M, de Jong WHA, Bouma G, Meijer C, Walenkamp AME, et al. Use of selective serotonin reuptake inhibitors is associated with very low plasma-free serotonin concentrations in humans. Annals of Clinical Biochemistry. 2020;57(1):59-63.
17. Li R, Qu J, Wu C, Fang Z, Hong X, Xu H. Demonstration of an action pathway in mouse platelets leading to prolongation of bleeding time by fluoxetine. European Journal of Pharmacology. 2020;883:173385.
18. Tang J, Sharma U, Desai S, Molnar J, Perlmuter L, Feller A, et al. A study of proton pump inhibitors and other risk factors in warfarin-associated gastrointestinal bleeding. Cureus. 2021;13(1).
19. Gahr M, Connemann BJ, Muche R, Zeiss R. The Impact of Serotonin Transporter Binding Affinity on the Risk of Bleeding Related to Antidepressants. Journal of clinical psychopharmacology. 2021;41(4):470-3.
20. Nguyen TTH, Roussin A, Rousseau V, Montastruc J-L, Montastruc F. Role of serotonin transporter in antidepressant-induced diabetes mellitus: a pharmacoepidemiological–pharmacodynamic study in VigiBase®. Drug Safety. 2018;41(11):1087-96.
21. Nykamp MJ, Zorumski CF, Reiersen AM, Nicol GE, Cirrito J, Lenze EJ. Opportunities for Drug Repurposing of Serotonin Reuptake Inhibitors: Potential Uses in Inflammation, Infection, Cancer, Neuroprotection, and Alzheimer's Disease Prevention. Pharmacopsychiatry. 2022;55(01):24-9.
22. Niwa T, Yanai M, Matsumoto M, Shizuku M. Effect of cytochrome P450 (CYP) 2D6 genetic polymorphism on the inhibitory action of antidepressants on CYP2D6-mediated dopamine formation from p-tyramine. Journal of Pharmacy & Pharmaceutical Sciences. 2018;21:135-42.
23. Niwa T, Sugimoto S. Inhibitory and stimulatory effects of selective serotonin reuptake inhibitors on cytochrome P450 2D6-mediated dopamine formation from p-tyramine. Journal of Pharmacy & Pharmaceutical Sciences. 2019;22:585-92.
24. Deodhar M, Al Rihani SB, Arwood MJ, Darakjian L, Dow P, Turgeon J, et al. Mechanisms of CYP450 inhibition: understanding drug-drug interactions due to mechanism-based inhibition in clinical practice. Pharmaceutics. 2020;12(9):846.
25. Robinson AC, January SE, Botkin KW, Vader JM, Hartupee JC, Tellor Pennington BR. Association of bleeding with serotonergic antidepressants in patients receiving left ventricular assist device support. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2022;42(1):4-13.

Volume 5, Issue 4; July-August 2022; Page No 01-09

26. Revet A, Montastruc F, Roussin A, Raynaud J-P, Lapeyre-Mestre M, Nguyen TTH. Antidepressants and movement disorders: a postmarketing study in the world pharmacovigilance database. BMC psychiatry. 2020;20(1):1-13.
27. Na K-S, Jung H-Y, Cho S-J, Cho S-E. Can we recommend mirtazapine and bupropion for patients at risk for bleeding?: A systematic review and meta-analysis. Journal of Affective Disorders. 2018;225:221-6.
28. Schäfer W, Princk C, Kollhorst B, Schink T. Antidepressants and the Risk of Hemorrhagic Stroke in the Elderly: a Nested Case–Control Study. Drug Safety. 2019;42(9):1081-9.
29. Yuet WC, Derasari D, Sivoravong J, Mason D, Jann M. Selective serotonin reuptake inhibitor use and risk of gastrointestinal and intracranial bleeding. Journal of Osteopathic Medicine. 2019;119(2):102-11.
30. Hicks JK, Bishop JR, Gammal RS, Sangkuhl K, Bousman C, Leeder JS, et al. A call for clear and consistent communications regarding the role of pharmacogenetics in antidepressant pharmacotherapy. Clinical pharmacology and therapeutics. 2020;107(1):50.
31. Liu L, Fuller M, Behymer TP, Ng Y, Christianson T, Shah S, et al. Selective serotonin reuptake inhibitors and intracerebral hemorrhage risk and outcome. Stroke. 2020;51(4):1135-41.
32. Grech J, Chan MV, Ochin C, Lachapelle A, Thibord F, Schneider Z, et al. Serotonin-Affecting Antidepressant Use in Relation to Platelet Reactivity. Clinical Pharmacology & Therapeutics. 2022;111(4):909-18.
33. Douros A, Ades M, Renoux C. Risk of intracranial hemorrhage associated with the use of antidepressants inhibiting serotonin reuptake: a systematic review. CNS drugs. 2018;32(4):321-34.
34. McDonald DD, Srisopa P. Predictors of hemorrhagic stroke in older persons taking nonsteroidal anti-inflammatory drugs: Results from the Food and Drug Administration Adverse Event Reporting System. Journal of the American Association of Nurse Practitioners. 2021;33(11):959-66.
35. Pressman E, Penn D, Patel NJ. Intracranial hemorrhage from meningioma: 2 novel risk factors. World Neurosurgery. 2020;135:217-21.
36. Sheikh Rezaei S, Mittlböck M, Reichardt B, Wolzt M. SSRI co-medication with NOAC or VKA does not increase hospitalisation for bleeding: A retrospective nationwide cohort study in Austria 2010-2015. International Journal of Geriatric Psychiatry. 2019;34(8):1194-9.
37. Quinn GR, Hellkamp AS, Hankey GJ, Becker RC, Berkowitz SD, Breithardt G, et al. Selective serotonin reuptake inhibitors and bleeding risk in anticoagulated patients with atrial fibrillation: an analysis from the ROCKET AF trial. Journal of the American Heart Association. 2018;7(15):e008755.
38. Wilkins T, Wheeler B, Carpenter M. Upper gastrointestinal bleeding in adults: evaluation and management. American family physician. 2020;101(5):294-300.
39. Shao IY, Claxton JNS, Lutsey PL, Chen LY, MacLehose RF, Alonso A. Association of Type of Antidepressant Initiation with Bleeding Risk in Atrial Fibrillation Patients Taking Oral Anticoagulants. Drugs-Real World Outcomes. 2021;8(3):383-91.
40. Iasella CJ, Kreider MS, Huang L, Coons JC, Stevenson JM. Effect of selective serotonin reuptake inhibitors on cardiovascular outcomes after percutaneous coronary intervention: a retrospective cohort study. Clinical drug investigation. 2019;39(6):543-51.
41. Francescangeli J, Karamchandani K, Powell M, Bonavia A. The serotonin syndrome: from molecular mechanisms to clinical practice. International journal of molecular sciences. 2019;20(9):2288.
42. Jensen MP, Ziff OJ, Banerjee G, Ambler G, Werring DJ. The impact of selective serotonin reuptake inhibitors on the risk of intracranial haemorrhage: A systematic review and meta-analysis. European stroke journal. 2019;4(2):144-52.
43. Narouze S, Benzon HT, Provenzano D, Buvanendran A, De Andres J, Deer T, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American

Volume 5, Issue 4; July-August 2022; Page No 01-09

Society of regional anesthesia and pain medicine, the European Society of regional anaesthesia and pain therapy, the American Academy of pain medicine, the International neuromodulation Society, the North American neuromodulation Society, and the world Institute of pain. Regional Anesthesia & Pain Medicine. 2018;43(3):225-62.
44. Halperin D, Reber G. Influence of antidepressants on hemostasis. Dialogues in clinical neuroscience. 2022.
45. Kubanek A, Paul P, Przybylak M, Kanclerz K, Rojek JJ, Renke M, et al. Use of Sertraline in Hemodialysis Patients. Medicina. 2021;57(9):949.
46. Assimon MM, Brookhart MA, Flythe JE. Comparative cardiac safety of selective serotonin reuptake inhibitors among individuals receiving maintenance hemodialysis. Journal of the American Society of Nephrology. 2019;30(4):611-23.
47. Marquez-Romero JM, Reyes-Martínez M, Huerta-Franco MR, Ruiz-Franco A, Silos H, Arauz A. Fluoxetine for motor recovery after acute intracerebral hemorrhage, the FMRICH trial. Clinical Neurology and Neurosurgery. 2020;190:105656.
48. Spina E, Barbieri MA, Cicala G, Bruno A, de Leon J. Clinically relevant drug interactions between newer antidepressants and oral anticoagulants. Expert Opinion on Drug Metabolism & Toxicology. 2020;16(1):31-44.
49. Abramoff BA, Mahdi ND, Beran M, Belagaje SR. ICH Rehabilitation and Recovery. Intracerebral Hemorrhage Therapeutics: Springer; 2018. p. 161-83.
50. Schellen C, Ferrari J, Lang W, Sykora M. Effects of SSRI exposure on hemorrhagic complications and outcome following thrombolysis in ischemic stroke. International Journal of Stroke. 2018;13(5):511-7.
51. Ghanbarzamani A, Sefidaniforough A, Salamzadeh J, Fahimi F. Hemorrhagic Events in Patients Receiving Heparin or Enoxaparin in Combination With Oral Antithrombotics, NSAIDs, and Antiplatelet Medications: A Multi-Center Case-Series Study. Pharmaceutical and Biomedical Research. 2021;7(2):115-20.
52. Sarier M, Demir M, Emek M, Özgen A, Turgut H, Özdemir C. Association between selective serotonin and serotonin–noradrenaline reuptake inhibitor therapy and hematuria. Nordic Journal of Psychiatry. 2022:1-5.
53. Chi T-Y, Zhu H-M, Zhang M. Risk factors associated with nonsteroidal anti-inflammatory drugs (NSAIDs)-induced gastrointestinal bleeding resulting on people over 60 years old in Beijing. Medicine. 2018;97(18).
54. Bielsa-Fernández MV, Tamayo-de la Cuesta JL, Lizárraga-López J, Remes-Troche JM, Carmona-Sánchez R, Aldana-Ledesma JM, et al. The Mexican consensus on the diagnosis, treatment, and prevention of NSAID-induced gastropathy and enteropathy. Revista de Gastroenterología de México (English Edition). 2020;85(2):190-206.
55. Zapata LV, Hansten PD, Panic J, Horn JR, Boyce RD, Gephart S, et al. Risk of bleeding with exposure to warfarin and nonsteroidal anti-inflammatory drugs: a systematic review and meta-analysis. Thrombosis and haemostasis. 2020;120(07):1066-74.
56. Soriano LC, Fowkes FGR, Allum AM, Johansson S, Rodriguez LAG. Predictors of bleeding in patients with symptomatic peripheral artery disease: a cohort study using the health improvement network in the United Kingdom. Thrombosis and Haemostasis. 2018;118(06):1101-12.
57. Batool A, Bui RT. Patients on NSAIDs/Anticoagulation. Management of Occult GI Bleeding: Springer; 2021. p. 251-64.
58. Qazi JZ, Schnitzer ME, Côté R, Martel M-J, Dorais M, Perreault S. Predicting major bleeding among hospitalized patients using oral anticoagulants for atrial fibrillation after discharge. PloS one. 2021;16(3):e0246691.
59. Gaist D, García Rodríguez LA, Hald SM, Hellfritzsch M, Poulsen FR, Halle B, et al. Antidepressant drug use and subdural hematoma risk. Journal of Thrombosis and Haemostasis. 2020;18(2):318-27.
60. Mortensen JK, Andersen G. Safety considerations for prescribing SSRI antidepressants to patients at increased cardiovascular risk. Expert Opinion on Drug Safety. 2022;21(4):467-75.

Volume 5, Issue 4; July-August 2022; Page No 01-09

61. Sembill JA, Kuramatsu JB, Schwab S, Huttner HB. Resumption of oral anticoagulation after spontaneous intracerebral hemorrhage. Neurological Research and Practice. 2019;1(1):1-10.
62. Vajravelu RK, Mamtani R, Scott FI, Waxman A, Lewis JD. Incidence, risk factors, and clinical effects of recurrent diverticular hemorrhage: a large cohort study. Gastroenterology. 2018;155(5):1416-27.
63. Katsinelos P, Lazaraki G, Anastasiadis S, Chatzimavroudis G, Katsinelos T, Terzoudis S, et al. The impact of selective serotonin receptor inhibitors on post-endoscopic sphincterotomy bleeding, alone or with concurrent aspirin or nonsteroidal anti-inflammatory drugs. Annals of Gastroenterology. 2019;32(6):614.
64. Chollet F, Rigal J, Marque P, Barbieux-Guillot M, Raposo N, Fabry V, et al. Serotonin selective reuptake inhibitors (SSRIs) and stroke. Current Neurology and Neuroscience Reports. 2018;18(12):1-11.
65. Bakhireva LN, Sparks A, Herman M, Hund L, Ashley M, Salisbury A. Severity of neonatal opioid withdrawal syndrome with prenatal exposure to serotonin reuptake inhibitors. Pediatric Research. 2022;91(4):867-73.
66. Onuțu AH, Dîrzu DS, Petrișor C. Serotonin reuptake inhibitors and their role in chronic pain management. Serotonin: IntechOpen; 2018.
67. Piel-Julian ML, Mahévas M, Germain J, Languille L, Comont T, Lapeyre-Mestre M, et al. Risk factors for bleeding, including platelet count threshold, in newly diagnosed immune thrombocytopenia adults. Journal of Thrombosis and Haemostasis. 2018;16(9):1830-42.
68. Robbins AJ, Lusczek E, Bellin MD, Alwan FS, Hodges JS, Chapman SA, et al. Gastrointestinal Bleed After Total Pancreatectomy With Islet Autotransplant. Pancreas. 2021;50(6):841-6.

Volume 5, Issue 4; July-August 2022; Page No 01-09