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RESEARCH

Association of antidepressants plus antithrombotics and bleeding risk: a pharmacovigilance study

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Abstract

Aim The present study investigated the risk of bleeding when antidepressants are added to antithrombotics.

Methods Using data registered in VigiBase®, the WHO pharmacovigilance database, between 01/01/2000 and 31/12/2022, we compared the risk of reporting "serious" bleeding (Reporting Odds Ratio, ROR) with antidepressants + antithrombotics versus antithrombotics alone.

Results Increased values of ROR were found for the association Serotonin Reuptake Inhibitors (SRIs) + Direct Oral Anticoagulants (DOACs) versus DOACs alone (ROR=1.49(1.17-1.89)). Similar results were found for Factor Xa inhibitors or Thrombin inhibitors. This association was also found for other antithrombotics: Vitamin K Antagonists (ROR=1.37(1.12-1.68)), Platelet Aggregation Inhibitors PAIs (ROR=1.38(1.21-1.57)) and Heparins (2.04(1.59-2.62)) but not with other antidepressants (Non-Selective Monoamine Reuptake Inhibitors, NSMRIs).

Conclusion The present study suggests an increased risk of "serious" bleeding when SRIs (but not NSMRIs) are associated with antithrombotics (all antithrombotics and not only DOACs).

Keywords Antidepressants · Direct Oral Anticoagulants · Direct Factor Xa inhibitors · Direct Thrombin Inhibitors · Heparins · Platelet Agregation Inhibitors

Bleeding is an adverse drug reaction (ADR) largely discussed with serotonin reuptake inhibitors (SRIs) [1]. The problem of an increased bleeding when SRIs are combined with oral anticoagulants remains open to debate, mainly due to methodological problems [2, 3]. Since multi-source approaches are mandatory in pharmacoepidemiology [4], the present study used VigiBase®, the largest WHO pharmacovigilance database in the world, to investigate putative drug-drug interactions between antidepressants and antithrombotics in general with regards of bleeding.

We performed disproportionality analyses [5–7] with all "serious" reports (defined according to WHO) [8] with antithrombotics (B01, according to Anatomical Therapeutic Chemical (ATC) classification, registered between January 01, 2000 and December 31, 2022) as "suspected/interacting" in Vigibase® in adults (≥ 18 years) with age and sex known and reported by physicians. Antithrombotics were divided into Vitamin K Antagonists VKA (B01AA), direct factor Xa inhibitors (B01AF), direct thrombin inhibitors (B01AE), platelet aggregation inhibitors (PAIs) (B01AC), and heparins (B01AB). Cases were reports of bleeding (according to Standardized MedDRA Queries classification) with the drug(s) of interest and non-cases all other reports with the same drug(s) of interest. Antidepressants (N06) were divided into non-selective monoamine reuptake inhibitors (NSMRIs, N06AA) and SRIs (N06AB), thus excluding monoamine oxydase inhibitors (N06AF and N06AG). Data with antidepressants (and their different pharmacological classes as described above) + antithrombotics (and their different pharmacological classes) were compared with antithrombotics (and their different pharmacological classes) alone. Results are presented as reporting odds ratios (ROR) [6, 7].

Among the 2,396,829 reports registered in VigiBase®, according to the criteria defined above, 235,813 were bleeding. Table 1 shows the number of bleeding reports

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Table 1 Case non-case study of "serious" bleeding with the association antidepressants

	Cases	Non-cases	ROR	95% CI
Antidepressants + antithrombotics versus antithrombotics alone	1 463; 121,555	872; 80,605	1.11, 1.00	1.02–1.21
NSMRIs + antithrombotics versus antithrombotics alone	30; 121,555	230; 80,605	0.09, 1.00	0.06–0.13
SRIs + antithrombotics versus antithrombotics alone	1433; 121,155	642; 80,605	1.48, 1.00	1.35–1.63
SRIs + VKA versus VKA alone	627; 36,296	112, 8954	1.37, 1.00	1.12–1.68
SRIs + factor Xa inhibitors versus factor Xa inhibitors alone	193; 35,296	84; 21,294	1.39, 1.00	1.08–1.80
SRIs + thrombin inhibitors versus thrombin inhibitors alone	38; 11,864	10, 7324	2.35, 1.00	1.17–4.72
SRIs + DOACs versus DOACs alone	231, 47,160	94; 28,618	1.49, 1.00	1.17–1.89
SRIs + PAIs versus PAIs alone	624; 36,257	376; 30,187	1.38, 1.00	1.21–1.57
SRIs + heparins versus heparins alone	175, 12,380	97; 14,010	2.04, 1.00	1.59–2.62

Cases are reports of bleeding and non-cases all other reports registered in Vigibase®

NSMRIs non selective monoamine reuptake inhibitors, *SRIs* serotonin reuptake inhibitors + antithrombotics (and their different pharmacological classes: oral anticoagulants: *VKA* vitamin K antagonists, *DOACs* direct oral anticoagulants, *PAIs* platelet aggregation inhibitors, and heparins) versus antithrombotics alone (and their different pharmacological classes) registered in Vigibase® from January 01, 2000 to December 31, 2022 in adults. *ROR* reporting odds ratio, *95% CI* 95% confidence interval

with antithrombotics (and their different pharmacological classes) and their association with antidepressants (and their two different pharmacological classes). "Serious" bleeding with antidepressants + antithrombotics was mainly observed in patients aged more than 74 years: 67.5% for antidepressants + antithrombotics, 53.9% for antithrombotics alone. They caused/prolonged hospitalization in 66.2 and 81.2%, were fatal in 13.7 and 14.4%, respectively. A slight significant association was found for bleeding reports with the combination antidepressants + antithrombotics, driven by SRIs. The reporting risk was found with all antithrombotics, i.e., the 3 main clases of oral anticoagulants, as well as heparins and PAIs (Table 1).

The present study is, as far as we know, the first to investigate not only bleeding associated with SRIs alone [1] or with direct oral anticoagulants (DOACs) [2, 3] but also bleeding associated with antidepressants and antithrombotics in general. It confirms the excess risk for the association SRIs + DOACs (factor Xa inhibitors, thrombin inhibitors) and also extends this result to all antithrombotics. Interestingly, we found an increased reporting risk not only for VKA but also for heparins and PAIs, data not widely previously described in the literature. An association was only found for SRIs and not for NSMRIs, i.e., imipraminic antidepressants and related compounds. Once again, this result is new. The mechanism of this interaction is pharmacodynamic, i.e., addition of hemorrhagic effects of antithrombotics and SRIs, the latter being explained by the well-known role of serotonin and 5HT2A receptors on platelet aggregation [9].

Strengths and limits are well known; for example, the generalizability of VigiBase®, underreporting, and the fact that ROR evaluates the risk of bleeding reporting but not the true bleeding risk [5].

In conclusion, using an original and validated method, the present study allows generalizing the results of other previous studies: an excess of bleeding can be expected when SRIs (but not NSMRIs) are associated with antithrombotics (all antithrombotics and not only DOACs). Further studies using other pharmacoepidemiological methods are needed to confirm this pharmacovigilance signal.

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Data availability Data are available on request from the main author (JLM).

Declarations

Competing interests The authors declare no competing interests.

References

1. Laporte S, Chapelle C, Caillet P, Beyens MN, Bellet F, Delavenne X, Mismetti P, Bertoletti L (2017) Bleeding risk underrselective serotonin reuptake inhibitor (SSRI) antidepressants: a meta-analysis of observational studies. Pharmacol Res 118:19–32
2. Monteiro Machado C, Alves M, Caldeira D (2023) Impact of selective serotonin-reuptake inhibitors in hemorrhagic risk in anticoagulated patients taking non-vitamin K antagonist anticoagulants; a systematic review and meta-analysis. J Clin Psychopharmacol 43:267–267
3. Rahman AA, He N, Rej S, Platt RW, Renoux C (2023) Concomitant use of selective serotonin reuptake inhibitors and oral anticoagulants and risk of major bleeding: a systematic review and meta-analysis. Thromb Haemost 123:54–63
4. Montastruc JL, Benevent J, Montastruc F, Bagheri H, Despas F, Lapeyre-Mestre M, Sommet A (2019) What is pharmacoepidemiology? Definition, methods, interest and clinical applications. Therapie 74:169–174
5. Montastruc JL, Montastruc F, Bura-Riviere A (2023) Tramadol and the risk of bleeding complications in patients on oral anticoagulants: a pharmacovigilance study. Eur J Clin Pharmacol 79:701–702
6. Montastruc J-L, Sommet A, Bagheri H, Lapeyre-Mestre M (2011) Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol 22:905–908
7. Faillie J-L (2019) Case non-case studies: Principles, methods, bias and interpretation. Therapie 74:225–232
8. Edwards R, Aronson J (2000) Adverse drug reactions: Definitions, diagnosis, and management. Lancet 356:1255–1259
9. Nichols CD, Amara SG, Sibley DR (2023) 5-Hydroxytryptamine (serotonin) and dopamine. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th ed. New York McGraw-Hill, pp 285–304