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SYSTEMATIC REVIEW

Effect of the selective serotonin reuptake inhibitors over coagulation in patients with depressive disorders – a systematic review and retrospective analysis

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Abstract: *Several problems related to coagulation dysfunctions induced by selective serotonin reuptake inhibitors (SSRIs) were reported in literature, as serotonin is widely distributed in the human organism and it has significant contribution in various vascular and hematologic regulatory mechanisms. First, a systematic review has integrated main results from the field of SSRIs and anticoagulants pharmacologic interactions. Secondly, a retrospective analysis was performed, based on the medical charts of hospitalized patients diagnosed with SSRI-treated depressive disorders, who also received concomitant anticoagulant treatment with acenocoumarol. Platelet count, prothrombin time, activated partial thromboplastin time, and bleeding time were monitored during hospitalization and their values before and after SSRI initiation treatment were compared.*

Keywords: *major depressive disorder, antidepressants, anticoagulants, serotonin*

CURRENT STAGE OF RESEARCH IN THE FIELD OF SSRIs-ANTICOAGULANTS INTERACTIONS AND SSRIs-INDUCED COAGULATION DYSFUNCTIONS

Data in the literature regarding selective serotonin reuptake inhibitors (SSRI) treatment in patients diagnosed with depressive disorders and cardiovascular pathology for which they receive anticoagulants contain contradictions regarding the magnitude of antidepressants' effect over coagulation parameters.

Currently available informations suggest the existence of a decrease in platelets serotonin due to serotoninergic antidepressants action, and this phenomenon appears to be explained by a pharmacogenetic mechanism, through serotonin transporter promotor gene (5-HTTLPR) polymorphism [1, 2]. Also, it has been observed that serotoninergic antidepressants could mitigate the depression- and anxiety-related procoagulant action [3], while yet another studies reveal the lack of significant effect of sertraline over coagulation in patients after an acute myocardial infarction [4].

An independent analysis of clinical trials published in the main electronic databases (PubMed, Cochrane, Medscape, and EMBASE), using keywords "anti-depressant", "serotonin selective reuptake inhibitors", "major depressive disorder (MDD)", "coagulation", "anticoagulants", "paroxetine", "sertraline", "escitalopram", "citalopram", "fluoxetine", "fluvoxamine", "warfarine", and "acenocoumarol" was performed. Only articles published between 1996 and 2018 have been selected.

Specific inclusion and exclusion criteria had been formulated according to Table 1.

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Table 1. Selection criteria for literature research

Operationalized criteria	Inclusion criteria	Exclusion criteria
Population	Inferior age limit is 18, no superior limit had been established. Diagnoses of MDD, dysthymia, adjustment disorder with depressive features, bipolar depression, mixed depressive and anxious disorder. Diagnoses according to DSM, ICD criteria, or compatible with these classifications. Lack of substance related comorbidities.	Children and adolescents. Heterogenous populations, where statistical procedures didn't allow a separate conclusion for patients aged over 18. Other disorders than those with a significant depressive component
Intervention	Any agent from the SSRI class. Monitored anticoagulant treatment.	Other, non-SSRIs-antidepressants. SSRIs in combination with other antidepressants. Concomitant use of CYP450 iso-enzymes inductors or inhibitors. Supra-therapeutic doses of SSRI agents.
Environment	In-patient or out-patient. In vitro or in vivo analysis of coagulation variables.	Unspecified environment.
Primary and secondary variables	Any coagulation-related indicator, like platelet count, bleeding time, prothrombin time etc. Discontinuation of treatment due to severe adverse events from the hematological domain, like gastro-intestinal bleeding, hemorrhagic stroke etc.	Any trial without coagulation related parameters as primary variables was excluded
Design	Randomized clinical trials, open-label, single-blind or double-blind, placebo-controlled or not, prospective or retrospective trials, case control studies, case reports or case series.	Unspecified design. Lack of a specific method for coagulation monitoring
Language	English, French, German, Romanian	Other language except for those mentioned

A number of 9 trials corresponded to these criteria and were included in analysis. A synthetic overview of the selected studies is presented in Table 2.

Table 2. Synthetic indicators for selected trials

Overall number of subjects	Mean duration of interaction	Age at inclusion
n=391 43.4 SD=70.9 Minimum=1 Maximum=225	n=2 7.5 weeks SD=6.3 Minimum=3 Maximum=12	n=3 68 years old SD=19.9 Minimum=45 Maximum=80

Due to the fact that not all of the papers published contain complete data, synthetic indicators were calculated using only those studies which included specified variables, like the number of participants, mean duration of treatment or the patients' age at inclusion.

The most relevant research data are presented in Table 3.

SSRIs as a pharmacologic class induced lower serotonin levels in the patients' platelets [1] and had a significant effect over several indicators of coagulation [3].

Fluoxetine increased significantly the bleeding time, although not above the normal values [5]. Another trial showed no significant influence of fluoxetine over mean prothrombine time during warfarin treatment [6].

Escitalopram had no effect on coagulation according to one trial [5].

Fluvoxamine could induced an over-anticoagulation status during acenocoumarol maintenance treatment, unlike other SSRIs used as controls [7]. Fluvoxamine effect over coagulation is supported also by two cases treated with warfarine [8, 9].

Sertraline is relatively safe in patients after acute MI, as it induced no changes in bleeding time [4]. Sertraline could interfere with warfarine at circulating binding proteins and displaced the anticoagulant, increasing its free fraction [10].

In conclusion, escitalopram, sertraline and fluoxetine seem to be quite safe during anticoagulant treatment, while fluvoxamine has a tendency for inducing an over-anticoagulation status. Not enough data have been found to formulate a conclusion regarding paroxetine and citalopram, but these agents seem safer than fluvoxamine, in trials who compared various serotoninergic agents. SSRIs, as a pharmacological class, doesn't induce significant effects over

coagulation from a clinical point of view.

Table 3. Studies included in the systematic review

AUTHORS	DESIGN	RESULTS AND OBSERVATIONS
Reikvam AG, Hustad S, Reikvam H, et al., 2012 [1]	Case-control pilot study. In vitro measurements of platelet function. N=18. Blood donors using SSRIs vs. blood donors without treatment	Donors with SSRIs had significantly lower serotonin in their thrombocytes. Coagulation could be altered in patients using SSRIs based on lower serotonin platelet concentration.
Siddiqui R, Gawande S, Shende T, et al., 2011 [5]	Prospective, open-label, diagnosis of MDD. Bleeding time, clotting time, platelet count, prothrombin time, partial thromboplastin kaolin time – all were monitored for 12 weeks. N=40. Treatment with fluoxetine or escitalopram	At week 12 a significant increase in bleeding time was detected for fluoxetine, while escitalopram had no effect on coagulation variables. Fluoxetine is more powerful inhibitor of SERT than escitalopram. Fluoxetine increased significantly the bleeding time, but not beyond the normal values
Geiser F, Conrad R, Imbierowicz K, et al., 2011 [3]	Case-control study. Anxiety and comorbid depression. APTT, fibrinogen, factor VII, factor VIII, von Willebrand factor, von Willebrand ristocetin cofactor activity, prothrombin fragment 1 and 2, thrombin-antithrombin complex, d-dimer, alpha2-antiplasmin, PAP, tissue plasminogen activator and plasminogen activator inhibitor. N=62.	Fibrinogen, plasminogen activator inhibitor, PAP differentiated SSRIs treated patients from their matched controls. After controlling for smoke status and BMI, differences between groups were significant for PAP, von Willebrand ristocetin cofactor activity and APTT. Several coagulation indicators may be affected at significant levels ($p<0.05$) in anxious-depressive patients treated with SSRIs
Teichert M, Visser LE, Uitterlinden AG, et al., 2011 [7]	Prospective, populational-based cohort study. INR≥6 was the event monitored in patients treated with SSRIs during acenocumarol maintenance treatment. N=225 Age ≥ 45	The risk for over-anticoagulation during acenocoumarol maintenance treatment was increased in patients treated with fluvoxamine, but not with other SSRIs. Prothrombine time in users of acenocoumarol was increased by fluvoxamine above a critical value associated with bleeding risk. Number of exposed patients to other SSRIs except for fluvoxamine was low.
Limke KK, Shelton AR, Elliott ES, 2002 [8]	Case report. Warfarin+fluvoxamine 79 year old woman	Increased values of INR that persisted for 7 days. Fluvoxamine inhibits CYP1A2, 2C9, 2C19 and 3A4, while the metabolism of warfarine involves the same isoenzimes of CYP450.
Yap KB, Low ST, 1999 [9]	Case report. Warfarin + fluvoxamine. 80 year old woman	The interaction between fluvoxamine and warfarin could persist for up to 2 weeks after stopping the antidepressant
Shapiro PA, Lesperance F, Frasure-Smith N et al., 1999 [4]	Multicenter, open-label, pilot study. MDD patients identified 5 to 30 days after admission for acute MI. Serial bleeding time determinations. N=26	Bleeding time increased in 12 patients, decreased in 4 patients, was unchanged in 2 patients, 3 patients withdraw prematurely. No significant changes in coagulation measures. Sertraline seems to be relatively safe in patients after acute MI.
Ford MA, Anderson ML, Rindone JP, Jaskar DW, 1997 [6]	Open label. Stable dose of warfarin + fluoxetine. Prothrombine time was measured during the 22 days of the trial. N=6	No significant differences in mean prothrombine time before and during fluoxetine administration were detected. Fluoxetine at 20 mg/day doesn't influence the hypopro-thrombinemic response of warfarin.
Apseloff G, Wilner KD, Gerber N, Tremaine LM, 1997 [10]	Non-blinded, randomised, placebo-controlled. Healthy male volunteer. Warfarin+sertraline or placebo. N=12	Increased prothrombine time significantly during sertraline versus placebo ($p=0.02$). After 22 days a significant increase ($p=0.02$) in unbound warfarine was observed in sertraline vs. placebo group. Differences between groups were statistically, but not clinically significant. Sertraline has minimal effect on the CYP2C9/10 isoenzyme, while warfarin is principally mediated by this enzyme.

SERT = serotonin transporter, BMI = body mass index, APTT = activated partial thromboplastin time, PAP = plasmin-alpha2-antiplasmin complex, INR = International Normalised Ratio, MI = myocardial infarction

Nevertheless, pharmacokinetic interactions between SSRIs and anticoagulants are possible, at the plasma protein binding level and at the CYP450 isoenzymes level, therefore monitoring of the main coagulation parameters is recommended in patients who undergo serotoninergic antidepressant and anticoagulant treatment.

RETROSPECTIVE ANALYSIS IN PATIENTS USING SSRIs AND ANTICOAGULANTS

Patients diagnosed with depressive disorders admitted in the hospital who received an SSRI agent, and who also were diagnosed with various cardio-vascular or hematologic diseases for which they received anticoagulant treatment, were analysed from coagulation parameters perspective.

Objective

To detect if significant statistical and/or clinical variation of coagulation variables are detected during combined, SSRIs and anticoagulant treatment.

Methods

We analyzed retrospectively charts of all patients evaluated for depressive disorders during one year in our department (01 January 2017 – 31 December 2017), which had anti-coagulant treatment with acenocoumarol and also received treatment with escitalopram, citalopram, fluoxetine, paroxetine, fluvoxamine or sertraline. Platelet count, prothrombin time as reflected in the INR values, APTT, and bleeding time were analyzed in all cases which were monitored during hospitalization and their values before and after SSRI initiation treatment were compared.

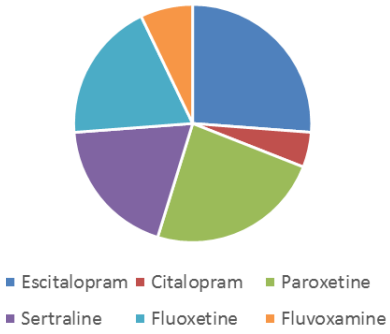
All included patients were over 18 years old, without previous treatment with an SSRI agent and were stabilized on acenocoumarol at time of the admission. Depressive disorders diagnoses were formulated according to ICD-10 criteria and included MDD, either first episode or recurrent, bipolar depression, dysthymia, adjustment disorder with depressive manifestations, mixed anxious-depressive disorder.

Patients diagnosed with comorbid substance related disorders were excluded from this analysis, and also those with mentioned history of non-adherence to their anticoagulation treatment.

Results

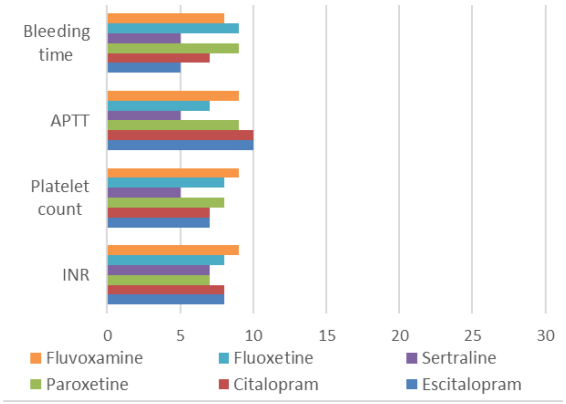
A number of 42 patients, mean age 56.6, 30 female and 12 male, diagnosed with MDD (n=23), mixed anxious-depressive disorder (n=10), bipolar depression (n=4), dysthymia and MDD (n=2) and adjustment disorder with depressive manifestations (n=3) were included in the statistical analysis. These patients had at least two determinations of INR and platelet count in their charts and most of them (62%) had at least 3 coagulation indicators recorded.

Figure 1: Treatment used during anticoagulation therapy



Patients received escitalopram (n=11), citalopram (n=2), paroxetine (n=10), sertraline (n=8), fluoxetine (n=8) or fluvoxamine (n=3).

Figure 2: SSRIs treatment influence over coagulation indicators (% of score variation)



No significant differences (at $p<0.05$) were detected in any coagulation indicator for SSRIs as a pharmacologic class, as reflected by t test for dependent samples, when platelet count ($p=0.166$), INR ($p=0.098$), APTT ($p=0.110$), and bleeding time ($p=0.102$) were analyzed pre-SSRIs administration and after at least 7 days (mean duration of SSRIs treatment before hospital discharge was 8.4 days). When translated in percentage of absolute values variation, all SSRIs changes ranged from 5 to 10% in all the monitored parameters.

ANOVA univariate test resulted in F values ranging between 1.67 and 1.28, lower than Fcrit, at $p<0.05$, and $\eta 2$ varied between 0.025 and 0.069, which signifies an influence of 2.5-6.9% of the SSRIs agent over INR, APTT, bleeding time, and platelet count variation during acenocoumarol treatment. A

post-hoc analysis showed a superior effect over bleeding time for fluvoxamine over escitalopram and sertraline (p=0.043 and 0.46), although the clinical impact of this difference wasn't relevant.

No significant adverse event in the hematologic area was recorded during hospitalization period and mixed (SSRI and anticoagulant) treatment.

Two cases (one treated with fluvoxamine 150 mg/day and one who received paroxetine 40 mg/day) registered values of INR above therapeutic value (5.2 and 6.1, respectively) after 8 days of treatment, and acenocumarol doses were adjusted.

CONCLUSIONS

SSRIs had a minor influence over main coagulation parameters (INR, APTT, platelet count, and bleeding time) during acenocoumarol treatment in patients with depressive disorder and comorbid cardio-vascular or hematologic diseases.

Fluvoxamine has been associated statistically with a lesser safe profile than escitalopram and sertraline, although differences in the clinical domain are not detectable.

Disclaimer

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Ethical considerations

All the analyzed medical charts included patients' informed consent for processing of their personal data for research and educational purposes.

List of abbreviations

5-HTTLPR= Serotonin-transporter-linked polymorphic region
APTT= Activated partial thromboplastin time
APTT= activated partial thromboplastin time,
BMI= body mass index
DSM= Diagnostic and Statistical Manual of mental Disorders
ICD= International Classification of Diseases
INR= International normalized ratio
MDD= major depressive disorder
MI= myocardial infarction
PAP= plasmin-alpha2-antiplasmin complex
SERT= serotonin transporter
SSRI= Selective serotonin reuptake inhibitor

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