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## Selective serotonin reuptake inhibitors and risk for gastrointestinal bleeding

### Key words:

selective serotonin reuptake inhibitors,  
gastrointestinal bleeding

### Abstract

The most of the known effects of selective serotonin reuptake inhibitors, beneficial or harmful, are associated with the inhibitory action of the serotonin reuptake transporter. This mechanism is present not only in neurons, but also in other cells such as platelets. Serotonergic mechanism seems to have an important role in hemostasis, which has long been underestimated. Abnormal activation may lead to a prothrombotic state in patients treated with selective serotonin reuptake inhibitors. On one hand there may be an increased risk of bleeding, and on the other hand reduction in thrombotic risk may be possible. Serotonin is critical to maintain a platelet haemostatic function, such as platelet aggregation. Evidences from the studies support the hypothesis that antidepressants with a relevant blockade of action of serotonin reuptake mechanism may increase the risk of bleeding, which can occur anywhere in the body. Epidemiological evidences are, however, the most robust for upper gastrointestinal bleeding. It is estimated that this bleeding can occur in 1 in 100 to 1 in 1.000 patient-years of exposure to the high-affinity selective serotonin reuptake inhibitors, with very old patients at the highest risk. The increased risk may be of particular relevance when selective serotonin reuptake inhibitors are taken simultaneously with nonsteroidal anti-inflammatory drugs, low dose of aspirin or warfarin.

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## Introduction

Selective serotonin reuptake inhibitors (SSRIs) are effective drugs partly due to their ability to block the proteins responsible for the transport of serotonin back into the presynaptic neuron. Most of the known effects of SSRIs, beneficial or harmful, are associated with the inhibitory action of the serotonin transporter (5-HTT). This mechanism is present not only in neurons, but also in other cells such as platelets. The serotonergic mechanism appears to play an important role in hemostasis, which has long been neglected. Abnormal activation may lead to a prothrombotic state in patients treated with SSRIs. On the one hand there may be an increased risk of bleeding, and on the other hand reduction in thrombotic risk is possible.

Serotonin is critical for maintenance of platelet haemostatic functions such as platelet aggregation. Evidences from the studies support the hypothesis that antidepressants with a relevant blockade of action mechanism of serotonin reuptake increase the risk of bleeding, which can occur anywhere in the body. The epidemiological evidences are, however, more robust for upper gastrointestinal bleeding. It has been estimated that upper gastrointestinal bleeding occurs at 1 in 100 to 1 in 1,000 patient-years of exposure to high-affinity drugs (the SSRIs), with the very old patients being at the highest risk. The increased risk may be of particular relevance when the SSRIs are associated with nonsteroidal anti-inflammatory drugs (NSAIDs), as well as low-dose aspirin<sup>1</sup>.

Bleeding from the upper gastrointestinal tract, caused by the SSRIs may appear through the SSRI induced inhibition of serotonin reuptake from platelets, leading to platelet serotonin depletion after several weeks of treatment. Impaired platelet aggregation can lead to gastrointestinal bleeding. The first epidemiological study was published in 1999 and since then 35 epidemiological studies from different areas (most of them included elderly patients in their study population), have been published with a variety of results. Most epidemiological evidences support a moderately increased risk of bleeding associated with the use of SSRIs which may depend on the patient's susceptibility and the presence of risk factors. Damage of primary hemostasis induced with SSRI may result in benefits that are manifested in the reduction of thrombotic risk. As the risk of gastrointestinal bleeding from the upper part increases with age, a useful approach for patients with a previous history of upper gastrointestinal bleeding or peptic ulcer disease, and those who are taking NSAIDs, oral anticoagulants, antithrombotic therapy and corticosteroids, is addition of drugs that suppress hydrochloric acid, especially in elderly patients<sup>2</sup>.

Bleeding disorders that occur in patients treated with SSRIs are a consequence of the reduction of serotonin in platelets, which results in impaired haemostatic function and consequently prolonged bleeding time. Specifically, serotonin

is required for the primary activation of platelets and plays a role in their aggregation. SSRIs may precipitate bleeding in patients with haemostatic defects, in postoperative patients, or those who are receiving concomitant medication associated with risk of bleeding. Evidences from the studies suggest that concomitant use of SSRIs with anticoagulants, such as low doses of heparin, increase the risk of bleeding. NSAIDs and/or aspirin, older age, history of previous bleeding were identified as the risk factors for upper gastrointestinal bleeding in the current observational studies. For this reason, primarily SSRIs may increase the risk of bleeding in patients with present increased risk of bleeding<sup>3</sup>.

In relation to the binding affinity, SSRIs can be divided into three groups: a) SSRIs with high affinity (fluoxetine, sertraline, paroxetine); b) SSRIs with intermediate affinity (venlafaxine, fluvoxamine); c) SSRIs with low affinity (mirtazapine, bupropion). Drugs with the highest degree of serotonin reuptake inhibition (fluoxetine, paroxetine and sertraline) are commonly associated with abnormal bleeding and modification of haemostatic markers. The most common abnormalities are reduction in platelet aggregability and activity, and prolongation of bleeding time. SSRIs with high affinity bear higher risk of hospitalization due to abnormal bleeding (OR=2.6 compared to the low affinity SSRIs), then SSRIs with intermediate affinity (OR=1.9 compared to the low affinity SSRIs). Patients with a history of coagulation disorders (documented thrombocytopenia or platelet disorder) need monitoring in the case of prescribing any SSRI<sup>3</sup>. Another important difference in the pharmacokinetics stems from the different abilities of individual SSRIs to inhibit CYP450 enzyme, so that physicians who prescribe SSRIs should be aware of the possible interactions, which is particularly applicable to drugs with a small therapeutic range.

There are no published randomized controlled clinical trials that evaluate correlation of bleeding from the upper gastrointestinal tract with the use of SSRIs. Sample and ethical issues of such studies would be disabling. Biological credibility supports the association between SSRIs and bleeding.

Consequently, bleeding from the upper part of the digestive system in people taking SSRIs was assessed primarily through observational studies and systematic reviews.

A recent Taiwan's cohort study quantified the risk of upper gastrointestinal bleeding induced by use of antidepressants with different affinities for serotonin transporters in psychiatric patients. This study used Taiwan's nationwide health insurance claims database and identified 304.606 psychiatric patients who initiated antidepressant treatment during the 2005-2006 period. Antidepressants are classified as high, intermediate and low affinity for serotonin reuptake inhibitors. The trend for elevated risk of upper gastrointestinal bleeding with increasing affinity of serotonin transporters was statistically significant ( $p < 0.01$ ). Elderly patients and those with previous bleeding from the upper gastrointestinal

tract were more susceptible to adverse effects. This suggests that the use of high-affinity SSRIs may increase the risk of bleeding from the upper gastrointestinal tract in psychiatric patients<sup>4</sup>. A systematic review of 34 studies about the association of antidepressants with the risk of bleeding concluded that antidepressants with high serotonin affinity can slightly increase the risk of upper gastrointestinal bleeding. The authors concluded that antidepressants are relatively safe as far as bleeding is concerned. Precautions can be taken in the case of high risk patients<sup>5</sup>.

A recently published study about the short-term use of SSRIs and the risk of upper gastrointestinal bleeding, which enrolled 5,377 hospitalized psychiatric patients who were on short-term SSRI treatment to 28 days, showed that short-term use of SSRIs was associated with a risk of upper gastrointestinal bleeding in male, but not in female patients. The adjusted odds ratio (OR) for the risk of upper gastrointestinal bleeding after SSRI exposure was 1.67 (95% CI=1.23–2.26) for the 7-day use, 1.84 (95% CI=1.42–2.40) for the 14-day use, and 1.67 (95% CI=1.34–2.08) for the 28-day use. SSRIs with high and intermediate affinity, but not with low affinity for serotonin transporter, were associated with upper gastrointestinal bleeding<sup>6</sup>.

## Interactions of SSRI and NSAIDs

The use of NSAIDs in patients who are taking SSRIs further increases the risk of bleeding from the upper gastrointestinal tract. Arbitrary use of NSAIDs is common in elderly patients, especially those with osteoarthritis. SSRIs probably contribute substantially to the risk of upper gastrointestinal bleeding in general population due to the large number of NSAIDs users.

According to the Scottish national clinical guideline for the management of acute upper and lower gastrointestinal bleeding, SSRIs should be used with caution in patients with increased risk of gastrointestinal bleeding, especially in those taking NSAIDs or aspirin. Non-selective SSRIs (venlafaxine, nefazodone, trazodone) could be an appropriate choice for this patients<sup>7</sup>.

Meta-analysis (Loke et al.), which examined gastrointestinal bleeding due to interaction between SSRIs and NSAIDs, included a total of 153,000 patients from one cohort study and three case control studies. This meta-analysis was obtained by searching the PubMed database, cited references, the Canadian database on side effects, systems for reporting side effects of the U.S. Food and Drug Administration FDA, the Web sites of trials registries for data on SSRIs and database research involving controlled information. Meta-analysis showed an odds ratio of 2.36 (95% CI: 1.44–3.85,  $p=0.0006$ ) for SSRI associated upper gastrointestinal bleeding. The odds ratio increased to 6.33 (95% CI: 3.40–11.8;  $p<0.00001$ ) with concomitant use of NSAIDs. In patients

aged above 50 years the risk of upper gastrointestinal bleeding occurred after a median of 25 weeks with SSRIs. Approximately 67% of these patients were on NSAIDs at the same time. A meta-analysis concluded that SSRIs use, alone or in combination with NSAIDs, substantially increases the risk of upper gastrointestinal bleeding. SSRIs more than double increase the risk of upper gastrointestinal bleeding, and concurrent use of NSAIDs increases the risk for more than 500%<sup>8</sup>.

On the other hand, analysis of the Canadian population based case-control studies concluded that the use of SSRIs is associated with a modest increase in the risk of upper gastrointestinal bleeding (OR, 1.43; 95% CI, 1.09–1.89). The addition of an SSRI to NSAID therapy did not significantly increase the risk of upper gastrointestinal bleeding (OR, 1.20; 95% CI, 0.78–1.92) over use of an NSAID alone. Addition of proton pump inhibitors significantly reduced the risk of SSRI induced bleeding from the upper gastrointestinal tract (OR, 0.39; 95% CI, 0.16–0.94). The authors concluded that the use of SSRIs is associated with a moderate increase in the risk of bleeding from the upper gastrointestinal tract, which can be significantly reduced with proton pump inhibitors. SSRIs use was not a major risk factor for upper gastrointestinal bleeding when they were used together with NSAID<sup>9</sup>.

A systematic review (Mort et al.), which included data from four retrospective studies about gastrointestinal side effects of the combination of SSRIs and NSAIDs found in MEDLINE between the 1996 and 2005, concluded that the risk ratio for an upper gastrointestinal bleeding from this drug combination ranged from 3.3–15.6, and the risk ratio for gastrointestinal adverse effects was 12.4. The authors concluded that the competitive use of SSRI and NSAID increases the risk of gastrointestinal bleeding. Clinicians must take care to avoid these negative outcomes by altering NSAID or SSRI therapy, or by providing ulcer-protective drugs<sup>10</sup>. NSAID such as piroxicam has a higher risk than ibuprofen<sup>11</sup>.

Canadian systematic review of studies on the population level concluded that the available evidences from epidemiological studies indicate that the concurrent use of NSAIDs or aspirin with SSRIs greatly increase the risk of upper gastrointestinal bleeding. The preventive strategies should be considered in SSRI users at high risk, especially the elderly, or those with a history of upper gastrointestinal bleeding and using NSAIDs or aspirin<sup>12</sup>.

Results of the study about significance of the interactions of drugs as a cause of adverse events, "Systematic review of pharmacological treatment with SSRI in France" showed that SSRI with the most frequent adverse reactions due to drug interactions was escitalopram, followed by fluoxetine and citalopram. Among these, 52.9% were "serious" adverse reactions, mainly bleeding, confusion and falls, hyponatremia, and serotonergic syndrome. The most frequent drug interactions occurred with psychotropic drugs (antipsychotics, benzodiazepines), followed by antithrombotic drugs

(vitamin K antagonists, antithrombotics), diuretics, and angiotensin receptor blockers. Authors concluded that around 40% of adverse drug reactions were related to drug interactions, especially in elderly<sup>13</sup>.

However, existing studies about interaction of SSRIs and NSAIDs did not explore the risk of upper gastrointestinal bleeding in correlation to specific individual agents, so there is no data to evaluate the potential difference between the specific combinations of drugs among more than a hundred possible. This requires a focus on the most frequently used combination of SSRIs and NSAIDs. Several therapeutic approaches could be considered, including the replacement of NSAIDs with acetaminophen if possible. In the case that NSAIDs are required, it is necessary to include COX-2 selective inhibitors that do not affect platelet function, and which reduce the risk of gastric irritation. Consider replacement SSRI with antidepressants that do not affect serotonin reuptake (tricyclic antidepressants, mianserin) or with low affinity SSRIs. For patients in whom this alternative therapy is not possible, addition of proton pump inhibitors will provide protection from irritation of the gastrointestinal tract caused by a combination of SSRIs and NSAIDs.

## Interactions of SSRI and antithrombotic drugs

Analysis of the French Spontaneous Reporting Database for a controversial adverse drug reactions of gastrointestinal bleeding, such as adverse drug reactions in patients with concomitant using of antithrombotic drugs and SSRI, concluded that total of 1,977 adverse reactions with antithrombotic drugs and antithrombotic drugs plus SSRI were collected in the period over three years in patients aged above 50 years, of which 1,331 (67.3%) concerned bleeding. Multivariate logistic regression analysis did not demonstrate a significant association between bleeding and exposure to a combination of SSRIs and antiplatelet therapy versus antiplatelets alone [adjusted ROR=0.8 (0.5-1.2)]. Considering other conflicting results, this risk should be kept in mind when treating patients with several risk factors<sup>14</sup>.

## Interactions of SSRI and anticoagulants

Bleeding is the most common and the most worrisome adverse effect of warfarin therapy, and one of the causes, among others, could be interactions with drugs that potentiate the effect of warfarin. A study about interaction of antidepressants and warfarin in correlation with the risk of bleeding (Shellman et al.) was an observational case-control study, which included data for a period 1999-2005. This study concluded that patients taking warfarin had 1.5 times increased risk of serious gastrointestinal bleeding after initiation of citalopram (OR=1.73 [95% CI, 1.25-2.38]), fluoxetine (OR=1.63

[95% CI, 1.11-2.38]) and paroxetine (OR=1.64 [95% CI, 1.27-2.12]). Also mirtazapine, which was not believed to interact with warfarin, increased the risk of gastrointestinal bleeding (OR=1.75 [95% CI, 1.30-2.35]). As it was expected, the risk of gastrointestinal bleeding in warfarin users generally declined after the first period of antidepressant prescription<sup>15</sup>.

## Conclusion

The association between serotonin reuptake inhibitors and the risk of upper gastrointestinal bleeding remains controversial. The use of selective serotonin reuptake inhibitors is associated with a twofold increase of incidence for upper gastrointestinal bleeding, hospitalization due to bleeding and perioperative transfusions. SSRIs with greater degree of serotonin reuptake inhibition have higher risk for bleeding. Concomitant use of nonsteroidal anti-inflammatory drugs or aspirin/warfarin further increases the risk of upper gastrointestinal bleeding. Serotonin reuptake inhibitors with low degree of inhibition, such as mirtazapine, and bupropion can be associated with a lower risk of bleeding, although the evidence is insufficient for a definitive conclusion.

Overview of cohort and case-control studies provides weak evidence that serotonin reuptake inhibitors can be associated with an increased risk of upper gastrointestinal bleeding, particularly in high risk patients or those who are receiving concomitant nonsteroidal anti-inflammatory drugs or aspirin. The relative risk is low for other antidepressants. Further investigations of these antidepressants are needed in order to examine whether these antidepressants are appropriate for patients with a high risk of abnormal bleeding. Non-selective serotonin reuptake inhibitors (venlafaxine, nefazodone, trazodone) can be an appropriate choice for these patients. In patients for whom this alternative therapy is not possible, proton pump inhibitors will provide protection against irritation of gastrointestinal mucosa.

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## Инхибитори поновног преузимања серотонина и ризик од гастроинтестиналног крварења

### Кључне речи:

инхибитори поновног преузимања серотонина,  
гастроинтестинално крварење

### Сажетак

Већина познатих ефеката инхибитора поновног преузимања серотонина, корисних или штетних, повезана је са инхибиторним дејством на транспортер поновног преузимања серотонина. Овај механизам је присутан не само у неуронима, већ и у другим ћелијама, као што су тромбоцити. Изгледа да серотонинергички механизам има важну улогу у хемостази, што је дуго времена запостављано. Абнормална активација може да доведе до протромботског стања пацијената лечених инхибиторима поновног преузимања серотонина. С једне стране, може постојати повећан ризик за крварење а, с друге стране, могућа је редукација ризика од тромбозе. Серотонин је критичан за одржавање тромбоцитне хемостатске функције, као што је агрегација тромбоцита. Докази из студија подржавају хипотезу да антидепресиви са релевантном блокадом дејства механизма поновног преузимања серотонина повећавају ризик од крварења, што може настати било где у организму. Епидемиолошки докази су, међутим, најубедљивији за крварење из горњег дела гастроинтестиналног тракта. Процењује се да ово крварење може наступити од 1 у 100 до 1 у 1.000 пацијент-година изложености високо афинитетним инхибиторима поновног преузимања серотонина, при чему су највећем ризику изложени веома стари пацијенти. Повишен ризик може да буде посебно важан када се инхибитори поновног преузимања серотонина узимају истовремено са нестероидним антиинфламаторним лековима, малим дозама аспирина или варфарина.

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