ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (2): 159-168
0114-5916/08/0002-0159/$48.00/0

Risk of Upper Gastrointestinal Bleeding and the Degree of Serotonin Reuptake Inhibition by Antidepressants

A Case-Control Study

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Abstract

Background and objective: Selective serotonin reuptake inhibitor (SSRI) antidepressants can inhibit uptake of serotonin by platelets, and their use may predispose patients to bleeding. Case reports and observational studies from databases have suggested an association between the use of SSRIs and gastrointestinal bleeding. Their risk appears to be increased if they are concurrently used with aspirin (acetylsalicylic acid) or with other NSAIDs. With the aim of establishing the risk of major upper gastrointestinal bleeding associated with various groups of drugs, we performed a multicentre case-control study. We present the results related to the use of antidepressants by the degree of serotonin reuptake inhibition they induce, the selectivity at monoamine transporters and the dose.

Methods: A population-based multicentre case-control study in 18 hospitals in Spain and in Italy, including 2813 incident cases of upper gastrointestinal bleeding and 7193 matched controls. Regression analyses are based on 2783 cases and 7058 controls because of missing variable data. Odds ratios (ORs) of upper gastrointestinal bleeding for antidepressant drugs grouped by affinity for the serotonin transporter, selectivity and dose, with adjustment for potential confounders were estimated.

Results: Overall, 84 (3.0%) cases and 160 (2.2%) controls had used a high-affinity serotonin reuptake inhibitor (SRI) antidepressant. Their use in the 7 days prior to the index day was not associated with a substantially increased risk of upper gastrointestinal bleeding (OR = 1.24; 95% CI 0.88, 1.76). Forty-one (1.5%) cases and 26 (0.4%) controls had concurrently used a high-affinity SRI antide-

pressant and an NSAID. The OR of upper gastrointestinal bleeding among these concurrent users (8.32; 95% CI 4.69, 14.76) did not differ from that in users of NSAIDs only (7.82; 95% CI 6.79, 9.00). No significant association was found between the use of SSRIs and the risk of upper gastrointestinal bleeding, neither with the degree of affinity for the serotonin transporter, by the selectivity of each individual agent (101 cases [3.6%] vs 192 controls [2.7%]; OR = 1.23; 95% CI 0.90, 1.68), nor by dose.

Conclusions: The risk of upper gastrointestinal bleeding is not increased by the use of SRIs. An interaction with coadministered NSAIDs was not observed. If there is a risk associated to these drugs, it seems to be low and not an important cause of hospital admission due to upper gastrointestinal bleeding. However, additional studies may be warranted in subgroup populations at potentially increased risk of bleeding, such as older adults and men.

Background

Peripheral serotonin is important in platelet aggregation and in the modulation of vascular tone. Antidepressants that act as selective serotonin reuptake inhibitors (SSRIs) block platelet uptake of serotonin, and the use of these agents may conceivably result in bleeding and vasospastic complications.[1] However, serotonin plays a minor part in the haemostatic process since it is a comparatively weak agonist for platelet aggregation.[2]

Several case reports and observational studies have suggested an association between the use of SSRIs and bleeding disorders.[3-10] Up until June 2006, seven epidemiological studies have provided data on the association between the use of SSRIs and upper gastrointestinal bleeding.[7-13] Four of these studies[7,9-11] have yielded estimates of the association, ranging from an odds ratio (OR) of 2.4 (95% CI 2.1, 2.7)[11] to a relative risk (RR) of 3.6 (95% CI 2.7, 4.7),[10] although the other studies were negative.[8,12,13] An interaction with NSAIDs leading to an increased risk beyond a simple additive effect has also been suggested.[7,10,14]

With the aim of establishing the risk of major upper gastrointestinal bleeding associated with various groups of drugs, we performed a multicentre, population-based, case-control study in Spain and in Italy.[15] In this study, we present the results related to the use of antidepressants by the degree of serotonin reuptake inhibition they induce, the selectivity at monoamine transporters and the dose.

Methods

Patients were recruited from September 1998 through December 2001 from ten hospitals in Spain, and from November 1999 through December 2001 from eight hospitals in Italy. Details on the methods and the process for patients' ascertainment and on primary and secondary exclusions can be found at http://www.icf.uab.es/SSRIs. The methods have also been described in detail in a previous publication.[15]

Records of all endoscopic procedures and lists of admission diagnoses in the participating hospitals were examined daily. Cases were patients aged >18 years who were admitted with a primary diagnosis of acute upper gastrointestinal bleeding from a duodenal or gastric ulcer, acute lesions of the gastric mucosa, erosive duodenitis or mixed lesions. Patients with endoscopic diagnoses other than bleeding from the specified lesions, those receiving anticoagulant drugs and those who were non-residents in the study area were excluded from the study.

Controls were patients who were admitted with non-alcohol-related trauma, for elective surgery for non-painful disorders or for acute clinical conditions thought to be unrelated to the intake of the drugs of main interest. To take into account the relationship between trauma and the use of drugs, patients who

experienced loss of consciousness before their trauma were excluded. For each case, up to three hospital controls were selected, matched according to centre, date of admission (within 2 months), sex and age (± 5 years). The same exclusion criteria as used for the cases were applied.

After obtaining informed consent, specially trained monitors interviewed patients with a structured questionnaire within 14 days of admission. The interview included detailed information on symptoms leading to the present admission, clinical and medication history.

Exposures to serotonin reuptake inhibitor (SRI) antidepressants, other drugs and alcohol were defined as any use in the 7 days before the index day. For each case, the index day (the day on which upper gastrointestinal bleeding started) was defined blindly to the use of drugs. For the controls, it was the day on which the accident occurred, the day of admission or when symptoms appeared.

Two classifications of antidepressant drugs were used to estimate the association with upper gastrointestinal bleeding. First, antidepressants were classified into three groups according to their affinity for the serotonin transporter,[9,16] e.g. high affinity (fluoxetine, paroxetine, sertraline and clomipramine), intermediate affinity (amitriptyline, fluvoxamine, citalopram, imipramine, dosulepin and venlafaxine) and low affinity (mirtazapine, nortriptyline, desipramine, trimipramine, maprotiline, trazodone, mianserin, amoxapine, bupropion, desipramine, doxepin, moclobemide and nefazodone). In a second analysis, a classification based on selectivity was used, which was based on the ratio of the equilibrium dissociation constants for the serotonin over the noradrenaline (norepinephrine) transporter.[7] Exposures to venlafaxine or mirtazapine were excluded in this analysis.

ORs and their 95% confidence intervals were estimated by means of a conditional logistic model. Individual drug terms were included in the primary analysis provided there was a minimum of five cases and five controls exposed to the particular drug. The reference category for each drug was made up of non-exposed cases and controls to this individual drug. In addition to each antidepressant group, the following variables were included in the conditional model: history of peptic ulcer, dyspepsia, upper gastrointestinal bleeding, diabetes mellitus, smoking habit, alcohol consumption and use of antacids, proton-pump inhibitors, sucralfate, nitrates, systemic NSAIDs, topical NSAIDs, analgesics, antiplatelet drugs, dihydropyridine calcium antagonists and HMG Co-A reductase inhibitors (statins) in the week before upper gastrointestinal bleeding symptoms started.

To estimate the effect of the dose, two dose categories were defined (low and high doses), based on the range of doses taken, those generally recommended and the number of exposed patients in each category.

The protocol was approved by the Ethics Committees of the participating hospitals.

Results

After a follow-up of 10 734 897 person-years, 4309 cases of upper gastrointestinal bleeding were identified. After secondary exclusions, 2813 cases and 7193 controls were included in the study. Table I shows the disease distribution of the control group. No differences between cases and controls were seen in educational level, median time between hospital admission and interview, illiteracy, interview refusal or unreliability of the interview (details can be found at http://www.icf.uab.es/SSRIs). Due to

Table I. Diagnostic categories in control patients

Diagnostic	Controls [n (%)]
Trauma	2729 (37.9)
trauma	2634 (36.6)
wounds	95 (1.3)
Elective surgery	3503 (48.7)
inguinal hernia	1824 (25.4)
prostatic adenoma	916 (12.7)
cataracts	613 (8.5)
other	150 (2.1)
Acute clinical conditions	961 (13.4)
appendicitis	763 (10.6)
pneumonia	190 (2.6)
foreign body	8 (0.1)
All	7193 (100)

Table II. Risk of upper gastrointestinal bleeding associated with antidepressants depending on affinity for the serotonin transporter[a]

Group	Cases (n = 2813) [n (%)]	Controls (n = 7193) [n (%)]	Adjusted OR (95% CI)
Non-users	2679 (95.2)	6917 (96.2)	Reference
Users			
high-affinity SRIs	84 (3.0)	160 (2.2)	1.24 (0.88, 1.76)
intermediate-affinity SRIs	43 (1.5)	92 (1.3)	0.97 (0.61, 1.54)
low-affinity SRIs	13 (0.5)	38 (0.5)	0.69 (0.32, 1.50)
All[b]	134 (4.8)	276 (3.8)	1.05 (0.80, 1.38)

a SRI affinity categories according to Tatsumi et al.[16]

b Six cases and 14 controls were taking two SRI antidepressants concurrently.

OR = odds ratio; **SRI** = serotonin reuptake inhibitor.

missing values in the variables included in the regression analyses, the results are based on 2783 cases and 7058 controls.

Overall, 134 (4.8%) cases and 276 (3.8%) controls had used an antidepressant in the week before the index day, resulting in an adjusted OR of 1.05 (95% CI 0.80, 1.38). Eighty-four (3.0%) cases and 160 (2.2%) controls had used a high-affinity SRI (1.24; 95% CI 0.88, 1.76) [table II]. In the second analysis, based on selectivity, 101 (3.6%) cases and 192 (2.7%) controls had used an SSRI antidepressant in the week before the index day (OR = 1.23; 95% CI 0.90, 1.68) [table III].

The median duration of use of any antidepressant drug was over 3 months for all drugs, both among the cases and the controls. For high-affinity SRIs, the median dose was similar to the recommended dose, both in the cases and in the controls. However, the doses of the other antidepressants were lower than recommended, both among cases and the controls. Table IV shows the main characteristics of high-affinity SRI use.

The analysis of SSRIs by age and sex gave a slightly increased risk for high-affinity SSRIs in males and with older age when compared with other subgroups; OR 1.49 (95% CI 0.88, 2.59) for males versus 1.11 (95% CI 0.70, 1.76) for females, and 1.57 (95% CI 0.97, 2.56) for patients aged >70 years versus 1.04 (95% CI 0.63, 1.73) for patients aged <70 years.

When patients with a history of gastrointestinal bleeding or peptic ulcers were excluded from the analysis, the OR for high-affinity SRIs was 1.38 (95% CI 0.96, 1.99) based on 1792 cases (56 exposed) and 6202 controls (131 exposed). If, in addition to these patients, those with a previous history of cardiovascular complications (diabetes, heart failure, angina pectoris, myocardial infarction, stroke or peripheral arteriopathy) were excluded then the OR was 1.21 (95% CI 0.76, 1.92), estimated with 1320 cases (32 exposed) and 4910 controls (97 exposed).

The use of high-affinity SRIs among the various diagnoses of the control group were as follows: 3.1% among patients admitted for trauma, 1.9% among those with acute medical conditions and

Table III. Risk of gastrointestinal bleeding associated with antidepressants on basis of selectivity of drug

Group	Cases (n = 2808) [n (%)]	Controls (n = 7180) [n (%)]	Adjusted OR (95% CI)
Non-users	2679 (95.2)	6917 (96.2)	Reference
Users			
SSRIs[a]	101 (3.6)	192 (2.7)	1.23 (0.90, 1.68)
non-SSRIs[b]	22 (0.8)	55 (0.8)	0.83 (0.45, 1.55)
other[c]	11 (0.4)	26 (0.4)	0.79 (0.33, 1.89)

a Fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, trazodone, clomipramine.

b Amitriptyline, dosulepin, imipramine, doxepine.

c Nortriptilyne, desipramine, trimipramine, maprotiline, amoxapine, mianserine.

OR = odds ratio; **SSRIs** = selective serotonin reuptake inhibitors.

Table IV. Frequency, dose and duration of use of high-affinity serotonin reuptake inhibitor antidepressants

Characteristic	Cases (n = 2813)	Controls			
		all (n = 7193)	emergency conditions (n = 961)	trauma (n = 2729)	elective surgery (n = 3503)
Antidepressant used [n (%)]					
clomipramine	14 (0.5)	18 (0.3)	4 (0.4)	7 (0.3)	7 (0.2)
fluoxetine	20 (0.7)	53 (0.7)	6 (0.6)	30 (1.1)	17 (0.5)
paroxetine	37 (1.3)	70 (1.0)	6 (0.6)	38 (1.4)	26 (0.7)
sertraline	13 (0.5)	20 (0.3)	2 (0.2)	10 (0.4)	8 (0.2)
Dosage in mg/day [median (IQR)]					
clomipramine	22.5 (30.6)	25.0 (20.6)	17.5 (28.1)	25.0 (10.0)	25.0 (50.0)
fluoxetine	20.0 (20.0)	20.0 (0)	20.0 (0)	20.0 (0)	20.0 (0)
paroxetine	20.0 (0)	20.0 (0)	20.0 (15.0)	20.0 (0)	20.0 (0)
sertraline	50.0 (25.0)	50.0 (0)	50.0 (0)	50.0 (0)	50.0 (37.5)
Duration of use in days [median (IQR)]					
clomipramine	1467.5 (2161.8)	1109.0 (3749.8)	923.5 (4276.3)	3629.0 (4319.0)	239.0 (1710.0)
fluoxetine	183.0 (670.5)	269.0 (660.0)	298.0 (284.5)	239.0 (666.8)	389.0 (733.5)
paroxetine	385.0 (632.5)	389.0 (680.3)	393.5 (1268.3)	374.0 (680.3)	389.0 (698.3)
sertraline	388.0 (525.5)	193.5 (429.0)	102.5 (–)	224.0 (367.5)	179.0 (613.0)
overall	387.0 (901.0)	359.0 (660.0)	387.5 (752.8)	269.0 (660.0)	389.0 (689.5)

IQR = interquartile range; – indicates not calculable.

Table V. Risk of upper gastrointestinal bleeding in relation to recent single use of antidepressants

Serotonin reuptake inhibitor[a]	Cases (n = 2813) [n (%)]	Controls[b] (n = 7193) [n (%)]	Adjusted OR (95% CI)
High-affinity			
clomipramine	14 (0.5)	18 (0.3)	1.42 (0.56, 3.55)
fluoxetine	20 (0.7)	53 (0.7)	1.02 (0.54, 1.93)
paroxetine	37 (1.3)	70 (1.0)	1.23 (0.72, 2.08)
sertraline	13 (0.5)	20 (0.3)	1.75 (0.69, 4.41)
Intermediate-affinity			
amitriptyline	19 (0.7)	47 (0.7)	0.83 (0.43, 1.63)
citalopram	12 (0.4)	19 (0.3)	1.13 (0.47, 2.71)
dosulepin	0 (0.0)	1 (0.0)	–
fluvoxamine	3 (0.1)	6 (0.1)	–
imipramine	3 (0.1)	7 (0.1)	–
venlafaxine	6 (0.2)	13 (0.2)	0.82 (0.22, 3.10)
Low-affinity			
desipramine	0 (0.0)	1 (0.0)	–
maprotiline	4 (0.1)	2 (0.0)	–
mianserine	5 (0.2)	17 (0.2)	0.53 (0.16, 1.74)
mirtazapine	0 (0.0)	2 (0.0)	–
nortriptyline	1 (0.0)	5 (0.1)	–
trazodone	2 (0.1)	10 (0.1)	–
trimipramine	1 (0.0)	1 (0.0)	–

a Affinity categories according to Tatsumi et al.[16]

b One control was exposed to both clomipramine and fluoxetine (high-affinity analysis) and a second was exposed to both amitriptyline and venlafaxine (intermediate-affinity analysis).

OR = odds ratio; **–** indicates not estimated.

1.6% among those admitted for elective surgery. The results of the analysis to estimate the association of high-affinity SRIs and upper gastrointestinal bleeding stratified by the different control groups were: OR 1.14 (95% CI 0.71, 1.84) for trauma; 1.26 (95% CI 0.51, 3.11) for acute medical conditions; and 1.42 (95% CI 0.85, 2.35) for elective surgery. A further analysis was performed after excluding trauma controls, which gave an OR of 1.43 (95% CI 0.92, 2.23).

The individual risks for each antidepressant drug are shown in table V. Although the group of high-affinity SRIs showed a point estimate that was slightly higher than those for the other groups, all estimates were close to one, and none reached statistical significance.

For each group of SRIs, no relationship between dose and risk of upper gastrointestinal bleeding was found. For high-affinity SRIs at low doses, the OR was 1.12 (95% CI 0.76, 1.65). For high-affinity SRIs at high doses, it was 1.58 (95% CI 0.69, 3.65).

Forty-one (1.5%) cases and 26 (0.4%) controls had used a high-affinity SRI concurrently with an NSAID. The OR of upper gastrointestinal bleeding among these concurrent users of a high-affinity SRI and an NSAID (8.32; 95% CI 4.69, 14.76) did not differ from that of users of NSAIDs only (7.82; 95% CI 6.79, 9.00). An interaction with low-dose aspirin (acetylsalicylic acid) was not seen (OR of the interaction term 1.21; 95% CI 0.46, 3.20). In addition, only one case and one control were concomitantly using an oral corticosteroid and a high-affinity SRI, precluding any attempt to estimate the interaction.

Discussion

In our study, the use of high-affinity SRIs did not substantially increase the risk of upper gastrointestinal bleeding. No significant association was found between the use of SSRIs and the risk of upper gastrointestinal bleeding, neither by the degree of serotonin reuptake inhibition, by the selectivity for

the serotonin transporter nor by dose. In addition, their use did not increase the risk of upper gastrointestinal bleeding associated with NSAIDs.

To our knowledge, this is one of the few epidemiological studies where an increased risk of upper gastrointestinal bleeding leading to hospital admission associated to the use of highly selective SRIs or high-affinity SRIs has not been seen.[8,12,13] In a prescription event monitoring study, no significant association between treatment with SSRIs and risk of upper gastrointestinal bleeding was seen.[8] In a recent nested case control study on the risk of upper gastrointestinal bleeding that resulted in hospital admission in patients who started using fluoxetine or fluvoxamine and who were already receiving warfarin, the initiation of SSRI use was not associated with a significant increase in the risk of upper gastrointestinal bleeding.[12] In a cohort study, treatment with a SSRI was not followed by an increase in the prescription of anti-ulcer drugs compared with starting treatment with non-selective antidepressants.[17] In another case-control study, with 579 cases of gastrointestinal bleeding, 193 of whom had upper gastrointestinal bleeding, and 1000 controls, no association was found between hospitalization for upper gastrointestinal bleeding and previous use of high and intermediate affinity SSRIs.[13]

Our results are also consistent with those of another case-control study where the risk associated with the concomitant use of both SSRIs and NSAIDs was only marginally higher than the risk associated with each group of drugs separately.[11]

Several observational studies have suggested an association between the use of SSRIs or high-affinity SRIs and upper gastrointestinal bleeding.[7,9-11] However, in these studies, information from administrative and health databases was used, which may not have captured all the events related to upper gastrointestinal disease and other various potential confounding factors, such as the wide variety of painful conditions potentially leading to the use of non-prescription analgesics and NSAIDs, or alcohol intake. In our study, exclusion of concomitant users of NSAIDs did not show an association between SSRIs or SRIs and upper gastrointestinal bleeding.

The results of the analysis excluding subjects with gastrointestinal or cardiovascular relevant history are very similar to those of the general analysis. As this subpopulation has a baseline risk of upper gastrointestinal bleeding lower than the global sample, higher ORs for true risk factors should be expected. However, this is not the case. This supports the absence of a relevant risk of upper gastrointestinal bleeding associated with SSRIs.

The classification of antidepressants used in some of the previous studies[7,11] has been a matter of debate. It has been suggested that the size of the association constants of each individual drug for the serotonin transporter should be the basis for classifying SSRIs and SRI antidepressants, rather than, or at least as well as, the selectivity.[9] However, the differences between both classifications are minor. The classification based on selectivity includes fluvoxamine, citalopram and trazodone in the group of selective SRIs, whereas the one based on affinity for the serotonin transporter includes fluvoxamine and citalopram in the intermediate affinity group, and trazodone in the low-affinity group. In our study, the results did not vary depending on the criteria for classifying individual SSRIs (i.e. the magnitude of the association constants or the old classification based on selectivity).[7,16]

The main difference between our data, those from a study using the General Practice Research Database[7] and those from a study that used The Health Improvement Network database[11] was the proportion of controls exposed to SSRIs (2.7% in ours, compared with 1.0% and 1.3%, respectively). The prevalence of use of SSRIs among controls in our study is compatible with consumption figures for the general population.[18] The use of consumption data has its own limitations, but due to the fact that antidepressants are often used long term and at fixed doses, they may provide a good estimation of their prevalence of use, specially if they refer to a well defined population in time and space. It should also be taken into account that differences in risk seen with the various SRI antidepressants in other studies have been inconclusive given the small numbers of exposed patients. Moreover, in one study

where the effect of dose has been examined, no relationship has been found between SSRIs or SRIs and upper gastrointestinal bleeding.[7]

It has been suggested that the disorder underlying the increased risk of upper gastrointestinal bleeding while on SSRIs is inhibition of platelet aggregation due to a limited uptake of serotonin by platelets. Platelets from patients treated with high doses of fluoxetine (40 mg/day), fluvoxamine (300 mg/day), paroxetine (60 mg/day), sertraline (250 mg/day) or citalopram (600 mg/day) for 6 weeks are highly depleted of serotonin.[19] It has also been shown that in most patients fluoxetine 20 mg or an equivalent dose of another SSRI is enough to reduce the serotonin content of platelets.[20] In our study, SSRIs had been taken at the recommended doses and for a median of over 3 months; therefore, the lack of association observed could not be attributed to low dose or short duration treatments. It is known that SSRIs limit the uptake of blood serotonin by platelets and that serotonin is released from platelets in response to vascular injury. However, serotonin plays a minor part in the haemostatic process. It is a comparatively weak agonist for platelet aggregation. It only induces a change in the shape of platelets but not on the platelet secretory processes, which are key to platelet activation. However, in the presence of other proaggregatory factors (adenosine diphosphate, adrenaline [epinephrine], collagen), serotonin significantly potentiates platelet aggregation.[1] This has led to the suggestion that SRIs may precipitate bleeding in patients with pre-existing haemostatic defects or who are taking concomitant antithrombotic treatment.[21,22]

Epidemiological studies on other bleeding outcomes have yielded controversial results. While three studies on abnormal bleeding and perioperative blood transfusion suggested an increase in risk associated with SSRIs,[14,23,24] in two other studies the use of SSRIs was not associated with an increase in the risk of haemorrhagic stroke.[25,26] Yet, the pathogenic mechanism of haemorrhagic stroke may be different from the one leading to gastrointestinal bleeding.

A major strength of our study was that detailed information on the patients' medical history and on the use of prescription and non-prescription medicines was collected by specifically trained monitors. This allows control for potential confounding factors. Detailed information on the clinical course leading to hospital admission was also carefully examined and, in order to avoid exposure misclassification, the index day was established blindly with respect to drug exposures. In addition, we tried to reduce selection bias by an ascertainment method, which was independent of previous exposures. Among controls, the prevalence of use of high-affinity SRIs was higher among those admitted because of trauma, but the risk estimations stratified by the different control groups did not differ substantially.

Two approaches were used to reduce information bias. First, patients were excluded if they could not be interviewed within 14 days of admission (87.4% of cases and 88.4% of controls were interviewed within 4 days of hospitalization). Second, information on exposures was carefully collected, by means of a structured questionnaire including three questions about the previous use of medicines, with a series of colour pictures including the top selling pharmaceutical agents of interest. The structured interview method overcomes the problem of lack of information about over-the-counter drugs, as they were named by the participants irrespective of how the drugs were obtained. Unfortunately, we can not distinguish if the consumed drugs were obtained as over-the-counter drugs or as prescriptions. Finally, potential confounding by various factors, including the main known risk factors for upper gastrointestinal bleeding, was controlled by multivariate analysis.

Less severe episodes of upper gastrointestinal bleeding, which did not result in hospital admission, were not included; therefore, we cannot rule out that SSRIs or high-affinity SRI antidepressants could be associated with less severe haemorrhagic events.

Overall, the differences in results, when compared with other studies, could be explained by variability in study design, the included population

and the ability to retrieve information. However, we cannot rule out that in some subgroup populations (e.g. older age and male sex), an association between the use of SSRIs and gastrointestinal bleeding could exist. Further studies should take this into consideration.

Conclusion

In conclusion, recent exposure to high-affinity SRIs does not seem to increase the risk of upper gastrointestinal bleeding resulting in hospital admission, and an interaction with coadministered NSAIDs or aspirin was not seen. If there is a risk associated with these drugs, it seems to be low and not an important cause of hospital admission due to upper gastrointestinal bleeding.

Acknowledgements

The Spanish-Italian Collaborative Group for the Epidemiology of Upper Gastrointestinal Bleeding consists of the following individuals.

The Central Management and Coordinating Group: L. Ibáñez, X. Vidal, L. Vendrell, J.R. Laporte, Fundació Institut Català de Farmacologia.

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Funding: In Spain, Almirall Prodesfarma, Aventis, Bayer, Boehringer Ingelheim, Ferrer Internacional, J Uriach y Cía, Knoll, Laboratorios del Dr Esteve, Lácer, Menarini, Merck Sharp and Dhome, Monsanto España, Novartis, Roche, Sanofi-Synthélabo and Vita-Invest. In Italy, Boehringer Ingelheim, Helsinn and Roche.

The design, conduct, analysis and interpretation of the study were totally independent from the sponsoring companies. These were approached for potential funding after approval of the protocol by the study group.

The Fundació Institut Català de Farmacologia and the Servizio di Farmacologia Medica have research contracts with the pharmaceutical companies supporting the present study. Personnel at these institutions do not receive any premium related to these contracts.

We would also like to acknowledge the patients who participated in this study.

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