ORIGINAL ARTICLE

Risk of Upper Gastrointestinal Tract Bleeding Associated With Selective Serotonin Reuptake Inhibitors and Venlafaxine Therapy

Interaction With Nonsteroidal Anti-inflammatory Drugs and Effect of Acid-Suppressing Agents

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Context: Selective serotonin reuptake inhibitors have been reported to increase the risk of upper gastrointestinal tract bleeding. The wide use of these drugs makes such potential risk a public health concern, and identification of factors that may increase or minimize such risk is necessary.

Objectives: To test the association of selective serotonin reuptake inhibitors and venlafaxine hydrochloride therapy with upper gastrointestinal tract bleeding, to identify subgroups of patients at particularly increased risk, and to explore whether acid-suppressing agents may be effective in minimizing risk.

Design: Nested case-control study.

Setting: General practice database from the United Kingdom.

Participants: One thousand three hundred twenty-one patients with upper gastrointestinal tract bleeding referred to a consultant or hospital and 10 000 control subjects matched for age, sex, and calendar year of the index date.

Main Outcome Measure: Risk of bleeding associated with selective serotonin reuptake inhibitors and effect of acid-suppressing agents.

Results: The percentage of current users of selective serotonin reuptake inhibitors (5.3%) or venlafaxine (1.1%) among case subjects was significantly higher than in matched control subjects (3.0% and 0.3%; adjusted odds ratio [OR], 1.6; 95% confidence interval [CI], 1.2-2.1, and OR, 2.9; 95% CI, 1.5-5.6, respectively). An interaction with nonsteroidal anti-inflammatory drugs (OR, 4.8; 95% CI, 2.8-8.3) was observed, in particular among those not using acid-suppressing agents (OR, 9.1; 95% CI, 4.8-17.3) compared with users of these drugs (OR, 1.3; 95% CI, 0.5-3.3). In addition, an interaction with antiplatelet drugs in nonusers of acid-suppressing agents was suggested (OR, 4.7; 95% CI, 2.6-8.3) compared with users of these drugs (OR, 0.8; 95% CI, 0.3-2.5).

Conclusions: Antidepressants with a relevant blockade action on the serotonin reuptake mechanism increase the risk of upper gastrointestinal tract bleeding. The increased risk may be of particular relevance when these drugs are associated with nonsteroidal anti-inflammatory drugs. Our study findings also provide evidence that use of acid-suppressing agents limits such increased risk.

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In the last few years, the possibility that selective serotonin reuptake inhibitors (SSRIs) may induce serious bleeding disorders has emerged as a new safety concern.[1,2] Since the early 1990s, the number of case reports suggesting the association, some of them also showing impairment in platelet aggregation, has accumulated in the medical literature and pharmacovigilance systems worldwide.[3-7] The depletion of serotonin from platelets caused by these drugs is postulated as the most likely mechanism of action.[7] In 1999, our group published the first epidemiologic study that showed that SSRIs increase the risk of upper gastrointestinal (GI) tract bleeding.[8] Although other authors using different populations and different study designs confirmed the finding,[9-11] the issue is still a matter of controversy.[12-14]

The wide use of this drug class requires research to provide more accurate risk estimates, to identify factors that may further increase the risk, and, in particular, to determine whether using acid-suppressing agents may reduce the risk.[1] It is also important to determine whether venlafaxine hydrochloride, a new antidepressant related to SSRIs also increases the risk of bleeding, as some individual case reports have suggested.[15,16] The present study was conducted in an attempt to clarify these concerns.

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METHODS

This study was part of a wider research initiative with the purpose of evaluating the risk of upper GI tract bleeding associated with several drugs, in particular, nonsteroidal anti-inflammatory drugs (NSAIDs).[17] We used the data from The Health Improvement Network database in the United Kingdom. The Health Improvement Network database is a population-based resource in which general practitioners store clinical information about their patients, including medical diagnoses, referrals to consultants and hospitals, prescriptions, and patient demographics and habits (smoking status and alcohol intake).

We performed a nested case-control study. The source cohort comprised persons aged 40 to 84 years who have been seen for at least 2 years by a general practitioner and with at least 1 year elapsed since the first recorded prescription. The study was conducted from January 1, 2000, to December 31, 2005. All subjects who at the start date had a history of cancer, liver disease, coagulopathy, Mallory-Weiss syndrome, esophageal varices, or alcohol-related disorders were excluded. In addition, persons aged 70 years or older at the start date with a follow-up of longer than 1 year and with no recording of data or with only 1 medical visit were excluded to avoid inclusion in the source cohort of individuals most likely to have seriously incomplete information. The source cohort members were followed up from the start date until the date of one of the following end points: age 85 years or older, case definition criteria, any of the exclusion criteria, death, or the end of the study, whichever came first.

CASE DEFINITION AND ASCERTAINMENT

The process of case selection and ascertainment has been described in full elsewhere.[17] In brief, a first computer search identified 5869 patients as potential cases. A "case patient" was defined as having an upper GI tract complication when no exclusion criteria were found up to 2 months after the computer date of case detection; the patient had not been discharged from the hospital in the previous month; the specific site of bleeding or perforation was the stomach or duodenum; the clinical diagnosis of the underlying lesion was erosion, peptic ulcer, or inflammation of gastric or duodenal mucosa; and the patient had been referred to a consultant or was hospitalized. Using these criteria, all potential cases were manually reviewed with us being blinded to all drug exposure information. This review yielded 1561 cases. A random sample of cases was sent to the general practitioners with a questionnaire to validate the case status, with a confirmation rate of 97%. In addition, a distinction was made between bleeding and perforating lesions.

SELECTION OF CONTROL SUBJECTS

Eligible control subjects were randomly selected from the source population using a density-based sampling method.[18] Each patient in the study cohort was randomly assigned a date in the study period. If the date was within the period of observation of the subject, he or she was considered an eligible control subject. This sampling procedure enabled the probability of being selected as a control subject to be proportional to the person-time at risk. Ten thousand control subjects were randomly selected from the pool of eligible control subjects frequency-matched to case patients by age (within 1 year), sex, and calendar year of the index year.

EXPOSURE DEFINITION

The index date for cases was the date of first symptoms or the date of first diagnosis. For controls, the random date assigned in the process of selection was considered the index date. As in our previous article,[8] we defined patients as "current users" if prescribed antidepressants lasted until the index date or were discontinued within 30 days of the index date, "past users" if the prescribed antidepressants were discontinued before the 30 days defined for current users, and "nonusers" if no antidepressants were prescribed before the index date. Current users were subdivided into "single users" and "multiple users." Multiple users included those patients using 2 or more antidepressants during the current-use window. Similar exposure categories were used for all other drugs considered.

Antidepressants were classified into 4 groups on the basis of their inhibitory action on the serotonin reuptake mechanism: (1) SSRIs, including sertraline hydrochloride, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, citalopram hydrobromide, and escitalopram oxalate; (2) selective serotonin and norepinephrine reuptake inhibitors (SNRIs), including venlafaxine and duloxetine hydrochloride; (3) tricyclic antidepressants with an inhibitory action on the reuptake of serotonin, including dothiepin hydrochloride, amitriptyline hydrochloride, imipramine hydrochloride, clomipramine hydrochloride, and doxepin hydrochloride; and (4) tricyclic antidepressants with a predominant action on the reuptake of norepinephrine and other antidepressants with no relevant action on serotonin reuptake, including nortriptyline hydrochloride, protriptyline hydrochloride, desipramine hydrochloride, lofepramine hydrochloride, trimipramine maleate, maprotiline hydrochloride, amoxapine, mirtazapine, mianserin hydrochloride, trazodone hydrochloride, and nefazodone hydrochloride. Other authors have used a classification based on the affinity (dissociation constant [K_D]) for the human serotonin transporter shown in experimental models.[19] We consider that this latter classification may be misleading because a greater affinity may not necessarily translate into an increased biological effect, in particular when the dose used is not the same across drugs; for example, a drug with lower affinity can have the same efficacy as another drug with higher affinity if the dose is accordingly increased. The relevant mechanistic feature would have been to use the relative effect on the platelet serotonin content at therapeutic doses; however, to our knowledge, this information is lacking for most antidepressants. For some analyses, SSRIs and SNRIs were combined in a single category (SRIs) to increase the precision of the estimates when there was homogeneity of effect.

We studied the effect of daily dose and treatment duration in current users. The daily dose was divided into 2 categories (low vs medium to high), with the cutoff point of the doses equivalent to fluoxetine hydrochloride, 20 mg; venlafaxine hydrochloride, 75 mg; or amitriptyline hydrochloride, 75 mg. These cutoff points were determined using both pharmacologic and statistical criteria to ensure a sufficient number of patients in each dose category. Duration was evaluated by summing the "periods of consecutive prescriptions," defined as an interval of less than 2 months between 2 prescriptions.

STATISTICAL ANALYSIS

To determine the association between upper GI tract bleeding and current use of antidepressants compared with nonuse, we built unconditional logistic regression models and computed the odds ratios (ORs) and 95% confidence intervals (95% CIs). Owing to the selection process of controls, ORs were considered as unbiased estimates of rate ratios (RRs; also referred to in the text as "relative risks") in the underlying source cohort. All estimates were adjusted for the matching variables (age, sex, and calendar year), smoking status, alcohol intake, antecedents of GI disorder, and concomitant use of other medications

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associated with upper GI tract bleeding (NSAIDs, systemic corticosteroids, warfarin sodium, and low-dose aspirin and other antiplatelet drugs). Other variables (comorbidities, number of referrals, use of other drugs, number of general practitioner visits, and previous hospitalization) that seemed to be more prevalent among cases than controls were assessed for confounding, but none modified the primary OR by more than 10% and they were not included in the final model.

The interaction between 2 factors, A and B, was evaluated by constructing a variable with 5 categories: (1) nonexposure to any factor; (2) current exposure to factor A and nonexposure to factor B (abbreviated as "A only"); (3) current exposure to factor B and nonexposure to factor A (abbreviated as "B only"); (4) current exposure to both factors ; and (5) any other exposure combination. In the logistic model, this variable was factored as 4 dummy variables, with the first category (nonexposure to any factor) representing the reference. Through the corresponding adjusted ORs (estimates of RRs) associated with these variables, we calculated the relative excess risk due to interaction (RERI) to identify departures from additivity using the following formula[18]:

$$\mathrm{RERI} = \mathrm{RR}_{\text{factors A and B}} - [(\mathrm{RR}_{\text{factor A}} + \mathrm{RR}_{\text{factor B}}) - 1].$$

The RERI values indicated the following: 0, additivity of independent effects (no interaction); greater than 0, superadditivity (positive interaction or synergism); and less than 0, subadditivity (negative interaction or antagonism).

The effect of acid-suppressing drugs on the effect of SRIs, as well as on the combined effect of SRIs and NSAIDs or SRIs and antiplatelet drugs, was studied by stratifying patients as current users or nonusers of acid-suppressing agents. To improve the statistical precision of this analysis, "remote users" of acid-suppressing agents, defined as those in whom the last prescription of these drugs ended more than 365 days before the index date, were added up to the nonuser category.

The measures of association found in the study were translated into more clinically interpretable figures by calculating the number of patients needed to be treated for 1 additional patient to be harmed (NNTH) using the following formula[20]:

$$\mathrm{NNTH} = 1/[(\mathrm{OR} - 1)\ UER],$$

where *UER* is the unexposed event rate (unexposed rate of GI tract bleeding).[20] The unexposed event rate was estimated to be 0.5 per 1000 person-years.[21]

RESULTS

During the study, use of SSRIs and SNRIs in controls who were currently exposed to antidepressants at the index date increased from 34% (32% and 2%, respectively) in 2000 to 60% (50% and 10%, respectively) in 2005. The use of tricyclic antidepressants (most of them with an inhibitory action on serotonin reuptake) decreased from 59% to 34%.

RISK OF UPPER GI TRACT BLEEDING

The final analysis included 1321 case patients with upper GI tract bleeding and 10 000 matched controls. There was a similar distribution of age, sex, and calendar year at the index date in cases and controls owing to the matching procedure, but cases included a higher prevalence of smokers, heavy alcohol drinkers, antecedents of upper GI disorders, and current use of acid-suppressing agents (**Table 1**), NSAIDs, antiplatelet drugs, systemic corticosteroids, and oral anticoagulants (eTable 1) (http://www.archgenpsychiatry.com). The percentages of current users of SSRIs (5.3%) and SNRIs (1.1%) were significantly higher in cases than in controls (3.0% and 0.3%, respectively), yielding adjusted ORs of 1.6 (95% CI, 1.2-2.1) for SSRIs and 2.9 (95% CI, 1.5-5.6) for SNRIs compared with nonuse of antidepressants (**Table 2**). When both groups of drugs were combined in a single category (SRIs), the adjusted OR was 1.8 (95% CI, 1.4-2.3). No statistically significant association was found with other groups of antidepressants after adjustment for confounders.

The effect of individual antidepressants with more than 5 exposed cases was analyzed. Sertraline (OR, 2.3; 95% CI, 1.0-5.1), citalopram or escitalopram (OR, 2.0; 95%

Table 1. Characteristics of Case Patients and Control Subjects

Characteristic	No. (%) Cases (n=1321)	No. (%) Controls (n=10 000)	Crude OR[a] (95% CI)
Male sex	772 (58.4)	5674 (56.7)	1.1 (0.9-1.2)
Age, y			
40-59	324 (24.5)	2760 (27.6)	1 [Reference]
60-69	299 (22.9)	2145 (21.5)	1.2 (1.0-1.4)
70-79	482 (36.5)	3450 (34.5)	1.2 (1.0-1.4)
80-84	216 (16.4)	1645 (16.5)	1.1 (0.9-1.3)
Year of index date			
2000-2001	422 (31.9)	2905 (29.1)	1 [Reference]
2002-2003	500 (37.9)	3436 (34.6)	1.0 (0.9-1.2)
2004-2005	399 (30.2)	3659 (36.6)	0.8 (0.6-0.9)
Smoking status			
Nonsmoker	613 (46.4)	5215 (52.2)	1 [Reference]
Ex-smoker	329 (24.9)	2142 (21.4)	1.3 (1.1-1.5)
Current smoker	271 (20.5)	1529 (15.3)	1.5 (1.3-1.8)
Unknown	108 (8.2)	1114 (11.1)	0.8 (0.7-1.0)
Alcohol intake, No. drinks/wk			
0	491 (37.2)	3641 (36.4)	1 [Reference]
1-9	379 (28.7)	2855 (28.6)	1.0 (0.9-1.1)
10-29	204 (15.4)	1515 (15.1)	1.0 (0.8-1.2)
>30	40 (3.0)	174 (1.7)	1.7 (1.2-2.4)
Unknown	207 (15.7)	1815 (18.2)	0.8 (0.7-1.0)
Antecedents of GI tract disorders			
None	747 (56.6)	7611 (76.1)	1 [Reference]
Dyspepsia	346 (26.2)	1813 (18.1)	1.9 (1.7-2.2)
Ulcer	131 (9.9)	372 (3.7)	3.6 (2.9-4.4)
Upper GI tract complications	97 (7.3)	204 (2.0)	4.8 (3.8-6.2)
Use of acid-suppressing agents[b]			
Nonuse or remote use	965 (73.1)	8539 (85.4)	1 [Reference]
Current use, 0-30 d	257 (19.5)	1115 (11.2)	2.5 (2.2-3.0)
Past use, 31-365 d	99 (7.5)	346 (3.5)	3.2 (2.5-4.0)
No. of visits to a GP during the study			
0-5	32 (2.4)	764 (7.6)	1 [Reference]
6-20	237 (17.9)	2742 (27.4)	2.1 (1.4-3.0)
21-100	823 (62.3)	5625 (56.3)	3.5 (2.4-5.0)
>100	229 (17.3)	869 (8.7)	6.3 (4.3-9.2)

Abbreviations: CI, confidence interval; GI, gastrointestinal; GP, general practitioner; OR, odds ratio.
[a] Adjusted only for the matching factors.
[b] For an explanation of type of users, see the "Exposure Definition" subsection of the "Methods" section.

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Table 2. Risk of Upper GI Tract Bleeding in Association With Current Use Compared With Nonuse of Various Pharmacologic Groups of Antidepressants

Category	No. (%) Cases (n=1321)	No. (%) Controls (n=10 000)	Crude OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Current use, 0-30 d				
SSRIs[c]	70 (5.3)	304 (3.0)	2.2 (1.7-2.9)	1.6 (1.2-2.1)
SNRIs[d]	15 (1.1)	34 (0.3)	4.2 (2.3-7.7)	2.9 (1.5-5.6)
TCAs-ser[e]	59 (4.5)	297 (3.0)	1.8 (1.4-2.4)	1.3 (0.9-1.7)
Other agents[f]	14 (1.1)	80 (0.8)	1.7 (0.9-3.3)	1.3 (0.7-2.7)
Multiple agents[g]	6 (0.5)	40 (0.4)	1.5 (0.6-3.5)	0.9 (0.4-2.3)
Past use, >30 d	290 (22.0)	1520 (15.2)	1.8 (1.6-2.1)	1.4 (1.2-1.7)
Nonuse	867 (65.6)	7725 (77.3)	1 [Reference]	1 [Reference]

Abbreviations: CI, confidence interval; GI, gastrointestinal; OR, odds ratio; SNRIs, selective norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs-ser, tricyclic antidepressants with inhibitory action on serotonin reuptake.

[a] Adjusted for matching factors (age, sex, and calendar year).

[b] Adjusted for matching factors, history of GI tract disorder (ulcer, bleeding ulcer, or dyspepsia), alcohol intake, smoking status, and use of corticosteroids, nonsteroidal anti-inflammatory drugs, anticoagulants, and antiplatelet drugs (low-dose aspirin, dipyridamole, clopidogrel bisulfate, or ticlopidine hydrochloride). Further adjustment for acid-suppressing agents did not materially change risk estimates.

[c] Sertraline hydrochloride, fluoxetine hydrochloride, paroxetine hydrochloride, citalopram hydrochloride, or escitalopram oxalate. There were no current users of fluvoxamine maleate among cases or controls.

[d] Venlafaxine hydrochloride or duloxetine hydrochloride (only 2 controls).

[e] Doxepin hydrochloride, dothiepin hydrochloride, clomipramine hydrochloride, imipramine hydrochloride, or amitriptyline hydrochloride.

[f] Tricyclic antidepressants with no relevant action on serotonin reuptake (nortriptyline hydrochloride, protriptyline hydrochloride, trimipramine maleate, or lofepramine hydrochloride) and other antidepressants (mirtazapine, maprotiline hydrochloride, flupentixol, trazodone hydrochloride, mianserin hydrochloride, nefazodone hydrochloride, reboxetine mesilate, or tryptophan).

[g] Two or more antidepressants.

CI, 1.2-3.2), and venlafaxine (OR, 2.9; 95% CI, 1.5-5.7) demonstrated the highest increased risks. Fluoxetine, paroxetine, dothiepin, and amitriptyline demonstrated a significant increased risk in the crude analysis; however, the risk was decreased and rendered nonsignificant after adjustment for confounding (eTable 2).

We did not identify a dose-response effect or a clear-cut duration effect in current users of SSRIs or SNRIs, although the effect was more consistent when treatment duration was longer than 3 months (eTable 3). An increased RR of SRIs vs nonuse of antidepressants was observed both in female patients (OR, 2.0; 95% CI, 1.4-2.8) and male patients (OR, 1.5; 95% CI, 1.0-2.4), as well as in patients with or without antecedents of upper GI tract disorders such as an ulcer or upper GI tract complications (OR, 2.1; 95% CI, 1.1-3.9), dyspepsia (OR, 1.9; 95% CI, 1.2-3.1), or no history of GI disorders (OR, 1.6; 95% CI, 1.1-2.4). In patients aged 70 years or older, the effect seemed to be lower (OR, 1.3; 95% CI, 0.9-2.0) than in younger subjects (OR, 2.3; 95% CI, 1.6-3.3), probably owing to a higher background rate of upper GI tract bleeding in the older group; however, the CIs overlapped, indicating no heterogeneity of effects.

INTERACTION WITH OTHER DRUGS

The concomitant use of SRIs and NSAIDs induced an increased risk (OR, 4.8; 95% CI, 2.8-8.3) greater than the sum of the independent effects (RERI, +1.2) (**Table 3**). Likewise, a synergism was suggested with the concomitant use of SRIs and systemic corticosteroids (OR, 4.0; 95% CI, 1.3-12.3; RERI, +1.7). In contrast, no positive interaction was observed with the concomitant use of SRIs and antiplatelet drugs (primarily low-dose aspirin) (antiplatelet drugs only: OR, 2.4; 95% CI, 1.7-3.3; SRIs only: OR, 2.2; 95% CI, 1.9-2.6; concomitant use: OR, 2.6; 95% CI, 1.6-4.2; RERI, –1.0) or oral anticoagulants (oral anticoagulants only: OR, 2.4; 95% CI, 1.7-3.3; SRIs only: OR, 1.9; 95% CI, 1.5-2.5; concomitant use: OR, 2.9; 95% CI, 1.0-8.9; RERI, –0.4). No interaction was observed between tricyclic antidepressants and NSAIDs (tricyclic antidepressants only: OR, 1.4; 95% CI, 0.8-2.6; NSAIDs only: OR, 2.8; 95% CI, 2.3-3.5; concomitant use: OR, 3.1; 95% CI, 1.9-5.1; RERI, –0.1).

EFFECT OF ACID-SUPPRESSING AGENTS

Prevalence of current use of acid-suppressing drugs (proton pump inhibitors, or H_2 antihistamines) was 11.2% in controls and 19.5% in case patients with upper GI tract bleeding, which suggests an important confounding by indication (crude OR, 2.0; 95% CI, 1.7-2.4) compared with nonusers or remote users that was not completely eliminated after full adjustment (adjusted OR, 1.2; 95% CI, 1.0-1.4). In controls, the prevalence of current use of acid-suppressing agents was higher in persons aged 70 years or older than in younger individuals (14.2% vs 8.0%), in those with antecedents of GI tract disorders (dyspepsia, 27.6%; ulcer or upper GI tract complications, 33.3%; no antecedents of GI tract disorders, 5.6%) and in users compared with nonusers of NSAIDs (18.8% vs 9.1%), antiplatelet drugs (18.6% vs 8.8%), systemic corticosteroids (30.0% vs 10.1%), warfarin (19.8% vs 10.8%), and antidepressants (25.2% vs 9.1%). The RR of upper GI tract bleeding associated with SRIs was lower in those taking acid-suppressing agents (OR, 1.4; 95% CI, 0.8-2.3) than in those not having a prescription for acid-suppressing agents or having only a record of remote use (OR, 2.0; 95% CI, 1.5-2.8). Current use of

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acid-suppressing drugs greatly reduced the joint effect of SRIs and NSAIDs (OR, 9.1; 95% CI, 4.8-17.3 in nonusers vs OR, 1.1; 95% CI, 0.3-3.4 in current users) (**Figure 1**), as well as the joint effect of SRIs and antiplatelet drugs (OR, 4.7; 95% CI, 2.6-8.3 in nonusers vs OR, 0.8; 95% CI, 0.3-2.5 in current users) (**Figure 2**) (eTable 4 and eTable 5). The effect of acid-suppressing agents on the interaction observed between SRIs and systemic corticosteroids could not be evaluated because of the small number of patients.

NUMBER OF PATIENTS NEEDED TO BE TREATED FOR 1 ADDITIONAL PATIENT TO BE HARMED

Assuming a background rate of upper GI tract bleeding in the general population of 0.5 in 1000 person-years and an OR of 2.0 associated with the use of SRIs in those not using acid-suppressing agents, 2000 patients per year would need to be treated with SRIs in order for 1 case of upper GI tract bleeding to be attributed to such drugs. When both SRIs and NSAIDs are concomitantly used (OR of 9 among those not treated with acid-suppressing agents), it would be sufficient to treat 250 patients per year for 1 case of upper GI tract bleeding to be attributed to such combination, and 500 patients per year if SRIs are concomitantly used with antiplatelet drugs (OR of approximately 5 in those not treated with acid-suppressing agents). The use of acid-suppressing agents would reduce the relative risk to 1.4 or less, thus increasing to 5000 or more the number of patients needed to be treated with an SRI or the combination of an SRI with NSAIDs or antiplatelet drugs in order for 1 case to be attributed to these drugs. That is, the use of acid-suppressing agents would prevent 10 to 20 cases of upper GI tract bleeding for every 5000 patients per year treated concomitantly with SRIs and antiplatelet drugs or with SRIs and NSAIDs.

RISK OF UPPER GI TRACT PERFORATION

We also collected information for 240 patients with an upper GI tract perforation. Current use of SRIs was found in 14 cases with perforation (5.8%) and 338 controls (3.4%), resulting in a nonsignificant adjusted OR of 1.4 (95% CI, 0.8-2.6). Nine of 14 exposed cases (64%) were also current users of NSAIDs, whereas concomitant use was noted in 44 controls (13%), which suggests an interaction of effects. The combined effect of SRIs and NSAIDs yielded an adjusted OR of 10.3 (95% CI, 4.6-22.9), whereas the independent effects yielded an adjusted OR of 4.6 (95% CI, 3.1-6.7) for NSAIDs only and 0.8 (95% CI, 0.2-3.3) for SRIs only (RERI, +5.9).

Table 3. Evaluation of the Interaction Between Current Use of NSAIDs and SRIs on Risk of Upper GI Tract Bleeding Compared With Nonuse of NSAIDs and Antidepressants

Category[a]	No. (%) Cases (n=1321)	No. (%) Controls (n=10 000)	Adjusted OR[b] (95% CI)
Current use			
NSAIDs only	173 (13.1)	642 (6.4)	2.8 (2.3-3.5)
SRIs only	22 (1.7)	105 (1.1)	1.8 (1.1-2.9)
Both NSAIDs and SRIs[c]	23 (1.7)	44 (0.4)	4.8 (2.8-8.3)
Nonuse	339 (25.7)	3625 (36.3)	1 [Reference]

Abbreviations: CI, confidence interval; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; SRIs, selective serotonin reuptake inhibitors plus venlafaxine hydrochloride.

[a] An additional dummy variable (not shown) was included in the model to group all of the remaining combinations (past users of NSAIDS, past users of SRIs, and current and past users of antidepressants other that SRIs) (see "Statistical Analysis" subsection of the "Methods" section).

[b] Adjusted for matching factors, history of GI tract disorder, alcohol intake, smoking status, and use of anticoagulant agents, corticosteroids, and antiplatelet drugs.

[c] Only 2 cases and 7 controls were exposed to selective cyclooxygenase-2 inhibitors.

COMMENT

The results obtained in the present study support the hypothesis that SSRIs as a group increase the risk of upper GI tract bleeding. An important increased risk was also found for venlafaxine, the only SNRI with enough exposure during the study; however, we did not observe a significant association for other groups of antidepressants after adjustment for confounding factors. The increased risk was apparent across different subgroups of patients (sex, age, antecedents of GI tract disorders), although the magnitude varied. No significant differences were found among different categories of dose and duration. A positive interaction was suggested with the concomitant use of SRIs and NSAIDs and with SRIs and systemic corticosteroids. The results also suggest that use of acid-suppressing agents lowers the risk of upper GI tract bleeding associated with SRIs and, in particular, the combined effect of their concomitant use with NSAIDs and antiplatelet drugs.

The hypothesis that use of SSRIs would increase the risk of bleeding received the first epidemiologic support in 1999 when our group reported a 3-fold increased risk of upper GI tract bleeding. For that study, we used data from the United Kingdom–based general practice research database for a study conducted from April 1, 1993, to September 30, 1997. In the present study, we used essentially the same methods using another United Kingdom–based general practitioner database in a more recent study period, January 1, 2000, to December 31, 2005, and obtained qualitatively similar results including the lack of a dose and duration effect. The magnitude of the increased RR, however, is smaller in the current study. A similar reduction in the RR estimates has also been observed for NSAIDs as a group (from 3.7 to 2.8; Table 3). Both reductions may be explained by better selection of patients over the years, an increasing use of proton pump inhibitors (from 2.3% in controls in the previous study to 7.9% in the present study), and declining cohort prevalence of *Helicobacter pylori* infection and its widespread treatment. The risk estimates obtained in the present study for SRIs are similar to those observed for antiplatelet drugs, which supports the idea that both act on the same end target.

Although some anecdotal cases of major bleeding and impaired platelet function in association with venlafaxine

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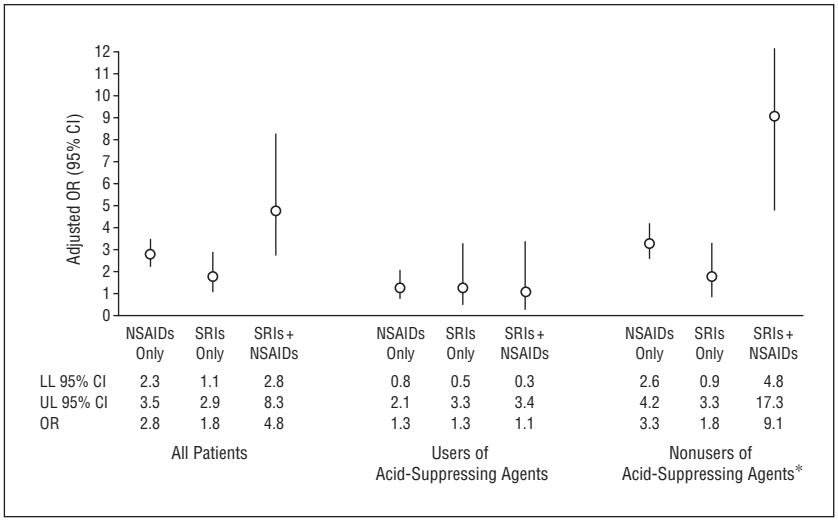

Figure 1. Effect of current use of nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors plus venlafaxine hydrochloride (SRIs) and both groups combined on upper gastrointestinal tract bleeding risk, and effect of acid-suppressing agents (proton pump inhibitors or H_2-antihistamines combined). *For this analysis, this category also included remote users of these agents (past use more than 365 days previously). CI represents confidence interval; LL, lower limit; OR, odds ratio; and UL, upper limit.

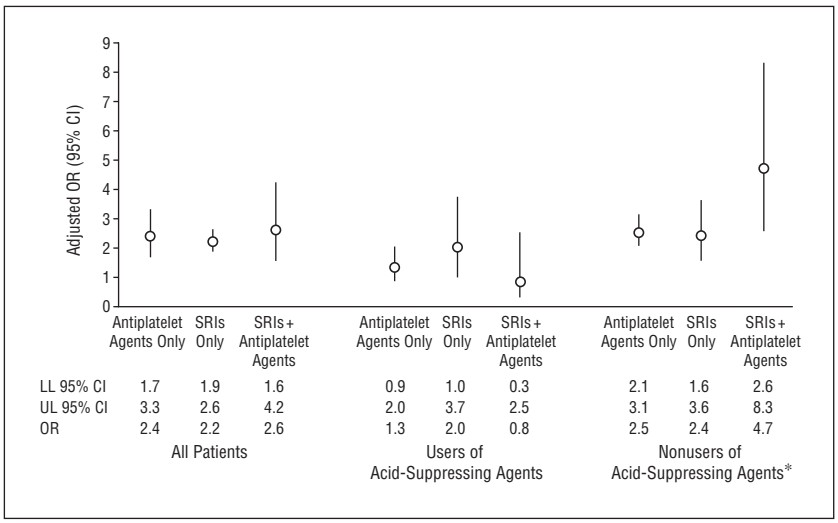

Figure 2. Effect of current use of antiplatelet agents, selective serotonin reuptake inhibitors (SRIs) plus venlafaxine therapy and both groups combined on upper gastrointestinal tract bleeding risk, and effect of acid-suppressing agents (proton pump inhibitors or H_2-antihistamines combined). *For this analysis, this category also included remote users of these agents (past use more than 365 days previously). CI represents confidence interval; LL, lower limit; OR, odds ratio; and UL, upper limit.

have been published,[15,16] there has been no epidemiologic evidence until now. Recently, Opatrny et al[22] reported an increased risk of upper GI tract bleeding using the general practice research database. The affinity of venlafaxine for the serotonin receptor is lower than that of most SSRIs,[19] but the daily dose normally used is 3- to 7-fold greater, which may compensate in vivo for a lower potency shown in vitro. The risk estimates of venlafaxine and SSRIs are different but with widely overlapping CIs, which impedes drawing any conclusion of a greater effect of venlafaxine on the basis of these data. The low level of use of duloxetine precluded any specific risk estimation for this drug, but there is no apparent reason to think that duloxetine may demonstrate a different risk pattern.

Our results support an interaction between SSRIs and NSAIDs, as has been reported previously.[8,10,11] Tata et al,[13] however, did not find a relevant interaction. Their study was performed using The Health Improvement Network database, the same database we used for the present study, with 2 important differences. First, we performed a thorough ascertainment of all potential cases after the computer search, resulting in the exclusion of 73% of those initially identified, whereas Tata et al[13] seemed to include without further evaluation all cases obtained directly with the computer search; therefore, misclassification of the outcome is more likely in their study than in ours. Second, they did not control for the important effect of acid-suppressing agents on the interaction itself. The effect modification exerted by these drugs is an important finding because it enables the observation of the interaction between SRIs and NSAIDs in a much clearer manner and, more importantly, it confirms in a real-life setting that acid-suppressing drugs are an effective measure to reduce the increased risk of upper GI tract bleeding resulting from the interaction.

In our previous study, we also found support for a similar, although smaller, interaction between SSRIs and low-dose aspirin.[8] This result has not been confirmed in the present study, perhaps owing to the strong influence of acid-suppressing agents. In the nonusers of these drugs, an interaction was clearly suggested. Therefore, caution should be exercised when both types of drugs are used in combination. The use of acid-suppressing drugs would greatly limit such excess risk.

If our risk estimates are correct, it would be necessary to treat approximately 2000 patients per year with SRIs for 1 case of upper GI tract bleeding to be attributed to them, which indicates that the risk is rather low

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Table 4. Epidemiologic Studies That Tested the Hypothesis of an Association Between SSRI Use and Upper GI Tract Bleeding

Source/Year	Study Design	Population/ Age, y	No. of Persons Exposed to SSRIs	No. of Cases Exposed to SSRIs	RR (95% CI) vs Nonuse of SSRIs	RR (95% CI) vs Other Antidepressants	Interaction With NSAIDs
de Abajo et al[8]/ 1993-1997	Nested case-control	General/40-79	69 593	52	3.0 (2.1-4.4)	3.4 (1.1-14.2)	Yes
Dunn et al[12]/before 2000	Cohort/PEM	General	237 609[a]	103[b]	1.2 (0.9-1.7)[c]	. . .	. . .
Van Walraven et al[9]/1992-1998	Cohort	Elderly/>65	101 397	404	. . .	10.7% Per each higher inhibition group (3 groups)	. . .
Dalton et al[10]/ 1991-1995	Cohort	General/>16	17 320	55	3.6 (2.7-4.7)	2.0 (1.0-4.6)	Yes
Tata et al[13]/ 1990-2003	Nested case-control	General/>18	. . .	362	2.4 (2.1-2.7)	. . .	No
Wessinger et al[11]/ 2003-2004	Hospital-based case-control	Hospital/>18	. . .	111[b]	1.3 (0.8-1.9)	. . .	Yes
Opatrny et al[22]/ 2000-2005	Nested case-control	General	. . .	NA	SSRIs: 1.3 (1.1-1.6) Venlafaxine hydrochloride: 1.9 (1.3-2.6)	. . .	. . .
Helin-Salmivaara et al[23]/2000-2004	Population-based case-control	Hospital	. . .	473	SSRIs, excluding NSAID users: 1.3 (1.1-1.5)	. . .	Yes
Lewis et al[24]/NS	Hospital-based case-control	Hospital/22-80	. . .	High affinity: 40[d]	High affinity: 2.1 (1.3-3.3)	. . .	No
Vidal et al[25]/ 1998-2001	Hospital-based case-control	Hospital/>18	. . .	101	SSRIs: 1.2 (0.9-1.7) SSRIs (>70 y): 1.6 (1.0-2.6) Venlafaxine: 0.8 (0.2-3.1)	. . .	No
Present study/ 2000-2005	Nested case-control	General/40-85	169 721 SSRIs:149 320 Venlafaxine: 19 490	85 SSRIs: 70 Venlafaxine: 15	SSRIs: 1.6 (1.2-2.1) Venlafaxine: 2.9 (1.5-5.6) SRIs: 1.8 (1.4-2.3)	SRIs vs other antidepressants: 1.4 (1.0-2.1)	Yes

Abbreviations: CI, confidence interval; GI, gastrointestinal; NS, not specified; NSAID, nonsteroidal anti-inflammatory drug; PEM, prescription event monitoring; RR, relative risk; SRIs, selective serotonin reuptake inhibitors plus venlafaxine hydrochloride; SSRI, selective serotonin reuptake inhibitor.

[a] Indicates patient-months.

[b] Indicates any kind of GI tract hemorrhage.

[c] SSRIs vs moclobemide and salmeterol.

[d] Indicates toxic reaction in the upper GI tract.

in the general population treated with these drugs. However, when SRIs are combined with NSAIDs or antiplatelet drugs, the number of patients needed to be treated per year for 1 case of upper GI tract bleeding decreases remarkably. These data indicate that in such a high-risk population, the use of acid-suppressing agents would save a relevant number of cases and is worthwhile.

To our knowledge, 11 epidemiologic studies, including ours, have been published that provide data about the association between use of SSRIs and upper GI tract bleeding.[8-13,22-25] Most of these studies showed an increased risk, although the magnitude varied (**Table 4**). Seven additional epidemiologic studies have been published that proposed to assess the risk of bleeding outcomes, other than upper GI tract bleeding, in users of SSRIs and other antidepressants.[26-32] Four of 5 with focus on abnormal bleeding and perioperative blood transfusion suggested an increased risk,[26-30] whereas the other 2 studies, both on intracranial hemorrhage, did not.[31,32]

Current techniques to measure platelet function have clearly shown that several SSRIs may impair both the platelet secretory response and the platelet aggregation induced by thrombin, collagen, and adenosine diphosphate[33,34] and cause inhibition of platelet plug formation.[35,36] These actions have been related to the important depletion these drugs produce in the platelet serotonin content,[7] although other mechanisms have also been suggested (eg, a direct antiplatelet effect of sertraline[37] and venlafaxine[16]). The clinical effect of these actions are not yet clear, but they provide a biological explanation for the increased trend of bleeding observed in users of these drugs, although a certain predisposition would be necessary for such actions to have clinical expression. The synergisms observed between SRIs and other groups, primarily NSAIDs, imply that the corresponding biological mechanisms involved in upper GI tract bleeding are complementary, resulting in mutually reinforced actions. Few patients were exposed to selective cyclooxygenase-2 inhibitors, and we were unable to examine their effect. The preventive effect of acid-suppressing agents suggests that acid secretion is a necessary step in the causal pathway leading to upper GI tract bleeding induced by these drugs, in particular when they are associated with other gastrotoxic drugs.

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The finding that SRIs may further increase the risk of ulcer perforation induced by NSAIDs is unexpected and should be treated with caution, in particular because it is based on small numbers and the lack of increased risk in the absence of concomitant use of NSAIDs. Takeuchi et al[38] reported that paroxetine and fluvoxamine worsen the development of antral ulcers induced by diclofenac sodium, flurbiprofen sodium, or indomethacin sodium in a animal model and that this effect can be significantly prevented by omeprazole and 5-HT3 serotonin antagonists. These findings suggest that serotonin, and, in turn, SSRIs, may have a direct harmful effect on the GI tract mucosa, but further research is needed in this area.

The current study has several strengths and limitations. Although the study is retrospective, there are a number of elements that make highly unlikely the possibility of selection bias: drug use was recorded prospectively by general practitioners before the occurrence of the outcome of interest; cases were selected by us and we were blinded to the exposure; and controls were randomly sampled from the source population from which the cases were obtained. Computer profiles of all potential cases were manually reviewed, including the free text, and a patient was considered a case only if he or she had been hospitalized or referred to a consultant, minimizing the probability of false-positive outcomes. The validity of our case ascertainment was confirmed in a sample of patients for whom we requested direct confirmation of the episode of upper GI tract bleeding from their general practitioners. The record of prescriptions is almost complete, and, therefore, misclassification of antidepressant exposure and other prescription drugs is unlikely. In addition, efforts were made to control for potential confounders; however, as in any epidemiologic study, there is the possibility of residual confounding as a result of unmeasured or inaccurately measured risk factors. For example, as in most automated databases, nonprescription drugs such as some analgesics (eg, aspirin, ibuprofen, or naproxen sodium) are not systematically recorded in The Health Improvement Network database, which may lead to misclassification of such exposure. If this misclassification were differential with respect to the use of antidepressants (eg, if use of nonprescription analgesics were more frequent in current users of antidepressants than in nonusers), a spurious inflation of the risk of upper GI tract bleeding associated with SRIs or any other antidepressants would be expected. To test the sensitivity of our results to this potential bias, we compared current users of SRIs with current users of other antidepressants and found that a significant excess risk was still present (OR, 1.4; 95% CI, 1.0-2.0), which suggests a rather specific effect of SRIs.

In conclusion, the results of the present study provide additional evidence to that derived from clinical reports, pharmacologic research, and previous epidemiologic studies and lend support to the hypothesis that antidepressants with a relevant blockade action on the serotonin reuptake mechanism, in particular, SSRIs and SNRIs, increase the risk of upper GI tract bleeding to a similar extent as with antiplatelet drugs. Moreover, they confirm that the increased risk may be of particular relevance when SRIs are associated with other gastrotoxic drugs, primarily NSAIDs. Our study also provides clear evidence that use of acid-suppressing agents limits such an increased risk.

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