Association of Risk of Abnormal Bleeding With Degree of Serotonin Reuptake Inhibition by Antidepressants

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Background: Serotonin plays a role in platelet aggregation. Because antidepressants influence blood serotonin levels, their use may be associated with an increased risk of abnormal bleeding. However, previous studies were inconclusive regarding this association. The aim of this study was to estimate the risk of abnormal bleeding associated with the use of antidepressants and to establish the relationship between serotonin reuptake inhibition and the risk of bleeding.

Methods: We used data collected from 1992 through 2000 to conduct a nested case-control study of a cohort of more than 64 000 new antidepressant users. Cases were identified as all patients hospitalized for a primary diagnosis of abnormal bleeding, and they were matched with controls for age and sex. We classified exposure according to the degree (high, intermediate, or low) of serotonin reuptake inhibition and performed logistic regression analysis to calculate odds ratios.

Results: There were 196 cases of abnormal bleeding. The risk of hospitalization increased with the use of inhibitors providing intermediate (odds ratio, 1.9; 95% confidence interval, 1.1-3.5) and high degrees of serotonin reuptake inhibition (odds ratio, 2.6; 95% confidence interval, 1.4-4.8).

Conclusions: In a large population of new antidepressant users we found a significant association between degree of serotonin reuptake inhibition by antidepressants and risk of hospital admission for abnormal bleeding as the primary diagnosis. An increased risk of abnormal bleeding was strongly associated with the degree of serotonin reuptake inhibition.

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CASE REPORTS AND OBSERVATIONAL studies have both shown an association between use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), and abnormal bleeding. Case reports have described patients with various bleeding disorders (eg, ecchymoses, purpura, epistaxis, and vaginal bleeding[1-7]), while observational studies have focused on upper gastrointestinal bleeding, intracranial bleeding, and bleeding during surgery.[8-13]

The suggested mechanism underlying these adverse effects is that SSRIs limit uptake of blood serotonin by platelets.[14] Since platelets are unable to synthesize serotonin, this leads to a lower concentration of serotonin within the platelets, and because one of the functions of serotonin within the platelets is to promote platelet aggregation, a decreased amount of serotonin in the platelets may increase the risk of abnormal bleeding.[15]

The first large case-control study that demonstrated an association between the use of SSRIs and upper gastrointestinal bleeding found moderately higher risk with the use of SSRIs than with the use of non-SSRI antidepressants.[9] This result proved consistent with the findings of another large cohort study that reported a higher (though not statistically significantly higher) risk of abnormal bleeding for patients taking SSRIs than for those taking other psychiatric drugs.[11] Another cohort study classified the antidepressants based on their affinity for the serotonin transporter and found an increased risk of bleeding with the use of SSRIs that provide a higher degree of serotonin reuptake inhibition compared with those providing a moderate or low degree of inhibition.[10] Old age, a history of gastrointestinal problems, and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) were identified in another study as risk factors, and the most recent cohort study found, again, an increased risk of upper gastrointestinal bleeding with SSRI use in individuals also taking NSAIDs.[12] The risk differences seen with the use of different SSRIs remain inconclusive because of the

Table 1. Primary Admission Diagnosis of 196 Patients Hospitalized With Abnormal Bleeding

Abnormal Bleeding	No. (%)
Uterus bleeding (metorrhagia, menorrhagia, postmenopausal bleeding)	93 (47.4)
Upper gastrointestinal tract bleeding (all bleeding ulcers, hematemesis, melena, gastrointestinal bleeding NOS)	31 (15.8)
Cerebral bleeding (subarachnoidal bleeding, intracerebral bleeding, subdural bleeding, intracranial bleeding NOS)	21 (10.7)
Blood abnormalities (thrombocytopenia, anemia due to blood loss)	6 (3.1)
Other bleeding abnormalities (hematuria, epistaxis, hemoptosys, hemarthorsis, hematoma, excessive bleeding following a surgical procedure, bleeding NOS)	45 (23.0)

Abbreviation: NOS, not otherwise specified.

small numbers of cases found. Another recent retrospective study in orthopedic patients undergoing surgery reported an association between the use of serotonergic antidepressants and an increased risk of bleeding and subsequent need for blood transfusion during orthopedic surgery and attributed this increased risk to inhibition of serotonin-mediated platelet activation.[13]

We investigated the risks of all types of abnormal bleeding associated with the use of antidepressants and aimed to establish the relationship between degree of serotonin reuptake inhibition and risk by performing a large case-control study in a cohort of antidepressant users in the Netherlands from 1992 through 2000.

METHODS

DESIGN AND COHORT

We conducted a case-control study nested within a cohort of new antidepressant users.

Data were collected from the PHARMO database, which, at the time of the study, contained prescription medication histories for 850 000 patients in the Netherlands. Prescription data were linked to hospital discharge data. Drugs were coded according to the Anatomical Chemical Therapeutic coding system. Discharge diagnoses were coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). All patients 18 years or older who received a first prescription for an antidepressant (Anatomical Chemical Therapeutic code N06A) from 1992 through 2000 were included in the cohort. A prescription was considered a first prescription if a patient had an available medication history of at least 1 year and was not known to have received previous antidepressant prescriptions. Patients joined the cohort at the date of their first prescription for an antidepressant and were followed up during their subsequent use of any antidepressant. Follow-up ended when a gap in antidepressant prescriptions of more than 30 days occurred, when patients were admitted to the hospital with a diagnosis related to bleeding as reason for admission, or at the end of data collection, whichever came first. Data on patients with a single prescription of an antidepressant were discarded to exclude incidental visitors to the pharmacy.

CASES AND CONTROLS

Cases were defined as all patients hospitalized with a primary diagnosis of abnormal bleeding while taking any antidepressant (*ICD-9-cm* diagnostic codes for these patients are available from the corresponding author).

For cases, the index date was the date of first hospitalization for abnormal bleeding during antidepressant use. For each case, up to 5 nonhospitalized controls were randomly selected during the case's follow-up. Controls were matched for age (± 5 years), sex, and initiation date of antidepressant therapy. Data were available for controls at least as long as the follow-up duration of the case they were matched with. The index dates for controls were the dates of antidepressant therapy initiation of the case they were matched with.

EXPOSURE DEFINITION

Antidepressants were classified according to their degree of inhibition (high, intermediate, or low) of serotonin reuptake.[10] This distribution is based on the antidepressant's dissociation constant (Kd) for the serotonin transporter, which was categorized into the following ranges: 0-1 nmol/L, 1 to 10 nmol/L, and 10 nmol/L and greater.[16,17] Lower dissociation constants reflect a higher affinity of antidepressants for the serotonin transporter and therefore a higher inhibition of serotonin reuptake.

Current use and dosage of an antidepressant, prior use of antidepressants, and current as well as prior use of other medications were determined. Current use of any drug was defined as use within 30 days before the index date. History of use of a drug was defined as use 180 to 30 days before the index date. History of hospitalization for abnormal bleeding during 1 year before inclusion in the cohort was determined from the hospital admission records.

STATISTICAL ANALYSIS

Conditional logistic regression was used on the matched sets to estimate the risk of bleeding associated with the degree of serotonin reuptake inhibition of an antidepressant, expressed as odds ratio (OR) with 95% confidence interval (CI). We adjusted for potential confounding in the regression model by including current and prior use of other medications (aspirin, other NSAIDs, anticoagulants, glucocorticoids, estrogens, progestagens, histamine$_2$ blockers, proton pump inhibitors, and antidiabetic agents) and history of hospitalization for bleeding. Age, sex, and date of inclusion were controlled for through matching. Stratified analyses were performed for abnormal uterus and upper gastrointestinal bleeding. Log-linear regression was used to estimate OR vs K_d trends. All analyses were performed using the statistical software packages Egret, version 2.03 (Cytel Software Corperation, Cambridge, Mass), and SPSS, version 10 (SPSS Inc, Chicago, Ill).

RESULTS

Of 69 342 new users of antidepressants, 4695 (6.7%) were excluded because they had received only 1 prescription. The initial cohort was thus made up of 64 647 individuals, with an average follow-up duration of 229 days. During the follow-up of these first-time antidepressant users, 196 individuals were hospitalized with a primary diagnosis of abnormal bleeding (an incidence of 4.9 per 1000 person-years). **Table 1** gives an overview of the

Table 2. Risk of Hospitalization for Bleeding Associated With Type of Antidepressant Used: Nested Matched Case-Control Analysis

Degree of Inhibition of Serotonin Reuptake	Cases, No. (%) (n = 196)	Controls, No. (%)* (n = 972)	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)†
Low	18 (9.2)	148 (15.2)	Reference	Reference
Mirtazapine	2 (1.0)	39 (4.0)	Reference	Reference
Maprotiline	3 (1.5)	36 (3.7)	1.5 (0.2-10.0)	1.8 (0.2-14.1)
Mianserine	1 (0.5)	16 (1.6)	1.3 (0.1-15.8)	2.9 (0.2-39.6)
Nefazodone	0	1 (0.1)	NA	NA
Trazodone	4 (2.0)	14 (1.4)	5.8 (0.9-35.9)	7.1 (0.9-53.2)
Doxepin	1 (0.5)	8 (0.8)	2.8 (0.2-35.3)	2.3 (0.1-36.7)
Nortriptyline	4 (2.0)	16 (1.6)	5.3 (0.9-32.5)	7.2 (1.0-53.6)
Desipramine	0	3 (0.3)	NA	NA
Bupoprion	1 (0.5)	7 (0.7)	2.7 (0.1-31.7)	2.5 (0.1-34.2)
Moclobemide	2 (1.0)	8 (0.8)	5.1 (0.6-41.0)	4.4 (1.1-114.0)
Intermediate	75 (38.3)	362 (37.2)	1.9 (1.1-3.3)	1.9 (1.1-3.5)
Venlafaxine	5 (2.6)	23 (2.4)	4.6 (0.8-26.0)	3.4 (0.5-24.9)
Dothiepin	2 (1.0)	17 (1.7)	2.3 (0.5-15.5)	2.0 (0.5-15.1)
Amitriptyline	48 (24.5)	200 (20.6)	5.0 (1.1-21.9)	5.6 (1.1-29.1)
Fluvoxamine	20 (10.2)	103 (10.6)	4.2 (0.9-19.2)	7.0 (1.3-37.5)
Imipramine	0	10 (1.0)	NA	NA
Citalopram	0	11 (1.1)	NA	NA
High	103 (52.6)	462 (47.5)	2.1 (1.2-3.6)	2.6 (1.4-4.8)
Fluoxetine	18 (9.2)	88 (9.1)	4.4 (1.0-20.3)	7.6 (1.4-41.9)
Sertraline	3 (1.5)	14 (1.4)	4.4 (0.7-29.1)	4.9 (0.6-39.6)
Clomipramine	21 (10.7)	83 (8.5)	5.1 (1.1-24.1)	9.4 (1.7-52.6)
Paroxetine	61 (31.1)	275 (28.3)	4.6 (1.1-19.8)	6.4 (1.3-32.6)

Abbreviation: NA, not applicable.
*Matched for age, sex, and date of initiation of antidepressant use.
†Adjusted for history and current use of aspirin, other nonsteroidal anti-inflammatory drugs, anticoagulants, steroids, estrogens, progestagens, anti-ulcer drugs, and history of hospitalization for bleeding by conditional logistic regression.

type of bleeding complications identified. We randomly matched cases for age and sex with up to 5 controls, which resulted in a total of 972 controls. Most participants were women (73.5%), with a mean age of 58 years. The risk (expressed as ORs with 95% CIs) of hospitalization for bleeding with use of each antidepressant drug compared with the risk of hospitalization for bleeding with use of mirtazapine, the antidepressant with the lowest affinity for the serotonin transporter, is shown in **Table 2**.

Inhibition of serotonin reuptake was associated with a higher risk of abnormal bleeding, as depicted in the **Figure**. When categorizing the antidepressants according to their affinity for the serotonin transporter we found that, for the 103 study subjects (53.1%) who were using antidepressants with a high affinity for the serotonin transporter (0-1 nmol/L), the adjusted OR was 2.6 (95% CI, 1.4-4.8) compared with patients using antidepressants with a low affinity (>10 nmol/L). Antidepressants with an intermediate affinity showed an OR of 1.9 (95% CI, 1.1-3.5) (Table 2). (An appendix showing antidepressants categorized according to their affinity for the serotonin transporter is available from the corresponding author.)

Despite small numbers of cases, we performed stratified analyses in the subgroup with abnormal uterus bleeding and in the subgroup with upper gastrointestinal bleeding to specify the results in the various categories of abnormal bleeding. We found an increased risk of abnormal uterus bleeding in women using antidepressants with intermediate (adjusted OR, 1.7 [95% CI, 0.7-4.1]) and high (adjusted OR, 3.0 [95% CI, 0.8-4.9]) inhibition of serotonin reuptake compared with women using antidepressants with a low level of inhibition. We observed a similar pattern among individuals presenting with upper gastrointestinal bleeding, who showed increased risks of hospitalization with increased inhibition of serotonin. The use of antidepressants with an intermediate degree of inhibition of serotonin reuptake showed an adjusted OR of 1.7 (95% CI, 0.4-6.6) compared with the use of antidepressants with low inhibition, while the use of antidepressants with a high degree of inhibition resulted in an adjusted OR of 2.1 (95% CI, 0.6-8.3). In both subgroups, associations were not statistically significant.

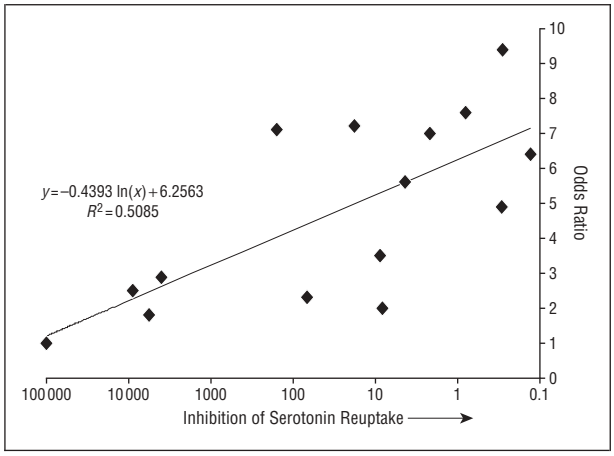

Figure. Relation between inhibition of serotonin reuptake and risk of hospitalization for bleeding.

COMMENT

We found a significant association between degree of serotonin reuptake inhibition by antidepressants and risk of hospital admission for abnormal bleeding. Antidepressants with a high degree of inhibition of serotonin reuptake were associated with a 2.6-fold increased risk of bleeding events compared with antidepressants with a low degree of serotonin reuptake inhibition.

How do our findings compare with those of other studies on the risk of bleeding associated with antidepressants[9-13]? In a large-scale case-control study, de Abajo et al[9] found a 3-fold increase in risk of gastrointestinal bleeding in primary care patients using SSRIs, especially in those concurrently using NSAIDs compared with patients using non-SSRIs. In a cohort study by van Walraven et al,[10] a higher risk of gastrointestinal bleeding was associated with a higher degree of serotonin reuptake inhibition. In addition, they found greater differences in risks between antidepressant use in patients older than 80 years and in patients with a history of gastrointestinal bleeding. Therefore, in our analyses we adjusted for age (through matching) and previous hospitalization for bleeding.

Layton et al[11] reported results from a cohort study of 50 000 patients taking SSRIs. They found only small, nonsignificant increased risks of abnormal bleeding events in patients using SSRIs. Their definition of abnormal bleeding events included not only those leading to hospital admission, as in our study, but any new bleeding diagnosis or complaint possibly related to impaired platelet aggregation. A problem in their study was the low response rate (51%). Furthermore, they compared the effect of SSRIs and other psychiatric and nonpsychiatric drugs categorized by indication, without taking into account the possible effects of these medications on the serotonin reuptake mechanism. Most recently, Dalton et al[12] found in a large cohort study an increased in risk of upper gastrointestinal bleeding in patients using SSRIs, a moderate increase in those using non-SSRIs, and no increase in those using antidepressants with no effect on serotonin levels. In our study, to be able to compare the effects of the different degrees of serotonin reuptake inhibition, we included all patients receiving a new prescription for any antidepressant and we defined the outcome as hospitalization for all categories of abnormal bleeding.

To avoid possible confounding, we adjusted for current and prior use of other medications (aspirin, other NSAIDs, anticoagulants, glucocorticoids, estrogens, progestagens, histamine$_2$ inhibitors, proton pump inhibitors) and a history of hospitalization for abnormal bleeding. Confounding by indication was unlikely because all patients were new users of antidepressants, and there is no association between the indications for which antidepressants are prescribed and bleeding.

A limitation of our study is that misclassification may have occurred by using hospital records for diagnosing. Moreover, we missed bleeding events that did not result in hospitalization or that resulted in death before the patient came to the hospital, which most likely led to an underestimation of the actual risk.

In a phase 1 study in which healthy volunteers received paroxetine in a randomized, double-blind, placebo-controlled, cross-over trial, paroxetine use substantially decreased platelet serotonin content, and thereby platelet plug formation and responsiveness to platelet activation.[15] Paroxetine is a strong serotonin reuptake inhibitor, and it is conceivable that the underlying mechanism of serotonin inhibition is associated with bleeding. However, the available clinical studies showed diverse results.[9-11] Our results show that a higher degree of inhibition of serotonin reuptake is associated with a higher risk of admission for various categories of bleeding, indicating a similar underlying pharmacological action.

This study broadens the view of the previously reported associations between the use of antidepressants and bleeding. In a population of 64 000 new antidepressant users we found 196 cases of admission to a hospital with abnormal bleeding as the primary diagnosis. The increase in risk that we found for the various categories of bleeding depended on the level of inhibition of serotonin reuptake.

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REFERENCES

1. Alderman CP, Moritz CK, Ben-Tovim DI. Abnormal platelet aggregation associated with fluoxetine therapy. *Ann Pharmacother.* 1992;26:1517-1519.
2. Gunzberger DW, Martinez D. Adverse vascular effects associated with fluoxetine [letter]. *Am J Psychiatry.* 1992;149:1751.
3. Ottervanger JP, Stricker BH, Huls J, Weeda JN. Bleeding attributed to the intake of paroxetine. *Am J Psychiatry.* 1994;151:781-782.
4. Baldwin D. SSRIs and sexual side effects. *Int J Psych Clin Pract.* 1997;1:47-58.
5. Tielens JA. Vitamin C for paroxetine- and fluvoxamine-associated bleeding. *Am J Psychiatry.* 1997;154:883-884.
6. Cooper TA, Valcour VG, Gibbons RB, O'Brien-Falls K. Spontaneous ecchymoses due to paroxetine administration. *Am J Med.* 1998;104:197-198.
7. Vandel P, Vandel S, Kantelip JP. SSRI-induced bleeding: two case reports. *Therapie.* 2001;56:445-447.
8. Bak S, Tsiropoulos I, Kjaersgaard JO, et al. Selective serotonin reuptake inhibitors and the risk of stroke: a population-based case-control study. *Stroke.* 2002; 33:1465-1473.
9. de Abajo FJ, Rodriguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ.* 1999;319:1106-1109.
10. van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ.* 2001;323:655-658.
11. Layton D, Clark DW, Pearce GL, Shakir SA. Is there an association between selective serotonin reuptake inhibitors and risk of abnormal bleeding? results from a cohort study based on prescription event monitoring in England. *Eur J Clin Pharmacol.* 2001;57:167-176.
12. Dalton SO, Johansen C, Mellemkjaer L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch Intern Med.* 2003;163:59-64.
13. Movig KL, Janssen MW, de Waal Malefijt J, Kabel PJ, Leufkens HG, Egberts AC. Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. *Arch Intern Med.* 2003;163:2354-2358.
14. Skop BP, Brown TM. Potential vascular and bleeding complications of treatment with selective serotonin reuptake inhibitors. *Psychosomatics.* 1996;37:12-16.
15. Hergovich N, Aigner M, Eichler HG, Entlicher J, Drucker C, Jilma B. Paroxetine decreases platelet serotonin storage and platelet function in human beings. *Clin Pharmacol Ther.* 2000;68:435-442.
16. Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol.* 1997;340:249-258.
17. Richelson E. Pharmacology of antidepressants: clinical relevance of effects on neurotransmitter systems and their receptors. In: Den Boer JA, Westenberg HGM, eds. *Antidepressants: Selectivity or Multiplicity.* Amsterdam, the Netherlands: Benecke NI; 2001:43-60.