

## Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study

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### Abstract

**Objectives** To determine the association between inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding.

**Design** Retrospective cohort study from population based databases.

**Setting** Ontario, Canada.

**Participants** 317 824 elderly people observed for more than 130 000 person years. The patients started taking an antidepressant between 1992 and 1998 and were grouped by how much the drug inhibited serotonin reuptake. Patients were observed until they stopped the drug, had an upper gastrointestinal bleed, or died or the study ended.

**Main outcome measure** Admission to hospital for acute upper gastrointestinal bleeding.

**Results** Overall, 974 bleeds were observed, with an overall bleeding rate of 7.3 per 1000 person years. After controlling for age or previous gastrointestinal bleeding, the risk of bleeding significantly increased by 10.7% and 9.8%, respectively, with increasing inhibition of serotonin reuptake. Absolute differences in bleeding between antidepressant groups were greatest for octogenarians (low inhibition of serotonin reuptake, 10.6 bleeds/1000 person years *v* high inhibition of serotonin reuptake, 14.7 bleeds/1000 person years; number needed to harm 244) and those with previous upper gastrointestinal bleeding (low, 28.6 bleeds/1000 person years *v* high, 40.3 bleeds/1000 person years; number needed to harm 85).

**Conclusions** After age or previous upper gastrointestinal bleeding were controlled for, antidepressants with high inhibition of serotonin reuptake increased the risk of upper gastrointestinal bleeding. These increases are clinically important for elderly patients and those with previous gastrointestinal bleeding.

### Introduction

Serotonin potentiates platelet aggregation.<sup>1</sup> Selective serotonin reuptake inhibitors decrease serotonin uptake from the blood by platelets. Because platelets do not synthesise serotonin, these inhibitors decrease the amount of serotonin in platelets.<sup>2</sup> Case reports sug-

gest that serotonin reuptake inhibitors are associated with a variety of bleeding events.<sup>3-10</sup>

The strongest evidence linking the use of selective serotonin reuptake inhibitors with bleeding comes from a case-control study.<sup>11</sup> After potential confounders were controlled for, this study found the odds of gastrointestinal bleeding for users of the inhibitors were three times that of the controls. Patients taking tricyclic antidepressants had no increased risk of upper gastrointestinal bleeding.

The study did, however, have potential limitations, which we have addressed in this study.<sup>12-15</sup> In particular, the study could not provide the absolute risk of serious bleeding associated with antidepressant use. Clinicians need this information when choosing antidepressants for patients.

We conducted a retrospective cohort study to determine the overall risk of serious upper gastrointestinal bleeding in elderly patients taking antidepressants. We also aimed to determine if this risk varied with the extent of inhibition of serotonin reuptake by antidepressants.

### Patients and methods

#### Cohort definition

We obtained our data from administrative databases for Ontario, Canada, where services provided by physicians, drugs, and hospital services for patients aged over 65 are provided by a universally funded health programme.

We used a retrospective cohort design that included all residents of Ontario aged over 65 who received a new prescription for any antidepressant (see table A1 on website). Drug use was determined from the Ontario drug benefits database, which records the type of drug, quantity, and date of all prescriptions for all residents aged 65 and over.

#### Patient observation

We began our surveillance on 1 July 1992. Patients entered the cohort on the date they were first prescribed an antidepressant (see table A1 on website). Patients were grouped by the affinity of the antidepressant for the transporter responsible for serotonin reuptake. This affinity was categorised before the

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analysis as low, intermediate, or high, on the basis of the drug's dissociation constant.<sup>16</sup>

Observation ended when exposure to the drug, as defined by the duration of the prescription, ended. Observation also ended when patients were admitted to hospital with upper gastrointestinal bleeding, or died or the study ended. Admissions to hospital with the primary diagnosis of upper gastrointestinal bleeding were identified from the discharge abstract database, which records all admissions to Ontario hospitals. We identified upper gastrointestinal bleeds by using a series of ICD-9 (international classification of

diseases, 9th revision) codes that have been shown to have a positive predictive value of 86% for upper gastrointestinal bleeds.<sup>17</sup> Patient deaths were identified from the Registered Patient Database, which records all deaths for residents of Ontario, including those occurring out of the province. Our study ended 1 April 1998.

### Potential confounders

We controlled for factors that are associated with upper gastrointestinal bleeding, including age, sex, previous upper gastrointestinal bleeding, and diabetes.<sup>18 19</sup> Confounding drugs included non-steroidal anti-inflammatory drugs, acetylsalicylic acid, glucocorticoids, anticoagulants, H<sub>2</sub> blockers, and proton pump inhibitors. We considered that patients were exposed to these drugs if they were prescribed within 30 days of the end of observation. Capture of non-steroidal anti-inflammatory drugs and acetylsalicylic acid that can be acquired without prescription is likely to be incomplete.

Finally, given the long duration of our study and the potential for changes in patient care over that time, we thought it necessary to control for year of study entry. To do this we stratified the analysis by year of entry to the study.

### Results

During the study period, 383 911 of 1 798 382 (21.3%) elderly patients were prescribed antidepressants. Of these, 317 824 (82.8%) started their drug during the study period and were included. They were observed for 132 812 person years, during which time there were 974 admissions to hospital for upper gastrointestinal bleeding. Patients entering the study in later years were much more likely to be prescribed antidepressants with greater inhibition of serotonin reuptake.

The overall risk of upper gastrointestinal bleeding was 7.3 per 1000 person years (table). The risk of upper gastrointestinal bleeding was significantly associated with each confounder. This was especially so with increasing age and previous upper gastrointestinal bleeding.

The risk of upper gastrointestinal bleeding increased slightly with inhibition of serotonin reuptake, rising from 6.6 bleeds per 1000 person years for antidepressants with the lowest inhibition to 7.9 bleeds per 1000 person years in the highest group (table). This trend did not reach significance.

However, significant increases in upper gastrointestinal bleeding with increasing inhibition were seen after controlling for variables strongly associated with upper gastrointestinal bleeding (table). When we controlled for age, the risk of bleeding increased by 10.7% for each higher inhibition group. For octogenarians, bleeding rates increased from 10.6 per 1000 person years in the lowest group to 14.7 per 1000 person years in the highest group. This corresponded with a number needed to harm of 244—that is, one extra upper gastrointestinal bleed would be expected when 244 patients were treated with an antidepressant from the high rather than the low serotonin reuptake inhibitors. When we controlled for previous upper gastrointestinal bleeding, bleeding risk increased by 9.8%. For patients with a history of active peptic ulcer disease, bleeding rates increased from 28.6 per 1000

Rates of gastrointestinal bleeding per 1000 person years of observation in antidepressant groups by serotonin reuptake inhibition. Values in brackets are 95% confidence intervals

| Factor or stratum                      | Cohort           | Antidepressant group |              |      | % increase in bleeding with increased serotonin inhibition |
|----------------------------------------|------------------|----------------------|--------------|------|------------------------------------------------------------|
|                                        |                  | Low                  | Intermediate | High |                                                            |
| Cohort                                 | 7.3              | 6.6                  | 7.4          | 7.9  | 9.2 (-3.7 to 23.9)                                         |
| Study entry:                           |                  |                      |              |      |                                                            |
| 1992                                   | 6.2              | 5.4                  | 6.7          | 8.4  | 10.7 (4.6 to 17.2)                                         |
| 1993-5                                 | 7.3              | 7.0                  | 8.3          | 6.8  |                                                            |
| 1995-7                                 | 6.9              | 6.5                  | 6.7          | 7.2  |                                                            |
| 1997-8                                 | 8.5              | 7.5                  | 7.2          | 9.5  |                                                            |
| Relative risk                          | 1.4 (1.1 to 1.7) |                      |              |      |                                                            |
| <b>Patient factors</b>                 |                  |                      |              |      |                                                            |
| Age:                                   |                  |                      |              |      |                                                            |
| 65-70                                  | 4.1              | 3.9                  | 4.2          | 4.1  | 10.7 (4.6 to 17.2)                                         |
| 70-75                                  | 7.2              | 7.5                  | 6.6          | 7.3  |                                                            |
| 75-80                                  | 8.8              | 6.4                  | 11.5         | 8.6  |                                                            |
| >80                                    | 12.3             | 10.6                 | 11.1         | 14.7 |                                                            |
| Relative risk                          | 3.0 (2.6 to 3.6) |                      |              |      |                                                            |
| Sex:                                   |                  |                      |              |      |                                                            |
| Female                                 | 6.0              | 5.7                  | 6.0          | 6.3  | 7.6 (-1.6 to 17.7)                                         |
| Male                                   | 10.0             | 8.6                  | 10.5         | 10.8 |                                                            |
| Relative risk                          | 1.7 (1.5 to 1.9) |                      |              |      |                                                            |
| <b>Medical history</b>                 |                  |                      |              |      |                                                            |
| Diabetes:                              |                  |                      |              |      |                                                            |
| No                                     | 7.0              | 6.3                  | 7.2          | 7.5  | 7.1 (-2.1 to 17.2)                                         |
| Yes                                    | 9.1              | 8.9                  | 8.4          | 9.9  |                                                            |
| Relative risk                          | 1.3 (1.1 to 1.5) |                      |              |      |                                                            |
| Previous gastrointestinal bleeding:    |                  |                      |              |      |                                                            |
| No                                     | 6.7              | 6.1                  | 6.8          | 7.1  | 9.8 (0.3 to 20.0)                                          |
| Yes                                    | 33.2             | 28.6                 | 29.1         | 40.3 |                                                            |
| Relative risk                          | 5.0 (4.1 to 6.1) |                      |              |      |                                                            |
| <b>Drugs</b>                           |                  |                      |              |      |                                                            |
| Non-steroidal anti-inflammatory drugs: |                  |                      |              |      |                                                            |
| No                                     | 6.4              | 5.8                  | 6.2          | 7.0  | 6.6 (-2.5 to 16.7)                                         |
| Yes                                    | 17.9             | 16.7                 | 17.4         | 19.3 |                                                            |
| Relative risk                          | 2.8 (2.4 to 3.3) |                      |              |      |                                                            |
| Acetylsalicylic acid:                  |                  |                      |              |      |                                                            |
| No                                     | 7.0              | 6.3                  | 7.1          | 7.5  | 4.5 (-4.4 to 14.3)                                         |
| Yes                                    | 11.6             | 11.8                 | 10.7         | 12.2 |                                                            |
| Relative risk                          | 1.7 (1.4 to 2.0) |                      |              |      |                                                            |
| Glucocorticoids:                       |                  |                      |              |      |                                                            |
| No                                     | 7.2              | 6.5                  | 7.2          | 7.8  | 8.9 (-0.4 to 19.2)                                         |
| Yes                                    | 12.2             | 9.6                  | 15.7         | 11.2 |                                                            |
| Relative risk                          | 1.7 (1.2 to 2.3) |                      |              |      |                                                            |
| Anticoagulant:                         |                  |                      |              |      |                                                            |
| No                                     | 7.1              | 6.3                  | 7.2          | 7.6  | -0.4 (-9.0 to 8.9)                                         |
| Yes                                    | 15.4             | 17.3                 | 14.3         | 14.9 |                                                            |
| Relative risk                          | 2.2 (1.7 to 2.8) |                      |              |      |                                                            |
| Peptic ulcer treatment:                |                  |                      |              |      |                                                            |
| No                                     | 6.3              | 5.6                  | 6.4          | 6.8  | 7.8 (-1.5 to 17.9)                                         |
| Yes                                    | 12.9             | 12.0                 | 12.4         | 14.1 |                                                            |
| Relative risk                          | 2.1 (1.8 to 2.4) |                      |              |      |                                                            |

Relative risks compare bleeding risk in bottom stratum with that of top stratum. Final column presents relative change in risk of gastrointestinal bleeding when switching to next higher serotonin blocking group.

person years in the lowest group to 40.3 per 1000 person years in the highest group. This corresponded with a number needed to harm of 85. Finally, we also found a period effect. When we controlled for the year of study entry, the relative risk of upper gastrointestinal bleeding increased significantly by 10.7% with increasing inhibition of serotonin reuptake.

## Discussion

We found a trend towards an increased risk of upper gastrointestinal bleeding for patients taking antidepressants with greater inhibition of serotonin reuptake. This association was significant when we controlled for age or previous upper gastrointestinal bleeding. We believe that the increased bleeding rates are clinically important for octogenarians or patients with previous upper gastrointestinal bleeding and should be considered when selecting antidepressants. For most patients, however, such precautions are probably unnecessary.

Our conclusions are similar to those of de Ajabo et al<sup>11</sup> and corroborate them in a distinct patient population using a different study design. We believe that this strengthens the association between inhibition of serotonin reuptake by antidepressants and gastrointestinal bleeding.

Octogenarians and patients with previous upper gastrointestinal bleeding are at especially high risk from antidepressants with high inhibition of serotonin reuptake.<sup>20</sup> It is possible that increased bioavailability of selective serotonin reuptake inhibitors in elderly patients results in a stronger antiplatelet effect at the same dose, thereby increasing the risk of gastrointestinal bleeding. These findings might also be a function of particular vulnerability to gastrointestinal bleeding in elderly patients<sup>21</sup> and those with previous upper gastrointestinal bleeding, thereby allowing the antiplatelet effect of the antidepressant to become apparent. These factors would explain why the association between bleeding risk and inhibition of serotonin reuptake was seen only after these strong confounders were controlled for.

Two factors could explain why upper gastrointestinal bleeding was associated with inhibition of serotonin reuptake after the year of study entry was controlled for (table). Firstly, the number of octogenarians who were prescribed antidepressants with high inhibition increased from 892 in 1992 to 11 179 in 1997. Secondly, the use of upper endoscopy in elderly patients increased noticeably during the study. Therefore major changes during the study in the bleeding risk of patients taking selective serotonin reuptake inhibitors and the use of an important technology to diagnose upper gastrointestinal bleeds may explain the cohort effect in our base analysis.

We believe that our study is valid and provides new information that is useful to clinicians. It is population based and includes a large number of participants. This increased the precision of point estimates for bleeding rates and allowed us to limit the analysis to patients taking antidepressants. It also allowed us to measure absolute differences in bleeding risks, which are essential for determining clinical relevance. The validity of our methods to calculate bleeding rates is supported by our rates being similar to those in two other cohort studies.<sup>21 22</sup> Although drug exposure was measured by

## What is already known on this topic

A case-control study found that the risk of upper gastrointestinal bleeding increases with intake of antidepressants that extensively inhibit serotonin reuptake

The study's validity was questioned because antidepressants were not specifically classified by the extent that they inhibit serotonin reuptake, and absolute differences in bleeding rates between antidepressants were unavailable

## What this study adds

The risk of upper gastrointestinal bleeding in elderly and depressed patients increases with antidepressants having the greatest extent of inhibition of serotonin reuptake

This increased risk of bleeding is clinically important for patients with a high risk of bleeding—namely, octogenarians and those with previous upper gastrointestinal bleeding

The extent that an antidepressant inhibits serotonin reuptake should be considered when drugs are required for depression in high risk patients

prescription only, this method agrees well with self reported use of drugs.<sup>23</sup> Our study outcome of admission to hospital with upper gastrointestinal bleeding was explicitly determined by using diagnostic codes that are highly indicative of such bleeding.

Our results potentially have two minor limitations. Firstly, although we controlled for important confounders, we did not control for all of the factors that de Ajabo et al considered, such as smoking or “antecedents of upper gastrointestinal disorders.” Because the independent risks of bleeding associated with these factors were not provided,<sup>11</sup> we are unsure of the importance of their control when studying upper gastrointestinal bleeding. Secondly, we considered only upper gastrointestinal bleeds that resulted in admission to hospital. We may therefore have missed those patients whose bleed resulted in death before admission to hospital or that did not require admission. Despite this potential misclassification bias,<sup>24</sup> we found a significant association between the inhibition of serotonin reuptake and gastrointestinal bleeding when important confounders were controlled for.

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Contributors: CvW conceived the study; he will act as guarantor for the paper. CvW, MMM, PSW, and JIW contributed to the design, analysis, and interpretation of the data. CvW drafted the paper, and all investigators helped revise the paper.

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## Is voice therapy an effective treatment for dysphonia? A randomised controlled trial

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### Abstract

**Objectives** To assess the overall efficacy of voice therapy for dysphonia.

**Design** Single blind randomised controlled trial.

**Setting** Outpatient clinic in a teaching hospital.

**Participants** 204 outpatients aged 17-87 with a primary symptom of persistent hoarseness for at least two months.

**Interventions** After baseline assessments, patients were randomised to six weeks of either voice therapy or no treatment. Assessments were repeated at six weeks on the 145 (71%) patients who continued to this stage and at 12-14 weeks on the 133 (65%) patients who completed the study. The assessments at the three time points for the 70 patients who completed treatment and the 63 patients in the group given no treatment were compared.

**Main outcome measures** Ratings of laryngeal features, Buffalo voice profile, amplitude and pitch perturbation, voice profile questionnaire, hospital anxiety and depression scale, clinical interview schedule, SF-36.

**Results** Voice therapy improved voice quality as assessed by rating by patients ( $P=0.001$ ) and rating by observer ( $P<0.001$ ). The treatment effects for these two outcomes were 4.1 (95% confidence interval 1.7 to 6.6) points and 0.82 (0.50 to 1.13) points. Amplitude perturbation showed improvement at six weeks but not on completion of the study. Patients with dysphonia had appreciable psychological distress and lower quality of life than controls, but voice therapy had no significant impact on either of these variables.

**Conclusion** Voice therapy is effective in improving voice quality as assessed by self rated and observer rated methods.

### Introduction

Many patients have transient, self limiting changes in voice, but those who have been hoarse for more than three weeks need specialist assessment to exclude underlying laryngopharyngeal pathology. Once conditions that need surgery have been excluded, patients are usually referred to a speech and language therapist for voice therapy. Up to 40 000 patients with dysphonia are referred for voice therapy annually in the United Kingdom.<sup>1</sup> At the time of referral, many patients with vocal dysfunction have entered a vicious cycle in which psychological factors exacerbate voice pathology and poor voice quality adversely affects psychological wellbeing.<sup>2-9</sup>

We aimed to examine the efficacy of voice therapy in patients with dysphonia and to identify those patients for whom voice therapy might be most beneficial.

### Participants and methods

We recruited consecutive outpatients attending the department of otorhinolaryngology and head and neck surgery of Glasgow Royal Infirmary with a primary complaint of dysphonia (hoarseness) present for a minimum of two months and without any relevant organic pathology (for example, polyp, papilloma, tumour, vocal cord palsy) or need for surgery.