BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2008.03154.x

Gastro-intestinal haemorrhage risks of selective serotonin receptor antagonist therapy: a new look

Lucie Opatrny,[1,2] J. A. 'Chris' Delaney[1,3] & Samy Suissa[1,3]

[1]Division of Clinical Epidemiology, [2]Division of Internal Medicine, McGill University Health Center and [3]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada

Correspondence
Dr Samy Suissa PhD, Division of Clinical Epidemiology, Royal Victoria Hospital, 687 Pine Avenue West, Ross 4.29, Montreal, Quebec, Canada, H3A 1A1.
Tel.: + 1 51 4843 1564
Fax: + 1 51 4843 1493
E-mail: samy.suissa@clinepi.mcgill.ca

Keywords
selective serotonin, reuptake inhibitors, warfarin, gastro-intesinal haemorrhage, alcohol, confounding

Received
21 July 2007
Accepted
24 January 2008
Published *OnlineEarly*
6 May 2008

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The known biological effects of selective serotonin reuptake inhibitors (SSRI) on platelets are consistent with an increased risk of gastrointestinal haemorrhage in patients on SSRI therapy.
- Previous research supports this increased risk among SSRI users with a large increase in bleeding risk observed.

WHAT THIS STUDY ADDS

- This large study was able to compare the effects of different classes of antidepressant as well as to test for drug–drug interactions with warfarin.
- The discovery of alcohol abuse as a strong confounder may partially explain the very high risks of bleed seen in previous studies that did not adjust for this confounder.

AIMS

(i) To determine the effects of selective serotonin reuptake inhibitors (SSRI) and other classes of antidepressants on upper gastro-intestinal (GI) haemorrhage and (ii) to assess the drug–drug interaction effects of antidepressants and warfarin or clopidogrel on the risk of GI haemorrhage.

METHODS

This was a population-based case control study in the General Practice Research Database (GPRD). Cases with a first episode of upper GI haemorrhage between 2000 and 2005 were matched with up to 10 controls. Exposure to the study drugs was defined by a prescription issued in the 90 days before the index date. Rate ratios were estimated using conditional logistic regression.

RESULTS

Four thousand and twenty-eight cases of GI haemorrhage and 40 171 controls were identified. The excess risk of GI haemorrhage with SSRI use was small (Rate Ratio [RR]: 1.3; 95% confidence interval [CI]: 1.1, 1.6) and null with exposure to tricyclic antidepressants (TCAs) (RR 1.0; 95% CI: 0.8, 1.3). The risk of GI haemorrhage was highest with venlafaxine use (RR: 1.9; 95% CI: 1.3, 2.6). There was no drug–drug interaction between warfarin anticoagulation and antidepressant use.

CONCLUSIONS

This study supports a small increased risk of upper GI haemorrhage with the use of SSRI antidepressants compared with the older TCA drugs, but to a lesser extent than previously reported due to confounding by alcohol use. The small elevation in risk of GI haemorrhage with SSRI and venlafaxine should be weighed against the therapeutic benefit of their use.

Introduction

The incidence of gastro-intestinal (GI) haemorrhage is a significant source of morbidity and mortality in the British general population. Studies have reported an incidence rate of approximately 103 per 100 000 people [1]. It is important to understand the risk factors for GI haemorrhage in order to reduce morbidity and mortality especially for high risk populations. An important contributor of risk for GI haemorrhage is adverse events related to medication use. Properly defining this risk represents clinically important information especially when different treatment options represent different levels of risk. Recent work has suggested that use of the newer class of antidepressants, selective serotonin reuptake inhibitors (SSRI), is associated with an increased risk of GI haemorrhage [2–5]. This is thought to be the result of blocked serotonin reuptake by platelets with resulting platelet serotonin depletion and potentially impaired haemostasis. However, unanswered questions remain about this empirical relationship.

First, editorials have noted that the purported increase in the risk of bleeding due to SSRI use is higher than seen in clinical practice [6]. Could it be that the risk of SSRI on GI bleed has been exaggerated, as occurs in some observational studies? Few studies were able to control for important confounders. Also, few studies have concurrently examined the possible risk of traditional antidepressants on GI haemorrhage, or atypical antidepressants such as venlafaxine, classified as a serotonin-norepinephrine-dopamine reuptake inhibitor. This is important in order to determine whether the excess bleeding risk is a class effect of SSRI *vs.* being a feature of the type of patient who is prescribed an antidepressant. Most studies have excluded patients concurrently on medications known to increase bleeding risk in order to isolate the effect of antidepressant use. This approach ignores the possibility of clinically important effect modification between the drugs due to drug–drug interaction.

In addition, since anticoagulants, such as warfarin, and antiplatelet agents, such as clopidogrel, are well known to increase the risk of GI haemorrhage it is important to determine what is the total risk for patients exposed to these drugs as well. Since approximately 3% of the UK population is on warfarin therapy [7] and warfarin is known to have a broad range of important interactions with other drugs [8], detecting an interaction between antidepressants and anticoagulants on bleeding risk could be an important clinical consideration when treating patients with multiple indications for these therapies.

Database studies have played an important part in finding risk factors for GI haemorrhages [3, 9, 10] and this study was performed to refine knowledge of the empirical risk of antidepressants as well as to assess for drug–drug interactions at the population level to address concerns of residual confounding in previous studies.

Methods

The General Practice Research Database (GPRD) is a United Kingdom population-based database containing information entered from over 400 GP practices and having approximately 25 million patient years of data from the late 1980s until today [11]. Each practice entering the GPRD has a 'run in' period to ensure proper recording of information prior to it converting to an 'up to standard' practice where the information is considered to have a high degree of accuracy and validity [12]. The GPRD is prospectively updated and the accuracy of data entry is periodically controlled by on-site visits. Studies have shown that the GPRD is an accurate reflection of the general population in terms of demographics, investigation and treatments ordered [11–15]. Furthermore, linkage to other databases has shown accurate and valid recordings of specific diagnoses. This database is also ideal for pharmacovigilence and investigating the association between drug use and rare adverse events in the general population [15].

Using the GPRD, all cases with a first diagnosis of upper GI haemorrhage were identified in the database between January 2000 and December 2005 using a READ or OMXIS medical code recorded by the general practitioner. The date of the first GI haemorrhage recorded in the database was defined as the index date for the cases. All patients (cases or controls) were required to have at least 3 years of follow-up time between their first registration at a GPRD practice and their index date, otherwise they were excluded from the study.

The time period of the study was restricted from 2000 to 2005 in order to focus on more recent time periods as the primary study question involved drugs that were relatively recently introduced to the UK market. Up to 10 controls were selected for every case matched on GPRD practice, age ($\pm$ 2 years) and index date [16]. Incidence density sampling was used to match cases and controls on index date.

Exposure definition

Exposure to study drugs was defined by any prescription issued for a given medication in the 90 days prior to the index date. This was chosen as an assessment period as many of these drugs are issued for chronic use. The primary hypothesis of the study was to consider the independent effects of antidepressants, notably SSRIs, TCAs and an atypical antidepressant, venlafaxine, on the risk of GI haemorrhage. A secondary hypothesis was to assess for drug–drug interaction effects between the concurrent prescription of antidepressants and warfarin or clopidogrel on the risk of GI haemorrhage.

In order to control for confounding, drugs previously considered to be either protective against or conversely to promote GI haemorrhage were included in the analysis. These drugs were: the concomitant use of proton pump inhibitors, diuretics, histamine H_2-receptor antagonists,

antidepressants, antibiotics, corticosteroids and paracetamol. All drugs were defined using the British national formulary classification system.

Co-morbidity definition

Demographic characteristics of the cases and controls were compared, including age, sex, smoking status, body mass index (BMI) and history of heavy alcohol use, and past or current smoking. A BMI of less than 18 was considered underweight, a BMI greater than 30 but less than 40 to be obese and a BMI of 40 or greater was considered morbid obesity. The presence of a comorbid condition was defined as being any previous history (as defined by a GPRD medical code recorded by the General Practitioner) for a medical condition prior to the index date. In order to control robustly for confounding by health status, a broad range of indicators of patient morbidity as well as risk factors for GI bleeds or indications for warfarin use were considered.

A past history (defined as at least one GPRD medical for the condition recorded in the database prior to the index date) of the following diseases was also considered as a potential confounder: gastro-esophageal reflux, peptic ulcer disease, a recorded positive test for *Helicobacter pylori*, a high blood pressure reading in the past 1 year (systolic blood pressure above 160 mmHg or diastolic blood pressure above 100 mmHg), an elevated blood pressure reading in the past year but no high reading (systolic blood pressure above 140 mmHg or diastolic blood pressure above 85 mmHg), no blood pressure reading in the past year, liver failure, renal failure, rheumatoid arthritis, other types of arthritis (either unspecified or oesteoarthritis), diabetes, cancer (any type), chronic obstructive pulmonary disease and any form of dementia. The indication for warfarin use, including cardiac arrhythmia, pulmonary embolism, deep vein thrombosis, congestive heart failure, myocardial infarct, angina and stroke were also analyzed. Alcohol abuse was a comorbidity newly defined in the GPRD.

Other medications (as listed in Table 1) that were concommitantly taken by the patient were also included in the analysis as covariates. This included known risk factors like aspirin and other nonsteroidal anti-inflammatory drugs.

Data analysis

The primary data analysis was done using conditional logistic regression on a nested case control study design [17]. All covariates were entered into the model as well as multiplicative or statistical interactions between anticoagulants and antidepressants. Odds ratios (OR) were estimated using conditional logistic regression. Because we used incidence density sampling to select the controls, the OR can be considered an approximation of the rate ratio (RR) for the outcome [16, 18]. All analyses were performed using PROC PHREG in SAS version 9.1.3 software.

Table 1

Characteristics of upper gastrointestinal haemorrhage case-control study population

Covariates	Cases (n = 4028)	Controls (n = 40 171)
Personal characteristics		
Age (per year)	69.3/17.6	69.1/17.7
Mean/Standard deviation (Range)	(18–104)	(18–105)
Male sex	2171 (53.9%)	17 237 (42.9%)
Female sex	1857 (46.1%)	22 934 (57.1%)
Body mass index (kg m^{-2})		
<18	105 (2.6%)	690 (1.7%)
30–39.9	514 (12.8%)	4 780 (11.9%)
40+	56 (1.4%)	399 (1.0%)
Missing BMI	1064 (26.4%)	10 666 (26.6%)
18–29.9	2289 (56.8%)	23 636 (58.8%)
Blood pressure (BP)		
High blood pressure	959 (23.8%)	8 848 (22.0%)
Borderline blood pressure	978 (24.3%)	8 264 (20.6%)
No BP reading in the past year	1350 (33.5%)	17 541 (44.7%)
Normal blood pressure	741 (18.4%)	5 518 (13.7%)
Smoking		
Smoker	1797 (44.6%)	13 780 (34.3%)
No smoking recorded	468 (11.6%)	5 689 (14.2%)
Non-smoker	1763 (43.8%)	20 702 (51.5%)
Heavy alcohol use	395 (9.8%)	791 (2.0%)
Comorbid conditions*		
Acid reflux disease	431 (10.7%)	3 321 (8.3%)
Peptic ulcer	76 (1.9%)	403 (1.0%)
H. pylori	56 (1.4%)	228 (0.6%)
Pulmonary embolism	89 (2.2%)	410 (1.0%)
Deep vein thrombosis	139 (3.5%)	907 (2.3%)
Myocardial infarct	358 (8.9%)	2 014 (5.0%)
Angina	672 (16.7%)	4 477 (11.1%)
Stroke	329 (8.2%)	1 489 (3.7%)
Arrthymia	536 (13.3%)	3 362 (8.4%)
Congestive heart failure	472 (11.7%)	2 290 (5.7%)
Rheumatoid arthritis	101 (2.5%)	616 (1.5%)
Other arthritis	1252 (31.1%)	10 841 (27.0%)
Diabetes	512 (12.7%)	3 204 (8.0%)
Cancer	143 (3.6%)	852 (2.1%)
Dementia	171 (4.3%)	1 029 (2.6%)
Liver failure	89 (2.2%)	62 (0.2%)
Renal failure	125 (3.1%)	490 (1.2%)
COPD	354 (8.8%)	1 875 (4.7%)
Drug related covariates:		
Not NSAID or anticoagulant*		
Antibiotics	1009 (25.1%)	5 990 (14.9%)
Corticosteroids	599 (14.9%)	4 729 (11.8%)
Diuretics	1370 (34.0%)	10 348 (25.8%)
Histamine H_2-receptor antagonists	268 (6.7%)	1 287 (3.2%)
Heparin	4 (0.1%)	7 (0.02%)
Lithium	10 (0.2%)	69 (0.2%)
NSAIDs†	1627 (40.4%)	10 569 (26.3%)
Paracetamol	1336 (33.2%)	7 934 (19.8%)
Proton pump inhibitors	930 (23.1%)	3 985 (9.9%)

*Previous history of condition in GPRD medical records prior to index date. †This drug class includes aceclofenac, aspirin, celecoxib, dexketoprofen, diclofenac, difunisal, etololac, fenbufen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumeton, naproxen, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofanic acid and tolfenamic acid.

Results

There were 4028 cases identified in our study with a first-ever episode of GI haemorrhage in our study period. These cases were matched by age, general practice and index date to 40 171 controls. The demographic characteristics of the cases and controls are described in Table 1. Demographic variables that are associated with increased GI bleed risk included male sex and heavy alcohol use.

There were a number of comorbid conditions that we observed to be independently related to a higher rate of GI bleeds (Table 1) after multivariate analysis. These included liver failure and renal failure but additionally congestive heart failure (CHF) (Adjusted RR 2.34, 95% CI: 2.10, 2.62), diabetes (Adjusted RR 1.71, 95% CI: 1.54, 1.89) and cancer (Adjusted RR 1.73, 95% CI: 1.44, 2.08). Also, heavy alcohol use was found to be a highly significant confounder in the association between antidepressant use and GI haemorrhage, present in 9.8% of cases *vs.* only 2.0% of controls (Adjusted RR 4.00; 95% CI. 3.15, 4.63).

Among this general population, there was a small increased risk of GI bleed among users of SSRI medications. This risk decreased appreciably but remained significant after multivariate analysis (adjusted RR 1.33, 95% CI: 1.09, 1.62). Among users of tricyclic antidepressants, there was an elevated risk of GI bleed in univariate analysis that was eliminated with multivariate analysis (crude RR 1.52, adjusted RR 1.04). Venlafaxine was associated with the largest increase in GI haemorrhage risk (adjusted RR 1.85, 95% CI: 1.34, 2.55). In use as a single agent, the risk of GI haemorrhage on warfarin therapy was similar, if higher, to that observed among users of clopidogrel alone (adjusted RR 2.17, 95% CI: 1.82, 2.59 *vs.* RR 2.07, 95% CI: 1.6, 2.58). Both of these RR were substantially higher than the haemorrhage risk of SSRI use (Table 2).

We did find not find any evidence of statistical interaction (effect modification) for the co-ingestion of SSRI and warfarin ($P = 0.43$), SSRI and clopidogrel ($P = 0.30$) or TCA and warfarin ($P = 0.88$) or TCA and clopidogrel ($P = 0.79$).

Table 2

Effect of anticoagulants and antidepressants drugs on the rate of gastrointestinal haemorrhage

Agent	Cases ($n = 4028$)	Controls ($n = 40\,171$)	Crude rate ratio	Adjusted rate ratio*	95% confidence interval
Antidepressants					
SSRI	335 (8.3%)	1780 (4.4%)	1.97	1.33	1.09, 1.62
TCA	262 (6.5%)	1764 (4.4%)	1.52	1.04	0.83, 1.30
Venlafaxine	56 (1.4%)	229 (0.6%)	2.48	1.85	1.34, 2.55
Anticoagulant					
Warfarin	281 (7.0%)	1130 (2.8%)	2.64	2.17	1.82, 2.59
Clopidogrel	160 (4.0%)	532 (1.3%)	3.16	2.07	1.66, 2.58

*Adjusted for all of the variables in Table 1 (including concurrent medication use) as well as warfarin, clopidogrel and antidepressants.

We did not have enough power to analyze for potential interactions with the use of venlafaxine.

Discussion

The main finding of this study was the confirmation of increased GI bleeding risk of SSRI medications. However, this relative risk was small, and significantly less than the risk observed in earlier studies [2–4]. The risk from exposure to tricyclics was null. We also found that venlafaxine increased the risk of GI haemorrhage above that of traditional SSRIs.

Our other major finding was the absence of statistical interaction (i.e. effect modification) for bleeding for the concurrent use of warfarin with either SSRI or TCA medications. This finding supports other recent studies which also found no evidence of interaction between these drugs [19, 20]. Patients at higher risk should still exercise caution when adding an additional bleeding risk factor when at elevated risk due to current drug therapy.

A study by Dalton *et al*. [2] using a Danish database study found that SSRI use was associated with a RR = 3.6 of GI haemorrhage. These authors excluded patients deemed at higher risk of haemorrhage in order to control confounding as an alternative to multivariate analysis. In our study, multivariate analysis served to decrease the RR of SSRI on GI haemorrhage by controlling for confounders. Although the Dalton *et al*. study attempted to control for confounding by restriction, there was almost certainly residual confounding. This may explain the elevated RR for bleeding seen relative to our results. In particular, the addition of alcohol abuse as a novel covariate reduced the size of the associations observed between antidepressant use and GI bleeding. This finding is logical, as alcohol abuse is well known as a risk factor for both GI bleed and depression.

This is the first time, to our knowledge, that heavy alcohol use has been defined and used as a confounder in the GPRD. De Abajo *et al.* [3] also described an adjusted RR of 3 for SSRI on upper GI haemorrhage using the GPRD. Again, these results may be discrepant from ours due to residual confounding as the results were mainly adjusted for pharmacological agents and not for clinical covariates and disease comorbidities. It is crucial to adjust for comorbidities such as diabetes and cancer, as they have been described as independent risk factors for GI bleed as well as for depression and thus are classical confounders [21–24].

Another previous study by Meijer et al. [4] studied the effect of SSRI on the risk of 'abnormal bleeding' and also found a large effect. This definition included GI haemorrhage as well as bleeding from other sites (haematuria, cerebral, etc.). A minority of the bleeds that were reported

by Meijer et al. were upper gastrointestinal (15.8%) which makes directly comparing our results with their results difficult.

The strength of our study includes a widely validated database with millions of person-years follow-up that is representative of the United Kingdom population [12]. This allows us to look at the population level effects of this drug without the selection issues in a typical case control study.

As in all observational studies, there is always the possibility of unknown confounders that could bias the results of our study. However, we made extensive attempts to broadly control for confounding, including the novel use of heavy alcohol intake. Given the large number of conditions and medications that we have controlled for, it seems unlikely that there is a strong unmeasured confounder that would alter our results. However, it is always possible that there is a small degree of residual confounding due to variable measurement error as there is in any epidemiological study.

The ability for studies in the GPRD to control for potential confounders such as clinical blood pressure, alcohol use and smoking are key advantages that this study has over prescription claims database studies on these drugs. These results should be reassuring for physicians treating patients with depression who might be at high risk of GI haemorrhage. Although we are reporting a minimally increased risk of GI haemorrhage for patients exposed to SSRIs, it is significantly less than previously reported and not necessarily of clinical importance. In addition, we did not show an effect of tricylcic antidepressants, which is consistent with what is known about the pharmacology of these drugs.

The different risks of GI haemorrhage seen with different classes of antidepressants must be weighed in the balance of their other side-effects when making a prescription decision for the individual patient. The mechanism leading to increased risk due to venlafaxine exposure is unclear, but there are several possible explainations. As a newer drug, venlafaxine may be given more selectively to patients who have failed previous therapies and so the bleeding effect could be due to the characteristics of patients who are likely to fail initial antidepressant therapy. Another possibility could be that venlafaxine raises blood pressure [18]. While we adjusted for blood pressure in our analysis, the high degree of missing data creates the potential for residual confounding of this result.

The lack of evidence in our study of a statistical interaction with the concomitant use of warfarin or clopidogrel with antidepressant therapy is also reassuring to patients who are exposed to many different drugs in the course of treatment. While the power to find interactions between warfarin and antidepressants was limited in this study, other studies in the GPRD have successfully found warfarin drug–drug interactions in similar populations [25]. This suggests that any such drug–drug interaction is unlikely to be large.

The results of this study suggest that the risk of antidepressants is much lower than reported in previous observational research. Future research into medication-based risk factors for GI haemorrhage should consider the potential for confounding due to health status in populations at risk of GI haemorrhage.

Competing interests: None declared.
Funding: This study was funded by the Canadian Institutes of Health Research (CIHR) and the Canadian Foundation for Innovation. Dr Samy Suissa is the recipient of a Distinguished Scientist Award from CIHR. Dr Lucie Opatrny is a supported scholar from the Fondation de recherche en sante du Quebec.
Ethical approval: Ethical review for this study was done by the Independent Scientific Advisory Committee for MHRA database research.

REFERENCES

1 Rockall T, Logan R, Devlin H, Northfield T. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. BMJ 1995; 311: 222–6.

2 Dalton S, Johansen C, Mellemkjoer L, Norgard B, Sorensen H, Olsen J. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding. Arch Intern Med 2003; 163: 59–64.

3 de Abajo F, Garcia-Rodriguez L, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding; population based case-control study. BMJ 1999; 319: 1106–9.

4 Meijer W, Heerdink E, Nolen W, Herings R, Leufkens H, Egberts A. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. Arch Intern Med 2004; 164: 2367–70.

5 van Walraven C, Mamdani M, Wells P, Williams J. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. BMJ 2001; 323: 655–8.

6 Po A. Antidepressants and upper gastrointestinal bleeding. BMJ 1999; 319: 1081–2.

7 Pirmohamed M. Warfarin: almost 60 years old and still causing problems. Clin Pharmacol 2006; 62: 509–11.

8 Holbrook A, Pereira J, Labiris R, McDonald M, Douketis J, Crowther M, Wells P. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med 2005; 165: 1095–106.

9 Suissa S, Bourgault C, Barkun A, Sheehy O, Ernst P. Antihypertensive drugs and the risk of gastrointestinal bleeding. Am J Med 1998; 105: 230–5.

10 Jick S. The risk of gastrointestinal bleed, myocardial infarction, and newly diagnosed hypertension in users of meloxicam, diclofenac, naproxen, and piroxicam. Pharmacotherapy 2000; 20: 741–4.

11 Jick S, Kaye J, Vasilakis-Scaramozza C, Garcia Rodriguez L, Ruigomez A, Meier C. Validity of the general research practice database. Pharmacotherapy 2003; 23: 686–9.

12 Walley T, Mantgani A. The UK general practice research database. Lancet 1997; 350: 1097–9.

13 Garcia Rodriguez L, Perez Gutthann S. Use of the UK general research database for pharmacoepidemiology. Br J Clin Pharmacol 1998; 45: 425.

14 Lawrenson R, Williams T, Farmer R. Clinical information for research: the use of general practice databases. J Public Health Med 2006; 23: 299–304.

15 Wood L, Martinez C. The general research practice database: role in pharmacovigilence. Drug Saf 2004; 27: 871–81.

16 Clayton D, Hills M. Statistical Models in Epidemiology. Oxford: Oxford University Press, 1993; 161–2.

17 Suissa S. Novel approaches to pharmacoepidemiology study design and statistical analysis. In: Strom BL, ed. Pharmacoepidemiology. Chichester: John Wiley & Sons 2000; 785–805.

18 Feighner JP. Cardiovascular safety in depressed patients: focus on venlafaxine. J Clin Psychiatry 1995; 56: 574–9.

19 Wessinger S, Kaplan M, Choi L, Williams M, Lau C, Sharp L, Crowell M, Keshavarzian A, Jones M. Increased use of selective serotonin reuptake inhibitors in patients admitted with gastrointestinal haemorrhage: a multicentre retrospective analysis. Aliment Pharmacol Ther 2006; 23: 937–44.

20 Kurdyak P, Juurlink D, Kopp A, Hermann N, Mamdani M. Antidepressants, warfarin and the risk of hemorrhage. J Clin Psychopharmacol 2005; 25: 561–4.

21 Thomsen R, Riis A, Christensen S, Norgaard M, Sorensen HT. Diabetes and 30-day mortality from peptic ulcer bleeding and perforation: a Danish population basedcohort study. Diabetes Care 2006; 29: 805–10.

22 Nakaya N, Saito-Nakaya K, Akizuki N, Yoshikawa E, Kobayakawa M, Fujimori M, Nagai K, Nishiwaki Y, Fukudo S, Tsubono Y, Uchitomi Y. Depression and survival in patients with non-small cell lung cancer after curative resection: a preliminary study. Cancer Sci 2006; 97: 199–205.

23 Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. JAMA 1993; 270: 1819–25.

24 Engum A. The role of depression and anxiety in onset of diabetes in a large population-based study. J Psychosom Res 2007; 62: 31–8.

25 Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ 2007; 177: 347–51.