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Article

Serotonin-Norepinephrine Reuptake Inhibitors and the Risk of AKI: A Cohort Study of Eight Administrative Databases and Meta-Analysis

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Abstract

Background and objectives A safety signal regarding cases of AKI after exposure to serotonin-norepinephrine reuptake inhibitors (SNRIs) was identified by Health Canada. Therefore, this study assessed whether the use of SNRIs increases the risk of AKI compared with selective serotonin reuptake inhibitors (SSRIs) and examined the risk associated with each individual SNRI.

Design, setting, participants, & measurements Multiple retrospective population-based cohort studies were conducted within eight administrative databases from Canada, the United States, and the United Kingdom between January 1997 and March 2010. Within each cohort, a nested case-control analysis was performed to estimate incidence rate ratios (RRs) of AKI associated with SNRIs compared with SSRIs using conditional logistic regression, with adjustment for high-dimensional propensity scores. The overall effect across sites was estimated using meta-analytic methods.

Results There were 38,974 cases of AKI matched to 384,034 controls. Current use of SNRIs was not associated with a higher risk of AKI compared with SSRIs (fixed-effect RR, 0.97; 95% confidence interval [95% CI], 0.94 to 1.01). Current use of venlafaxine and desvenlafaxine considered together was not associated with a higher risk of AKI (RR, 0.96; 95% CI, 0.92 to 1.00). For current use of duloxetine, there was significant heterogeneity among site-specific estimates such that a random-effects meta-analysis was performed showing a 16% higher risk, although this risk was not statistically significant (RR, 1.16; 95% CI, 0.96 to 1.40). This result is compatible with residual confounding, because there was a substantial imbalance in the prevalence of diabetes between users of duloxetine and users of others SNRIs or SSRIs. After further adjustment by including diabetes as a covariate in the model along with propensity scores, the fixed-effect RR was 1.02 (95% CI, 0.95 to 1.10).

Conclusions There is no evidence that use of SNRIs is associated with a higher risk of hospitalization for AKI compared with SSRIs.

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Introduction

Antidepressants represent one of the most prescribed classes of drugs in developed countries and a steadily increasing use has been noted, with an estimated prevalence around 10% in the general population (1–4). The introduction of selective serotonin reuptake inhibitors (SSRIs)—as well as the newer agents, the serotonin-norepinephrine reuptake inhibitors (SNRIs)—contributed to this increase. SNRIs are a class of antidepressants that includes duloxetine, venlafaxine, and desvenlafaxine. Aside from its indication for major depressive disorder, venlafaxine is also indicated in most countries for the treatment of generalized anxiety disorder, social anxiety disorder, and panic disorder, whereas duloxetine is also indicated for generalized anxiety disorder, neuropathic pain associated with diabetic neuropathy, fibromyalgia, chronic low back pain, and osteoarthritis of the knee. Desvenlafaxine, the active metabolite of venlafaxine, is indicated for the treatment of major depressive disorder only.

The reasons for the success of SSRIs and SNRIs, which have now superseded older antidepressants as the first-line treatment of depression, include their better tolerability and safety profiles (5). However, a recent safety signal was identified by Health Canada regarding SNRIs. A series of 16 spontaneous reports of AKI in association with duloxetine were identified in the designated Medical Event Surveillance of the Canada Vigilance database. Moreover, there were 157 reports of AKI associated with duloxetine in the World Health Organization (WHO) Adverse Reaction Database. There were also postmarketing reports of AKI with the two other

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SNRIs, venlafaxine and desvenlafaxine. The biologic mechanism linking exposure to SNRIs and AKI is unknown, and there is limited evidence in the cases and in the scientific literature. However, this safety issue should be investigated in more depth, because of its severity and the large numbers of individuals exposed to these drugs in the general population.

The primary objective of our study was therefore to assess whether the use of SNRIs increased the risk of AKI compared with the use of SSRIs. The secondary objective was to examine the risk of AKI associated with each individual SNRI drug. SSRIs were chosen as the comparator to help the clinically relevant decision of which antidepressant medication to use as opposed to the question of whether to prescribe an antidepressant.

Materials and Methods

Study Design

We conducted a retrospective population-based cohort study within each of eight databases comprising the Canadian Network of Observational Drug Effect Studies (CNODES) (6), using a common analytical protocol. Within each cohort, a nested case-control analysis was performed to estimate incidence rate ratios (RRs) of AKI associated with SNRIs compared with SSRIs, and the overall effect was then estimated using meta-analytic methods. Research ethics approval was obtained from the relevant institutions in each site.

Data Sources

The eight CNODES databases used in this study included the health administration databases of the provinces of Alberta, Manitoba, Ontario, Nova Scotia, Quebec, and Saskatchewan, as well as the UK Clinical Practice Research Datalink (CPRD) and the US MarketScan database, corresponding to a total source population of >43 million patients.

Cohort Definition

The cohort comprised all patients in each database aged ≥12 years (or ≥65 years in Alberta, Nova Scotia, and Ontario) with a first prescription of an SNRI (duloxetine, venlafaxine, or desvenlafaxine) or an SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline) between January 1, 1997 (or 1 year after the beginning of data availability) and March 31, 2010. The indication for an antidepressant was not considered for cohort entry. We defined a new-users cohort by selecting only patients newly treated with an SNRI or SSRI (*i.e.*, without any SSRIs or SNRIs dispensed in the previous 365 days). Patients were excluded if they had (*1*) <1 year of information in the database before the date of cohort entry, (*2*) a prescription or dispensation of an SNRI or SSRI in the year preceding cohort entry, or (*3*) a history of kidney transplantation, dialysis, or AKI in the year preceding cohort entry. Patients were also excluded if they had a prescription for both an SNRI and an SSRI the day of cohort entry. Cohort entry was taken as the date of the first new prescription for an SNRI or SSRI. Patients were followed until the date of their first outcome event (AKI), death, 730 days (2 years) after cohort entry, or the end of the study period, whichever occurred first. Each individual was allowed to enter the cohort only once.

Case Definition

The primary end point was defined, using a validated algorithm (7–9), as hospitalization with a diagnosis of AKI within 730 days of initiation of treatment with an SNRI or SSRI (diagnosis code for AKI in any of the listed diagnoses; International Classification of Diseases, Ninth Revision, Clinical Modification codes 584, 584.5, 584.6, 584.7, 584.8, or 584.9; International Classification of Diseases, Tenth Revision, codes N17, N17.0, N17.1, N17.2, N17.8, or N17.9).

Control Selection

For each case, up to 10 controls were randomly selected among the cohort members in the risk sets defined by the case, after matching on age (±1 year), sex, and date of cohort entry (±1 year). The matching on calendar time permitted control for trends over time in the use of antidepressant drugs and changes in incidence of the outcome. Because controls were selected from the risk set defined by each case, all controls were necessarily alive and event free when matched to their corresponding case. The index date for each case was the date of hospital admission for the outcome event, and the index date for the controls was chosen in order for the controls to have the same duration of follow-up as their matched cases.

Definition of Exposure

The clinically relevant exposure period considered for data analysis was a maximum of 2 years preceding the index date, and exposure to SNRIs and SSRIs was classified according to prescriptions issued during this time period (Figure 1). Current exposure to SNRIs and SSRIs was defined as a prescription dispensed in the 60 days before the index date. A 60-day observation period was chosen based on the assumption of a 30-day duration of prescription with a 30-day grace period. Past recent use was defined as a prescription dispensed 60–180 days before the index date. Finally, past use was defined as a prescription issued >180 days, but not >730 days, before the index date. Patients currently exposed to both an SNRI and an SSRI (*i.e.*, switching between classes within the 60 days before the index date) were classified according to the last prescription issued during the 60-day current exposure period. Among the SNRI and SSRI current exposure categories, we also defined categories of switchers and nonswitchers. A SNRI switcher was a current SNRI user with an SSRI prescription at any time during follow-up including the 60 days before the index date. An SSRI switcher was a current SSRI user with an SNRI prescription at any time during follow-up including the 60 days before the index date.

Covariates

In addition to the inherent adjustment by matching factors, control for confounding was achieved using high-dimensional propensity scores (hdPSs) (10). The hdPSs were estimated for all patients in the cohorts using information up to and including the 365 days before cohort entry. Briefly, all available variables in the study databases such as demographics,

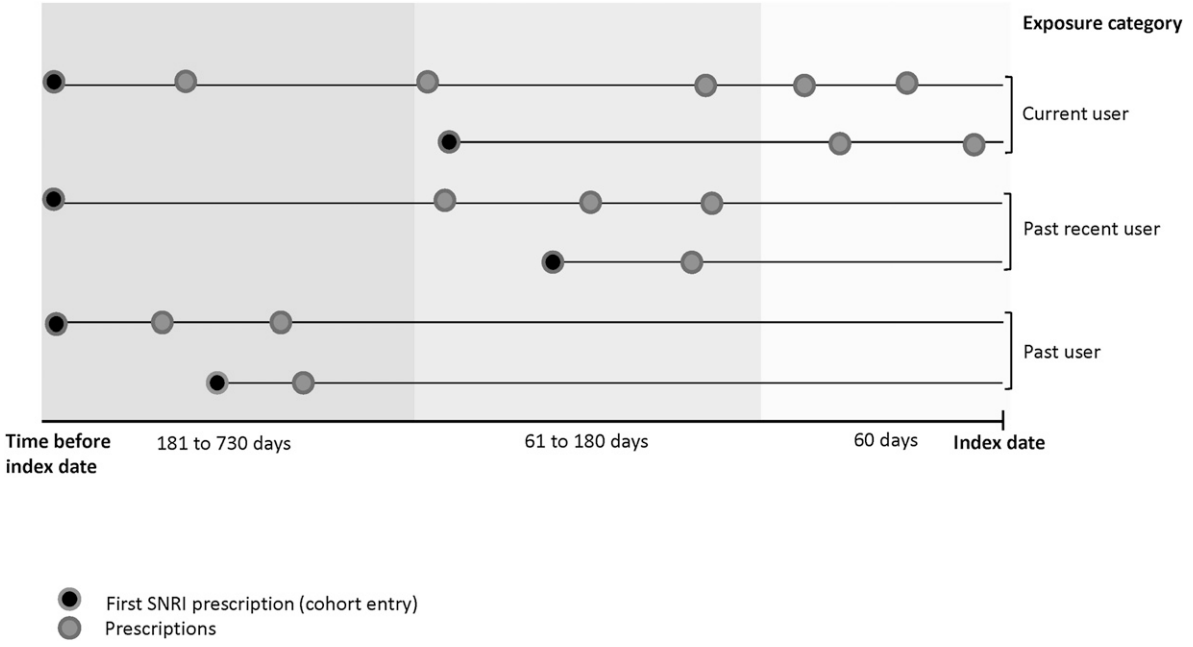

Figure 1. | **Definition of drug exposure.** SNRI, serotonin-norepinephrine reuptake inhibitor.

diagnostics, procedures, drugs dispensed, and use of health services were classified according to their potential to cause bias in the estimate of the exposure-outcome association. The 500 variables most likely to cause bias were included in a propensity score model. Important potential confounding variables—namely, calendar year of cohort entry, hypertension (defined as disease diagnosis or hypertensive drugs), diabetes (defined as disease diagnosis or antidiabetic drugs), and CKD—were forced into the hdPS. Logistic regression was used to estimate the predicted probability (hdPS) of exposure to SNRIs or SSRIs, conditional on all of the included covariates. The cohorts were trimmed by excluding the 5% of patients (or more if needed) at either end of the distribution of the hdPS to ensure overlap in the distribution of covariates for SNRI and SSRI users.

Statistical Analyses

A time-matched, nested case-control analysis of the cohorts was used to assess the effects of SNRIs and SSRIs in relation to the date of AKI. This nested case-control approach is computationally more efficient than a time-dependent survival analysis while producing equivalent

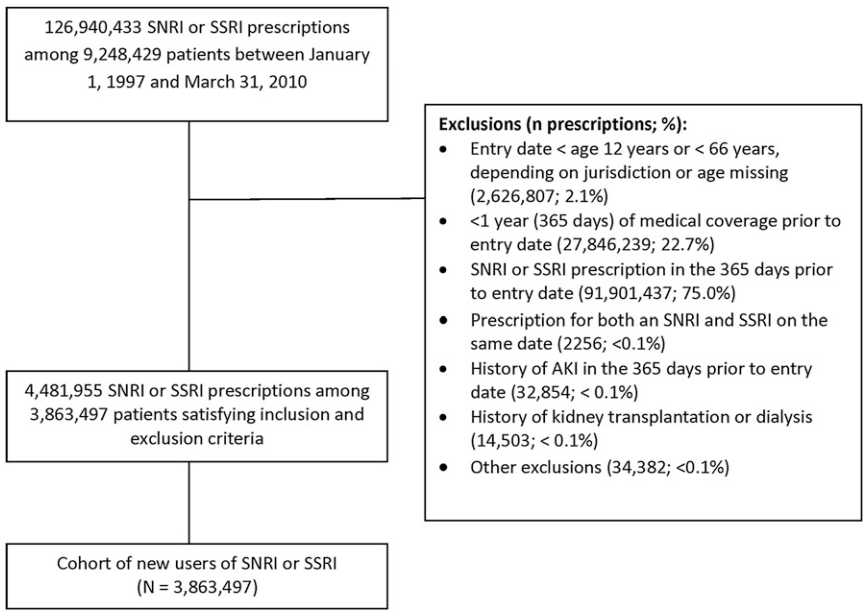

Figure 2. | **Flowchart of cohort definition.** SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

estimates (11,12). Incidence RRs of AKI associated with current use of SNRIs compared with SSRIs and their corresponding 95% confidence intervals (95% CIs) were estimated from the odds ratios calculated using conditional logistic regression. By the matching process, all RRs were adjusted for sex, age, duration of follow-up, and calendar time. In addition, we adjusted for hdPS deciles and income quintiles. The primary analysis estimated the risk of AKI associated with a 60-day period of current use for SNRIs compared with a 60-day period of current use for SSRIs. Secondary analyses were performed to determine the risk of AKI associated with current exposure to each SNRI separately compared with SSRIs. In sensitivity analyses, the current windows of exposure were defined as 30 days and 120 days, and past recent use and past use were also investigated using a 60-day exposure window. All site-specific analyses were conducted independently at each site using SAS software (versions 9.2–9.4; SAS Institute, Cary, NC).

Meta-Analysis

Results from the individual databases were combined using fixed-effects meta-analytic techniques. Of note, the Ontario, Quebec, and the US MarketScan databases represent more than one-half of the weight in the meta-analysis. A random-effects model was adopted if there was evidence of significant heterogeneity, based on the I^2 statistic (I^2 of ≥50%) (13). After the initial analysis demonstrated heterogeneity in the results for the risk of AKI with use of duloxetine (I^2 = 72%), we included an independent analysis from the US MarketScan database for patients aged >65 years. The original protocol included only patients aged <65 years from that database. The data were summarized using RevMan Review Manager software (version 5.2; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Including all participating sites, a total of 641,184 new users of SNRIs and 3,222,313 new users of SSRIs were identified (Figure 2). Their baseline characteristics are presented in Supplemental Table 1. The incidence rates of AKI varied across the data sets, from 1.98 per 1000 person-years in the CPRD database to 2.39 in the Manitoba database (in which both databases included individuals aged ≥12 years), and 12.94 in Alberta, 14.28 in Ontario, and up to 31.32 in the US

Table 1. Baseline characteristics of cases and their matched controls

Characteristic	Cases	Controls
Participants	38,974 (100)	384,034 (100)
Age (yr)		
12–17	52 (0.1)	481 (0.1)
18–24	184 (0.5)	2012 (0.5)
25–44	1601 (4.1)	16,113 (4.2)
45–64	7608 (19.5)	76,058 (19.8)
65–74	8265 (21.2)	82,400 (21.1)
≥75	21,249 (54.5)	206,970 (54.2)
Sex		
Female	20,710 (53.1)	205,185 (53.1)
Male	18,264 (46.9)	178,849 (46.9)
Calendar year of cohort entry		
1997–1999	1816 (4.7)	18,408 (4.8)
2000–2002	5452 (14.0)	55,087 (14.3)
2003–2005	6043 (15.5)	59,622 (15.5)
2006–2008	16,022 (41.1)	157,649 (41.1)
2009–2010	9641 (24.7)	93,268 (24.2)
Hypertension	32,134 (82.5)	255,705 (66.6)
Diabetes	14,228 (36.5)	73,452 (20.9)
Congestive heart failure	8433 (21.6)	28,733 (7.5)
Cirrhosis	1066 (2.7)	2968 (0.7)
Depression	7591 (19.5)	72,539 (18.6)
Number of hospitalizations		
0	20,103 (51.6)	275,585 (71.9)
1	10,374 (26.6)	71,811 (18.6)
2	4547 (11.7)	23,747 (6.2)
≥3	3950 (10.1)	12,891 (3.3)
Nonsteroidal anti-inflammatory drugs	10,362 (26.6)	100,794 (25.6)
Angiotensin-converting enzyme inhibitors	16,427 (42.1)	105,842 (27.2)
Angiotensin II receptor blockers	7843 (20.1)	55,642 (14.2)
Diuretics	15,908 (40.8)	101,780 (26.3)
Follow-up time (d), mean (SD)	312.9 (219.2)	312.8 (219.2)

Data are presented as *n* (%) unless otherwise indicated. Cases and controls were matched for age, sex, date of cohort entry, and duration of follow-up. For controls, means (SDs) and percentages are weighted by the inverse of the number of controls matched to each case.

MarketScan database (in which the databases include only patients aged >65 years). These variable rates of AKI are likely explained by the age differences in the eight cohorts. Of note, and to contrast the rates of AKI with those of other diseases, the rate of myocardial infarction varied from 1.53 to 15.69 per 1000 person-years, whereas the rate of hyperglycemic emergencies varied from 0.2 to 1.91 per 1000 person-years. The baseline characteristics for the cases of AKI and their matched controls are presented in Table 1. As expected, cases had a higher prevalence of comorbidities, such as hypertension and diabetes, than controls as well as a higher exposure to angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics at cohort entry.

Figure 3 displays a forest plot for the primary analysis of the risk of AKI associated with current use of SNRIs compared with SSRIs, using a 60-day exposure window. There was no excess risk of AKI (RR, 0.97; 95% CI, 0.94 to 1.01) associated with current use of SNRIs compared with current use of SSRIs. Similarly, there was no excess risk associated with past recent use of SNRIs (RR, 1.02; 95% CI, 0.95 to 1.09) or with past use using this same exposure window (RR, 1.00; 95% CI, 0.95 to 1.04) compared with SSRI use (Supplemental Figures 1 and 2).

Restricting the analysis to current users who did not switch from SSRIs to SNRIs or *vice versa* during the study period yielded similar results to the primary analysis (RR, 0.98; 95% CI, 0.94 to 1.02) (Supplemental Figure 3). The results were also consistent when changing the definition of current exposure to SNRIs and SSRIs to 30 days or 120 days before the index date (Supplemental Figures 4 and 5). We performed two stratified analyses to check the consistency of our results. First, we repeated the primary analysis, stratified by calendar time to assess the potential effect of increasing sensitivity of diagnostic codes over time (Supplemental Figure 6). Second, we restricted our primary analysis to cases of AKI as a primary diagnostic (Supplemental Figure 7). The results were virtually unchanged in these analyses.

Figures 4 and 5 describe the risk of AKI comparing the different SNRIs to current SSRI use. Current use of venlafaxine and desvenlafaxine considered together was not associated with a higher risk of AKI (RR, 0.96; 95% CI, 0.92 to 1.00) compared with current SSRI use (Figure 4). For current use of duloxetine, although there was no clear evidence of a higher risk (RR, 1.07; 95% CI, 0.99 to 1.16), there was significant heterogeneity (I^2 = 72%) among site-specific estimates (Figure 5), such that a random-effects meta-analysis was performed (Supplemental Figure 8). Although the RR of 1.16 (95% CI, 0.96 to 1.40) was not statistically significant in this analysis, the size of this estimate may be of concern. Therefore, we examined indications for use of duloxetine in Quebec and Ontario, where the individual estimates suggested an excess risk of AKI associated with duloxetine. In Quebec, use of duloxetine is limited to patients with diabetes, such that almost 95% of users of duloxetine had diabetes as opposed to 18.6% of venlafaxine users. In Ontario, the corresponding figures were 36.8% of users of duloxetine having diabetes compared with 20.5% of venlafaxine users. Hence, we performed a supplementary analysis including diabetes as an additional covariate in the model, along with hdPS deciles and income quintiles. The resulting RR in the fixed-effects meta-analysis was 1.02 (95% CI, 0.95 to 1.10) (Supplemental Figure 9).

Discussion

In this large new-users cohort, we found no evidence of an excess risk of hospitalization for AKI with use of SNRIs compared with SSRIs. The results were consistent between databases, and they did not change when varying the time windows of current exposure to 30 and 120 days or when eliminating patients who had switched between SSRIs and SNRIs.

When looking specifically at duloxetine, the estimates of risk of AKI were somewhat higher, although they were not statistically significant. Because the hdPS adjustment was carried out for SNRIs combined, insufficient adjustment for concomitant diabetes likely explains the slightly higher risk of AKI with duloxetine. Indeed, we found no higher risk of AKI with current use of duloxetine once diabetes was added to the model.

Recently, several cases of AKI after exposure to SNRIs, in particular to duloxetine, were reported to Health Canada and the WHO. After the identification of this safety signal, Health

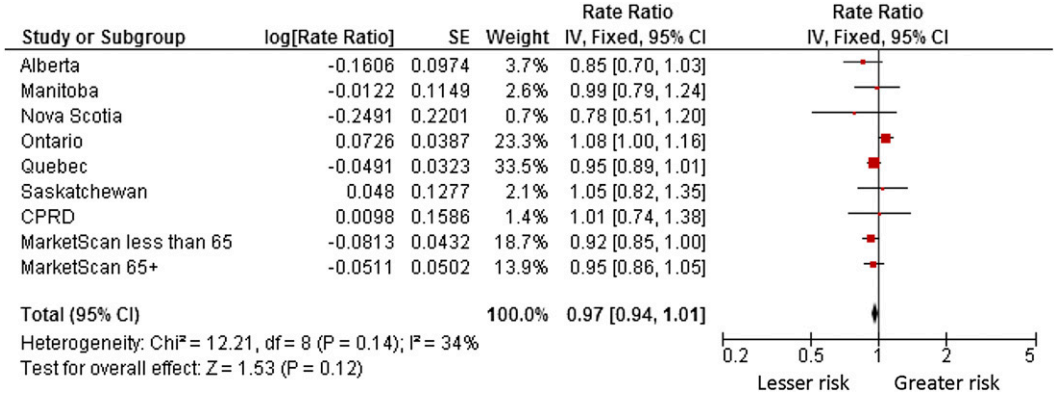

Figure 3. | Adjusted rate ratios of AKI associated with current use of SNRIs compared with current use of SSRIs. Results are based on a 60-day observation window to define current use. For example, current SNRI use is defined as ≥1 SNRI prescription dispensed within or including 60 days before the index date, regardless of prescriptions dispensed between 61 and 730 days before the index date. Current SSRI use is defined in a consistent way. IV, inverse variance; 95% CI, 95% confidence interval; CPRD, Clinical Practice Research Datalink; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

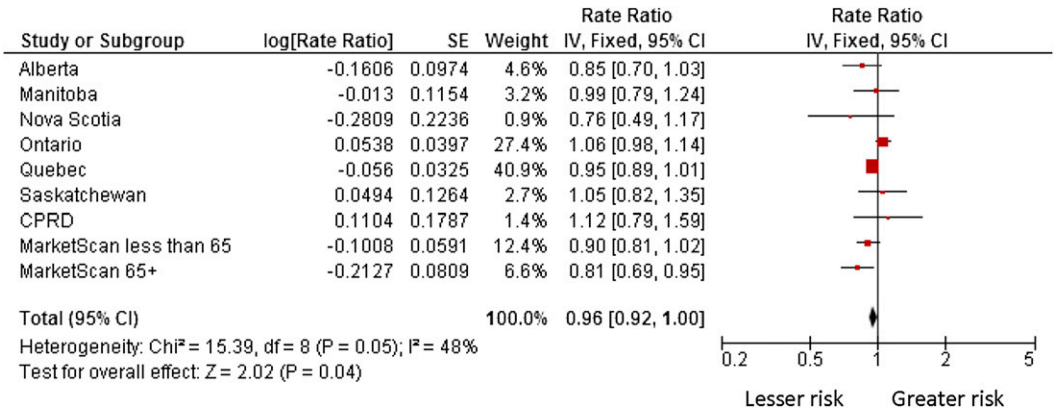

Figure 4. | **Adjusted rate ratios of AKI associated with current use of venlafaxine and desvenlafaxine compared with current use of SSRIs.** Results are based on a 60-day observation window to define current use. IV, inverse variance; 95% CI, 95% confidence interval; CPRD, Clinical Practice Research Datalink; SSRI, selective serotonin reuptake inhibitor.

Canada requested CNODES to further investigate this potential risk (14), owing to the potential severity of AKI as well as the extent and steadily increasing use of SNRIs in the population. Moreover, patients using antidepressants may represent a vulnerable population because antidepressants are most frequently used to treat depression or chronic pain, conditions often associated with comorbidities. In particular, it has been shown that major depressive disorders worsen the outcome of other comorbid illness, including kidney disease (15). Aside from this safety signal, the scientific literature is scarce on the potential risk of AKI after exposure to SNRIs. To our knowledge, only one study reported a higher risk of renal failure (and several other outcomes) associated with exposure to SNRIs or SSRIs (as one category) compared with nonuse in a cohort of patients who underwent coronary artery bypass grafting (16). Aside from the fact that it was a selected population, the time of measurement of exposure to antidepressants was not specified, and the exposure group likely included both incident and prevalent users. Moreover, the use of a nontreated group as a comparator increases the potential for residual confounding, particularly because the exposed group had more comorbidities, including renal disease, at baseline. In any case, the direct comparison with our result is difficult because the authors did not directly compare SNRI use to SSRI use.

This large population-based study has several strengths. First, we used a new-users design to avoid potential biases related to the inclusion of prevalent users (17). Second, the selection of cases and controls among a well defined cohort in each jurisdiction eliminates the potential for selection bias. Finally, we used a validated algorithm for the definition of AKI in administrative databases, previously used in another CNODES study (7). Of note, this definition includes hospitalized AKI only; therefore, we did not capture milder cases that did not require hospitalization. In addition, the sensitivity of diagnostic codes for AKI is only modest, ranging from 35% in adults discharged from the hospital to 61% in elderly patients at hospital admission (8,9). However, there is no reason to believe that this misclassification would be differential between those exposed to SSRIs and SNRIs. Other limitations related to the observational nature of the study need to be considered. In particular, confounding by indication may be an issue, but confounding was minimized by the use of an active comparator group (SSRIs) and the use of hdPSs estimated at cohort entry, with follow-up time set at a maximum of 2 years to lessen the effect of confounders varying with time. However, the control for confounding using hdPSs was implemented at the exposure class level (*i.e.*, among SNRI and SSRI users). Therefore, residual confounding likely explains the trend toward a small higher risk of AKI

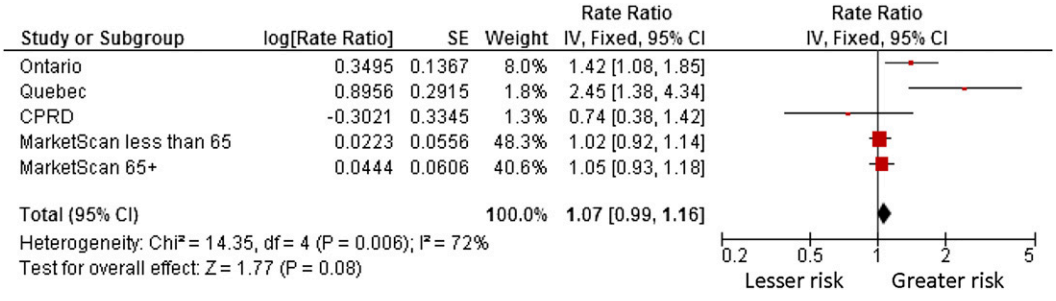

Figure 5. | **Adjusted rate ratios of AKI associated with current use of duloxetine compared with current use of SSRIs.** Fixed-effects meta-analysis. Results are based on a 60-day observation window to define current use. IV, inverse variance; 95% CI, 95% confidence interval; SSRI, selective serotonin reuptake inhibitor; CPRD, Clinical Practice Research Datalink.

associated with duloxetine compared with SSRIs, because no excess risk was found after adjustment for diabetes in the supplementary analysis. Some degree of exposure misclassification is also likely to be present. For instance, some patients classified as currently exposed may not be compliant or may not have had more than one prescription. However, this misclassification is unlikely to be different between those exposed to SSRIs and SNRIs. Another limitation is the lack of knowledge as to the biologic mechanism underlying the potential risk of AKI with exposure to SNRIs, resulting in uncertainty regarding the relevant period of exposure. Therefore, sensitivity analyses were conducted to explore the effect of different exposure time windows with no evidence of a higher risk of AKI whatever the exposure definition chosen.

In conclusion, our analysis does not support a higher risk of AKI associated with SNRI use, collectively or individually, compared with SSRI use. Therefore, when an antidepressant is indicated, prescribers may not need to take AKI into account in their choice between these two classes.

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Disclosures

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