**CNODES**

**Scientific Protocol**

**Serotonin-norepinephrine reuptake inhibitors and acute kidney injury**

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# Document Control

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| --- | --- | --- |
| Version | Author(s) | Type of Change |
| 1.0 | CR, PE | Initial first draft  |
|  | BH, CD | suggestions throughout |
| 2.0 | CR, PE | Based on discussion by Team |
| 2.1 | CR, PE | Based on comments received |

Abbreviations: CR: Christel Renoux; PE: Pierre Ernst.

# Background

 Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressants that include duloxetine, venlafaxine and desvenlafaxine. Aside from its indication for depression, venlafaxine is also indicated for the treatment of generalized anxiety disorder, social anxiety disorder and panic disorder whereas duloxetine is also prescribed for generalized anxiety disorder, neuropathic pain associated with diabetic neuropathy, fibromyalgia, chronic low back pain and osteoarthritis of the knee. Desvenlafaxine is indicated for the treatment of major depressive disorder only.

 According to data obtained from IMS Health Canada Inc, a steadily increasing use of SNRIs has been noted, with 1.2 million prescriptions of duloxetine, 6.7 million prescriptions of venlafaxine and 280 000 of desvenlafaxine dispensed in 2011 in Canada.

 A series of 16 spontaneous reports of renal failure in association with duloxetine were identified in the designated Medical Event Surveillance of the Canada Vigilance database. Moreover, there were 157 reports of acute kidney injury (AKI) associated with duloxetine in the WHO Adverse Reaction Database. There were also post-marketing reports of acute/chronic renal failure with the two other SNRIs, venlafaxine and desvenlafaxine. The mechanism for AKI associated with SNRIs is unknown.

 As the signal assessment focused on SNRIs and AKI, information was not provided on AKI in users of selective serotonin reuptake inhibitor (SSRIs) antidepressants. However, the review of the product monographs for SSRIs available in Canada suggests that there have been post-marketing cases of AKI with many of the SSRIs. Therefore, an increased risk of AKI may not be limited to SNRIs but may extend to related classes of antidepressants such as SSRIs.

# Justification of the proposed study

AKI is a serious potential health risk.

SNRIs are widely used by Canadians.

The population treated with these medications is highly vulnerable given that the indications for use are psychiatric disorders and chronic pain.

SNRIs and SSRIs being widely used, particularly as first line treatment for depression, it is important to examine if SNRIs are associated with a higher risk of AKI compared with SSRIs to guide the choice of antidepressant according to patients’ characteristics.

# Objectives

## Primary objective

 To assess whether the use of SNRIs increases the risk of acute kidney injury (AKI) compared to the use of SSRIs in a new users’ cohort.

## Secondary objectives

1. To assess whether the use of duloxetine increases the risk of AKI compared to the use of SSRIs.
2. To assess whether the use of venlafaxine increases the risk of AKI compared to the use of SSRIs.
3. To assess whether the use of desvenlafaxine increases the risk of AKI compared to the use of SSRIs.

# Methods

## Study Design

 We will conduct a retrospective population-based cohort study to assess the risk of AKI associated with SNRIs compared with SSRIs in a cohort of newly treated patients within each of 8 CNODES databases. The results of these database-specific analyses will then be pooled via meta-analysis across databases to obtain summary treatment effects. We will use both cohort and nested case-control analyses within the CNODES population to estimate the rate ratios of AKI associated with SNRI treatment as compared to treatment with SSRIs.

## Data sources

 The provincial health administration databases of the provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec and Nova Scotia, as well as the Clinical Practice Research Datalink (CPRD) in the U.K. and the U.S. Market scan data.

## Cohort definition

 The cohort will be formed of all patients in the database aged 12 or older (or 65 or older in some of the databases) with a first prescription of an antidepressant of the SNRI or SSRI class of any dose between January 1, 1997 and March 31, 2010. The antidepressants used to define cohort entry will include the following drugs:

* SNRI: duloxetine, venlafaxine, desvenlafaxine.
* SSRI: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

 The indication for antidepressant treatment will not be considered for cohort entry. To reduce the potential for confounding by progression and severity of the medical condition, we will define a new-user cohort by selecting only patients newly treated with antidepressants.

Exclusion criteria:

 Subjects will be excluded if:

* They are <12 years old at the time of cohort entry.
* They have less than 1 year of information in the database prior to the date of cohort entry.
* They have a prescription of an SNRI or SSRI in the year before the date of cohort entry.
* They have a have a prescription for both an SNRI and an SSRI the day of cohort entry.
* They have a history of chronic kidney disease (including kidney transplantation and dialysis) or AKI in the year preceding cohort entry.
* The subject was previously included in the cohort.

 Cohort entry (time zero) will be taken as the date of the first new prescription for an SNRI or an SSRI which occurs once the subject has met all the inclusion and none of the exclusion criteria. Patients will be followed until the date of their first outcome event i.e., AKI, death, 730 days (2 years) after cohort entry, or end of the study period, whichever occurs first. Each subject will be allowed to enter the cohort only once.

## Case definition

 The primary endpoint is acute kidney injury (AKI) occurring after cohort entry and defined, using a validated algorithm (1), as hospitalization for AKI within 730 days of initiation of treatment with an antidepressant (diagnosis code for acute kidney injury in any of the listed diagnoses; ICD-9-CM codes 584, 584.5, 584.6, 584.7, 584.8, or 584.9; ICD-10 N17, N17.0, N17.1, N17.2, N17.8, or N17.9). This outcome has been defined and used in a previous CNODES study. Therefore, each center will use the previously created algorithm to define AKI.

## Control selection

 For each case, up to 10 controls will be 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 permits to control for trends over time in the use of antidepressant drug and changes in incidence of the outcome. Because controls will be selected from the risk set defined by each case, which includes all individuals who are still at risk of the event at the time of this event for the case, all controls will necessarily be alive, covered by health plan, and event-free when matched to their corresponding case. The index date for each case is the date of the outcome event and the index date for the controls will be chosen in order for the controls to have the same duration of follow-up as their matched cases (i.e., an index date that corresponds to the sum of their cohort entry date and the case’s duration of follow up).

## Definition of exposure

 The clinically relevant exposure period considered for data analysis will be a maximum of 2 years preceding the index date, and exposure to SNRIs and SSRIs will be classified according to prescriptions dispensed (or written for CPRD) during this time period. Thus, for all cases and their matched controls, we will identify all prescriptions for SNRIs and SSRIs from the database during up to 2 years after cohort entry or between cohort entry and the index date.

*As treated analysis with nested case-control analysis:* Current exposure to SNRIs and SSRIs will be defined as a prescription lasting until the index date or dispensed or written in the 60 days before the index date. A 60 days period has been chosen based on the assumption of a 30 days duration of prescription with a 30 days grace period. Past recent use will be defined as a prescription dispensed 180 to 60 days prior to the index date. Finally, past use will be defined as a prescription issued more than 180 days before the index date. Patients currently exposed to SNRI and SSRI will be classified according to the last prescription issued during the 60 days current exposure time period. Consequently, current users, past recent users and past users will represent mutually exclusive exposure categories. The reference category for the primary analysis will consist of current users of SSRIs. In sensitivity analyses, the current time windows of exposure will be defined as 30 days and 120 days.

 After defining the cohorts of SNRIs and SSRIs users, we will examine patterns of use to determine the frequency of switching from SNRIs to SSRIs and vice versa. If this occurs in more than 10% of cohort members, we will form a cohort of switchers and examine rates of the outcome in this group separately.

*As treated analysis with Cox model:* Subjects will be censored at the date of any switch to the other study antidepressant or discontinuation of cohort entry antidepressant, Current use will be defined as a prescription dispensed within the 30-day period of the date defined by the risk set of the Cox model

## Covariates

 In addition to the inherent adjustment by matching factors (age, sex and date of cohort entry), control for confounding will be achieved using high-dimensional propensity scores (hd-PS) which will be estimated for all patients in the cohorts using information for the year prior to cohort entry including the day of cohort entry. Hd-PS is an empirically driven, multistep process to adjust for confounding bias in observational studies.(2) The hd-PS algorithm prioritizes thousands of drug, diagnostic, procedure and demographic variables according to their potential to cause bias in the estimate of a multiplicative estimate of an exposure-outcome association (e.g. rate ratio). Typically, the 200 to 500 variables most likely to cause bias are included in a propensity score model. Logistic regression will used to estimate the predicted probability (propensity score) of exposure to SNRIs or SSRIs, conditional on all of the included covariates. Theoretically, balancing or adjusting a study dataset for treatment propensity score should remove confounding from any confounders that were included. Important potential confounding variables such as hypertension and diabetes will be forced into the hd-PS. Matching variables (age, sex and calendar time) will not be included in the hd-PS.

## Data analysis

Two different as treated analyses will be performed:

1/A time-matched, nested case-control analysis of the cohort will be used to assess the effects of SNRIs and SSRIs in relation to the date of AKI, while simultaneously adjusting for the potentially confounding variables described above. This nested case-control approach is computationally simpler than a time-dependent survival analysis while producing equivalent estimates. Incidence rate ratios of AKI associated with current use of SNRIs compared with SSRIs and their corresponding 95% confidence intervals (CI) will be estimated from the odds ratios calculated using conditional logistic regression. By the matching process, all rate ratios will be inherently adjusted for sex, age, duration of follow-up, and calendar time. In addition, we will adjust for deciles of propensity score. The primary analysis will estimate the risk of AKI associated with 60 days current use of SNRIs compared with 60 days current use of SSRIs. Secondary analyses will be performed to determine separately the risk of AKI associated with current exposure to the each SNRI separately as compared to SSRIs, sample size permitting.

2/A Cox proportional hazard regression model will be used to assess the effect of current use of SNRIs versus SSRIs on the occurrence of AKI. In this analysis, patients will be censored at the date of end of treatment or switching to the other antidepressant

Sensitivity analysis

 We will conduct the following sensitivity analyses to assess the robustness of our results:

 First, we will repeat the nested case-control analysis using a current exposure definition of 30 days and 120 days.

 Second, we will repeat the cohort analysis extending the current exposure period to 60 days.

## Power calculations

 Using the population database of 43.5 million patients in the statins AKI project (3) (seven Canadian provinces (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, Quebec, and Saskatchewan; source population 33 million in 2011), two international databases in the United Kingdom (General Practice Research Database (CPRD), 6 million in the HES subcohort) and the US (MarketScan, 4.5 million)), and assuming that 7.5% will be exposed to antidepressants (4;5), we will constitute a cohort of 3.2625 million patients. We expect to follow this cohort for a maximum of 2 years after the first antidepressant prescription, for a total follow-up of 6.525 million person-years. According to previous studies (6;7) we assume the AKI incidence rate to be within 0.93/10,000 person-years and 2.12/10,000 persons-year. The cohort is therefore expected to generate from 300 to 1383 cases of AKI during the study period.

 The table below shows that, given the above assumptions and assuming the lowest rate of 0.93/10,000, 100% of patients still exposed to antidepressants, 45% exposed to SNRI and 55% to SSRIs there will be 91% power to detect an odds ratio for incident AKI of 1.5 or greater for SNRI compared to SSRIs. . Assuming that 50% would still be exposed to antidepressants, the power will be 94% to detect an odds ratio of 1.35 comparing SNRI to SSRIs.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| SNRI vs.SSRI |  |  |  |  |  |  |  |
|   |   |   |   | **OR** |   |   |   |
| **Cases** | **1.1** | **1.2** | **1.3** | **1.35** | **1.4** | **1.45** | **1.5** |
| **300** | 0.1209985  | 0.3259889  | 0.5821311  | 0.6972305  | 0.7919986  | 0.8640978  | 0.9152478  |
| **424.9** | 0.1535931  | 0.4339146  | 0.7311989  | 0.8374581  | 0.9094281  | 0.9532207  | 0.9774621  |
| **485.6** | 0.1693350  | 0.4826924  | 0.7861912  | 0.8822266  | 0.9410541  | 0.9729952  | 0.9885869  |
| **546.3** | 0.1850303  | 0.5287565  | 0.8313111  | 0.9155943  | 0.9621635  | 0.9846684  | 0.9943319  |
| **607** | 0.2006792  | 0.5719837  | 0.8678843  | 0.9400971  | 0.9760086  | 0.9914223  | 0.9972325  |
| **691** | 0.2222491  | 0.6270326  | 0.9068146  | 0.9632611  | 0.9874534  | 0.9962403  | 0.9989986  |
| **800** | 0.2500563  | 0.6902827  | 0.9417414  | 0.9809381  | 0.9947325  | 0.9987509  | 0.9997418  |
| **968.1** | 0.2924091  | 0.7707350  | 0.9726458  | 0.9933464  | 0.9986853  | 0.9997845  | 0.9999701  |
| **1106.4** | 0.3266324  | 0.8230263  | 0.9856689  | 0.9972866  | 0.9995957  | 0.9999514  | 0.9999952  |
| **1244.7** | 0.3601695  | 0.8646308  | 0.9926319  | 0.9989192  | 0.9998791  | 0.9999894  | 0.9999992  |
| **1383** | 0.3929177  | 0.8973006  | 0.9962737  | 0.9995783  | 0.9999647  | 0.9999977  | 0.9999999  |

# Meta-Analysis

Fixed effect or random effects models estimates will be pooled according to results of χ2 tests for heterogeneity 8. Matched ORs will be reported as rate ratios. Inverse variance weighted ORs and 95% CIs will be calculated to estimate the total effect across all study populations.

# Potential limitations

Several potential biases in relation with the observational nature of the study need to be considered. In particular, confounding by indication may be an issue that will be minimised by the use of an active comparator group (SSRIs). Moreover, residual confounding will be limited by the use of high dimensional propensity scores estimated at cohort entry. The short follow-up time (maximum 2 years) will limit the impact of confounders varying with time. Another limitation is the lack of background information on the biological mechanism underlying the risk of AKI with exposure to SNRIs, and the uncertainty regarding the relevant period of exposure. Sensitivity analyses will be conducted to explore the impact of different exposure definitions.

Finally, the rarity of the outcome under study and the potential limited exposure may limit the power of our study, especially regarding the assessment of the risk of AKI associated with each individual SNRI.

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