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Original Investigation

Second-Generation Antidepressants and Hyponatremia Risk: A Population-Based Cohort Study of Older Adults

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Background: Hyponatremia may occur after initiation of a second-generation antidepressant drug. However, the magnitude of this risk among older adults in routine care is not well characterized.

Study Design: Retrospective, population-based, matched-cohort study.

Setting & Participants: In Ontario, Canada, 2003 to 2012, we compared older adults with a mood or anxiety disorder who were dispensed 1 of 9 second-generation antidepressant drugs with matched adults with comparable indicators of baseline health who were not dispensed an antidepressant drug (n = 138,246 per group). A similar comparison was made in a subpopulation with available laboratory data (n = 4,186 per group).

Predictor: Second-generation antidepressant prescription versus no antidepressant prescription.

Outcomes: The primary outcome was hospitalization with hyponatremia. A secondary outcome was hospitalization with both hyponatremia and delirium.

Measurements: We assessed hospitalization with hyponatremia using a diagnosis code and, in the subpopulation, serum sodium values. We assessed hospitalization with hyponatremia and delirium using a combination of diagnosis codes.

Results: Second-generation antidepressant use versus nonuse was associated with higher 30-day risk for hospitalization with hyponatremia (450/138,246 [0.33%] vs 84/138,246 [0.06%]; relative risk [RR], 5.46 [95% CI, 4.32-6.91]). This association was consistent in the subpopulation with serum sodium values (73/4,186 [1.74%] vs 18/4,186 [0.43%]; RR, 4.23 [95% CI, 2.50-7.19]; absolute risk increase, 1.31% [95% CI, 0.87%-1.75%]). Second-generation antidepressant use versus nonuse was also associated with higher 30-day risk for hospitalization with both hyponatremia and delirium (28/138,246 [0.02%] vs 7/138,246 [0.005%]; RR, 4.00 [95% CI, 1.75-9.16]).

Limitations: Measures of serum sodium could be ascertained in only a subpopulation.

Conclusions: Use of a second-generation antidepressant in routine care by older adults is associated with an approximate 5-fold increase in 30-day risk for hospitalization with hyponatremia compared to nonuse. However, the absolute increase in 30-day incidence is low.

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INDEX WORDS: Hyponatremia; serum sodium; syndrome of inappropriate antidiuretic hormone secretion (SIADH); electrolyte disorder; antidepressants; second-generation antidepressant; older adults; citalopram; escitalopram; paroxetine; fluoxetine; fluvoxamine; venlafaxine; duloxetine; mirtazapine; sertraline; mood disorder; anxiety disorder.

Mood and anxiety disorders are common and affect approximately 1 in 8 older adults.[1-3] Second-generation antidepressants are frequently recommended in the treatment of these disorders, with more than 180 million prescriptions dispensed in the United States in 2013.[4-7] Although generally well tolerated, a potential adverse effect of these medications is hyponatremia. Hyponatremia can lead to adverse sequelae such as confusion, seizures, and even death.[8] The accepted mechanism of hyponatremia with antidepressants occurs through the syndrome of inappropriate antidiuretic hormone.[9,10]

Most prior studies of antidepressant-induced hyponatremia are descriptive, with variable definitions of hyponatremia and lengths of follow-up. Reported estimates of incidence range widely from

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<1% to 40% for selective serotonin reuptake inhibitors (SSRIs) and up to 70% for venlafaxine, with most events observed in older adults within 4 weeks of antidepressant therapy initiation.[11-18] In 3 small retrospective studies of risk (maximum sample size, 812 patients), older antidepressant users were up to 6 times more likely to develop hyponatremia compared with nonusers.[19-21]

Whether results of prior studies generalize to the contemporary North American outpatient setting remains uncertain because most studies consisted of small samples of patients, did not investigate newer second-generation antidepressants used in practice today, and were limited to patients admitted to psychiatric hospitals or long-term care facilities, where patient health and monitoring differ from those in the community. Thus, using a population-based cohort, we aimed to investigate the 30-day risk for hospitalization with hyponatremia in older adults who were newly dispensed a second-generation antidepressant in a nonhospitalized setting.

METHODS

Study Design and Setting

We conducted a retrospective population-based cohort study of older adults from June 1, 2003, through March 1, 2012, using linked health care databases in Ontario, Canada. Ontario has approximately 2.2 million residents older than 65 years who are eligible to receive universal access to hospital care, physician services, and prescription drug coverage.[22] These data sets were linked using unique encoded identifiers and were analyzed at the Institute for Clinical Evaluative Sciences (ICES). We conducted this study according to a prespecified protocol that was approved by the Institutional Review Board at Sunnybrook Health Sciences Centre, Toronto, Canada. Participant informed consent was not required for this study. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for the reporting of our study.[23]

Data Sources

We used records from 9 linked databases to identify patient characteristics, drug use, covariate information, and outcome data. We used the Ontario Registered Persons Database to obtain vital statistics. This database contains demographic information for all residents who have been issued a provincial health card. We identified drug information using the Ontario Drug Benefit Program database. This database documents all outpatient prescriptions dispensed to patients 65 years and older (error rate, <1%).[24] We used the Canadian Institute for Health Information (CIHI) Discharge Abstract Database to obtain diagnostic and procedural information about all hospital admissions. Similarly, we used the CIHI National Ambulatory Care Reporting System database to identify information relating to emergency department visits. We also used the Ontario Mental Health Reporting System database to identify diagnostic information for admissions to mental health facilities. We obtained covariate information from the Ontario Health Insurance Plan database, which includes health claims for inpatient and outpatient physician services. We also used the ICES Physician Database to ascertain antidepressant prescriber information. We obtained hospital-based serum sodium measurements from Cerner (a medical laboratory service provider) for a subpopulation in Southwestern Ontario residing in the catchment area of 12 hospitals in which linked laboratory data were available (this catchment area has been previously defined).[25] We also identified outpatient serum sodium measurements using Gamma-Dynacare Medical Laboratories, which is an outpatient laboratory service provider in Ontario. We have previously used these databases to research adverse drug events and health outcomes in several studies (including outcomes of hyponatremia and health services).[26-30]

We used *International Classification of Diseases, Ninth Revision* (*ICD-9*; pre-2002) and *Tenth Revision* (*ICD-10*; post-2002) codes to assess baseline comorbid conditions in the 5 years prior to cohort entry. Only *ICD-10* codes were used to identify outcomes because these events were ascertained following implementation of this coding system. Codes used to ascertain baseline comorbid conditions and outcomes are detailed in Table S1 (provided as online supplementary material). The databases were complete for all variables used in this study, with the exception of income quintile, rural residence, and prescriber information, which were missing in <0.5%, 0.1%, and 12% of older adults, respectively.

Patients

We established a cohort of older adults who had evidence of a hospital diagnosis or physician claim for a mood or anxiety disorder in the 5 years prior to a new prescription for 1 of 9 second-generation study antidepressants: citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, venlafaxine, duloxetine, mirtazapine, or sertraline (referred to as the users group). We defined new use as no prescription for any type of antidepressant drug in the prior 6 months. The date of the first eligible prescription served as the index date (cohort entry date) for users. We restricted the cohort to those who had a prescription for only one type of study second-generation antidepressant on their index date in order to compare mutually exclusive groups in subgroup analyses. We also established a control group from the Ontario population who were not prescribed antidepressants (referred to as the nonusers group) and randomly assigned them an index date based on the distribution of index dates among users.[28,31]

We excluded the following patients from both groups: (1) those who were discharged from a hospital in the 2 days prior to their index date to ensure (in the case of the users) that the medication was not initiated in a hospital setting (because patients continuing antidepressant drug treatment would have their oral outpatient prescription dispensed the day of or the day after hospital discharge) and (2) those with evidence of end-stage renal disease prior to their index date because in these patients, sodium blood levels are regulated through dialysis. Among nonusers, we excluded those who did not have at least one outpatient medication dispensed in the 90 days prior to their index date to ensure active use of the health care system.

We derived a propensity score for the predicted probability of receiving a new second-generation antidepressant drug from a logistic regression model in which treatment status was regressed on more than 100 variables that were potentially associated with second-generation antidepressant use or the outcome (Table S2).[32] We used greedy matching to match each user to a nonuser (1:1) based on the following characteristics: the logit of the propensity score (within a caliper of ±0.2 standard deviations); age (within 2 years); sex; index date (within 1 year); residential status (community dwelling or long-term care); evidence of a mood disorder, anxiety disorder, chronic kidney disease, or congestive heart failure; diuretic use; and constituency in the catchment area for which linked laboratory data were available. We matched on these characteristics to ensure good balance of prognostically important characteristics and facilitate subgroup analyses (to keep matched pairs intact).[32] We applied matching without replacement when users and nonusers could be selected only once for inclusion in the study. Greedy matching without replacement within specified