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Association of Baclofen With Encephalopathy in Patients With Chronic Kidney Disease

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➕ Supplemental content

IMPORTANCE At least 30 case reports have linked the muscle relaxant baclofen to encephalopathy in patients with chronic kidney disease (CKD).

OBJECTIVE To compare the 30-day risk of encephalopathy in patients with CKD and newly prescribed baclofen at greater than or equal to 20 mg per day vs less than 20 mg per day. The secondary objective was to compare the risk of encephalopathy in baclofen users vs nonusers.

DESIGN, SETTING, AND PARTICIPANTS Retrospective population-based cohort study in Ontario, Canada (2007-2018) using linked health care data. Participants comprised 15 942 older adults (aged 66 years or older) with CKD (defined as an estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 but not receiving dialysis). The primary cohort was restricted to patients who were newly prescribed baclofen; participants in the secondary cohort were new users and nonusers.

EXPOSURES Prescription for oral baclofen greater than or equal to 20 mg per day vs less than 20 mg per day.

MAIN OUTCOMES AND MEASURES Hospital admission with encephalopathy, defined as a main diagnosis of delirium, disorientation, transient alteration of awareness, transient cerebral ischemic attack, or unspecified dementia within 30 days of starting baclofen. Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health. Weighted risk ratios (RRs) were obtained using modified Poisson regression and weighted risk differences (RDs) using binomial regression. Prespecified subgroup analyses were conducted by eGFR category.

RESULTS The primary cohort comprised 15 942 patients with CKD (9699 [61%] women; median age, 77 years [interquartile range, 71-82]; 9707 [61%] patients started baclofen at ≥20 mg/d and 6235 [39%] at <20 mg/d). The primary outcome, hospitalization with encephalopathy, occurred in 108/9707 (1.11%) patients who started baclofen at greater than or equal to 20 mg per day and in 26/6235 (0.42%) who started baclofen at less than 20 mg per day; weighted RR, 3.54 (95% CI, 2.24 to 5.59); weighted RD, 0.80% (95% CI, 0.55% to 1.04%). In subgroup analysis, the absolute risk increased progressively at lower eGFR (weighted RD eGFR 45-59, 0.42% [95% CI, 0.19%-0.64%]; eGFR 30-44, 1.23% [95% CI, 0.62%-1.84%]; eGFR <30, 2.90% [95% CI, 1.30%-4.49%]; *P* for interaction, <.001]). In the secondary comparison with 284 263 nonusers, both groups of baclofen users had a higher risk of encephalopathy (<20 mg/d weighted RR, 5.90 [95% CI, 3.59 to 9.70] and ≥20 mg/d weighted RR, 19.8 [95% CI, 14.0 to 28.0]).

CONCLUSIONS AND RELEVANCE Among older patients with CKD who were newly prescribed baclofen, the 30-day incidence of encephalopathy was increased among those prescribed higher doses compared with lower doses. If verified, these risks should be balanced against the benefits of baclofen use.

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Baclofen is a centrally acting γ-amino butyric acid ago-nist that was prescribed more than 8.3 million times in the United States in 2016.[1] It is primarily used as a muscle relaxant for patients with spasticity, but it is also prescribed off-label for alcoholism, gastroesophageal reflux disease, nystagmus, and trigeminal neuralgia.[2] Unlike other muscle relaxants that are primarily metabolized by the liver, baclofen is eliminated primarily unchanged in the urine, with a step-wise prolongation in the elimination half-life as kidney function declines.[3] Chronic kidney disease (CKD) was estimated to affect 20% of older adults in 2011-2012,[4] and at least 30 case reports have linked baclofen use to encephalopathy in patients with CKD within days of initiating the drug.

Despite these case reports, no clinical study has quantified the risk of baclofen-associated encephalopathy in patients with CKD. The objective of the present study was to examine the 30-day risk of hospitalization with encephalopathy in patients with CKD who were new users of oral baclofen. The primary objective was to compare the risk in patients prescribed greater than or equal to 20 mg per day vs less than 20 mg per day; a comparison of 2 dosing groups helps minimize concerns that the results are confounded by indication. The secondary objective was to examine the risk in these patient groups compared with nonusers (ie, patients with CKD with no evidence of baclofen use).

Methods

Study Design and Setting

This study was conducted using linked administrative health care databases in the province of Ontario, Canada (2007-2018). All Ontario residents (≈13 million) have universal access to hospital care and physician services through a government-funded single-payer system.[5] Those aged 65 years and older (≈2.2 million) also receive universal prescription drug coverage. The use of data in this study was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board. Study reporting follows recommended guidelines for observational studies that use routinely collected health data (eTable 1 in the Supplement).[6,7]

Data Sources

Patient characteristics, prescription drug use, covariate information, and outcome data were obtained from 8 health care databases at the Institute for Clinical Evaluative Sciences (ICES).[8] The data sets were linked using unique encoded identifiers and analyzed at ICES (Canadian Institute for Health Information–Discharge Abstract Database, ICES Physician Database, National Ambulatory Care Reporting System, Ontario Drug Benefit Database, Ontario Health Insurance Plan Database, Ontario Laboratories Information System, Ontario Mental Health Reporting System, and the Registered Persons Database). Information on hospital admissions and diagnoses are coded by trained personnel using the *International Classification of Diseases,*

Key Points

Question Is there an increased risk of encephalopathy among patients with chronic kidney disease (CKD) initiating treatment with a higher vs lower dose of baclofen?

Findings In this retrospective cohort study that included 15 942 patients with CKD, the 30-day incidence of encephalopathy among those prescribed baclofen at greater than or equal to 20 mg per day compared with less than 20 mg per day was 1.11% vs 0.42%, a difference that was statistically significant.

Meaning Baclofen use among patients with CKD, particularly at higher doses, may be associated with an increased risk of encephalopathy.

10th Revision (*ICD-10*) system; personnel only consider physician-recorded diagnoses in a patient's medical chart when assigning codes and do not review or interpret symptoms or test results. Additional information on the databases, variable definitions, and administrative codes are provided in eTable 2 in the Supplement.

Patients

The primary cohort included adults aged 66 years and older with CKD (defined as having an estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m² but not receiving dialysis) and who were newly dispensed oral baclofen from an outpatient pharmacy between January 1, 2007, and March 1, 2018. The prescription fill date was the patient's cohort entry date (the index date); patients could enter the cohort only once. The age restriction was applied to ensure that all patients in the study had at least 1 year of prescription drug coverage. The GFR was estimated using the most recent outpatient serum creatinine measurement before the index date (using the isotope dilution mass spectroscopy-traceable enzymatic method), and eGFR was calculated using the chronic kidney disease epidemiology (CKD-EPI) equation (justification for use of this equation to guide baclofen dosing is provided in eTable 3 in the Supplement).[9] In Ontario, many older adults have at least 1 outpatient serum creatinine measurement in routine care each year, in which a single value represents a stable (or long-term) value.[10] Patients with no serum creatinine measurement in the year before the index date were excluded.

To ensure that patients were new baclofen users, those with any evidence of baclofen use (including combination drug prescriptions) in the 180-day period before the index date were excluded, as were those who were discharged from the hospital or emergency department within 2 days before the index date (in Ontario, patients who start a baclofen prescription during a hospital admission would have their outpatient prescription dispensed on the same day or the day after hospital discharge). Patients with an implausible baclofen dose (<5 mg/d or >80 mg/d) were excluded.

The secondary cohort included all patients in the primary cohort, as well as patients without any evidence of baclofen use (ie, nonusers). Nonusers were randomly assigned

an index date (a simulated baclofen start date) that followed the same distribution of index dates as baclofen users.[11]

Exposure

The primary exposure of interest was oral baclofen of greater than or equal to 20 mg per day, which is the median dose reported in cases of baclofen toxicity in patients with CKD (eTable 4 in the Supplement; literature search in eTable 5 in the Supplement). An active comparator, oral baclofen at less than 20 mg per day, was chosen for the primary comparison to reduce the influence of indication bias. Other active comparators were considered (eg, other types of muscle relaxants including dantrolene and tizanidine); however, these drugs are prescribed infrequently in Ontario. For the secondary objective, each group of baclofen users (ie, those prescribed ≥20 mg/d and those prescribed <20 mg/d) were compared separately with nonusers (ie, patients with CKD with no evidence of baclofen use).

Outcomes

All primary and secondary outcomes were prespecified. The primary outcome was the 30-day risk of a hospital admission with encephalopathy, defined as a main diagnosis of delirium, disorientation, transient alteration of awareness, transient cerebral ischemic attack, or unspecified dementia (unclear diagnosis of dementia). Transient ischemic attack was included as one of the encephalopathy outcomes since baclofen-related toxicity in patients with CKD has been characterized in some case reports by symptoms (visual disturbances, numbness, slurred speech) similar to those observed in transient ischemic attack (eTable 4 in the Supplement). The outcome and time frame were defined based on a review of the literature (studies summarized in eTable 4 in the Supplement); in these studies, the median time to encephalopathy after baclofen initiation was 2.5 days (interquartile range [IQR], 1-4). To improve the specificity of this outcome, we only considered *ICD* codes that were entered in the main diagnosis field of the database; this field contains a single diagnosis that most influenced the patient's length of hospital stay, that was responsible for the greatest proportion of resource use, or both. Alternative definitions of encephalopathy were examined in sensitivity analyses. Secondary outcomes were hospitalization with delirium as the main diagnosis, hospitalization for any cause, and all-cause mortality. Diagnostic codes for all outcome variables and information on their validation and interpretation are provided in eTable 6 in the Supplement.

Statistical Analysis

Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on recorded indicators of baseline health, including known indications for baclofen use (including off-label indications).[12-14] The propensity score was estimated using multivariable logistic regression with 164 covariates chosen a priori (defined in eTable 7 in the Supplement). Patients in the reference group were weighted (propensity score/[1−propensity score]).[12-14]

This method produces a weighted pseudo sample of patients in the reference group with the same distribution of measured covariates as the exposed group.[12,13] Between-group differences in baseline characteristics were compared using standardized differences in both the unweighted and weighted samples[15] (differences >10% were considered meaningful). Weighted risk ratios and 95% CIs were obtained using modified Poisson regression,[16] and weighted risk differences and 95% CIs were obtained using a binomial regression model with an identity link function. Two-tailed *P* values of less than .05 were interpreted as statistically significant. Because of the potential for type I error due to multiple comparisons, findings of the secondary, subgroup, and sensitivity analyses should be interpreted as exploratory. All variables in this study were complete except for baclofen prescriber specialty (7% missing; defined in a separate category) and patient income quintile (0.3% missing; recoded as the middle quintile). Emigration from the province, which occurs at a rate of 0.5% per year, was the only reason for lost follow-up designation.[17]

Prespecified sensitivity analyses were conducted to examine 2 alternative definitions of encephalopathy: (1) any hospital admission or emergency department visit with encephalopathy (ie, all relevant diagnostic codes considered, not just those entered in the main diagnostic field), and (2) hospital admission with receipt of an urgent computed tomography scan of the head. A prespecified subgroup analysis by baseline eGFR (grouped into 3 categories) was conducted by including an interaction term in the model. To address the secondary objective, each group of baclofen users (≥20 mg/d and <20 mg/d) was compared separately with nonusers on the risk of encephalopathy; inverse probability of treatment weighting was performed separately for these comparisons.

Five post hoc sensitivity analyses were conducted to assess the robustness of the main results: (1) a survival analysis (with 30-day follow-up censoring on death) that met the proportional hazards assumption (nonsignificant high dose × follow-up time interaction term; *P* = .06); (2) an analysis that accounted for the correlation between patients who received a prescription from the same physician[18]; (3) an E-value analysis to assess the extent of unmeasured confounding that would be required to negate the observed results[19]; (4) an analysis using a negative control exposure[20] (in which the index date was defined to be 90 days before the baclofen start date); and (5) an analysis using a negative control outcome[20] (in which the outcome was defined as hospitalization with heart failure). Analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc).

Results

Patients

The primary cohort included 15 942 older adults with an eGFR of less than 60 mL/min/1.73 m² (median age, 77 years; 61% women) who were newly dispensed baclofen at an

Table 1. Baseline Demographic Characteristics of Older Adults With Chronic Kidney Disease Newly Prescribed Baclofen in Ontario, Canada (2007-2018)[a]

Demographic Characteristics	Observed Data (N = 15 942)			Weighted Data (N = 19 387)[b]		
	Baclofen Dose, No. (%)[c]			Baclofen Dose, No. (%)[c]		
	≥20 mg/d (n = 9707)	<20 mg/d (n = 6235)	Standardized Difference, %[d]	≥20 mg/d (n = 9707)	<20 mg/d (n = 9680)	Standardized Difference, %[d]
Women	5719 (58.9)	3980 (63.8)	10	5719 (58.9)	5702 (58.9)	2
Men	3988 (41.1)	2255 (36.2)	10	3988 (41.1)	3978 (41.1)	0
Age, mean (SD), y	76.5 (6.9)	78.0 (7.4)	21	76.5 (6.9)	76.5 (8.8)	0
Residence						
Urban	8870 (91.4)	5800 (93.0)	6	8870 (91.4)	8845 (91.4)	0
Rural	837 (8.6)	435 (7.0)	6	837 (8.6)	835 (8.6)	0
Long-term care facility	210 (2.2)	379 (6.1)	20	210 (2.2)	217 (2.2)	0
Income quintile[e]						
1 (Lowest)	2313 (23.8)	1508 (24.2)	1	2313 (23.8)	2309 (23.9)	0
2	2098 (21.6)	1345 (21.6)	0	2098 (21.6)	2121 (21.9)	1
3 (Middle)	2010 (20.7)	1280 (20.5)	0	2010 (20.7)	1988 (20.5)	0
4	1893 (19.5)	1145 (18.4)	3	1893 (19.5)	1871 (19.3)	1
5 (Highest)	1393 (14.4)	957 (15.3)	3	1393 (14.4)	1389 (14.4)	0

[a] Unless otherwise specified, baseline characteristics were assessed on the date the patient filled the baclofen prescription—the index date.

[b] Weighted using inverse probability of exposure weighting, based on propensity scores. The propensity score was estimated using multivariable logistic regression with 164 covariates chosen a priori (defined in eTable 7 in the Supplement). Patients in the reference group were weighted as (propensity score/[1−propensity score]).[12-14] This method produces a weighted pseudo sample of patients in the reference group with the same distribution of measured covariates as the exposure group.[12,13]

[c] Values are reported as No. (%) unless otherwise indicated.

[d] The difference between the groups divided by the pooled standard deviation; a value greater than 10% is interpreted as a meaningful difference.[15]

[e] Income was categorized into fifths of average neighborhood income on the index date.

outpatient pharmacy. The flow diagram for the cohort build is shown in eFigure 1 in the Supplement. Baclofen prescriptions were dispensed by 4128 unique pharmacies and prescribed by 4977 unique physicians (86% were primary care physicians). Overall, 66% of patients had an eGFR between 45 and 59 mL/min/1.73 m², 27% between 30 and 45 mL/min/1.73 m², and 7% had an eGFR less than 30 mL/min/1.73 m². The median prescribed dose of baclofen in each eGFR category was 20 mg per day (IQR, 10-30).

Of 15 942 patients prescribed baclofen, 9707 (60.9%) started at greater than or equal to 20 mg per day (median, 30 mg/d [IQR, 20-30]) and 6235 (39.1%) started at less than 20 mg per day (median, 10 mg/d [IQR, 10-10]). While the baclofen product monograph indicates that the initial dose may be increased by 5 mg every 3 days until a desired clinical response is reached, no change in follow-up was observed in the initial median daily dose for either group (eTable 8 in the Supplement). In those prescribed greater than or equal to 20 mg per day, the median duration of continuous baclofen dispensing was 15 days (IQR, 10-30), and in those prescribed less than 20 mg per day, the median duration was 30 days (IQR, 14-30) (eTable 9 in the Supplement).

Characteristics of patients who started baclofen at greater than or equal to 20 vs less than 20 mg per day are shown in **Table 1** and **Table 2** (the full set of 164 characteristics is shown in eTable 10 in the Supplement). Before weighting, all standardized differences were less than 10% except for age, sex, living in a long-term care residence, and dementia. After weighting, the 2 groups were balanced on

these and the other 160 variables, including type of prescriber, recorded indications for baclofen use, comorbidities, baseline eGFR, and concurrent medications (eTable 10 in the Supplement).

Hospitalization With Encephalopathy

The primary outcome, hospitalization with encephalopathy, occurred in 108 of 9707 patients (1.11%) who started baclofen at greater than or equal to 20 mg per day and in 26 of 6235 patients (0.42%) who started at less than 20 mg per day. The median time from starting baclofen to hospitalization was 3 days (IQR, 2-5) for patients who started baclofen at greater than or equal to 20 mg per day and 8 days (IQR, 3-12) for patients who started baclofen at less than 20 mg per day. Additional descriptive characteristics of these patients are shown in eTable 11 in the Supplement. Aggregate event rates for outcome type (ie, delirium, disorientation, transient cerebral ischemic attack, transient alteration of awareness, and unspecified dementia) are shown in eTable 12 in the Supplement.

Starting baclofen at greater than or equal to 20 mg per day vs less than 20 mg per day was associated with a higher 30-day risk of hospitalization with encephalopathy (weighted risk ratio, 3.54 [95% CI, 2.24 to 5.59]; weighted risk difference, 0.80% [95% CI, 0.55% to 1.04%]). Starting baclofen at greater than or equal to 20 mg per day vs less than 20 mg per day was also associated with a higher risk of hospitalization with delirium and all-cause hospitalization, but not all-cause mortality (**Table 3**).

Table 2. Baseline Clinical Characteristics of Older Adults With Chronic Kidney Disease Newly Prescribed Baclofen in Ontario, Canada (2007-2018)[a]

Clinical Characteristics	Observed Data (N = 15 942)			Weighted Data (N = 19 387)[b]		
	Baclofen Dose, No. (%)[c]			Baclofen Dose, No. (%)[c]		
	≥20 mg/d (n = 9707)	<20 mg/d (n = 6235)	Standardized Difference, %[d]	≥20 mg/d (n = 9707)	<20 mg/d (n = 9680)	Standardized Difference, %[d]
Kidney function						
eGFR,[e] mean (SD), mL/min/1.73 m^2	47.5 (10.1)	47.3 (10.2)	2	47.5 (10.1)	47.5 (12.6)	0
eGFR category, mL/min/1.73 m^2						
<30	687 (7.1)	468 (7.5)	2	687 (7.1)	711 (7.4)	1
30-<45	2616 (26.9)	1682 (27.0)	0	2616 (26.9)	2580 (26.7)	0
45-<60	6404 (66.0)	4085 (65.5)	1	6404 (66.0)	6388 (66.0)	0
Baclofen prescriber						
General practitioner	8433 (86.9)	5208 (83.5)	1	8433 (86.9)	8399 (86.8)	0
Other	665 (6.9)	533 (8.5)	6	665 (6.9)	669 (6.9)	0
Missing	609 (6.3)	494 (7.9)	6	609 (6.3)	611 (6.3)	0
Comorbidities[f]						
Gastroesophageal reflux disease	3050 (31.4)	1958 (31.4)	0	3050 (31.4)	3050 (31.5)	0
Nystagmus or irregular eye movements	2962 (30.5)	1889 (30.3)	0	2962 (30.5)	2931 (30.3)	0
Kidney disease	2543 (26.2)	1593 (25.5)	2	2543 (26.2)	2572 (26.6)	1
Dementia	945 (9.7)	885 (14.2)	14	945 (9.7)	953 (9.8)	0
Cramps and spasms	384 (4.0)	232 (3.7)	2	384 (4.0)	394 (4.1)	1
Trigeminal neuralgia	233 (2.4)	156 (2.5)	1	233 (2.4)	241 (2.5)	1
Ischemic stroke	191 (2.0)	171 (2.7)	5	191 (2.0)	195 (2.0)	0
Hemiplegia	70 (0.7)	50 (0.8)	1	70 (0.7)	63 (0.7)	0
Multiple sclerosis	69 (0.7)	46 (0.7)	0	69 (0.7)	78 (0.8)	1
Hemorrhagic stroke	28 (0.3)	24 (0.4)	2	28 (0.3)	30 (0.3)	0
Charlson Comorbidity Index, mean (SD)[g]	0.55 (1.3)	0.57 (1.3)	2	0.55 (1.3)	0.56 (1.6)	1
Health care visits and tests[h]						
Primary care visits, mean (SD)	11.2 (9.6)	11.8 (10.2)	6	11.2 (9.6)	11.2 (11.4)	0
Emergency department visits, mean (SD)	0.7 (1.4)	0.7 (1.4)	4	0.7 (1.4)	0.7 (1.9)	1
Serum creatinine tests						
0	196 (2.0)	133 (2.1)	1	196 (2.0)	223 (2.3)	2
1	3253 (33.5)	2077 (33.3)	0	3253 (33.5)	3272 (33.8)	1
2	2449 (25.2)	1570 (25.2)	0	2449 (25.2)	2398 (24.8)	1
≥3	3809 (39.2)	2455 (39.4)	0	3809 (39.2)	3788 (39.1)	0
Medication use[i]						
Statins	5782 (59.6)	3693 (59.2)	1	5782 (59.6)	5767 (59.6)	0
Benzodiazepines	1897 (19.5)	1152 (18.5)	3	1897 (19.5)	1885 (19.5)	0
Antipsychotics	376 (3.9)	284 (4.6)	3	376 (3.9)	378 (3.9)	0

Abbreviation: eGFR, estimated glomerular filtration rate.

[a] Unless otherwise specified, baseline characteristics were assessed on the date the patient filled the baclofen prescription—the index date.

[b] Weighted using inverse probability of exposure weighting, based on propensity scores. The propensity score was estimated using multivariable logistic regression with 164 covariates chosen a priori (defined in eTable 7 in the Supplement). Patients in the reference group were weighted as (propensity score/[1−propensity score]).[12-14] This method produces a weighted pseudo sample of patients in the reference group with the same distribution of measured covariates as the exposure group.[12,13]

[c] Values are reported as No. (%) unless otherwise indicated.

[d] The difference between the groups divided by the pooled standard deviation; a value greater than 10% is interpreted as a meaningful difference.[15]

[e] The most recent eGFR measurement in the period (7-365 days) before the index date; eGFR was calculated using the Chronic Kidney Disease (CKD)–Epidemiology (EPI) equation: 141 × min([serum creatinine concentration in μmol/L/88.4]/κ, 1)α × max([serum creatinine concentration in μmol/L/88.4]/κ, 1)−1.209 × 0.993 age × 1.018 (if female) × 1.159 (if African American); κ = 0.7 if female and 0.9 if male; α = −0.329 if female

and −0.411 if male; min = the minimum of serum creatinine concentration/κ or 1; max = the maximum of serum creatinine concentration/κ or 1. Information on race was not available in our data sources and all patients were assumed not to be of African Canadian race/ethnicity; African Canadians comprised less than 5% of the population of Ontario in 2006.

[f] Baseline comorbidities were assessed in the 5-year period before the index date.

[g] The Charlson Comorbidity Index was calculated based on hospital admission data in the 3-year period before the index date. Admissions data reported as no hospital admissions received a score of 0. The Charlson score considers each person with a hospital admission with the disease of interest (ie 17 diseases). For each person, it assigns a point score based on disease mortality risk and sums them to generate an overall score of disease burden. The final risk scores range between 0 and 13, with higher values associated with higher mortality. Each disease in the index has an assigned weight of 1,2,3, or 6, with HIV/AIDS and metastatic cancer having the highest weight of 6. Patients with no prior hospitalizations have a score of 0.

[h] Total number of health care visits and tests in the 12-month period before the index date.

[i] Medication use was examined in the 120-day period before the index date (the Ontario Drug Benefit Program dispenses a maximum 100-day supply).

Table 3. Risk of Encephalopathy in Older Adults With Chronic Kidney Disease Who Started a New Prescription for Baclofen (≥20 mg/d vs <20 mg/d)

	Unweighted				Weighted[a]			
	Baclofen Dose, No. of Events (%)		Risk Difference (95% CI), %	Risk Ratio (95% CI)	Baclofen Dose, No. of Events (%)		Risk Difference (95% CI), %	Risk Ratio (95% CI)
	≥20 mg/d (n = 9707)	<20 mg/d (n = 6235)[b]			≥20 mg/d (n = 9707)	<20 mg/d (n = 9680)[b]		
Primary outcome								
Hospitalization with encephalopathy (main diagnosis)[c]	108 (1.11)	26 (0.42)	0.70 (0.43 to 0.96)	2.67 (1.74 to 4.09)	108 (1.11)	30 (0.31)	0.80 (0.55 to 1.04)	3.54 (2.24 to 5.59)
Secondary outcomes								
Hospitalization with delirium	59 (0.61)	15 (0.24)	0.37 (0.17 to 0.56)	2.53 (1.43 to 4.45)	59 (0.61)	17 (0.17)	0.43 (0.25 to 0.62)	3.48 (1.88 to 6.45)
All-cause hospitalization	674 (6.94)	305 (4.89)	2.05 (1.32 to 2.79)	1.42 (1.24 to 1.62)	674 (6.94)	451 (4.66)	2.29 (1.53 to 3.05)	1.49 (1.29 to 1.72)
All-cause mortality	91 (0.94)	80 (1.28)	−0.35 (−0.68 to −0.01)	0.73 (0.54 to 0.99)	91 (0.94)	95 (0.98)	−0.04 (−0.37 to 0.29)	0.96 (0.68 to 1.35)
Additional outcomes								
Any hospital admission with encephalopathy[d]	320 (3.30)	106 (1.70)	1.60 (1.12 to 2.08)	1.94 (1.56 to 2.41)	320 (3.30)	137 (1.42)	1.88 (1.41 to 2.34)	2.32 (1.83 to 2.95)
Hospital admission with urgent CT head scan[e]	309 (3.18)	124 (1.99)	1.19 (0.70 to 1.69)	1.60 (1.30 to 1.97)	309 (3.18)	163 (1.68)	1.50 (1.02 to 1.98)	1.89 (1.51 to 2.37)

Abbreviation: CT, computed tomography.

a Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health.[12-14] The propensity score was estimated using multivariable logistic regression with 164 covariates chosen a priori (defined in eTable 7 in the Supplement). Patients in the reference group were weighted (propensity score/[1−propensity score]).[12-14] This method produced a weighted pseudo sample of patients in the reference group with the same distribution of measured covariates as the exposed group.[12,13] Weighted risk ratios (95% CIs) were obtained using modified Poisson regression,[16] and weighted risk differences (95% CIs) were obtained using a binomial regression model with an identity link function.
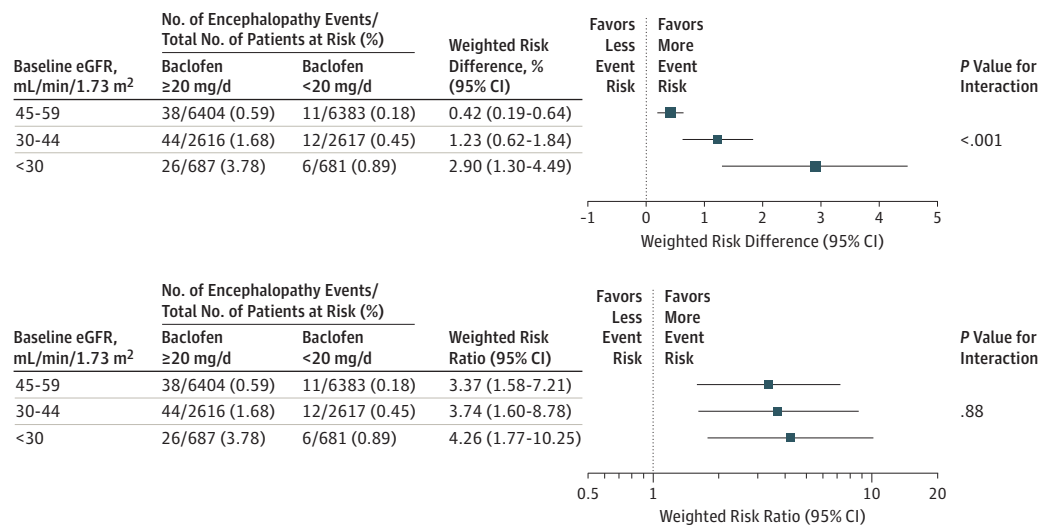
b Indicates the reference group.

c Category indicates the 30-day risk of a hospital admission with encephalopathy, defined as a main diagnosis of delirium, disorientation, transient alteration of awareness, transient cerebral ischemic attack, or unspecified dementia. To improve the specificity of this outcome, only codes that were entered in the main diagnosis field of the database were considered; this field contains a single diagnosis that most influences the patient's length of hospital stay and/or is responsible for the greatest proportion of resource use.

d Category indicates any hospital admission or emergency department visit with encephalopathy (ie, all relevant diagnostic codes considered, not just those entered in the main diagnostic field).

e Indicates computed tomography scans of the head performed during the first 5 days of hospital admission or performed in the emergency department during the 2 days preceding admission.

Figure. Subgroup Analysis for Risk of Encephalopathy by eGFR Category (Weighted Risk Difference and Weighted Risk Ratio)

Baseline eGFR, mL/min/1.73 m²	No. of Encephalopathy Events/ Total No. of Patients at Risk (%)		Weighted Risk Difference, % (95% CI)	Favors Less Event Risk / Favors More Event Risk	P Value for Interaction
	Baclofen ≥20 mg/d	Baclofen <20 mg/d			
45-59	38/6404 (0.59)	11/6383 (0.18)	0.42 (0.19-0.64)		
30-44	44/2616 (1.68)	12/2617 (0.45)	1.23 (0.62-1.84)		<.001
<30	26/687 (3.78)	6/681 (0.89)	2.90 (1.30-4.49)		

Weighted Risk Difference (95% CI)

Baseline eGFR, mL/min/1.73 m²	No. of Encephalopathy Events/ Total No. of Patients at Risk (%)		Weighted Risk Ratio (95% CI)	Favors Less Event Risk / Favors More Event Risk	P Value for Interaction
	Baclofen ≥20 mg/d	Baclofen <20 mg/d			
45-59	38/6404 (0.59)	11/6383 (0.18)	3.37 (1.58-7.21)		
30-44	44/2616 (1.68)	12/2617 (0.45)	3.74 (1.60-8.78)		.88
<30	26/687 (3.78)	6/681 (0.89)	4.26 (1.77-10.25)		

Weighted Risk Ratio (95% CI)

The 30-day risk of a hospital admission with encephalopathy, defined as main diagnosis of delirium, disorientation, transient alteration of awareness, transient cerebral ischemic attack, or unspecified dementia. To improve the specificity of this outcome, we only considered codes that were entered in the main diagnosis field of the database; this field contains a single diagnosis that most influences the patient's length of hospital stay and/or is responsible for the greatest proportion of resource use. Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health.[12-14] The propensity score was estimated using multivariable logistic regression with 164 covariates chosen a priori (defined in eTable 7 in the Supplement). Patients in the reference group were weighted (propensity score/[1−propensity score]).[12-14] This method produces a weighted pseudo sample of patients in the reference group with the same distribution of measured covariates as the exposed group.[12,13] Weighted risk ratios and 95% CIs were obtained using modified Poisson regression,[16] and weighted risk differences and 95% CIs were obtained using a binomial regression model with an identity link function. eGFR indicates estimated glomerular filtration rate.

Prespecified Sensitivity and Subgroup Analyses

Results were consistent when the outcome was defined as (1) any hospital admission or emergency department visit with encephalopathy; and (2) hospital admission with receipt of an urgent computed tomography scan of the head (Table 3). The results of the subgroup analyses by baseline eGFR categories are shown in the **Figure**. The weighted risk ratios and risk differences for encephalopathy increased progressively as eGFR declined; however, only the additive interaction was statistically significant ($P < .001$; $P = .88$ for multiplicative interaction).

Risk of Encephalopathy in Baclofen Users vs Nonusers

A hospital admission with encephalopathy occurred in 165/284 263 (0.06%) patients with no evidence of baclofen use. In comparison with nonusers, both groups of baclofen users had a higher risk of encephalopathy (<20 mg/d and ≥20 mg/d): (weighted risk ratio for patients with <20 mg/d, 5.90 [95% CI, 3.59 to 9.70]; weighted risk difference, 0.35% [95% CI, 0.18% to 0.51%]) (weighted risk ratio for patients with ≥20 mg/d, 19.8 [95% CI, 14.0 to 28.0]; weighted risk difference, 1.06% [95% CI, 0.85% to 1.27%]) (eTable 13 in the Supplement; characteristics of users and nonusers in eTable 14 and 15 in the Supplement).

Post Hoc Sensitivity Analyses

Results were consistent when the data were analyzed using a Cox proportional hazards regression (eTable 16 in the Supplement) and in an analysis that accounted for the correlation between patients who received prescriptions from the same physician (eTable 17 in the Supplement). The E-value for the risk ratio was 6.54, and the lower confidence bound for the primary outcome was 3.91, indicating that substantial unmeasured confounding would be needed to reduce the observed association or its 95% CI to the null (eFigure 2 in the Supplement). Study results were also supported by sensitivity analyses that used a negative exposure control (eTable 18 in the Supplement) and a negative outcome control (eTable 19 in the Supplement).

Discussion

In this study of older adults with CKD, those who started a prescription for baclofen at greater than or equal to 20 mg per day had a significantly greater risk of hospitalization with encephalopathy compared with those who started baclofen at less than 20 mg per day. Results were consistent in multiple sensitivity analyses and when alternative definitions of encephalopathy were analyzed. In a secondary comparison with patients who had no evidence of baclofen use, both groups of baclofen users (<20 mg/d and ≥20 mg/d) had a greater risk of encephalopathy.

Many patients benefit from using baclofen as a muscle relaxant or for several off-label indications including alcoholism, gastroesophageal reflux disease, nystagmus, and trigeminal neuralgia.[2] This study was not designed to answer the question of whether the potential benefits of

baclofen outweigh its risks, and clinicians will need to judge this on a patient-by-patient basis.

This population-based study of 15 942 older adults confirms and extends the findings of 30 international case reports linking baclofen use with encephalopathy in patients with CKD (eTable 4 in the Supplement). The findings of the present study are generalizable. The study was conducted in the setting of usual clinical care and included a representative sample of older adults with CKD in Ontario, Canada, where older adults have universal prescription drug coverage. Inverse probability of treatment weighting was used to help ensure that comparison groups were similar on baseline characteristics; however, even before weighting, groups were balanced on 98% of measured characteristics. Several sensitivity analyses were conducted and all supported the main findings. In particular, the magnitude of the E-values suggests that the observed association is unlikely to be explained by unmeasured confounding.

Limitations

This study has several limitations. First, the observational study design precludes reaching causal conclusions about the association between baclofen and encephalopathy, and the study requires replication before definitive conclusions can be reached. Second, despite the use of accurate information on baclofen dispensing, it was not possible to know the proportion of patients who took their medication as prescribed. Third, the patients studied were aged 66 years and older (likely to be at higher risk of encephalopathy), and so generalizability of the study findings to younger patients (who may be less prone to adverse drug events) is uncertain,

although approximately half of the patients described in the case report studies were younger than 66 years. Fourth, the benefit-risk ratio of baclofen use was not assessed in this study. Fifth, the use of administrative data meant that the primary outcome definition was restricted to diagnostic codes recorded for the patients' hospital stays, and granular data on patient symptoms were lacking. For example, baclofen use has been associated with several manifestations of encephalopathy, including confusion, drowsiness, and decreased consciousness, but occasionally vertigo, visual disturbances, numbness, nystagmus, and slurred speech. Many of these symptoms would not warrant hospital admission, and thus the overall incidence of baclofen-associated encephalopathy may be underestimated in this study. Sixth, information on serum baclofen levels was not available in the laboratory database, which precluded any corroboration in this study that excessive serum concentrations of baclofen were the cause for encephalopathy. Seventh, some misclassification in the outcome of encephalopathy is expected in this study because the codes are likely insensitive; however, there is no reason to believe that misclassification occurred differentially between exposure groups.

Conclusions

Among older patients with CKD who were newly prescribed baclofen, the 30-day incidence of encephalopathy was increased among those prescribed higher compared with lower doses. If verified, these risks should be balanced against the benefits of baclofen use.

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