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RESEARCH LETTER

Association of Baclofen With Falls and Fractures in Patients With CKD

To the Editor:

Baclofen is a popular muscle relaxant that is eliminated primarily unchanged in the urine.[1] We recently reported a higher risk of encephalopathy in a cohort of 15,942 older adults with chronic kidney disease (CKD) who started baclofen at ≥20 versus <20 mg/d; a higher risk was also observed in all baclofen users versus nonusers.[2] In another study of patients receiving dialysis, 1 in 14 were hospitalized with encephalopathy within 3 days of starting baclofen.[3]

In the present study, we analyzed the same cohort of 15,942 older adults with CKD not receiving dialysis,[2] and examined the 30-day risk of a hospital encounter with a fall, a fracture, or hypotension in patients newly prescribed baclofen at ≥20 versus <20 mg/d. The data source, design, and methods were the same as in our prior report[2] and are described in Table S1.

Briefly, we analyzed linked administrative health care data housed at ICES in Ontario, Canada, where all residents aged ≥65 years have universal prescription drug coverage. The primary cohort included adults aged ≥66 (to ensure at least 1 year of drug coverage) who had an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² and who were newly dispensed oral baclofen from an outpatient pharmacy between January 1, 2007, and March 1, 2018. Patients with evidence of baclofen use in the 180-day period before the prescription start date were excluded (this period was extended to 5 years in a sensitivity analysis).

The primary exposure was baclofen ≥ 20 mg/d (20 mg/d is the median dose reported in cases of baclofen toxicity, and the median dose prescribed during the study period [Table S2]).[2] To reduce the potential for indication bias, the prespecified reference group was baclofen < 20 mg/d.

In a secondary analysis, study outcomes in each group of baclofen users (≥20 and <20 mg/d) were compared separately to nonusers (ie, patients with CKD not taking baclofen). Nonusers were randomly assigned a simulated baclofen start date that followed the same distribution of start dates as baclofen users.

Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on 164 indicators of baseline health, including indications for

Table 1. Baseline Characteristics of Older Adults With CKD Newly Prescribed Baclofen in Ontario, Canada (2007-2018)

	Observed Data (N = 15,942)			Weighted Data (N = 19,387)[a]		
	Baclofen Dose			**Baclofen Dose**		
	≥20 mg/d (n = 9,707)	<20 mg/d (n = 6,235)	Std Diff[b]	≥20 mg/d (n = 9,707)	<20 mg/d (n = 9,680)	Std Diff[b]
Demographics						
Women	5,719 (58.9%)	3,980 (63.8%)	10%	5,719 (58.9%)	5,702 (58.9%)	2%
Men	3,988 (41.1%)	2,255 (36.2%)	10%	3,988 (41.1%)	3,978 (41.1%)	0%
Age, y	76.5 ± 6.9	78.0 ± 7.4	21%	76.5 ± 6.9	76.5 ± 8.8	0%
Residence						
Urban	8,870 (91.4%)	5,800 (93.0%)	6%	8,870 (91.4%)	8,845 (91.4%)	0%
Rural	837 (8.6%)	435 (7.0%)	6%	837 (8.6%)	835 (8.6%)	0%
Long-term care	210 (2.2%)	379 (6.1%)	20%	210 (2.2%)	217 (2.2%)	0%
Income quintile[c]						
1 (lowest)	2,313 (23.8%)	1,508 (24.2%)	1%	2,313 (23.8%)	2,309 (23.9%)	0%
2	2,098 (21.6%)	1,345 (21.6%)	0%	2,098 (21.6%)	2,121 (21.9%)	1%
3 (middle)	2,010 (20.7%)	1,280 (20.5%)	0%	2,010 (20.7%)	1,988 (20.5%)	0%
4	1,893 (19.5%)	1,145 (18.4%)	3%	1,893 (19.5%)	1,871 (19.3%)	1%
5 (highest)	1,393 (14.4%)	957 (15.3%)	3%	1,393 (14.4%)	1,389 (14.4%)	0%

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Older Adults With CKD Newly Prescribed Baclofen in Ontario, Canada (2007-2018)

	Observed Data (N = 15,942)			Weighted Data (N = 19,387)[a]		
	Baclofen Dose			Baclofen Dose		
	≥20 mg/d (n = 9,707)	<20 mg/d (n = 6,235)	Std Diff[b]	≥20 mg/d (n = 9,707)	<20 mg/d (n = 9,680)	Std Diff[b]
Kidney function						
eGFR, mL/min/1.73 m²[d]	47.5 ± 10.1	47.3 ± 10.2	2%	47.5 ± 10.1	47.5 ± 12.6	0%
eGFR category						
45-<60 mL/min/1.73 m²	6,404 (66.0%)	4,085 (65.5%)	1%	6,404 (66.0%)	6,388 (66.0%)	0%
30-<45 mL/min/1.73 m²	2,616 (26.9%)	1,682 (27.0%)	0%	2,616 (26.9%)	2,580 (26.7%)	0%
<30 mL/min/1.73 m²	687 (7.1%)	468 (7.5%)	2%	687 (7.1%)	711 (7.4%)	1%
Baclofen prescriber						
General practitioner	8,433 (86.9%)	5,208 (83.5%)	1%	8,433 (86.9%)	8,399 (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]						
Anemia	2,667 (27.5%)	1,719 (27.6%)	0%	2,667 (27.5%)	2,548 (26.3%)	3%
Parkinson disease	197 (2.0%)	174 (2.8%)	5%	197 (2.0%)	198 (2.0%)	0%
Prior hypotension	190 (2.0%)	125 (2.0%)	0%	190 (2.0%)	190 (2.0%)	0%
Rheumatoid arthritis	636 (6.6%)	415 (6.7%)	0%	636 (6.6%)	640 (6.6%)	0%
Syncope	168 (1.7%)	112 (1.8%)	1%	168 (1.7%)	163 (1.7%)	0%
Ischemic stroke	191 (2.0%)	171 (2.7%)	5%	191 (2.0%)	195 (2.0%)	0%
Encephalopathy	352 (3.6%)	305 (4.9%)	6%	352 (3.6%)	346 (3.6%)	0%
Prior falls	371 (3.8%)	295 (4.7%)	4%	371 (3.8%)	366 (3.8%)	0%
Prior fractures	627 (6.5%)	458 (7.3%)	3%	627 (6.5%)	627 (6.5%)	0%
Hemorrhagic stroke	28 (0.3%)	24 (0.4%)	2%	28 (0.3%)	30 (0.3%)	0%
Acute urinary retention	210 (2.2%)	161 (2.6%)	3%	210 (2.2%)	199 (2.1%)	1%
Health care visits and tests[e]						
Primary care visits	11.2 ± 9.6	11.8 ± 10.2	6%	11.2 ± 9.6	11.2 ± 11.4	0%
Emergency department visits	0.7 ± 1.4	0.7 ± 1.4	4%	0.7 ± 1.4	0.7 ± 1.9	1%
Serum creatinine tests	2.6 ± 2.2)	2.7 ± 2.3	0%	2.6 ± 2.2	2.6 ± 2.9	0%
Medication use[f]						
Selective serotonin reuptake inhibitors	991 (10.2%)	750 (12.0%)	6%	991 (10.2%)	994 (10.3%)	0%
Benzodiazepines	1,897 (19.5%)	1,152 (18.5%)	3%	1,897 (19.5%)	1,885 (19.5%)	0%
Antipsychotics	376 (3.9%)	284 (4.6%)	3%	376 (3.9%)	378 (3.9%)	0%
Opioids	2,749 (28.3%)	1,594 (25.6%)	6%	2,749 (28.3%)	2,734 (28.2%)	0%
Anticonvulsants	435 (4.5%)	261 (4.2%)	1%	435 (4.5%)	451 (4.7%)	1%

Unless otherwise specified, baseline characteristics were assessed on the date the patient filled the baclofen prescription. Values given as count (percentage) or mean ± SD.
[a]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.[2] Probabilities of treatment were determined separately for the primary and secondary analyses. Patients in the reference groups received a weight of [propensity score / (1 − propensity score)] and those in the exposed groups a weight of 1 (Table S1).[4-6] This method produces a weighted pseudosample of patients in the reference group with the same distribution of measured covariates as the exposure group.[4,5]
[b]Standardized difference: difference between the groups divided by the pooled SD; a value greater than 10% is interpreted as a meaningful difference.
[c]Based on average neighborhood income on the index date. Missing data on income quintile (0.3%) were recorded as the middle quintile.
[d]The most recent eGFR in the 7-365 days before the index date; eGFR calculated by CKD-EPI equation (Table S1); information on race was not available and all patients were assumed not to be of African-Canadian race (African-Canadians represented <5% of Ontario population in 2006).
[e]Baseline comorbidities were assessed in the 5-year (comorbidities) or 1-year (total visits or tests) period before the prescription start date.
[f]Medication use examined in the 120-day period before the prescription start date (the Ontario Drug Benefit program dispenses a maximum 100-day supply).

baclofen use.[4-6] Weighting methods are described in notes to Table 1 and in Table S1.[4-6] Weighted risk ratios (wRR) were obtained using modified Poisson regression,[7] and weighted risk differences (wRD) using a binomial regression model with an identity link function. A pre-specified subgroup analysis by baseline eGFR (in 3 categories) was conducted for the most common outcome (hospitalization with a fall).

The primary analysis included 15,942 patients. Weighting resulted in 2 well-balanced groups (Table S3); selected characteristics are shown in Table 1. The majority of prescribing physicians were primary care physicians (86%); <1% were nephrologists (Table 1). Less than 5% of patients received the recommended starting dose of 7.5 or 5.5 mg/d (Tables S4 and S5). Starting baclofen at ≥20 versus <20 mg/d was associated with a higher risk of

Table 2. Risk of a Fall, Fracture, and Hypotension in Older Adults With CKD Newly Prescribed Baclofen at ≥20 Versus <20 mg/d

Outcome: Hospital Encounter With	Observed No. of Patients, by Baclofen Dose		Weighted[a] No. of Patients, by Baclofen Dose		Risk Difference (95% CI)	Number Needed to Harm (95% CI)	Risk Ratio (95% CI)
	≥20 mg/d (n = 9,707)	<20 mg/d (n = 6,235)	≥20 mg/d (n = 9,707)	<20 mg/d (n = 9,680)			
Fall[b]	127 (1.31%)	65 (1.04%)	127 (1.31%)	92 (0.94%)	0.36% (0.03% to 0.70%)	278 (143-3333)[c]	1.38 (1.01-1.90)
Fracture[d]	36 (0.37%)	20 (0.32%)	36 (0.37%)	29 (0.30%)	0.07% (−0.12% to 0.26%)	Not available	1.23 (0.70-2.19)
Hypotension[e]	32 (0.33%)	6 (0.10%)	32 (0.33%)	10 (0.11%)	0.22% (0.08% to 0.37%)	456 (270-1250)[f]	3.06 (1.26-7.47)

Reference group: Baclofen dose < 20 mg/d.
[a]Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health[4-6]; further details in Table 1 and Table S1. Weighted risk ratios were obtained using modified Poisson regression[7]; weighted risk differences, by using a binomial regression model with an identity link function.
[b]Patient seen in the emergency department or admitted to the hospital with a fall diagnosis (ICD-10 code W00-W19).
[c]For every 278 patients prescribed baclofen at ≥20 vs <20 mg/d in the outpatient setting, 1 patient was hospitalized or visited an emergency department with a fall within 30 days of starting baclofen.
[d]Includes major fractures of hip (ICD-10 code S720, S721; S722. Canadian Classification of Health Interventions [CCI] code 1VA73, 1VC73, 1VA74, 1VA53, 1VC74, 1VA80), pelvis (ICD-10 code S321, S322, S324, S323, S325, S327, S328), humerus (ICD-10 code S422), and radius (ICD-10 code S52; CCI code 1TV73, 1TV74, 1TV03; Ontario Health Insurance Program [OHIP] code F014, F022, F023, F025, F026, F028, F030, F032, F033, F046, F024, F027, F031, Z203).
[e]Patient seen in the emergency department or admitted to the hospital with a hypotension diagnosis (ICD-10 code I95).
[f]For every 456 patients prescribed baclofen at ≥20 vs <20 mg/d in the outpatient setting, 1 patient was hospitalized or visited an emergency department with hypotension within 30 days of starting baclofen.

hospitalization with a fall (wRR, 1.38 [95% CI, 1.01-1.90]; wRD, 0.36% [95% CI, 0.03%-0.70%]) and hypotension (wRR, 3.06 [95% CI, 1.26-7.47]; wRD, 0.22% [95% CI, 0.08%-0.37%]), but not fracture (wRR, 1.23 [95% CI, 0.70-2.19]; wRD, 0.07% [95% CI, −0.12% to 0.26%]) (Table 2). Results were consistent in 2 sensitivity analyses (Tables S6 and S7). The association with falls was not significantly modified by baseline eGFR (Fig S1), acknowledging there was limited statistical power to detect it if it exists.

The secondary analysis included 15,942 baclofen users and 284,263 nonusers; characteristics of high-dose baclofen users versus nonusers and low-dose users versus nonusers are in Tables S8 and S9, respectively. Compared with nonusers, high-dose users had a higher risk of hospitalization with a fall, fracture, and hypotension; low-dose users had a higher risk of hospitalization with a fall, but not fracture or hypotension (Table S10).

In summary, older adults with CKD starting baclofen at ≥20 versus <20 mg/d were at higher risk for hospitalization with a fall and hypotension; for every 278 patients prescribed baclofen at ≥20 versus <20 mg/d, 1 was hospitalized with a fall. Although comparison groups were well balanced, residual confounding is still possible, and we did not account for dose changes in other medications such as opioids or benzodiazepines, which could influence study outcomes. Nonetheless, taken together the results of this study and others suggest that baclofen should be used with caution in older adults with CKD, and only at low doses.[2,3] To better protect patients with CKD, the product monograph should contain clear dose recommendations based on kidney function,[1] and computerized medication-order entry warnings with dosing prompts are also recommended.[8,9]

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Supplementary Material

Supplementary File (PDF)

Figure S1; Tables S1-S10.

Article Information

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any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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