

## Retrospective Cohort Study of the Prevalence of Off-label Gabapentinoid Prescriptions in Hospitalized Medical Patients

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Gabapentinoid prescriptions are increasing in North America, with frequent off-label use despite limited proven efficacy. This retrospective cohort study describes prescribing trends among hospitalized patients with a focus on dosing and deprescribing. We examined consecutive inpatients between December 2013 and July 2017 on a 52-bed medical unit in Montréal, Canada. Prevalence of off-label use, median doses prescribed, and deprescribing trends were analyzed over time. Of 4,103 hospitalized patients, 550 (13.4%) were prescribed gabapentinoids preadmission, with two patients being coprescribed gabapentin and pregabalin (total 552

prescriptions). A minority (94/552, or 17%) were for approved indications. Although it was uncommon for gabapentinoids to be newly prescribed in hospital, preadmission gabapentinoids were also seldom deprescribed (65/495 patients discharged alive, or 13%). Given a high prevalence of use, limited efficacy, and potential harms, gabapentinoids may represent an ideal target for re-evaluation of indication and effectiveness in hospitalized adults, with consideration given to deprescribing. *Journal of Hospital Medicine* 2019;14:547-550. Published online first May 10, 2019. © 2019 Society of Hospital Medicine

In the 1990s, gabapentin was licensed in the United States as an anticonvulsant and it became widely successful in the mid-2000s when marketed for the treatment of pain. Since then, prescriptions for gabapentinoids have accelerated dramatically.<sup>1,2</sup> Between 2012 and 2016, the total spending on pregabalin in the United States increased from \$1.9 to \$4.4 billion, with pregabalin ranking eighth overall for specific drug spending.<sup>3</sup>

Despite a finite number of indications, there has been a steady rise in off-label use, with an increased risk of adverse drug events (ADEs).<sup>4,5</sup> Several meta-analyses suggest either low-quality or no evidence of benefit for gabapentinoid use in settings including neuropathic pain in cancer, sciatica, and chronic low back pain.<sup>6-8</sup> Lack of efficacy is compounded by adverse effects such as altered mental status, fluid retention, sedation, and increased risk of traumatic falls in older adults.<sup>6,9,10</sup> Finally, dependency is a concern; opioids are coprescribed in up to 50% of patients,<sup>11</sup> increasing the odds of opioid-related death by up to 60%.<sup>12</sup>

To better characterize gabapentinoid use in hospitalized patients, we analyzed a retrospective cohort of patients admitted to our tertiary care medical teaching unit, examining preadmission and in-hospital prescribing trends, off-label use, and deprescribing.

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### METHODS

Patient data were collected from a retrospective cohort, including all consecutive admissions to our 52-bed medical clinical teaching unit in Montréal, Canada, since December 2013.<sup>13</sup> We reviewed admissions between December 17, 2013 and June 30, 2017 and identified three populations of gabapentinoid users from medication reconciliation documents: preadmission users continued at discharge, preadmission users deprescribed in hospital, and new in-hospital users continued at discharge. Deprescribing was defined as having the drug stopped at discharge or a prescribed taper that included stopping. The term “gabapentinoid users” refers to preadmission gabapentinoid use.

Gabapentinoid users were compared with nonusers with regard to demographic characteristics; select comorbidities; coprescription of opioids, benzodiazepines, and Z-drugs; length of stay (LOS); and inpatient mortality. Only the first eligible admission per patient was considered. Patients who had multiple admissions over the period of interest were classified as “users” in the patient-level analyses if they were taking a gabapentinoid at home or at discharge on at least one admission.

Doses and indications were collected from medication reconciliation performed by a clinical pharmacist, which included an interview with the patient or a proxy and a review of the indications for all drugs. These data were merged with any additional potential indications found in the admission notes (listing all chronic conditions from a detailed medical history) and review of the electronic medical record. The US Food and

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Additional Supporting Information may be found in the online version of this article.

**Received:** November 20, 2018; **Revised:** March 1, 2019;

**Accepted:** March 13, 2019

© 2019 Society of Hospital Medicine DOI 10.12788/jhm.3203

TABLE 1. Differences between Preadmission Users and Nonusers of Gabapentinoids<sup>a</sup>

	Gabapentinoid Preadmission Users (n = 550 <sup>b</sup> )	Gabapentinoid Nonusers (n = 3,553)
<b>Demographics</b>		
Age, median (IQR), years	71 (60-82)	72 (57-82)
Female	254 (46.2)	1,620 (45.6)
Pregabalin	408 (74.2)	–
Gabapentin	144 (26.2)	–
<b>Comorbidities</b>		
Hypertension <sup>c</sup>	346 (62.9)	1,880 (52.9)
Diabetes <sup>c</sup>	220 (40)	969 (27.3)
Receiving insulin <sup>c</sup>	96 (43.6)	239 (24.7)
Hemoglobin A1c, median (IQR); (n = 241)	7.6 (6.8-9.2)	7.3 (6.1-8.6)
Coronary artery disease <sup>d</sup>	136 (24.7)	664 (18.7)
Peripheral vascular disease <sup>c</sup>	61 (11.1)	127 (3.6)
Congestive heart failure <sup>d</sup>	84 (15.3)	383 (10.8)
Atrial fibrillation <sup>d</sup>	124 (22.5)	634 (17.8)
CHADS2 score, median (IQR)	2 (1-3)	2 (1-3)
Previous stroke <sup>e</sup>	77 (14)	369 (10.4)
Stage IV/V chronic kidney disease	75 (17.1)	402 (14.8)
Chronic obstructive pulmonary disease <sup>d</sup>	96 (17.5)	443 (12.5)
Active cancer	109 (19.8)	684 (19.3)
Ever smoker (n = 3,470)	262 (56.3)	1,528 (50.8)
<b>Other medications</b>		
Hypnotics, excluding benzodiazepines <sup>d</sup>	41 (7.5)	127 (3.6)
Benzodiazepines <sup>d</sup>	135 (24.5)	509 (14.3)
Opioids <sup>d</sup>	155 (28.2)	426 (12)
Benzodiazepines and opiates <sup>d</sup>	56 (10.2)	127 (3.6)
Proton pump inhibitor <sup>d</sup>	315 (57.3)	1,341 (37.7)
<b>Prescriptions (n = 3,621 discharged alive)</b>		
Home users continued at discharge	430 (86.9)	–
Home users deprescribed at discharge	65 (13.1)	–
Home users with dose decrease at discharge without further plan to taper	33 (6.7)	–
New users during admission	–	45 (1.4)
<b>Outcomes</b>		
Length of stay, median (IQR) <sup>e</sup>	6 (3-14)	6 (3-13)
Inpatient death	55 (10)	427 (12)

<sup>a</sup>All data are given as number (percentage) unless otherwise indicated.

<sup>b</sup>Includes two patients receiving both gabapentinoids preadmission.

<sup>c</sup>P < .001; <sup>d</sup>P < .01; <sup>e</sup>P < .05.

Abbreviation: IQR, interquartile range

Drug Administration (FDA) approved the indications and the recommended doses were taken from product monographs and compared with doses prescribed to patients. When documented, the reason for new prescriptions and justification for deprescribing at discharge were manually abstracted from discharge summaries and medication reconciliation documents.

Continuous variables were expressed as median and interquartile range (IQR) and compared using the Wilcoxon rank-sum test. Categorical variables were compared using the  $\chi^2$  test. Proportions of gabapentinoid use and deprescribing, including 95% confidence intervals around each proportion, were plotted and linear regression was performed versus fiscal quarter to evaluate for temporal trends. A two-sided  $\alpha$  value

of 0.05 was considered to be statistically significant. Statistical analyses were performed using Stata version 15 (StataCorp LLC, College Station, Texas). The McGill University Health Centre Research Ethics Board approved this study.

## RESULTS

A total of 4,103 unique patients were admitted from December 2013 to July 2017, of whom 550 (13.4%) were receiving a gabapentinoid before admission. Two preadmission users were coprescribed gabapentin and pregabalin for a total of 552 prescriptions. The prevalence of preadmission gabapentinoid use remained steady during the period of interest (Appendix 1;  $P = .29$  for temporal trend). There were no significant differences

TABLE 2. Proportion of Preadmission Gabapentinoid Use and Median Doses Prescribed by Indication<sup>a,14,15</sup>

Indications	Total (N = 552 <sup>b</sup> )	Gabapentin (n = 144)	Median Dose (mg, IQR)	FDA-recommended Dose (mg/day)	Pregabalin (n = 408)	Median Dose (mg, IQR)	FDA-recommended Dose (mg/day)
<i>FDA-approved indications for both pregabalin and gabapentin</i>							
Postherpetic neuralgia	19 (3.4)	2 (1.4)	2,450 (1,600-3,300)	900-1,800	17 (4.2)	150 (100-150)	150-300
Seizure disorder	5 (0.9)	3 (2.1)	200 (100-3,200)	900-,1800	2 (0.5)	87.5 (25-150)	150-600
<i>FDA-approved indications for pregabalin only</i>							
Diabetic neuropathic pain	86 (15.6)	32 (22.2)	600 (250-1,100)	–	54 (13.2)	112.5 (50-225)	150-300
Fibromyalgia	16 (2.9)	5 (3.5)	900 (300-900)	–	11 (2.7)	150 (100-300)	300-450
Spinal cord injury neuropathic pain	6 (1.1)	1 (0.7)	2,700	–	5 (1.2)	200 (150-500)	150-600
<i>Off-label use, or absence of a documented condition indicating a potential role for either pregabalin and gabapentin use</i>							
Other neuropathic pain	120 (21.7)	34 (23.6)	950 (600-1,750)	–	86 (21.1)	137.5 (75-200)	–
Musculoskeletal pain	88 (15.9)	20 (13.9)	400 (250-1,050)	–	68 (16.7)	150 (75-212.5)	–
Cancer-associated pain	49 (8.9)	6 (4.2)	650 (300-900)	–	43 (10.5)	100 (50-225)	–
Restless leg syndrome	7 (1.3)	2 (1.4)	1,450 (900-2,000)	–	5 (1.2)	150 (100-200)	–
Generalized anxiety disorder	1 (0.2)	0 (0)	–	–	1 (0.2)	50	–
Diabetes mellitus; absence of documented history of neuropathic pain	80 (14.5)	20 (13.9)	600 (300-750)	–	60 (14.7)	100 (75-162.5)	–
Not specified	75 (13.6)	19 (13.2)	900 (300-900)	–	56 (13.7)	75 (50-150)	–
Total	552 (100)	144 (100)	600 (300-1,200)	–	408 (100)	125 (68.75-200)	–

<sup>a</sup>All data are given as number (percentage) unless otherwise indicated.

<sup>b</sup>Includes 2 patients who were receiving both gabapentin and pregabalin preadmission

Abbreviations: FDA, United States Food and Drug Administration; IQR, interquartile range.

between gabapentinoid users and nonusers with regard to age or sex, but users had a higher prevalence of chronic disease (Table 1). In addition, compared with nonusers, gabapentinoid users were more likely to be coprescribed opioids (28.2% vs 12%;  $P < .01$ ), benzodiazepines (24.5% vs 14.3%;  $P < .01$ ), and nonbenzodiazepine sedative hypnotics (7.5% vs 3.6%;  $P < .01$ ). Of note, 10.2% of gabapentinoid users were simultaneously coprescribed both opioids and benzodiazepines versus 3.6% of nonusers ( $P < .01$ ; Table 1). Nonetheless, there was no statistically significant difference between users and nonusers with regard to inpatient mortality (10% vs 12%;  $P = .17$ ).

The indications for gabapentinoid use are presented in Table 2. Only a minority (17% or 94/552) had an approved indication. Among these 94 patients, 38 (40%) received FDA-recommended doses, 47 (50%) received doses below those demonstrated to be effective, and 9 (10%) received higher-than-recommended doses. New prescriptions at discharge were observed in 1.5% of patients, with the majority given for off-label indications (Appendix 2).

Gabapentinoids were deprescribed in 65/495 preadmission users who survived to discharge (13.1%) and 33/495 patients (6.7%) had their dose decreased without a further plan to taper

(Table 1). Approximately 50% of patients with a gabapentinoid deprescribed did not have a documented justification for cessation; however, when present, commonly cited reasons included ADEs (eg, impaired cognition, falls, edema) or the absence of an identified reason for ongoing use (Appendix 3). The proportion of patients who had a gabapentinoid deprescribed did not change over the study period (Appendix 4;  $P = .77$  for temporal trend).

## DISCUSSION

In this large cohort study of hospitalized medical patients, preadmission gabapentinoid use was present in one in every eight admitted patients. Most patients had off-label indications, including the small number of patients who had the drug started in hospital. Even for approved indications, the doses were often lower than what trials have suggested to be effective. Finally, although we have demonstrated that deprescribing occurred, it was uncommon and either precipitated by an adverse event or the justification was poorly documented.

To our knowledge, our study is one of the first to examine what happens to gabapentinoids in hospitalized patients and we present important new data with respect to dosing and prescribing patterns. The low rates of discontinuation, intent

to taper, or dose decreases in our cohort represent a potential area of improvement in deprescribing.

Deprescribing should be considered for patients with serious adverse events, for whom less serious adverse effects preclude achieving clinically effective doses, and for those who do not perceive benefit. Given the magnitude of the problems presented by polypharmacy, we propose that stopping priority be given to off-label use (especially when clinically ineffective) and for patients coprescribed opioids or sedatives. Up to a third of users in our cohort were coprescribed opioids or benzodiazepines, which is particularly concerning given the association with increased opioid-related mortality.<sup>12,15</sup> Although we did not observe a difference in inpatient mortality, such a study is underpowered for this outcome especially when considering the competing risks of death in hospital. Importantly, when deprescribing, the drug should be tapered over several weeks to limit symptoms of withdrawal and to prevent seizure.<sup>11</sup>

Presumed off-label use and subtherapeutic doses were common in our cohort, with only 17% of users having a clearly documented FDA-approved indication, in agreement with a previous study that reported only 5% on-label use.<sup>4</sup> High doses of gabapentinoids required for efficacy in clinical trials may be difficult to achieve because of dose-limiting side effects, which may explain the relatively low median doses recorded in our real-world cohort. Another possibility is that frail, older patients with renal dysfunction experience effectiveness at lower median doses than those quoted from study populations. In our study, patients on lower doses of gabapentinoids had a higher prevalence of stage IV or V chronic kidney disease (CKD). Stage IV/V CKD was identified in 16/47 (34.0%) patients on lower doses of gabapentinoids, compared to 4/38 (10.5%) on doses within the FDA-recommended range.

Our study has limitations; findings from a single Canadian tertiary care hospital may not be generalizable to other hospi-

tals or countries, particularly given the differences between the Canadian and US health systems. Indications were extracted from the patient chart and even with the best possible medication history and thorough review, sometimes they had to be inferred. Caution should also be exercised when interpreting the omission of an indication as equating to a lack of justifiable medication use; however, the rate of off-label use in our cohort is in agreement with prior research.<sup>4</sup> Moreover, with a retrospective design, the effectiveness of the drug on an individual basis could not be assessed, which would have allowed a more precise estimate of the proportion of patients for whom deprescribing might have been appropriate. The strengths of this study include a large sample of real-world, heterogeneous, general medical patients spanning several years and our use of trained pharmacists and physicians to determine the drug indication as opposed to reliance on administrative data.

## CONCLUSION

Gabapentinoid use was frequent in our cohort of hospitalized medical patients, with a high prevalence of off-label use, subtherapeutic doses, and coadministration with opioids and benzodiazepines. Deprescribing at discharge was uncommon and often triggered by an adverse event. The identification of gabapentinoids during hospitalization is an opportunity to reevaluate the indication for the drug, assess for effectiveness, and consider deprescribing to help reduce polypharmacy and ideally ADEs.

## Acknowledgment

For the purposes of authorship, Dr. McDonald and Dr. Lee contributed equally.

Disclosures: Dr. Emily McDonald and Dr. Todd Lee have a patent pending for MedSafer, a deprescribing software, and both receive research salary support from the *Fonds de Recherche Santé du Québec*. Dr. Gingras, Dr. Lieu, and Dr. Papillon-Ferland have nothing to disclose.

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