Antiepileptic use for epilepsy and nonepilepsy disorders

A population-based study (1998–2013)

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ABSTRACT

Objective: To examine the trends in antiepileptic drug (AED) use among individuals living in Manitoba with and without a history of epilepsy.

Methods: Using data obtained from administrative health databases in Manitoba, we assessed the quarterly prevalence of AED use between 1998 and 2013 among individuals with and without a history of epilepsy using cross-sectional time series analysis.

Results: Over the study period, the number of individuals prescribed AEDs increased more than 3-fold, from 8,883 to 27,246. The prevalence of AED use among patients with epilepsy increased by 3%, from 789.6 per 1,000 in 1998/1999 to 813.9 per 1,000 in 2012/2013 ($p < 0.001$ after 2006). In contrast, we observed a 210% increase in AED use among patients without epilepsy from 6.8 to 21.1 per 1,000 over the same period ($p < 0.001$). We observed a 55-fold rise in gabapentin use among patients without a seizure disorder (from 0.2 to 11.1 per 1,000; $p < 0.001$), while gabapentin use among those with epilepsy increased only 2-fold, from 21.6 to 41.3 per 1,000 ($p < 0.001$).

Conclusions: There has been a marked increase in the prevalence of AED users over the last 15 years, with a large shift towards the use of newer antiepileptic agents (primarily gabapentin) among those without epilepsy. Further research on the effect of these trends on health and economic outcomes will be of interest for clinicians and policymakers. **Neurology® 2016;86:939–946**

GLOSSARY

AED = antiepileptic drug; **DPIN** = Drug Program Information Network; **ICD** = *International Classification of Diseases*.

Antiepileptic drugs (AEDs) are a diverse class of medications that are increasingly used off-label for conditions other than epilepsy, such as migraine prophylaxis, neuropathic pain, and bipolar disorder.^{1–14} While previous studies suggest an increase in the use of newer AEDs,^{15–20} even newer agents have become available in practice, and no study to date has examined the prescribing trends of AEDs for seizure and nonseizure indications in a Canadian population. Understanding the trends in the use of such agents in a real-world setting will provide useful information from a policy perspective. Manitoba has one of the most comprehensive databases to examine the trend in drug use. In light of newer antiepileptic agents that have recently come into market, we aimed to examine temporal trends in AED use among individuals with and without epilepsy.

METHODS Design. We conducted a population-based retrospective time series analysis using data from April 1, 1998, to March 31, 2013.

Data sources. Data were obtained from the administrative Population Health Research Data Repository located at the Manitoba Centre for Health Policy. These databases have been used extensively for research.^{21,22} The Drug Program Information Network (DPIN) database captures outpatient prescription drug usage of all individuals living in Manitoba with the exception of medications received in hospital and by First Nations patients receiving care from nursing stations. Diagnoses were obtained from medical services (outpatient physician billings) and inpatient hospitalization files and identified using ICD-9-CM and ICD-10-CA codes. Patient records were

Supplemental data
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stored using an encrypted personal health identification number. Individual prescription data were linked with specific diagnoses from the health service contacts. The Manitoba Health Insurance Registry provided the number of residents in Manitoba and demographic information at the beginning of each 3-month interval. In Canada, universal health coverage is provided for all residents for medically necessary services, such as hospital care and physician visits. However, certain medications dispensed in the community setting are not always universally covered, and each province may differ in the provision of prescription drug coverage for residents. Restrictions are often made based on age or income. However, in Manitoba, all residents who are not covered by other provincial, federal, or private plans are eligible for drug coverage. Manitoba residents will have 100% of their prescription costs covered after an income-based deductible has been paid by the resident.

Patient population. We included 1.2 million individuals living in Manitoba. Individuals with epilepsy were defined as those with at least 3 primary care physician claims (separated by more than 30 days) or one hospitalization coded with a diagnostic code of ICD-9-CM 345 (or ICD-10-CA G40/G41, if applicable) within 2 years from the beginning of each quarter. This approach has been shown to have specificity of 99.8% and a positive predictive value of 79.5%.²³ Among individuals with and without a history of epilepsy, those receiving at least one prescription for an anticonvulsant within each index period (3-month interval) from April 1, 1998, to March 31, 2013, were identified as the population of AED users.

Antiepileptic agents. All oral AEDs (ATC code N03A) available in Canada were included in the analysis.

Quantification of use. The primary analysis examined the period prevalence of AED use every 3 months over the study period. Prevalent use was calculated by dividing the number of individuals filling a prescription for an AED by the total number of individuals alive in Manitoba at the beginning of the given interval, expressed as use per 1,000 individuals. The prevalent use of AEDs among individuals with a history of epilepsy, without a history of epilepsy, and total prevalent use of AEDs were calculated for each quarter.

Secondary analyses examined the quarterly prevalent use of AEDs grouped according to (1) users of older AEDs, defined as individuals using AEDs that entered the Canadian market prior to 1993; (2) users of newer AEDs, defined as individuals using AEDs that became available from 1993 onwards; and (3) mixed AED users, defined as individuals using both an older and newer AED in any given interval. Older AEDs included phenytoin, phenobarbital, methsuximide, ethosuximide, carbamazepine, primidone, and valproic acid. Newer AEDs included gabapentin, vigabatrin, lamotrigine, topiramate, oxcarbazepine, levetiracetam, pregabalin, lacosamide, rufinamide, and stiripentol. We also examined the quarterly prevalence of specific agents (carbamazepine, valproic acid, gabapentin, pregabalin, lamotrigine, and topiramate) at each interval in a secondary analysis. These agents were selected as they have been studied and used in the treatment of conditions other than epilepsy.¹⁻¹¹

Statistical analysis. Patient demographics were summarized based on the most recent year (i.e., April 1, 2012, to March 31, 2013) for AED users with and without epilepsy. The type of AED medications used among AED users with and without epilepsy was also summarized based on data from the most recent year. To assess trends in AED usage, the prevalence rates were analyzed using time series analysis including exponential

smoothing models and autoregressive integrated moving average models.²⁴ Time series analyses are well-established methods that employ a variety of techniques for modeling autocorrelation in temporally sequenced data. Numerous smoothing models were fit to the data by using the SAS software package for Windows, version 9.3 (SAS Institute, Inc., Cary, NC). The autocorrelation, partial autocorrelation, and inverse autocorrelation functions were further assessed for model parameter appropriateness and seasonality. Schwarz-Bayesian criteria were used to guide model selection. Stationarity was assessed with use of the autocorrelation function and the augmented Dickey-Fuller test. The presence of white noise was assessed by examining the autocorrelations at various lag points using the Ljung-Box χ^2 statistic.

Standard protocol approvals, registrations, and patient consents. This study was conducted in full compliance with the Privacy of Health Information Act of Manitoba and approved by the Research Ethics Board of the University of Manitoba and the Manitoba Health Information Privacy Committee.

RESULTS The population of Manitoba increased by 11% over the study period, from 1,073,508 to 1,186,862. The number of individuals who used AEDs increased more than 3-fold, from 8,883 (8,017 older AEDs and 322 newer AEDs) to 27,246 (7,617 older AEDs and 17,823 newer AEDs) during the study period. The population demographics for the most recent fiscal year are shown in table 1. AED users without epilepsy were more likely to be older, female, and have a concurrent prescription for an antidepressant, antipsychotic, or opioid.

Overall AED use increased dramatically, from 8.3 per 1,000 in the first fiscal quarter of 1998/1999 to 23.0 per 1,000 in the last fiscal quarter of 2012/2013 ($p < 0.001$). This was prominent among AED users without epilepsy who experienced a 210% increase in use ($p < 0.001$; figure e-1 on the *Neurology*[®] Web site at Neurology.org), while the rate in AED use among individuals with epilepsy showed only a modest 0.8% relative increase in use after 2008 ($p < 0.001$; figure e-2).

We observed an approximate 50-fold increase in AED use among individuals using newer AEDs, from 0.3 per 1,000 to 15.0 per 1,000 during the study period ($p < 0.001$). In contrast, the use of older AEDs decreased slightly from 7.5 per 1,000 to 6.4 per 1,000 during the same time period ($p < 0.001$). Among individuals with epilepsy, the use of older AEDs decreased by more than 30% between 1998/1999 and 2005/2006 ($p < 0.001$), while the use of newer and mixed (combination old and new AED) increased by almost 7-fold ($p < 0.001$) and 2-fold ($p < 0.001$), respectively (figure 1). Those without epilepsy represented the fastest-growing subgroup of new AED users ($p < 0.001$; figure 2). The most striking finding was the considerable 55-fold increase in gabapentin use among nonepilepsy users from 0.2 per 1,000 in the first quarter of 1998/1999 to 11.1

Table 1 Demographics of antiepileptic drug (AED) users in 1998/1999 and 2012/2013

Variable	1998/1999		2012/2013	
Total Manitoba population (on April 1 of fiscal year)	1,113,940		1,242,142	
Epilepsy vs nonepilepsy population	2,937	1,111,003	3,879	1,238,263
Total number of AED users ^a	AED users with epilepsy only (2,527)	AED users without epilepsy (9,510)	AED users with epilepsy only (3,366)	AED users without epilepsy (34,338)
Median (IQR) age, y	41 (28-57)	50 (36-68)	43 (24-57)	55 (43-67)
Age group, y, n (%)				
<13	173 (6.8)	477 (5.0)	420 (12.5)	298 (0.9)
13-18	132 (5.2)	342 (3.6)	226 (6.7)	456 (1.3)
19-64	1,795 (71.0)	5,820 (61.2)	2,196 (65.2)	23,308 (67.9)
>64	427 (16.9)	2,871 (30.2)	524 (15.6)	10,276 (29.9)
Female, n (%)	1,225 (48.5)	5,171 (54.4)	1,611 (47.9)	20,431 (59.5)
Urban residence, n (%)	1,478 (58.5)	6,065 (63.8)	2,131 (63.3)	21,440 (62.4)
Concurrent medications, n (%)				
Antidepressants	1,015 (40.0)	5,274 (55.5)	1,275 (37.9)	23,993 (69.9)
Tricyclic	434 (17.1)	2,980 (31.3)	569 (16.9)	15,703 (45.7)
SSRI	706 (27.9)	3,311 (34.8)	887 (26.4)	14,621 (42.6)
SNRI	228 (9.0)	1,474 (15.5)	356 (10.6)	8,722 (25.4)
Antipsychotics	587 (23.2)	3,084 (32.4)	648 (19.3)	8,736 (25.4)
Benzodiazepines	1,517 (60.0)	5,614 (59.0)	2,178 (64.7)	20,831 (60.7)
Opioids	1,806 (71.5)	6,950 (73.1)	2,258 (67.1)	30,044 (87.5)
Health care utilization in past year				
Hospitalizations, n (%)	685 (27.1)	2,191 (23.0)	780 (23.1)	6,450 (18.8)
Emergency department visits, n (%) ^b	Not available	Not available	1,032 (2.7)	8,982 (23.8)
Hospitalizations, mean (SD)	0.5 (1.3)	0.4 (1.1)	1.9 (1.7)	1.7 (1.4)
Emergency department visits, mean (SD) ^b	Not available	Not available	2.7 (3.5)	2.4 (3.3)
Psychiatry visits, mean (SD)	0.5 (4.4)	2.3 (9.0)	0.7 (5.2)	1.3 (6.9)
Neurology visits, mean (SD)	0.9 (1.6)	0.4 (1.1)	2.3 (4.3)	0.5 (1.5)
No. (%) AEDs used per patient				
1	1,471 (58.2)	8,029 (84.4)	1,812 (53.8)	31,098 (90.6)
2	746 (29.5)	1,304 (13.7)	1,001 (29.7)	2,826 (8.2)
3	244 (9.7)	162 (1.7)	399 (11.9)	369 (1.1)
4+	66 (2.6)	15 (0.2)	154 (4.6)	45 (0.1)
Type of AED, n (%)				
Newer	56 (2.2)	555 (5.8)	527 (15.7)	25,905 (75.4)
Older	2,052 (81.2)	8,523 (89.6)	1,885 (56.0)	6,871 (20.0)
Combination	419 (16.6)	432 (4.5)	954 (28.3)	1,562 (4.6)

Abbreviations: IQR = interquartile range; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = serotonin reuptake inhibitor.

^aDemographics described using number of AED users as the denominator.

^bEmergency visit data not available for 1998/1999 year.

per 1,000 in the last quarter of 2012/2013 ($p < 0.001$; figure 3). Among AED users with epilepsy, a 347% rise in lamotrigine was observed from 33.8 per 1,000 to 151.2 per 1,000 during the study period ($p < 0.001$), whereas the quarterly prevalence of the other agents remained relatively constant during

the same time period (figure 4). In compliance with the Manitoba Health Information Privacy Committee, the use of pregabalin could not be reported due to low numbers. Phenytoin, carbamazepine, valproic acid, and lamotrigine were the top 4 AEDs used among individuals with epilepsy in 2012/2013, and

Figure 1 Crude prevalence rates of antiepileptic drug (AED) users among individuals with epilepsy

All trends depicted are significant at $p < 0.001$.

gabapentin, pregabalin, valproic acid, and carbamazepine were the top 4 AEDs used among individuals without epilepsy in 2012/2013 (table e-1).

DISCUSSION In this 15-year population-based study, we found that AED use increased dramatically, with a large shift towards the use of newer antiepileptic agents, particularly among those without epilepsy. The increase in AED users observed in our study was consistent, yet markedly higher, compared with findings from previous

studies.^{15–20} Few studies have examined the use of AEDs in the nonepilepsy population.^{19,20} Tsiropoulos et al.²⁰ reported a decline in AED use of 19.7% among those with epilepsy, but an increase in AED use of 11.2% and 8.4% for those with pain and mood disorder, respectively. Landmark et al.¹⁹ found a substantial increase in the use of AEDs for indications other than epilepsy: neuropathic pain 1.4 defined daily dose/1,000 inhabitant days (360%), psychiatry 1.59 (200%), and migraine 0.005 (642%). It is important to note, however,

Figure 2 Crude prevalence rates of antiepileptic drug (AED) users among individuals without epilepsy

Older AED users significantly declined after 2004 ($p < 0.001$), while newer AED users significantly increased throughout the study period ($p < 0.001$). Mixed users significantly increased ($p < 0.001$) then plateaued after 2010 ($p = 0.994$).

Figure 3 Crude prevalence rates of specific antiepileptic drugs used among individuals without epilepsy

Gabapentin and lamotrigine users significantly increased ($p < 0.001$ for both). Topiramate users significantly increased ($p < 0.001$), then represented a weaker but significant increase after 2006 ($p = 0.045$).

that the determination of AED use for specific indications other than epilepsy in both of these studies has not been validated previously.

The increased use of the newer AEDs observed in our study was expected due to the introduction of new AEDs during the study period. Gabapentin, lamotrigine, and topiramate became available just prior to the start of the time period studied (between 1994 and 1997). Oxcarbazepine, levetiracetam, and pregabalin were introduced in the early

2000s, and lacosamide, rufinamide, and stiripentol were only introduced within the last 4 years. In Canada, carbamazepine, valproic acid, topiramate, and pregabalin are the only AEDs that have a Health Canada–approved indication for a condition apart from epilepsy. Other AEDs, such as gabapentin and lamotrigine, are only approved for use in epilepsy, and our study observed a rise in use of these agents among individuals without epilepsy. Accumulating literature and clinical guidelines

Figure 4 Crude prevalence rates of specific antiepileptic drugs used among individuals with epilepsy

Gabapentin users remained stable with a trend in increase in use after 2011 ($p = 0.07$). Lamotrigine users significantly increased ($p < 0.001$).

support the off-label use of newer AEDs for conditions other than epilepsy, including neuropathic pain (secondary to diabetic neuropathy, postherpetic neuralgia, cancer, and multiple sclerosis), migraine prophylaxis, restless legs syndrome, and fibromyalgia.^{4–6,25} These conditions often represent a significant challenge for patients and clinicians given the limited availability of safe and effective therapeutic options to optimally manage them. The rise in use of the newer AEDs among nonepilepsy patients could reflect a rise in the number of people who are benefiting from treatment. However, this cannot be concluded based on the findings of this study. In light of the limited long-term safety and efficacy data for the newer AEDs in the treatment of conditions other than epilepsy, further investigation on the long-term use and appropriateness of these agents is warranted.

The most striking finding is the rapid growth in gabapentin use. Gabapentin is widely used off-label for neuropathic pain; however, there is growing concern over its potential for abuse.^{26–31} Gabapentin imparts psychoactive effects and may be regarded as safe by many clinicians.²⁶ Reports of gabapentin abuse have been documented among individuals with a history of cocaine or alcohol dependency, and recreational abuse is widely reported on the Internet.^{28,29} For neuropathic pain, the effective target dose of gabapentin can be as high as 3,600 mg/d.^{26,32,33} In our study, more than half of all AED users were using gabapentin in 2012/2013. The high use of gabapentin warrants further exploration in the context of appropriate prescribing, especially in populations at risk for abuse. Pregabalin is the only antiepileptic agent with a Health Canada–approved indication for neuropathic pain and fibromyalgia.³⁴ However, this agent is not covered by public health plans in many jurisdictions (table e-2).³⁵ The limited accessibility of pregabalin may explain the shift in the off-label use of gabapentin for pain conditions. It is unclear whether the widespread use of off-label gabapentin in place of pregabalin for neuropathic pain is appropriate. Medications used off-label is an important concern, as the efficacy and safety of these agents may not have been adequately studied in this setting. As a result, patients may be exposed to the risks associated with the medication without any significant added benefit.

Strengths of this study include the length of the study period and the comprehensiveness of the administrative databases, which capture nearly all residents of Manitoba who contact the health care system regardless of age, socioeconomic status, and reimbursement plans. The DPIN database allows for a complete real-world examination of drug

utilization unaffected by sampling errors or restrictions based on health coverage. Access to nearly all antiepileptic agents is unrestricted to the study population with the exception of pregabalin and stiripentol, which are not covered for any indication, and oxcarbazepine, levetiracetam, lacosamide, and rufinamide are covered for seizure disorders if patients meet specific criteria. However, some limitations of our study merit emphasis, such as the lack of clinical information and validated case definitions for specific conditions other than epilepsy (e.g., neuropathic pain). It is also not possible to identify the change in indication of AED use over time for an individual. Although we used a validated algorithm to define individuals with epilepsy, some degree of misclassification is likely.

Despite the widespread use of some of the newer AEDs for specific nonseizure conditions, the cost-effectiveness remains inconclusive. Findings from this study will provide foundational information for future research that aims to study the appropriateness and cost-effectiveness of off-label prescribing for nonseizure conditions. The relative risk of suicide and long-term safety risks associated with each type of AED for both seizure and nonseizure indications would be a next step for future research. Moreover, this study provides the basis for studying health outcomes associated with AED use on populations typically underrepresented in clinical trials, including pregnant patients and the elderly population. Understanding trends in AED utilization and their potential effects on improving health and economic outcomes will be of interest for clinicians and policymakers.

AUTHOR CONTRIBUTIONS

Dr. Leong has full access to all of the results and has the right to publish any and all results separate and apart from any sponsor, developed the original concept and design of the protocol, drafted and revised the manuscript based on feedback provided by the coauthors, gave final approval of the version to be published, and agrees to act as a guarantor of the work. Dr. Mamdani contributed to the analysis and interpretation of the data, tested the data for significant trends, revised the manuscript critically for important intellectual content, and gave final approval of the version to be published. T. Gomes contributed to the analysis and interpretation of the data, tested the data for significant trends, revised the manuscript critically for important intellectual content, and gave final approval of the version to be published. Dr. Juurlink contributed to the analysis and interpretation of the data, tested the data for significant trends, revised the manuscript critically for important intellectual content, and gave final approval of the version to be published. E. Macdonald contributed to the analysis and interpretation of the data, tested the data for significant trends, revised the manuscript critically for important intellectual content, and gave final approval of the version to be published. M. Yogendran has full access to all of the data, contributed to the preparation, analysis, and interpretation of data, revised the manuscript critically for important intellectual content, and gave final approval of the version to be published.

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DISCLOSURE

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This Week's *Neurology*[®] Podcast

Transient ischemic attack service provision: A review of available service models (see p. 947)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the March 8, 2016, issue of *Neurology*. In the second segment, Dr. Bryan Eckerle talks with Dr. Anna Ranta about her paper on transient ischemic attacks as predictors of high risk for subsequent strokes. Dr. Ted Burns interviews Dr. Yian Gu about her paper on the Mediterranean diet and brain structure in a multiethnic elderly cohort in our “What’s Trending” feature of the week. In the next

part of the podcast, Dr. Nick Brenton focuses his interview with Dr. Daniela Pohl on the topic of disease-modifying therapy management in pediatric multiple sclerosis.

Disclosures can be found at Neurology.org.

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