ORIGINAL CONTRIBUTION

Association of Antiepileptic Drugs With Nontraumatic Fractures

A Population-Based Analysis

Nathalie Jetté, MD, MSc; Lisa M. Lix, PhD; Colleen J. Metge, PhD; Heather J. Prior, MSc; Jane McChesney, BN; William D. Leslie, MD

Objective: To explore the relationship between antiepileptic drug (AED) use and nontraumatic fractures in those aged 50 years and older.

Design: Retrospective matched cohort study.

Participants: A total of 15 792 persons, identified through the Population Health Research Data Repository from Manitoba, Canada, with nontraumatic fractures of the wrist, hip, and vertebra occurring between 1996 and 2004. Each patient was matched for age, sex, ethnicity, and comorbidity with up to 3 controls (n=47 289).

Interventions: Prior AED use (carbamazepine, clonazepam, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproic acid, and vigabatrin) was determined from pharmacy data in the repository. Odds ratios (OR) for fracture from AED exposure were adjusted for sociodemographic and comorbidity factors known to affect fracture risk.

Results: A significant increase in fracture risk was found for most of the AEDs being investigated (carbamazepine, clonazepam, gabapentin, phenobarbital, and phenytoin). The adjusted ORs ranged from 1.24 (95% confidence interval [CI], 1.05-1.47) for clonazepam to 1.91 (95% CI, 1.58-2.30) for phenytoin. The only AED not associated with increased fracture risk was valproic acid (adjusted OR, 1.10; 95% CI, 0.70-1.72).

Conclusions: Most AEDs were associated with an increased risk of nontraumatic fractures in individuals aged 50 years or older. Further studies are warranted to assess the risk of nontraumatic fractures with the newer AEDs and to determine the efficacy of osteoprotective medications in this population.

Arch Neurol. 2011;68(1):107-112

Author Affiliations: Department of Clinical Neurosciences, University of Calgary, Foothills Hospital, Calgary, Alberta, Canada (Dr Jetté and Ms McChesney); School of Public Health, University of Saskatchewan, Saskatoon, Saskatchewan, Canada (Dr Lix); and Manitoba Centre for Health Policy (Dr Metge and Ms Prior), Faculty of Pharmacy (Dr Metge), and Department of Medicine (Dr Leslie), University of Manitoba, Winnipeg, Manitoba, Canada.

OSTEOPOROSIS AFFECTS more than 50 million people worldwide, with 9 million osteoporosis-related fractures reported annually.[1,2] More than 80% of fractures in those aged 60 years and older are osteoporosis related.[3] In the United States alone, costs of treatment of incident osteoporotic fractures exceeded $30 billion in 2004.[4]

There are many secondary risk factors for osteoporosis.[5] Antiepileptic drugs (AEDs) are of particular concern, considering that epilepsy is highly prevalent in elderly persons, a population already at risk for osteoporosis.[6]

Antiepileptic drugs are associated with greater bone density reduction in postmenopausal women with epilepsy compared with controls.[7] Two population-based studies also confirmed that AED use increases the rate of bone loss in adults older than 65 years but, aside from phenytoin and gabapentin, these studies were unable to examine the association of individual AEDs with bone loss.[8,9]

A meta-analysis and 2 population-based studies described an association between AEDs and fractures, but most studies focused on patients with epilepsy.[10-12] The use of AEDs extends beyond seizure management (eg, pain and psychiatric disorders). One large population-based study that included persons using an AED for any indication found that carbamazepine, oxcarbamazepine, clonazepam, phenobarbital, and valproate were associated with fractures.[13]

Population-based studies assessing the association between AEDs and fractures are scarce, and none have focused solely on older individuals. With expected increases in the incidence of osteoporosis owing to the aging population, we embarked on a population-based, pharmaco-epidemiological, matched cohort study to explore the relationship between AED use and nontraumatic fractures in those older than 50 years.

METHODS

DATA SOURCE

The data source used to carry out this retrospective matched cohort study was the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy, a comprehensive health care–use database of nearly all residents of the province of Manitoba, Canada (population, 1.18 million).[14] Because of universal health care coverage in Canada, these data capture virtually all residents of the province. Manitoba residents are provided with a unique personal health number by the provincial health department that is scrambled to preserve anonymity during data linkage.

The Research Data Repository has been extensively validated for determining the prevalence of osteoporotic fractures and their risk factors.[15,16] This database is therefore well suited to investigate the association between the use of AEDs and fractures of the hip, vertebra, and wrist.

IDENTIFICATION OF PARTICIPANTS

Cases were included in the study if they were aged 50 years or older and had continuous health care coverage between April 1, 1988, and March 31, 2004, or until death. Nontraumatic (osteoporosis-related) fractures were identified in physician claims or hospital discharge abstracts coded with the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* using diagnosis codes for vertebral (*ICD-9-CM* 805), wrist (*ICD-9-CM* 813), or hip fracture (*ICD-9-CM* 820-821 plus a physician claim for hip fracture reduction or fixation, open or closed). High-trauma fractures, defined by an external cause of the injury (E codes), were excluded. The date of fracture became the index date for the case and any matched controls.

Cases were excluded if they had used osteoprotective medications (selective estrogen receptor modulators, natural and semisynthetic estrogens, bisphosphonates, parathyroid hormone analogues, or calcitonin) in the year prior to the fracture. Residents of long-term care facilities were also excluded, as they are one of the rare groups whose prescription medication history is not fully captured in the Research Data Repository.

Each case was matched with up to 3 controls without a history of hip, wrist, or vertebral fractures. Controls were matched by age (within 5 years), sex, degree of comorbidity, and ethnicity (Aboriginal) status. The degree of comorbidity was defined using the John Hopkins aggregated diagnosis groups (ADG).[17] The number of ADGs for which the patient had received a diagnosis in the year before the fracture was calculated and categorized based on the total number of ADGs (0, 1-2, 3-5, ≥6). The use of ADGs to quantify comorbidity and fracture risk has previously been validated in the Manitoba databases.[15]

DETERMINATION OF AED EXPOSURE

The Drug Program Information Network database was used to determine AED exposure. This pharmaceutical database has been validated and found to be accurate at capturing drug dispensations and prescription details.[18] The database contains virtually all pharmacy dispensations, and the drugs are coded using the World Health Organization Anatomical Therapeutic Chemical classification system.[19]

The AEDs studied were carbamazepine (N03AF01), clonazepam (NO3AE01), ethosuximide (N03AD01), gabapentin (N03AX12), phenobarbital (N03AA02), phenytoin (N03AB02), and valproic acid (N03AG01). Owing to smaller numbers of users, felbamate (N03AX10), lamotrigine (N03AX09), levetiracetam (N03AX14), pregabalin (N03AX16), primidone (N03AA03), oxcarbazepine (N03AF02), topiramate (N03AX11) and vigabatrin (N03AG04) were grouped together as "other AEDs."

Antiepileptic drug exposure was classified as (1) nonusers with no AED dispensations in the year prior to the index date; (2) past users with 1 or more AED dispensations in the period 4 to 12 months prior to the index date; and (3) current users, identified as those who had 1 or more AED dispensations within 4 months of the index date.

ASSESSMENT OF POTENTIAL CONFOUNDERS

We adjusted for potential confounders that have previously been assessed using administrative data and found to be associated with fracture risk.[20] Specifically, we controlled for area of residence (urban, rural south, rural north) and income (based on 2001 Canada census public files and grouped into the lower 2 quintiles and upper 3 quintiles).[21] We controlled for the following comorbidities using *ICD-9-CM* diagnosis codes from physician claims or hospital discharge abstracts during the 3 years prior to the index date (case fracture): epilepsy, diabetes, ischemic heart disease, hypertension, rheumatoid arthritis, chronic obstructive pulmonary disease (proxy for smoking), substance use, depression (as a marker of psychotropic drug use such as selective serotonin reuptake inhibitors), schizophrenia (as a marker of psychotropic drug use), and dementia. Epilepsy was defined using 2 physician visits or hospitalizations coded with *ICD-9-CM* 345 for the 3 years prior to the index date. We also controlled for home care use (proxy for frailty) during the year prior to the index date.

STATISTICAL ANALYSIS

Conditional logistic regression models were developed for each agent to assess the association between fractures and individual AED use. Model 1 adjusted for sociodemographic variables and past AED use. Model 2 adjusted for sociodemographic variables, home care use, comorbidities, and past AED use. Model 3 adjusted for sociodemographic variables, home care use, comorbidities, and for all the AEDs simultaneously. Specifically, separate variables were defined for each of the AEDs, including the other AEDs group. One final model was tested (model 4), in which each AED was included as a separate subgroup if it was currently being used in monotherapy (ie, patient only taking 1 of the AEDs studied) or in polytherapy (patients taking more than 1 of the AEDs studied). The final model was adjusted for sociodemographic variables, home care use, and comorbidities. Odds ratios (ORs) for the risk of fracture in AED vs non–AED users with 95% confidence intervals (CI) were obtained. All regression analyses were performed using SAS version 9.1.3 (SAS Inc, Cary, North Carolina).

RESULTS

A total of 15 792 patients met our case definition for nontraumatic (osteoporotic) fracture between April 1996 and March 2004. These cases were successfully matched for age, sex, ethnicity, and number of ADGs to 47 289 controls. Baseline characteristics of cases and controls are shown in **Table 1**. Fracture cases were more likely to live in urban dwellings (OR, 1.07; 95% CI, 1.03-1.10), fall in the lowest income group (OR, 1.10; 95% CI, 1.06-1.14), and have used home care services (OR, 1.74; 95% CI, 1.66-1.82) compared with controls. The most common fracture site was the wrist (52.0%) followed by the hip (26.2%) and, lastly, the vertebra (21.7%).

Table 1. Baseline Characteristics of Fracture Cases and Matched Nonfractured Controls

Characteristic	No. (%) Cases (n=15 792)	Controls (n=47 289)	Univariate OR (95% CI)[a]
Age, y			
50-59	2755 (17.5)	8393 (17.8)	NA
60-69	3142 (19.9)	9340 (19.8)	NA
70-79	4512 (28.6)	13 749 (29.1)	NA
≥80	5283 (34.1)	15 807 (33.4)	NA
Sex			
Male	4696 (29.7)	14 080 (29.8)	NA
Female	11 096 (70.3)	33 209 (70.2)	NA
ADGs, No.[b]			
0	1243 (7.9)	3721 (7.9)	NA
1-2	3999 (25.3)	11 975 (25.3)	NA
3-5	5901 (3704)	17 686 (37.4)	NA
≥6	4649 (29.4)	13 907 (29.4)	NA
Fracture site			
Vertebra	3431 (21.7)	0 (0.0)	NA
Wrist	8216 (52.0)	0 (0.0)	NA
Hip	4145 (26.2)	0 (0.0)	NA
Residence			
Rural north	9143 (57.9)	26 647 (56.4)	1.02 (0.92-1.13)
Urban	546 (3.5)	1603 (3.4)	**1.07 (1.03-1.10)**
Rural south	6103 (38.7)	19 039 (40.3)	**0.93 (0.90-0.97)**
Income			
Low	7805 (49.4)	22 291 (47.1)	**1.10 (1.06-1.14)**
High	7987 (50.6)	24 998 (52.9)	**0.91 (0.88-0.95)**
Home care use	3891 (24.6)	7486 (15.8)	**1.74 (1.66-1.82)**

Abbreviations: ADG, aggregated diagnosis group; CI, confidence interval; NA, not applicable; OR, odds ratio.
[a] Statistically significant results (α=.05) are in boldface.
[b] Johns Hopkins ADGs were used as an index of comorbidity. For each patient, we determined the number of aggregated diagnosis groups in the year before the fracture index date.

Table 2. Prevalence of Comorbidities in Fracture Cases and Controls

Comorbidity	No. (%) Cases (n=15 792)	Controls (n=47 289)	Univariate OR (95% CI)[a]
Epilepsy	79 (0.5)	82 (0.2)	**2.89 (2.12-3.94)**
Diabetes	2419 (15.3)	7123 (15.1)	1.02 (0.97-1.07)
Ischemic heart disease	2190 (13.9)	6884 (14.6)	0.95 (0.90-1.00)
Myocardial infarction	576 (3.7)	1688 (3.6)	1.02 (0.93-1.13)
Hypertension	5362 (34.0)	17 838 (37.7)	**0.85 (0.82-0.88)**
Arthritis	311 (2.0)	725 (1.5)	**1.29 (1.13-1.48)**
COPD	2665 (16.9)	7203 (15.2)	**1.13 (1.08-1.19)**
Substance abuse	532 (3.4)	742 (1.6)	**2.19 (1.95-2.45)**
Depression	1574 (10.0)	3313 (7.0)	**1.47 (1.38-1.56)**
Schizophrenia	142 (0.9)	197 (0.4)	**2.17 (1.75-2.69)**
Dementia	999 (6.3)	1572 (3.3)	**1.96 (1.81-2.13)**

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.
[a] Statistically significant results (α=.05) are in boldface.

The prevalence of comorbidities in fracture cases and controls is shown in **Table 2**. Cases were more likely to have epilepsy (OR, 2.89; 95% CI, 2.12-3.94), arthritis (OR, 1.29; 95% CI, 1.13-1.48), COPD (OR, 1.13; 95% CI, 1.08-1.19), substance abuse (OR, 2.19; 95% CI, 1.95-2.45), depression (OR, 1.47; 95% CI, 1.38-1.56), schizophrenia (OR, 2.17; 95% CI, 1.75-2.69), or dementia (OR, 1.96; 95% CI, 1.81-2.13). Those with fractures were less likely to have hypertension (OR, 0.85; 95% CI, 0.82-0.88).

The odds of fracture, based on the type of AED, are shown in **Table 3** and the **Figure**. In both the partially (models 1 and 2) and fully adjusted (model 3) models, all AEDs except for valproic acid were associated with fractures. Odds ratios in the fully adjusted model ranged from a low of 1.24 (95% CI, 1.05-1.47) for clonazepam to 1.49 (95% CI, 1.10-2.02) for gabapentin, 1.60 (95% CI, 1.16-2.19) for phenobarbital, 1.81 (95% CI, 1.46-2.23) for carbamazepine, and a high of 1.91 (95% CI, 1.58-2.30) for phenytoin. The odds of fracture was 1.65 (95% CI, 1.07-2.56) for other AEDs group. Similar results were obtained when we tested the effect size of AEDs in monotherapy on fractures (Table 3, model 4), with the greatest risk seen for those in the polytherapy subgroup (OR, 2.97; 95% CI, 2.26-3.89). All AEDs used in monotherapy were associated with significantly increased fracture risk except for valproic acid (OR, 0.71; 95% CI, 0.36-1.37), phenobarbital (OR, 1.31; 95% CI, 0.80-2.16), and other AEDs (OR, 1.29; 95% CI, 0.69-2.43).

COMMENT

A significant increase in fracture risk was found for most individual AEDs studied (except for valproic acid) in this large population-based pharmaco-epidemiologic study of older adults. This increased risk persisted after adjusting for sociodemographic variables, comorbidities, and use of home care services.

Our study is consistent with other population-based studies, demonstrating an increased risk of fractures in individuals receiving AEDs.[10-12] Most of these studies were small, poorly controlled, or focused on individuals with epilepsy. One large pharmaco-epidemiologic study by Vestergaard et al[13] examined the risk of fractures in individuals on AEDs, regardless of epilepsy status. One difference compared with our study is that they included patients of all ages, unlike our study, which focused on older individuals. Although their results were similar to ours, some contradictory findings are worth noting. First, our study found an association between phenytoin and the risk of fracture, while the study by Vestergaard et al[13] did not report such an association. This is surprising considering that phenytoin has been associated with bone loss.[8,22,23] For example, Pack et al[23] followed up 93 premenopausal women with epilepsy who were receiving AED monotherapy (carbamazepine, lamotrigine, phenytoin, or valproate) and noted significant bone loss at the femoral neck as little as 1 year after treatment initiation in the phenytoin group but not in the other groups. These results must be interpreted cautiously, as no control groups were enrolled in the latter study.[23] Second, the study by Vestergaard et al,[13] contrary to our study, reported an association between valproic acid and fractures. Once again, the literature on the association between valproic acid and bone loss or fracture is inconsistent. In our study, valproic acid was significantly as-

Table 3. Odds Ratios and 95% Confidence Intervals for the Association Between Current Use of Antiepileptic Drugs and Fractures

AED[b]	OR (95% CI)[a]			
	Model 1	Model 2	Model 3[c]	Model 4
Carbamazepine	2.21 (1.81-2.70)	1.91 (1.55-2.35)	**1.81 (1.46-2.23)**	1.77 (1.40-2.24)
Clonazepam	1.59 (1.36-1.87)	1.26 (1.06-1.49)	**1.24 (1.05-1.47)**	1.27 (1.06-1.51)
Gabapentin	1.74 (1.30-2.34)	1.57 (1.16-2.13)	**1.49 (1.10-2.02)**	1.61 (1.15-2.25)
Phenobarbital	2.62 (1.97-3.48)	2.17 (1.61-2.94)	**1.60 (1.16-2.19)**	1.31 (0.80-2.16)
Phenytoin	2.64 (2.23-3.12)	2.10 (1.75-2.52)	**1.91 (1.58-2.30)**	1.85 (1.50-2.29)
Valproic acid	2.09 (1.36-3.19)	1.25 (0.80-1.95)	1.10 (0.70-1.72)	0.71 (0.36-1.37)
Other AEDs[d]	2.73 (1.80-4.13)	2.05 (1.33-3.14)	**1.65 (1.07-2.56)**	1.29 (0.69-2.43)
Multiple current AEDs				2.97 (2.26-3.89)

Abbreviations: AED, antiepileptic drug; CI, confidence interval; OR, odds ratio.
[a] Model 1 was adjusted for sociodemographic variables + past AED use; model 2, for sociodemographic variables + homecare use + comorbidities + past AED use; model 3, for sociodemographic variables + homecare use + comorbidities and all AEDs simultaneously; model 4, all AEDs were tested for monotherapy (subjects currently taking a single AED) or polytherapy (subjects currently using more than 1 AED).
[b] In the first 3 models, the AEDs are included as variables whether or not they are used in monotherapy (subjects taking a single AED) or polytherapy (subjects taking multiple AEDs).
[c] Statistically significant results ($\alpha = .05$) are in boldface.
[d] Other AEDs includes felbamate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, primidone, topiramate, and vigabatrin (sample size for these too small to test individually).

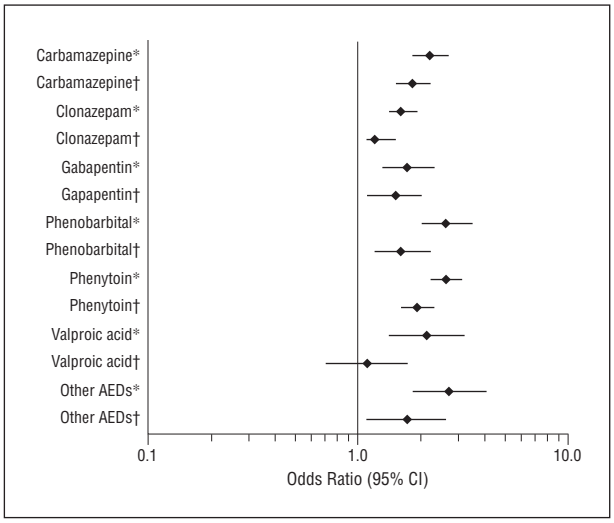

Figure. Odds ratio with 95% confidence intervals (CIs) for the association between current use of antiepileptic drugs (AEDs) and nontraumatic fractures. *Unadjusted model; † fully adjusted model. Odds ratios greater than 1 indicate increased risk of fracture.

sociated with the odds of fracture in a model only adjusted for sociodemographic variables but, after adjusting for home care use and the presence of comorbid conditions, this association was no longer statistically significant. Similar to prior studies by Vestergaard et al[13,24] and Souverein et al,[12] the odds of fracture were statistically significant for carbamazepine, clonazepam, and phenobarbital, but the association between phenobarbital and fracture risk was no longer significant once examined as monotherapy, possibly owing to the smaller sample size. Our finding of an association between gabapentin and nontraumatic fracture has not, to our knowledge, been described in previous research. However, an association between gabapentin and bone loss has previously been described in men in 1 large prospective study.[9] The association between gabapentin and fractures is surprising, although it is frequently used to treat chronic pain syndromes. It is plausible that many persons who are taking gabapentin are limited in their mobility (owing to pain), which can result in deconditioning, bone loss, and fractures.

It is interesting that those with fractures were less likely to have hypertension compared with those without fractures, suggesting a possible osteoprotective benefit from hypertension. This is consistent with prior studies suggesting higher bone mineral density in those with hypertension (possibly mediated through associations with overweight and obesity)[25-27] but contrary to other studies reporting that hypertension is associated with fractures[28,29] and bone density loss.[30] Antihypertensives have been found to be osteoprotective by reducing blood pressure, which can lead to decreased urinary calcium loss and subsequent decreased fracture risk or increased bone mineral density.[31-35]

Four different logistic regression models to assess effect size were used in the current study, each of varying complexity. The OR of sustaining a fracture decreased in magnitude when we added markers of frailty (eg, home care use) and comorbidity measures, suggesting a common mechanism to promote fracture risk in this population that may not be specifically AED related. Some of these mechanisms may be related to underlying health issues such as deconditioning, lack of antigravity activity, lack of sun exposure, low calcium intake, and overall poor vitamin D intake.[8] Unfortunately, we did not have the ability to specifically adjust for these in our study, although adjustment for home care use was chosen as a surrogate marker for lack of antigravity activity and deconditioning.

There are other confounding factors that could contribute to bone loss in our population besides the ones for which we were able to adjust. For example, psychotropic drugs, in particular selective serotonin reuptake inhibitors, have been associated with bone density loss and fracture risk.[36,37] There is often overlap between antidepressant and antiepileptic drug use. However, to minimize confounding from psychotropic agents, we adjusted for depression as a surrogate marker for psychotropic drug use.

There are strengths and limitations to our study. One strength is the population-based nature of the data source,

making it unlikely that selection bias occurred. Another is the large sample size with matching for important risk factors (age, sex, ethnicity, and number of comorbidities). We were able to adjust for many potential confounders (sociodemographic variables, multiple diagnoses, and home care use) but could not specifically adjust for vitamin D or calcium intake, physical activity level, or other lifestyle factors. We also did not have bone mineral density measurements for these individuals, and only fractures for which medical attention was sought are captured in administrative databases. Similarly, we had inadequate sample size to study some of the newer AEDs individually (eg, lamotrigine, pregabalin, topiramate).

Our study was not designed to address the possible mechanisms explaining the association between AEDs and fractures, but proposed mechanisms of AED-related bone disease include hepatic induction of cytochrome P450 enzymes leading to increased vitamin D metabolism, direct action of AEDs on osteoblasts, impaired calcium absorption, elevated homocysteine, inhibition of response to parathyroid hormone, hyperparathyroidism, reduced reproductive sex hormones, and reduced vitamin K level.[38]

In conclusion, our study showed that most AEDs except for valproic acid are associated with an increased likelihood of nontraumatic fracture in individuals aged 50 years or older. Future prospective studies of AEDs in newly treated drug-naive patients are needed to better examine the individual effects of AEDs on bone health. Second, the benefits of screening with bone densitometry also need to be studied before any recommendations can be made regarding the timing and frequency of bone densitometry screening in those on AEDs. Finally, randomized controlled trials assessing the effects of vitamin D and calcium prophylaxis as well as other osteoprotective medications in individuals who are receiving AEDs are also warranted.

Accepted for Publication: June 23, 2010.
Correspondence: Nathalie Jetté, MD, Department of Clinical Neurosciences, Foothills Medical Centre, 1403-29 St NW, Calgary, Alberta, Canada, T2N 2T9 (nathalie.jette@albertahealthsevices.ca).
Author Contributions: All authors had full access to all the data in the study and held final responsibility for the decision to submit for publication. *Study concept and design:* Lix, Metge, and Leslie. *Acquisition of data:* Leslie. *Analysis and interpretation of data:* Jetté, Lix, Metge, Prior, McChesney, and Leslie. *Drafting of the manuscript:* Jetté, Lix, and McChesney. *Critical revision of the manuscript for important intellectual content:* Jetté, Metge, Prior, McChesney, and Leslie. *Statistical analysis:* Jetté, Lix, and Prior. *Obtained funding:* Leslie. *Administrative, technical, and material support:* Jetté, Metge, and McChesney.
Financial Disclosure: Drs Lix and Metge report receiving an unrestricted research grants from Amgen Pharmaceuticals Canada; and Dr Leslie, speaker bureau and unrestricted research grants from Merck Frosst, research honoraria and unrestricted educational grants from Sanofi-Aventis and Procter & Gamble, unrestricted research grants from Novartis and Amgen, unrestricted educational grants from Genzyme, and serving on the advisory boards for Genzyme, Novartis, and Amgen.
Funding/Support: This study was supported in part by operating grant ACB-65731 (Dr Leslie) and New Investigator Awards (Drs Jetté and Lix) from the Canadian Institutes of Health research; and a research salary award from the Alberta Innovates Health Solutions (New Population Health Investigator; Dr Jetté).
Role of the Sponsor: The sponsors of the study had no role in study design, data collection, data analysis, data interpretation or writing of the manuscript.
Disclaimer: The results and conclusions are those of the authors, and no official endorsement by Manitoba Health is intended or should be inferred (File No. 2007/2008-08).
Additional Contributions: The authors are indebted to Shelley Derksen, MSc, for performing the cohort matching and to Manitoba Health for providing the data used in this study.

REFERENCES

1. Cole ZA, Dennison EM, Cooper C. Osteoporosis epidemiology update. *Curr Rheumatol Rep.* 2008;10(2):92-96.
2. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int.* 2006;17(12):1726-1733.
3. Goeree R, O'Brien B, Pettitt D, Cuddy L, Ferraz M, Adachi J. An assessment of the burden of illness due to osteoporosis in Canada. *J Soc Obstet Gynaecologists Canada.* 1996;18(suppl July):15-24.
4. Vanness D. Estimating the opportunity costs of osteoporosis in the United States. *Top Geriatric Rehab.* 2005;21(1):4-16.
5. Jacobs-Kosmin D, Hobar C, Chanmugam S. Metabolic and bone disease: osteoporosis. http://emedicine.medscape.com/article/330598-print. Accessed October 5, 2009.
6. Hauser WA. Incidence and prevalence. In: Engel J, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook.* Vol 1. Philadelphia, PA: Lippincott-Raven Publishers; 1998:45-57.
7. Lyngstad-Brechan MA, Taubøll E, Nakken KO, et al. Reduced bone mass and increased bone turnover in postmenopausal women with epilepsy using antiepileptic drug monotherapy. *Scand J Clin Lab Invest.* 2008;68(8):759-766.
8. Ensrud KE, Walczak TS, Blackwell T, Ensrud ER, Bowman PJ, Stone KL. Antiepileptic drug use increases rates of bone loss in older women: a prospective study. *Neurology.* 2004;62(11):2051-2057.
9. Ensrud KE, Walczak TS, Blackwell TL, Ensrud ER, Barrett-Connor E, Orwoll ES; Osteoporotic Fractures in Men (MrOS) Study Research Group. Antiepileptic drug use and rates of hip bone loss in older men: a prospective study. *Neurology.* 2008; 71(10):723-730.
10. Espallargues M, Sampietro-Colom L, Estrada MD, et al. Identifying bone-mass-related risk factors for fracture to guide bone densitometry measurements: a systematic review of the literature. *Osteoporos Int.* 2001;12(10):811-822.
11. Souverein PC, Webb DJ, Petri H, Weil J, Van Staa TP, Egberts T. Incidence of fractures among epilepsy patients: a population-based retrospective cohort study in the General Practice Research Database. *Epilepsia.* 2005;46(2):304-310.
12. Souverein PC, Webb DJ, Weil JG, Van Staa TP, Egberts AC. Use of antiepileptic drugs and risk of fractures: case-control study among patients with epilepsy. *Neurology.* 2006;66(9):1318-1324.
13. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. *Epilepsia.* 2004;45(11):1330-1337.
14. Roos NP. Establishing a population data-based policy unit. *Med Care.* 1999;37(6) (suppl):JS15-JS26.
15. Leslie WD, Lix LM, Prior HJ, Derksen S, Metge C, O'Neil J. Biphasic fracture risk in diabetes: a population-based study. *Bone.* 2007;40(6):1595-1601.
16. Leslie WD, Tsang JF, Caetano PA, Lix LM; Manitoba Bone Density Program. Effectiveness of bone density measurement for predicting osteoporotic fractures in clinical practice. *J Clin Endocrinol Metab.* 2007;92(1):77-81.
17. Starfield B, Weiner J, Mumford L, Steinwachs D. Ambulatory care groups: a categorization of diagnoses for research and management. *Health Serv Res.* 1991; 26(1):53-74.
18. Kozyrskyj AL, Mustard CA. Validation of an electronic, population-based prescription database. *Ann Pharmacother.* 1998;32(11):1152-1157.
19. WHO Collaborating Centre for Drug Statistics Methodology. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD). World

Health Organization Web site. http://www.who.int/classifications/atcddd/en/. Accessed November 10, 2010.
20. van Staa TP, Leufkens HG, Cooper C. Utility of medical and drug history in fracture risk prediction among men and women. *Bone*. 2002;31(4):508-514.
21. Manitoba Centre for Health Policy. Concept Dictionary 2007: income quintiles based on the 1996 census. University of Manitoba Web site. http://umanitoba.ca/faculties/medicine/units/community_health_sciences/departmental_units/mchp/resources/concept_dictionary.html. Accessed October 23, 2009.
22. Kinjo M, Setoguchi S, Schneeweiss S, Solomon DH. Bone mineral density in subjects using central nervous system-active medications. *Am J Med*. 2005;118(12):1414.
23. Pack AM, Morrell MJ, Randall A, McMahon DJ, Shane E. Bone health in young women with epilepsy after one year of antiepileptic drug monotherapy. *Neurology*. 2008;70(18):1586-1593.
24. Vestergaard P. Epilepsy, osteoporosis and fracture risk: a meta-analysis. *Acta Neurol Scand*. 2005;112(5):277-286.
25. Barbour KE, Zmuda JM, Strotmeyer ES, et al; Osteoporotic Fractures in Men (MrOS) Research Group. Correlates of trabecular and cortical volumetric bone mineral density of the radius and tibia in older men: the Osteoporotic Fractures in Men Study. *J Bone Miner Res*. 2010;25(5):1017-1028.
26. Cauley JA, Fullman RL, Stone KL, et al; Mr. OS Research Group. Factors associated with the lumbar spine and proximal femur bone mineral density in older men. *Osteoporos Int*. 2005;16(12):1525-1537.
27. Hill DD, Cauley JA, Sheu Y, et al. Correlates of bone mineral density in men of African ancestry: the Tobago bone health study. *Osteoporos Int*. 2008;19(2):227-234.
28. Vestergaard P, Rejnmark L, Mosekilde L. Hypertension is a risk factor for fractures. *Calcif Tissue Int*. 2009;84(2):103-111.
29. Orwoll ES, Bevan L, Phipps KR. Determinants of bone mineral density in older men. *Osteoporos Int*. 2000;11(10):815-821.
30. Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA; Study of Osteoporotic Fractures Research Group. High blood pressure and bone-mineral loss in elderly white women: a prospective study. *Lancet*. 1999;354(9183):971-975.
31. Rejnmark L, Vestergaard P, Mosekilde L. Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: a nationwide case-control study. *J Hypertens*. 2006;24(3):581-589.
32. Bauer DC, Browner WS, Cauley JA, et al; The Study of Osteoporotic Fractures Research Group. Factors associated with appendicular bone mass in older women. *Ann Intern Med*. 1993;118(9):657-665.
33. Morton DJ, Barrett-Connor EL, Edelstein SL. Thiazides and bone mineral density in elderly men and women. *Am J Epidemiol*. 1994;139(11):1107-1115.
34. Wasnich RD, Benfante RJ, Yano K, Heilbrun L, Vogel JM. Thiazide effect on the mineral content of bone. *N Engl J Med*. 1983;309(6):344-347.
35. Shimizu H, Nakagami H, Osako MK, et al. Angiotensin II accelerates osteoporosis by activating osteoclasts. *FASEB J*. 2008;22(7):2465-2475.
36. Bolton JM, Metge C, Lix L, Prior H, Sareen J, Leslie WD. Fracture risk from psychotropic medications: a population-based analysis. *J Clin Psychopharmacol*. 2008;28(4):384-391.
37. Richards JB, Papaioannou A, Adachi JD, et al; Canadian Multicentre Osteoporosis Study Research Group. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med*. 2007;167(2):188-194.
38. Pack A. Bone health in people with epilepsy: is it impaired and what are the risk factors? *Seizure*. 2008;17(2):181-186.