# The association of newer anticonvulsant medications and bone mineral density

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## Abstract

**Objective—**Previous studies have shown an association between the use of traditional anticonvulsants (e.g. phenytoin, carbamazepine, valproate) and decreased bone mineral density (BMD). However, there are limited data regarding the effects of newer anticonvulsants (e.g. gabapentin, levetiracetam, topiramate) on BMD. The aim of this study was to examine the association between the duration of anticonvulsant exposure and BMD, focusing on newer anticonvulsants.

**Methods—**This is a retrospective cohort study of patients at a single Veterans Affairs (VA) Medical Center. Longitudinal prescription histories, medical comorbidities, vital statistics, and BMD assessments by dual-energy X-ray absorptiometry (DXA), were abstracted from the computerized medical record. Among 1779 individuals with a DXA scan within the study period, 560 were prescribed at least one anticonvulsant.

**Results—**After adjusting for multiple confounders (including age, gender, body mass index, medical comorbidities, and other medication use), higher duration of use of newer, nonenzyme-inducing anticonvulsants was associated with a higher T-score at the total hip (0.05 standard deviations [SD], $p = 0.02$) and lumbar (0.10 SD, $p < 0.01$), compared to non-users referred for BMD assessment. In contrast, higher duration of use of traditional anticonvulsants had a lower total hip T-score. Furthermore, patients prescribed newer, nonenzyme-inducing anticonvulsants

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were less likely to have a diagnosis of osteoporosis at the lumbar spine (OR 0.80, 95% CI: 0.68 – 0.95), femoral neck (OR 0.82, 95% CI: 0.69 – 0.98), and total hip (OR 0.74, 95% CI: 0.56 – 0.98).

**Conclusion—**The results suggest that newer anticonvulsant medications are not associated with lower BMD.

### Keywords

Bone densitometry; anticonvulsants; osteoporosis; epidemiology

## Introduction

According to the Centers for Disease Control and Prevention, approximately 10% of persons in the United States will experience a seizure sometime during their lifetime and about 3% will have had a diagnosis of epilepsy by age 80 (1). Currently, it is estimated that 2 million Americans have a seizure disorder, with an annual incidence of 140,000 persons, highest among children and older adults (1,2). Therefore, a growing number of older adults are taking anticonvulsant medications. In the United States, over 1% of community-dwelling older adults are prescribed an anticonvulsant medication (3). The prevalence increases to approximately 10% among nursing home residents (4,5).

Furthermore, anticonvulsant medications are increasingly used for non-seizure indications including peripheral neuropathy, bipolar disorder, behavioral disturbance in dementia, and migraine headaches. Although traditional anticonvulsants (e.g., phenytoin, carbamazepine, valproate) continue to be used in older patients, newer anticonvulsant medications (e.g. gabapentin, lamotrigine, levetiracetam) have become increasingly more prevalent (3). This may be due to increased tolerability of the newer anticonvulsants compared to traditional agents (6).

Previous studies have shown an association between the use of traditional anticonvulsant medications and decreased bone mineral density (BMD), as well as increased risk of fractures (7–13). In a large, prospective cohort study of postmenopausal women over age 65 years, use of traditional anticonvulsants was associated with a mean rate of decline in total hip BMD of 1.16% per year (7). Moreover, the risk for non-spine fracture was increased in those taking anticonvulsants; however, the risk of hip fracture was not increased. The majority of participants in this cohort were prescribed phenytoin. Similarly, in a population-based, case-control study, there was an increased risk of any fracture associated with exposure to carbamazepine, phenobarbital, and valproic acid (12).

There are limited published data regarding the effects of newer anticonvulsant medications, such as gabapentin and levetiracetam, on BMD. We hypothesized that like traditional anticonvulsants, increased exposure to newer anticonvulsant medications was associated with lower BMD.

## Methods

### Study design and setting

This is a retrospective cohort study of patients at a single Veterans Affairs (VA) medical center, using data from the computerized medical record. All patients who had a BMD assessment by dual-energy x-ray absorptiometry (DXA) between May 2006 and January 2010 were identified and included in the analysis. In this center, it is standard practice in the neurology clinic for all patients taking anticonvulsants to be screened with DXA. The study

protocol was approved by the Institutional Review Board at the Durham VA Medical Center, Durham, NC.

### BMD data assessment

Data from bone density reports were abstracted for T-scores at the femoral neck, total hip, and lumbar spine, as well as BMD diagnosis of osteoporosis or osteopenia. BMD assessments were performed using the same densitometer (Discovery A, Hologic, Walham, MA, USA). The root mean square standard deviations are 0.014 g/cm$^2$ for the lumbar spine and 0.011g/cm$^2$ for the total hip. BMD measurements were assessed at the lumbar spine, femoral neck, and total hip. DXA results were reported by a clinician trained in bone densitometry using a uniform BMD report template. If more than one scan was performed in the study period, then the results from the most recent scan were used in the analysis.

### Medical and prescription history

Height and weight closest to the time of BMD assessment were abstracted from vital statistics and were used to calculate the body mass index (BMI). Prescription history prior to BMD assessment was obtained from the pharmacy records, including anticonvulsants, bisphosphonates, and corticosteroids. Longitudinal data included the drug name, dosage, and duration for each prescription. Medical history was obtained using ICD-9 diagnoses abstracted from outpatient, inpatient, and emergency department encounters for the occurrence of the following diagnoses: fracture (800–829), seizure disorder (354.xx), diabetes mellitus (250.xx), mood disorder (296.xx, 298.xx, 308.xx, 309.xx, 311.xx), cerebrovascular accident (430–436), tobacco abuse (305.1) and alcohol abuse (303, 305). Medical diagnoses were chosen based on major indications for anticonvulsant prescribing, as well as factors that are associated with changes in BMD.

### Statistical Analysis

The patients' exposures were classified according to the type of anticonvulsant prescribed:

**1)** newer, enzyme-inducing (e.g., topiramate, oxcarbazepine),

**2)** newer, nonenzyme-inducing (e.g., gabapentin, levetiracetam, lamotrigine),

**3)** traditional, enzyme-inducing (e.g., phenytoin, carbamazepine, phenobarbital),

**4)** traditional, nonenzyme-inducing (e.g., valproic acid)

**5)** no anticonvulsant prescription (i.e. non-users) – Reference Group.

Cumulative exposure to each anticonvulsant class, the predictor variable of primary interest, was expressed as total days of prescription for each anticonvulsant class. Due to the inherent non-normality of the distribution, cumulative exposure was re-parameterized as a 5-level ordinal categorical variable, using clinically meaningful time periods: 0 = “None,” 1 = “less than 90 days,” 2 = “between 90 and 365 days,” 3 = “between 1 and 3 years”, and 4 = “greater than 3 years.”

Subjects who had prescriptions for more than 1 anticonvulsant group (for example: traditional, nonenzyme-inducing and newer, nonenzyme-inducing) were included as members of both groups. Inferences from all statistical tests were made comparing each individual anticonvulant group to those with no anticonvulsant prescription (the reference group).

Baseline characteristics of the study population according to type of anticonvulsant class prescribed were described using proportions for categorical variables and means with standard deviations for continuous variables. Tests for differences between anticonvulsant

groups and the reference group (i.e. non-users) were performed using chi-square tests for categorical variables and Student t-tests for continuous variables. Patients who were prescribed medications from more than one class of anticonvulsant were classified in more than one category.

Multivariate linear models were used to compare average BMD T-score at each anatomic site (i.e., total hip, femoral neck, and lumbar spine) as a function of prior exposure to anticonvulsants. Exposure to anticonvulsants was included as the 5-level categorical variable, as described above. Models at each anatomic site were controlled for medication exposure (bisphosphonates, vitamin D supplements, and corticosteroids), medical comorbidities (seizure disorder, diabetes mellitus, cerebrovascular accident, mood disorder, and prior fracture), and patient demographics (age, race, gender, and BMI). Sensitivity analyses were performed to evaluate the effect of more than one category of exposure.

Similarly, multivariate logistic models were used to determine the association between exposure to class of anticonvulsant and diagnosis of osteoporosis at each anatomic site. Other model variables were the same as those used for the multivariate linear models of T-score. Statistical significance was assessed for $p < 0.05$. Analyses were performed using SAS Version 9.2 (SAS institute, Cary, NC).

## Results

### Study population

A total of 560 unique patients were prescribed at least one class of anticonvulsant medication; 245 of those were prescribed more than one class and are therefore included more than once in the summary tables. A total of 395 patients were prescribed traditional anticonvulsants, compared to 693 who were prescribed newer anticonvulsants. The most common traditional, enzyme-inducing anticonvulsant prescribed was phenytoin (n = 121), followed by carbamazepine (n = 110). One hundred seventeen patients were prescribed valproic acid. The most common newer anticonvulsant agent prescribed was gabapentin (n = 259), followed by levetiracetam (n = 152) and lamotrigine (n = 114). The median duration of exposure was 420 days (interquartile range [IQR]: 120 – 1258) among those prescribed newer, nonenzyme-inducing anticonvulsants and 270 days (IQR: 72 – 810) among those prescribed newer, enzyme-inducing anticonvulsants. The median duration of exposure was 345 days (interquartile range [IQR]: 90 – 900) among those prescribed traditional, nonenzyme-inducing anticonvulsants and 1245 days (IQR: 180 – 3030) among those prescribed traditional, enzyme-inducing anticonvulsants.

Characteristics of the study population are shown in Table 1. A total of 1779 individuals had a DXA within the study period, comprising 1901 scans. Compared to those not prescribed anticonvulsant medications (i.e. non-users), patients taking anticonvulsants were younger, more likely to be male, and more likely to have a diagnosis of a mood disorder. Patients prescribed newer, nonenzyme-inducing anticonvulsants were also more likely to have a higher BMI (mean 30.4 vs. 28.5 $kg/m^2$, p = 0.001). Patients prescribed traditional, enzyme-inducing anticonvulsants were less likely to be prescribed a bisphosphonate (16.2% vs. 10.5%, p = 0.02) or corticosteroid (38.3% vs. 25.8%, p < 0.001).

### Effect on T-score

Most of the non-users (reference group) had absolute T-scores in the osteopenic or osteoporotic range at the lumbar spine and femoral neck (Table 2). At the lumbar spine, 14.9% of non-users had absolute T-scores in the osteoporotic range, compared to 10.8% among those prescribed newer, nonenzyme-inducing ($p < 0.05$) 6.4% among those prescribed newer, enzyme-inducing anticonvulsants ($p < 0.05$). Similarly, at the femoral

neck, 12% of non-users had absolute T-scores in the osteoporotic range, compared to 7.2% among those prescribed newer, nonenzyme-inducing ($p < 0.01$) and 6.1% among those prescribed newer, enzyme-inducing anticonvulsants ($p < 0.01$). In contrast, there was no statistical difference in the absolute T-scores between non-users and those prescribed traditional agents, with 10.3% of enzyme-inducing and 9.7% of nonenzyme-inducing anticonvulsants in the osteoporotic range at the femoral neck.

In multivariate analysis, patients with greater duration of use of newer, nonenzyme-inducing anticonvulsants on average had higher T-scores at the total hip, femoral neck, and lumbar spine compared to non-users (Table 3). After adjusting for multiple potential confounders (including age, gender, BMI, use of corticosteroids, use of bisphosphonates, and comorbidities such as seizure disorder, diabetes mellitus, cerebrovascular accident, mood disorder, and history of prior fracture), the higher BMD at the total hip and lumbar spine remained statistically significant. The average T-score at the lumbar spine was 0.10 standard deviations (SD) higher for each interval increase in the period of anticonvulsant prescription, among those prescribed newer, nonenzyme-inducing anticonvulsants compared to non-users (reference group). As previously described, the period intervals were “None” (reference group), “less than 90 days,” “between 90 and 365 days,” “between 1 and 3 years”, and “greater than 3 years.” Therefore, for example, patients prescribed a newer, nonenzyme-inducing anticonvulsant for “1 to 3 years” had a higher T-score on average at the lumbar spine by 0.3 SD, compared to the reference group.

Similarly, the average T-score at the total hip was 0.05 SD higher for each interval increase in the period of prescription. Sensitivity analyses controlling for anticonvulsant class changes among those patients prescribed more than one class of agent did not change results. After adjusting for multiple confounders, there was no significant association in BMD with duration of exposure to newer, enzyme-inducing anticonvulsants at any of the three anatomic sites. Compared to non-users, patients with longer duration of use of traditional anticonvulsants (both enzyme-inducing and nonenzyme-inducing), had a lower T-score on average at the lumbar spine, femoral neck, and total hip, although the unadjusted differences were not statistically significant. However, after controlling for multiple confounders, there was a trend toward a lower BMD at the femoral neck (−0.04 SD for each interval increase in the period of prescription, p = 0.08) among those prescribed traditional, enzyme-inducing anticonvulsants.

### Effect on diagnosis of osteoporosis

After controlling for multiple confounders, those patients with longer duration of use of newer, nonenzyme-inducing anticonvulsants were significantly less likely to have a diagnosis of osteoporosis at the total hip (OR 0.74, 95% CI: 0.56 – 0.98) and femoral neck (OR 0.82, 95% CI: 0.69 – 0.98), and lumbar spine (OR 0.80, 95% CI: 0.68 – 0.95), compared to non-users (Table 4). Also, there was a lower likelihood of osteoporosis at the lumbar spine (OR 0.80, 95% CI: 0.68 – 0.95). Among those with longer duration of use of newer, enzyme-inducing anticonvulsants, there was a lower likelihood of osteoporosis at the lumbar spine and total hip, although these results did not reach statistical significance.

Among those prescribed traditional anticonvulsants, both enzyme-inducing and nonenzyme-inducing, there was no significant difference in the risk of osteoporosis at the total hip, femoral neck, or lumbar spine, compared to the reference group (i.e. non-users).

## Discussion

The results from the current study suggest that extended use of newer anticonvulsant medications may not be associated with a clinically meaningful lower BMD. Notably, after

controlling for a number of factors including age, gender, BMI, other medical comorbidities and use of other medications, increased duration of exposure to newer nonenzyme-inducing anticonvulsants were associated with a statistically significant higher T-score of 0.05 and 0.10 SD per period of prescription duration at the total hip and lumbar spine, respectively, compared to non-users referred to DXA for other reasons. In contrast, T-scores were lower among patients prescribed traditional anticonvulsants, consistent with observations in prior studies. However, in the current study, these results did not reach statistical significance. This may be due to the higher rates of vitamin D supplementation among those prescribed enzyme-inducing anticonvulsants, both newer and traditional. Also, there was a high prevalence of osteoporosis and osteopenia in the reference group (i.e. non-users), with over 12% and 15% in the osteoporotic range at the femoral neck and lumbar spine, respectively. Therefore, the differences between the current study and prior studies regarding traditional anticonvulsants are likely due to differences in the reference populations.

The limitations of this study should be considered. This was a retrospective cohort study in a single VA medical center with a large referral base, which may limit generalizability to other populations. The number of participants with more than one BMD assessment within the study period was limited; therefore, we were not able to determine a rate of change in BMD over time. Data were limited to that available in the electronic medical record. We could include only those patients who were referred for BMD assessment and the indications for referral were not available in the data set; therefore, there may be a resulting selection bias. While selection bias is mitigated by the neurology clinic protocol of referring all patients on anticonvulsant medications for BMD assessment, the comparison group (i.e. non-users) likely included patients with a higher risk for osteoporosis than the general population. Although we controlled for multiple potential risk factors (e.g. medical comorbidities, tobacco and alcohol abuse), residual confounding may remain due to unobserved or unrecorded covariates (e.g. falls propensity, other lifestyle behaviors).

Given the limited number of fractures, we were not able to assess the risk of fracture in the current study. Fracture risk may be increased in those patients taking newer anticonvulsant medications due to factors that do not influence BMD, such as increased falls risk. However, in a prior study of traditional anticonvulsants, the association with increased fracture risk was significantly attenuated after controlling for age and BMD (13). Given the higher BMD observed in the current study, an increased fracture risk among patients taking newer anticonvulsants is not predicted.

Nevertheless, our study adds to the existing literature because it includes a larger number of anticonvulsant users compared to previous studies. In addition, the medical database in this study included longitudinal prescription data, allowing us to incorporate the duration of exposure into our models. As part of the Study of Osteoporotic Fractures, Ensrud et al. examined the BMD at the total hip of 4,202 post-menopausal women, of whom 40 subjects were taking anticonvulsant medications, and the majority of patients (65%) used phenytoin alone or in combination with another traditional anticonvulsant (7). Total hip BMD declined 0.70% per year in subjects not taking anticonvulsants and 1.16% per year in continuous users of anticonvulsants ($p = 0.02$). As part of the MrOS study, Ensrud et al. examined 5,995 men over the age of 65 years, 100 of whom were taking nonenzyme-inducing anticonvulsants, with the majority taking gabapentin (8). Compared to men not taking anticonvulsants, those taking gabapentin had a greater decline in total hip BMD over the study period (0.35% vs. 0.50%, $p = 0.11$). The results of the current study suggest that increasing duration of exposure to newer, nonenzyme-inducing anticonvulsants is not associated with a clinically meaningful lower BMD. Greater exposure to this class of anticonvulsant was associated with significantly higher total hip T-score and trended toward

higher BMD at the femoral neck and lumbar spine, compared to those referred to DXA for other reasons.

Several mechanisms have been hypothesized to explain the impact of traditional anticonvulsants on BMD. The prevailing model describes induction of hepatic cytochrome P450 enzymes by anticonvulsant medications. Anticonvulsant medications, such as phenytoin and phenobarbital, activate nuclear receptors that increase the transcription of these hepatic enzymes, including CYP24B (14). The increase in hepatic enzymes accelerates the metabolism of vitamin D to inactive metabolites and depletes vitamin D stores, resulting in secondary hyperparathyroidism (15). Consequently, increased parathyroid hormone leads to increased bone resorption and ultimately reduced BMD and increased fracture risk. However, anticonvulsant use resulting in secondary hyperparathyroidism has not been consistently shown in other studies (16,17). Furthermore, while the enzyme-induction hypothesis suggests that inhibitors of hepatic enzyme activity would improve BMD, the hepatic enzyme-inhibitor valproic acid has been associated with decreased BMD and increased fracture risk in a number of studies (12,18,19). Therefore, anticonvulsants may affect BMD through mechanisms not associated with hepatic enzyme induction. However, the results of the current study suggest newer anticonvulsant medications, including gabapentin and levetiracetam which do not induce hepatic enzyme metabolism and topiramate which at higher doses induces hepatic enzymes, are not associated with lower BMD. This may be reassuring to patients and prescribers who are considering long-term therapy with newer anticonvulsant agents.

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**Table 1**

Subject characteristics by class of anticonvulsant prescribed

| Characteristic | No anticonvulsant use (reference) | Newer Nonenzyme-inducing | Newer Enzyme-inducing | Traditional Enzyme-inducing | Traditional Non-enzyme inducing |
|---|---|---|---|---|---|
| N | 1219 | 102 | 443 | 248 | 98 |
| Age, mean +/− SD | 63.4 (12.4) | 50.5 (12.3)[c] | 59.5 (12.3)[c] | 59.7 (12.9)[c] | 55.6 (10.6)[c] |
| Gender | | | | | |
| Male, % | 75.7 | 74.5 | 80.6[a] | 90.7[c] | 78.6 |
| Race | | | | | |
| White, % | 61.4 | 54.9 | 61.9 | 58.1 | 69.4 |
| BMI, mean +/− SD | 28.5 (5.9) | 30.4 (5.6)[b] | 28.8 (5.9) | 28.0 (5.4) | 29.0 (5.6) |
| Bisphophonate use, % | 16.2 | 12.8 | 12.6 | 10.5[a] | 12.2 |
| Corticosteroid use, % | 38.3 | 30.4 | 34.1 | 25.8[c] | 24.9[b] |
| Vitamin D use, % | 49.3 | 52.0 | 56.2[a] | 58.9[b] | 51.0 |
| Tobacco use, % | 30.2 | 31.4 | 39.7[c] | 35.9 | 46.9[c] |
| Alcoholism, % | 8.5 | 11.8 | 13.1[b] | 15.7[c] | 16.3[b] |
| Seizure disorder, % | 1.2 | 72.6[c] | 47.2[c] | 76.2[c] | 61.2[c] |
| Prior fracture, % | 15.3 | 11.8 | 15.8 | 14.1 | 16.3 |
| Diabetes mellitus, % | 30.3 | 28.4 | 33.4 | 31.1 | 27.6 |
| Mood disorder, % | 47.3 | 69.6[c] | 65.9[c] | 56.1[a] | 75.5[c] |

*p*-value reflects test compared to reference group: patients with "No anticonvulsant use" (i.e. "non-users")

[a] $p < 0.05$

[b] $p < 0.01$

[c] $p < 0.001$

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**Table 2**

T-score ranges of patients by anticonvulsant class prescribed

| | No anticonvulsant use (reference) | Newer Nonenzyme-inducing | Newer Enzyme-inducing | Traditional Enzyme-inducing | Traditional Non-enzyme inducing |
|---|---|---|---|---|---|
| **Anatomic site (T-score range)** | **% in T-score range** | | | | |
| T-score | | | | | |
| Lumbar | | | | | |
| ≥−1.0 | 47.3 | 53.0[a] | 58.5[b] | 52.4 | 43.0 |
| −1.0 to −2.5 | 37.8 | 36.2 | 35.1 | 33.5 | 39.5 |
| ≤−2.5 | 14.9 | 10.8 | 6.4 | 14.2 | 17.4 |
| Femoral neck | | | | | |
| ≥−1.0 | 33.0 | 39.3[b] | 50.5[b] | 33.5 | 40.9 |
| −1.0 to −2.5 | 55.0 | 53.5 | 43.4 | 56.2 | 49.5 |
| ≤−2.5 | 12.0 | 7.2 | 6.1 | 10.3 | 9.7 |
| Total hip | | | | | |
| ≥−1.0 | 55.9 | 58.0 | 69.7[b] | 52.9 | 59.8 |
| −1.0 to −2.5 | 38.7 | 39.4 | 29.3 | 42.1 | 37.0 |
| ≤−2.5 | 5.4 | 2.6 | 1.0 | 5.0 | 3.3 |

*p*-value reflects the test of proportions of each anticonvulsant class, compared to the reference group: those with "No anticonvulsant use" (i.e. "non-users")

[a] $p < 0.05$

[b] $p < 0.01$

## Table 3

Difference between average T-score at 3 anatomic sites by anticonvulsant class per interval increase in prescription period.

| | Newer enzyme-inducing | | Newer nonenzyme-inducing | | Traditional enzyme-inducing | | Traditional nonenzyme-inducing | |
|---|---|---|---|---|---|---|---|---|
| | ΔT-score[a] | *p* [b] | ΔT-score[a] | *p* [b] | ΔT-score[a] | *p* [b] | ΔT-score[a] | *p* [b] |
| Lumbar spine | | | | | | | | |
| Unadjusted | 0.12 | 0.07 | 0.10 | <0.01 | 0.04 | 0.28 | −0.05 | 0.42 |
| Adjusted[c] | 0.03 | 0.65 | 0.10 | <0.01 | −0.03 | 0.51 | −0.12 | 0.08 |
| Total hip | | | | | | | | |
| Unadjusted | 0.08 | 0.07 | 0.05 | 0.03 | −0.03 | 0.24 | 0.03 | 0.45 |
| Adjusted[c] | −0.04 | 0.25 | 0.05 | 0.02 | −0.03 | 0.20 | −0.03 | 0.46 |
| Femoral neck | | | | | | | | |
| Unadjusted | 0.14 | <0.01 | 0.06 | <0.01 | −0.02 | 0.49 | 0.08 | 0.05 |
| Adjusted[c] | −0.01 | 0.81 | 0.03 | 0.10 | −0.04 | 0.08 | −0.00 | 0.91 |

[a] ΔT-score is expressed as average difference between anticonvulsant class and non-users (the reference group) per interval increase in the prescription period: 1 = “less than 90 days,” 2 = “between 90 and 365 days,” 3 = “between 1 and 3 years”, and 4 = “greater than 3 years.”

[b] *p*-value reflects test compared to subjects with no anticonvulsant prescriptions prior to BMD assessment, i.e. “non-users” (reference group)

[c] Multivariate, linear regression model adjusting for medication exposure (bisphosphonates, vitamin D supplements, and corticosteroids), medical comorbidities (seizure disorder, diabetes mellitus, cerebrovascular accident, mood disorder, and prior fracture), and patient demographics (age, race, gender, and BMI).

## Table 4

Multivariate, logistic regression for diagnosis of osteoporosis at 3 anatomic sites by anticonvulsant class per interval increase in prescription period[a, b]

| | Newer enzyme-inducing | Newer nonenzyme-inducing | Traditional enzyme-inducing | Traditional nonenzyme-inducing |
|---|---|---|---|---|
| Anatomic site | | | | |
| Lumbar spine | 0.75 (0.50,1.12) | 0.80 (0.68,0.95) | 1.04 (0.87,1.25) | 1.23 (0.96, 1.58) |
| Total hip | 0.58 (0.17,2.00) | 0.74 (0.56, 0.98) | 1.09 (0.80,1.48) | 0.84 (0.46,1.52) |
| Femoral neck | 1.28 (0.90, 1.81) | 0.82 (0.69, 0.98) | 1.09 (0.88, 1.35) | 1.21 (0.89, 1.64) |

[a]Odds ratios (95% confidence interval) are expressed per interval increase in the prescription period: 1 = “less than 90 days” 2 = “between 90 and 365 days,” 3 = “between 1 and 3 years”, and 4 = “greater than 3 years,” compared to non-users (the reference group)

[b]Adjusted for medication exposure (bisphosphonates, vitamin D supplements, and corticosteroids), medical comorbidities (seizure disorder, diabetes mellitus, cerebrovascular accident, mood disorder, and prior fracture), and patient demographics (age, race, gender, and BMI).