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A Review of the Effect of Anticonvulsant Medications on Bone Mineral Density and Fracture Risk

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Abstract

Background—Osteoporosis and seizure disorders are common diagnoses in older adults and often occur concomitantly.

Objective—The goal of this review was to discuss the current hypothesis for the pathogenesis of anticonvulsant-induced bone density loss and the evidence regarding the risk for osteoporosis and fractures in older individuals.

Methods—A review of the literature was performed, searching in MEDLINE and CINAHL for articles published between 1990 and October 2009 with the following search terms: *anticonvulsant* OR *antiepileptic;* AND *osteoporosis* OR *bone density* OR *fracture* OR *absorptiometry, photon*. Studies within the pediatric population, cross-sectional studies, and studies whose results were published in a language other than English were excluded.

Results—A search of the published literature yielded >300 results, of which 24 met the inclusion and exclusion criteria and were included in this review. Hepatic enzyme induction by certain anticonvulsant medications appears to contribute to increased metabolism of 25-hydroxyvitamin D to inactive metabolites, which results in metabolic bone disease. There is increasing evidence that anticonvulsant use is associated with a higher risk of osteoporosis and clinical fractures, especially among older agents such as phenobarbital, carbamazepine, phenytoin, and valproate. Several observational studies suggest a class effect among anticonvulsant agents, associated with clinically significant reductions in bone mineral density and fracture risk. The use of anticonvulsant medications increases the odds of fracture by 1.2 to 2.4 times. However, only 2 large-scale observational studies have specifically examined the risk among those aged >65 years. This review also identified a randomized controlled trial whose results suggest that supplementation with high-dose vitamin D may be associated with increased bone mineral density in patients taking anticonvulsant medications. However, no randomized controlled trials investigating therapeutic agents to prevent fracture in this population were identified. Consequently, there are no formal practice guidelines for the monitoring, prevention, and management of bone disease among those taking anticonvulsants.

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Conclusions—Observational studies suggest an association between use of anticonvulsant medications, reduced bone mineral density, and increased fracture risk. Randomized clinical trials are needed to guide the management of bone disease among those who use anticonvulsants.

Keywords

anticonvulsants; bone density; osteoporosis; fractures

INTRODUCTION

Osteoporosis and seizure disorders are common diagnoses in older adults and may occur concomitantly. There is a bimodal distribution in the incidence of seizures and epilepsy, peaking in childhood but then increasing again after the age of 60 years.[1] In this older age group, the incidence of unprovoked seizures is 121 per 100,000 per year and the diagnosis of epilepsy nears 40 per 100,000 per year.[1,2] Likewise, the prevalence of epilepsy is 1% among individuals aged >60 years and increases with advancing age.[3] Anticonvulsants may also be prescribed for nonseizure indications such as neuropathic pain.[4]

Accordingly, the number of anticonvulsant prescriptions has increased in this population. In the United States and in European countries, ~1% of community-dwelling older adults are prescribed an anticonvulsant medication.[5–7] The prevalence increases to ~10% among nursing home residents.[8,9] Newer anticonvulsant medications are becoming increasingly more prevalent, although traditional anticonvulsants (eg, phenytoin, carbamazepine, valproic acid) continue to be used in older patients.[10,11]

The incidence of osteoporosis also increases after the age of 60 years.[12] In white populations, ~50% of women and ~20% of men aged >50 years will have a fragility fracture in their remaining lifetime.[13] Hip fractures carry an especially high burden of both morbidity and mortality.[14–16] The incidence of hip fracture is >700 per 100,000 person-years among women and >300 per 100,000 person-years among men, with wide variations within specific population groups, and with exponential increases in risk as age increases.[17] With the aging of the global population, if incidence rates remain stable, the number of hip fractures worldwide is projected to rise from 1.7 million in 1990 to 6.3 million in 2050.[18]

Despite the increasing prevalence and incidence of these diseases with age, few studies have specifically examined the risk of reduced bone mineral density (BMD) and fracture in older adults who use anticonvulsant medications. Data from a Veterans Affairs Cooperative Trial, following 593 patients aged >60 years with newly diagnosed seizures, suggest that the newer anticonvulsant medications, such as lamotrigine and gabapentin, may be better tolerated by older adults, with fewer early terminations due to adverse drug effects compared with the older agent carbamazepine (12.1% for lamotrigine, 21.6% for gabapentin, and 31% for carbamazepine; $P = 0.001$).[19] However, there are limited data regarding the impact of these medications on bone health.

In this article, the current hypothesis for the pathogenesis of anticonvulsant-induced bone density loss is discussed, and the evidence regarding the risk for osteoporosis and fractures in older individuals is reviewed.

METHODS

A review of the literature was performed to search MEDLINE and CINAHL for articles published between 1990 and October 2009 with the following search terms: *anticonvulsant* OR *antiepileptic;* AND *osteoporosis* OR *bone density* OR *fracture* OR *absorptiometry,*

photon. Studies within the pediatric population or among patients with neurodevelopmental disorders (eg, cerebral palsy), cross-sectional studies, and studies whose results were published in a language other than English were excluded. References from published articles were scanned for other relevant studies. Studies were evaluated using the Jadad criteria for randomized clinical trials or other published criteria for cohort studies,[20] and data specific to patients aged >65 years were abstracted.

RESULTS

A search of the published literature (using the specified databases and search terms) yielded >300 results, of which 24 met the inclusion and exclusion criteria and were included in this review.

Pathogenesis

Study of the mechanism by which anticonvulsant medications may be associated with metabolic bone disease has concentrated on vitamin D metabolism and bone turnover. The effects of anticonvulsant medications on bone were noted in the 1960s among children with rickets.[21] Observations that adult osteomalacic disease due to anticonvulsant use could be tempered by the administration of vitamin D were made in the 1970s. These observations led to studies on vitamin D metabolism as a mechanism for anticonvulsant-induced bone disease. In the 1970s, Hahn et al[22] reported that vitamin D was metabolized at a more rapid rate when administered to patients with long-term use of phenobarbital. Furthermore, they found that, in a rat model, this rapid metabolism was mediated by increased hepatic hydroxylation activity.[23] Similar results were noted with carbamazepine and oxcarbazepine.[24] Together, these findings suggest that hepatic enzyme induction led to increased metabolism of 25-hydroxyvitamin D to inactive metabolites, which resulted in metabolic bone disease.

Another study further elaborated this hypothesis. Pascussi et al[25] exposed human hepatocytes in tissue cultures to phenobarbital and carbamazepine for 48 hours. The expression of cytochrome P450 (CYP) 24 mRNA was increased 12-fold ($P < 0.01$) by phenobarbital compared with untreated cells, but carbamazepine was a weak and nonsignificant inducer. CYP24 is an enzyme involved in the 24-hydroxylation of 25-hydroxyvitamin D to 24,25-dihydroxyvitamin D, an inactive metabolite. Moreover, Pascussi et al reported that this induction was mediated through the pregnane X receptor (PXR) by binding to the vitamin D–responsive elements in the promoter region of the gene for CYP24. PXR is a nuclear receptor activated by xenobiotic compounds, including phenobarbital, valproic acid, and phenytoin.[26,27] PXR shares homology with the vitamin D receptor and, when activated, promotes expression of vitamin D–responsive genes, including CYP24.[25] This provides a molecular link between anticonvulsant administration and enzyme-induced vitamin D metabolism.

Increased 1,25-dihydroxyvitamin D inactivation can lead to increased parathyroid hormone (PTH) secretion, resulting in higher bone turnover. In a prospective cohort study, Pack et al[28] followed 93 premenopausal women with epilepsy for 1 year. Subjects were treated with 1 of 4 anticonvulsants in monotherapy. The majority were treated with carbamazepine (n = 41), followed by lamotrigine (n = 23), phenytoin (n = 15), and valproic acid (n = 14). In the phenytoin group, women with lower serum 25-hydroxyvitamin D concentrations had higher PTH levels ($r = –0.477$, $P = 0.025$), higher bone alkaline phosphatase ($r = –0.464$, $P = 0.013$), and higher urine *N*-telopeptide levels ($r = –0.338$, $P = 0.048$) than those with higher 25-hydroxyvitamin D concentrations; this biochemical pattern is consistent with secondary hyperparathyroidism and increased bone turnover.[29] These elevations in PTH, bone alkaline phosphatase, and *N*-telopeptide levels corresponded to a 2.6% decline (mean [SD] of 0.023

[0.03] g/cm^2) in BMD at the femoral neck, but not in the lumbar spine or total hip. Also, these findings were not noted among patients taking other agents, including carbamazepine and lamotrigine.

An association between anticonvulsant use, vitamin D levels, and PTH levels has not been shown consistently across studies. Filardi et al[30] evaluated 69 men, mean (SD) age of 37.6 (10.9) years, from a single out-patient clinic who were treated for >5 years with phenobarbital, phenytoin, or carbamazepine. Compared with 30 healthy subjects, they found no significant differences in PTH, 25-hydroxyvitamin D levels, or spine or femoral neck BMD. Similarly, Mintzer et al[31] identified 45 patients with epilepsy treated from outpatient clinics with carbamazepine or oxcarbazepine monotherapy. Compared with 24 healthy controls, there were no significant differences in PTH, bone alkaline phosphatase, or *N*-telopeptide levels. There were no significant differences in mean (SD) 25-hydroxyvitamin D levels between the oxcarbazepine group (19.4 [10.8] ng/mL), the carbamazepine group (20.4 [10.5] ng/mL), or the control group (27.5 [13.0] ng/mL).

Moreover, the enzyme-induction hypothesis would suggest that inhibitors of CYP would improve BMD. Valproic acid, a widely used anticonvulsant, is a known inhibitor of the CYP system.[32] Therefore, one would expect those who use valproic acid to have decreased metabolism of active vitamin D compounds and subsequent enhancement of BMD. However, valproic acid use is also associated with lower BMD and increased risk of fractures.[33–35]

Thus, evidence that anticonvulsants affect bone through vitamin D metabolism and secondary hyperparathyroidism is inconsistent and does not entirely explain the clinical presentation. Alternative mechanisms have been investigated, including decreased activation of vitamin D to 25-hydroxyvitamin D, direct inhibition of intestinal calcium absorption, and inhibition of osteoblast cell growth.[36] However, evidence for these alternative hypotheses is limited to in vitro and animal studies without correlation in humans.[37,38] They illustrate the complex biochemical and cellular interactions between anticonvulsants and bone metabolism.

Effects of Anticonvulsants on Bone density

Table I provides a summary of case–control and cohort observational studies that evaluated bone density and anticonvulsant use.[34,35,39–47] Only 4 studies included patients aged >65 years.[40,42,44,46] Among the case–control studies, only those by Stephen et al[40] and Lyngstad-Brechan et al[42] included older patients. Stephen et al identified 78 patients, including 47 post-menopausal women with epilepsy, who were matched by age, sex, height, and weight with 78 drug-naive individuals without epilepsy. The female patients with epilepsy had decreased BMD at the femoral neck, with a mean (SD) T-score of –2.18 (0.17), compared with –1.83 (0.20) among female controls ($P < 0.05$). Moreover, patients taking enzyme-inducing agents (eg, carbamazepine, phenytoin) and those taking non–enzyme-inducing agents (primarily valproic acid) had statistically significant lower BMD at the femoral neck than did controls ($P < 0.01$ and $P < 0.05$, respectively).

Lyngstad-Brechan et al[42] studied 26 postmenopausal women who were identified through an outpatient epilepsy clinic. The patients were matched by age and lifestyle parameters (eg, smoking habits, physical activity) with 26 control subjects who did not have epilepsy. The patients' ages ranged from 55 to 76 years. Compared with controls, patients taking anticonvulsants had lower mean BMD at the femoral neck (0.83 vs 0.94 g/cm^2; $P = 0.033$) and at the proximal forearm (0.58 vs 0.63 g/cm^2; $P = 0.037$). Similar results were seen among patients taking enzyme-inducing anticonvulsants (specifically, carbamazepine, in 13 of 21 patients).

In the largest prospective study, Ensrud et al[44] evaluated postmenopausal women who were part of the Study of Osteoporotic Fractures cohort. Participants in this study were women aged >65 years. Of the 9704 patients recruited, 4202 patients had baseline and follow-up hip BMD measurements, completed medication inventories, and were subsequently included in the analysis. They were categorized as *continuous users* (n = 40), *partial users* (n = 68), or *nonusers* (n = 4094), based on self-reported anticonvulsant use at multiple clinic visits. *Continuous users* reported anticonvulsant use at the baseline and fourth follow-up visit. *Partial users* reported use at only 1 of these visits, and *nonusers* reported no anticonvulsant use at both visits. After adjustment for confounders, including age, health status, body mass index, smoking status, and calcium and vitamin D intake, the mean rate of decline in total hip BMD steadily increased from 0.70% per year in nonusers to 0.87% per year in partial anticonvulsant users and 1.16% per year in continuous anticonvulsant users ($P = 0.015$ for trend), suggesting that anticonvulsant use may accelerate the rate of bone density loss with increasing exposure. Among continuous users, the majority of patients (65%) used phenytoin alone or in combination with another traditional anticonvulsant. The authors noted that, among those with continuous anticonvulsant use, the rate of hip bone loss would be expected to increase the risk of hip fracture by 29% within 5 years.

There are a number of limitations to these data. The method and site for determining BMD varied among studies. Case–control studies enrolled patients from epilepsy clinics, raising the possibility of selection bias. Moreover, given the observational studies' designs, there remains the possibility that uncontrolled confounders could explain the lower BMD that was noted in anticonvulsant users. It is difficult to assess publication bias, but there is a possibility that conflicting data may have been found in other studies but not published. Nevertheless, all of the studies reported significant differences in BMD between those taking anticonvulsants and con trols. Similar results were found across studies examining several anticonvulsants including enzyme-inducing agents (eg, phenytoin, carbamazepine) and non–enzyme-inducing agents (eg, valproate). Thus, the published literature is largely consistent and suggests a possible class effect among the anticonvulsant agents, associated with clinically significant reductions in BMD.

In a randomized controlled trial, Mikati et al[48] enrolled 106 adult patients, aged 18 to 54 years, and randomized them to receive either high-dose (4000 IU/d) or low-dose (400 IU/d) ergocalciferol. Patients were drawn from a single ambulatory clinic and had been receiving long-term treatment with anticonvulsants; 71% were using enzyme-inducing anticonvulsants. Participants were not blinded to treatment; however, investigators reading the dual-energy x-ray absorptiometry scans were blinded to treatment-group assignment. Twenty-four patients were lost to follow-up or discontinued treatment; therefore, data from only 72 participants were analyzed (37 in the high-dose group and 35 in the low-dose group). The investigators reported a statistically significant increase in BMD at 1 year in the lumbar spine and total hip among patients taking high-dose vitamin D ($P < 0.05$), compared with the low-dose group. However, T-scores remained below zero after 1 year of treatment. No significant changes were seen in BMD at the femoral neck or trochanter.

Effects of Anticonvulsants on Fracture risk

Table II provides a summary of case–control and cohort observational studies that evaluated the association between fracture risk and anticonvulsant use; a number of these studies included participants aged >65 years.[33,49–60]

Tsiropoulos et al[54] conducted a case–control study in a county hospital in Denmark, involving 7557 patients receiving anticonvulsants (>93% of the cohort were aged >60 years). Controls were age and sex matched. The investigators observed that fracture risk was increased among those who had ever used any anticonvulsant (odds ratio [OR] = 1.31 [95%

CI, 1.16–1.48]). The increased risk was limited to enzyme-inducing agents (1.31 [1.14–1.51]), and not with use of non– enzyme-inducing anticonvulsants (1.03 [0.77–1.37]). High daily dose and cumulative dose were associated with increased fracture risk, which was most notably seen with carbamazepine. There was no increased fracture risk seen with the use of clonazepam or gabapentin.

In the largest case–control study, Vestergaard et al[33] identified 124,655 cases through the National Hospital Discharge Register in Denmark. Cases were patients who had been discharged from the hospital after either an inpatient or an outpatient encounter, based on codes from the International Classification of Diseases, 10th Revision, for any fracture in the year 2000. Controls were obtained using the civil registration system, an electronic record of vital status, including date of death, for the Danish population. Controls were matched by sex and year of birth in a 1:3 ratio of cases to controls (n = 373,962). Drug histories were obtained from the national pharmacologic database, which registers drug purchases, including dosages sold. Cases had a mean (SD) age of 43.4 (27.4) years, and 51.8% were female. Cases were more likely than controls to use an antiresorptive medication (10.3% vs 7.5%; $P < 0.01$). After controlling for potential confounders, including comorbidities (as measured by Charlson index), previous fractures, and exposure to corticosteroids, an increased risk of any fracture was associated with exposure to carbamazepine (OR = 1.18 [95% CI, 1.10–1.26]), oxcarbazepine (1.14 [1.03–1.26]), clonazepam (1.27 [1.15–1.41]), phenobarbital (1.79 [1.64–1.95]), and valproic acid (1.15 [1.05–1.26]). However, the associated risk with other anticonvulsants did not reach statistical significance (eg, phenytoin: 1.20 [1.00–1.43]; topiramate: 1.39 [0.99–1.96]).

The largest prospective study by Ensrud et al[56] included postmenopausal women aged >65 years as part of the Study of Osteoporotic Fractures. (The study population and design have been described previously in the present review.) Of the 9704 cohort members, 8127 completed a medication inventory and were subsequently included in the analysis. Among women taking anticonvulsants, there was an increase in the risk for any nonspine fracture (hazard ratio = 1.68 [95% CI, 1.16–2.43]), but not for hip fracture (2.00 [0.94– 4.25]). In this group, 2% (n = 123) were taking anticonvulsant medications, with the majority taking phenytoin (n = 65), followed by phenobarbital (n = 34) and carbamazepine (n = 27). The association between anticonvulsant use and fracture risk was not significant after controlling for age and BMD. Likewise, after adjustment for other comorbidities (including poor health status, functional impairment, depressive symptoms, and weight change), the association was no longer significant. This suggests that, among older adults, anticonvulsants may have direct impact on fracture risk through effects on BMD, or their use may be a marker of increased fracture risk due to seizures or other conditions (eg, alcohol use, neuropathy). Indeed, seizures account for approximately one third of the fractures seen among patients with epilepsy who take anticonvulsants.[50] The increased risk of fracture among anticonvulsant users may have multiple causes affected by the neurologic condition, anticonvulsant treatment, and comorbidities associated with aging.

Despite the varying study populations, the effect sizes remained fairly consistent from study to study (**Table II**). In general, the use of anticonvulsant medications increased the odds of fracture by 1.2 to 2.4 times. Case–control and cohort studies yielded similar values, especially when comparing nested case–control and prospective cohort studies. The result by Scane et al[49] is conspicuously aberrant (OR = 6.1 [95% CI, 1.3–28.4]) and may be the result of a smaller study population or referral bias, because the population was drawn from a bone clinic. The relative consistency of the observed effect of anticonvulsants on fracture risk across other studies, regardless of population or particular agent, suggests a possible class effect.

There are limited data available regarding newer anticonvulsant medications. In the study by Vestergaard et al,[33] the risk of fracture among patients taking topiramate was not significantly increased (OR = 1.39 [95% CI, 0.99–1.96]). Ensrud et al[46] evaluated 84 men taking gabapentin who participated in a population-based cohort study of 5995 men aged >65 years. Men taking gabapentin had a rate of decline in total hip BMD of 0.50% per year, compared with 0.35% among men not taking any anticonvulsant (*P* = NS). Although these results did not reach statistical significance, there is a suggestion that these medications may have effects on bone density and fractures as well.[33,46]

DISCUSSION

Given the observational data concerning the risk of osteoporosis and fractures among patients who take anticonvulsant medications, evidence-based guidance regarding monitoring and treatment is needed. To date, there has been only 1 randomized controlled trial specifically designed to treat osteoporosis or low BMD among patients taking anticonvulsants. However, that trial did not include patients aged >65 years.[48] Moreover, there have been no randomized controlled trials to investigate therapeutic agents to prevent fractures specifically in patients taking anticonvulsants.

The National Institute for Health and Clinical Excellence in the United Kingdom recommended monitoring vitamin D levels and other measures of bone health and bone metabolism, including serum calcium and alkaline phosphatase, every 2 to 5 years among adults taking enzyme-inducing drugs,[61] but there are no guidelines from any US professional groups regarding monitoring and assessment of bone health, or any formal guidelines regarding treatment of bone disease, among patients taking anticonvulsant medications.

Further investigation is needed to assess whether newer anticonvulsant agents, such as levetiracetam and lamotrigine, have similar effects on bone density as the traditional agents such as phenytoin and valproic acid. However, given the possible class effect of these drugs, as suggested by the results of observational studies, clinicians should consider monitoring BMD in this population, even before such clinical trial results become available.

CONCLUSIONS

Several observational studies suggest an association between anticonvulsant medication use, reduced BMD, and increased fracture risk. The biological mechanism, although not yet completely understood, may involve the interaction of anticonvulsant medications with vitamin D metabolism and subsequent bone metabolism. Despite the recognition of particular anticonvulsants' impact on bone health, there are limited data regarding the monitoring and treatment of bone health and bone disease in this population. Likewise, few formal recommendations for practitioners have addressed osteoporosis prevention in patients who use anticonvulsants.

Further research is needed to elucidate the biological mechanism of anticonvulsants that may reduce BMD and contribute to osteoporosis. Improved biological understanding may lead to new therapeutic targets for those who take anticonvulsants. Additional investigation of newer anticonvulsants is needed to assess the relative risk with these agents compared with older medications. Also, randomized clinical trials are needed to guide and define treatment, specifically in this population. Currently, treatment decisions lie with the individual clinician, using the available medication options for treating bone disease, including calcium and vitamin D supplementation and bisphosphonates. Given the

increasing incidence and prevalence of seizures and epilepsy, as well as osteoporosis, among older adults, treatment guidelines based on randomized clinical trials are needed.

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Table I

Observational studies of the effect of anticonvulsants on bone mineral density.

Study (Year)	Population	No. of Participants	Anticonvulsive Agent	BMD Measurement	Result
Case–control design					
Kubota et al (1999)[39]	Neuropsychiatry clinic	Case: 44; control: 62	Phenytoin, barbiturates (mostly phenobarbital), acetazolamide	DEXA for lumbar spine and femoral neck	Mean (SD) BMD for lumbar spine, case vs control: 0.9779 (0.110) vs 1.0529 (0.114) g/cm^2 ($P < 0.01$). Mean (SD) BMD for femoral neck, case vs control: 0.7449 (0.121) vs 0.8279 (0.129) g/cm^2 ($P < 0.01$)
Stephen et al (1999)[40]	Epilepsy clinic	Case: 78; control: 78	Phenobarbital, phenytoin, carbamazepine, valproate, lamotrigine, vigabatrin, topiramate, gabapentin	DEXA for lumbar spine and femoral neck	Mean T-score for lumbar spine, case vs control: –1.46 vs –1.15. Mean T-score for femoral neck: –2.07 vs –1.54 ($P < 0.001$). No difference for enzyme-inducing vs non–enzyme-inducing drugs
Sato et al (2001)[35]	Neuropsychiatry clinic	Case: 40; control: 80 (40 untreated, 40 receiving phenytoin)	Valproate	Computer-linked x-ray densitometry for mid-second metacarpal	BMD reduction in patients vs healthy controls: valproate, 14% (12% in men, 16% in women); phenytoin, 13% (12% in men, 15% in women); $P < 0.001$ for both valproate and phenytoin
Boluk et al (2004)[34]	Epilepsy patients	Case: 50; control: 60	Valproate	DEXA for lumbar spine and femur	Mean (SD) BMD for lumbar spine, case vs control: 0.814 (0.157) vs 0.894 (0.102) g/cm^2 ($P = 0.003$). Mean (SD) BMD for femur, case vs control: 0.824 (0.144) vs 0.906 (0.104) g/cm^2 ($P = 0.001$)
Kulak et al (2007)[41]	Epilepsy clinic	Case: 55; control: 24	Carbamazepine, phenobarbital, phenytoin, valproate	DEXA for lumbar spine, femoral neck, and total femur	Mean (SD) BMD for lumbar spine, case vs control: 1.058 (0.1) vs 0.975 (0.13) g/cm^2 ($P < 0.03$). BMD for femoral neck, case vs control: no significant difference. Mean (SD) BMD for total femur, case vs control: 0.988 (0.12) vs 0.930 (0.1) g/cm^2 ($P < 0.02$)
Lyngstad-Brechan et al (2008)[42]	Epilepsy clinic	Case: 26; control: 26	Carbamazepine, phenobarbital, phenytoin, oxycarbazepine, valproate, lamotrigine	DEXA for femoral neck, total femur, distal forearm, and lumbar spine	Mean (range) BMD for femoral neck, case vs control: 0.83 g/cm^2 (0.61–1.22) vs 0.94 g/cm^2 (0.66–1.10) ($P = 0.033$). Mean (range) BMD for proximal forearm, case vs control: 0.58 g/cm^2 (0.44–0.75) vs 0.63 g/cm^2 (0.45–0.79) ($P = 0.037$). No significant difference in distal forearm or lumbar spine
Prospective cohort design					
Andress et al (2002)[43]	Outpatient seizure clinic, men	81	Phenytoin, carbamazepine, phenobarbital, valproate, gabapentin, lamotrigine, polytherapy (41%)	DEXA for femoral neck	No significant decline in BMD for femoral neck among those aged >45 years

Study (Year)	Population	No. of Participants	Anticonvulsive Agent	BMD Measurement	Result
Ensrud et al (2004)[44]	Community-dwelling women	9704	Phenytoin, carbamazepine, phenobarbital, primidone, valproate	DEXA for total hip, single X-ray absorptiometry for calcaneus	Mean rate of decline in BMD of total hip: 0.70%/y for nonusers, 0.87%/y for partial users, 1.16%/y for continuous users (P = 0.015 for trend). Rate of decline in BMD of calcaneus: 1.46%/y for nonusers, 1.74%/y for partial users, 2.35%/y for continuous users (P < 0.001 for trend)
Kim et al (2007)[45]	Newly diagnosed with epilepsy	33	Carbamazepine, valproate, lamotrigine	DEXA for right calcaneus	Mean (SD) change in BMD at initial visit after treatment and at 6 months after treatment with AED: carbamazepine, 0.42 (0.26) and –0.34 (0.35) (P = 0.043); valproate, 0.61 (0.41) and 0.06 (0.30) (P = 0.068); lamotrigine, 0.60 (0.17) and 0.48 (0.18) (P = 0.100)
Ensrud et al (2008)[46]	Community-dwelling men	4222	NEIAED: phenytoin, phenobarbital, primidone, carbamazepine, topiramate, oxcarbazepine. EIAED: gabapentin, valproate, lamotrigine, levetiracetam, pregabalin, tiagabine	DEXA for total hip, femoral neck, and trochanter	Rate of decline in BMD for total hip: no AED, –0.35%/y; nonenzyme inducers, –0.53%/y (P = 0.04); enzyme inducers, –0.46%/y (P = 0.31). Rate of decline in BMD for femoral neck: no AED, –0.33%/y; nonenzyme inducers, –0.58%/y (P < 0.05); enzyme inducers, –0.43%/y (P > 0.05). Rate of decline in BMD for trochanter: no AED, –0.32%/y; nonenzyme inducers, –0.53%/y (P < 0.05); enzyme inducers, –0.49%/y (P > 0.05)
Cohort design: twin/sibling pairs					
Petty et al (2005)[47]	Twin and sister longitudinal studies	35 Pairs	Carbamazepine, phenytoin, phenobarbital, primidone, valproate, lamotrigine, topiramate, gabapentin, ethosuximide, clonazepam	DEXA for lumbar spine, femoral neck, total hip, and total forearm	AED use >2 y vs ≤2 y: forearm BMD, 0.513 vs 0.534 (P = 0.016). Enzyme inducers vs nonenzyme inducers: forearm BMD, 0.508 vs 0.529 (P = 0.010). Age >40 y and AED use >2 y vs younger and/or less AED use: forearm BMD, 0.492 vs 0.524 (P = 0.017); lumbar spine, 0.884 vs 0.980 (P = 0.036). No significant differences at other sites

BMD = bone mineral density; DEXA = dual energy x-ray absorptiometry; AED = antiepileptic drug; NEIAED = nonenzyme-inducing AED; EIAED = enzyme-inducing AED.

Table II

Observational studies of the effect of anticonvulsants on fracture risk. Fracture risk is given as odds ratio (95% CI) unless otherwise noted.

Study (Year)	Population	No. of Participants	Fracture Type	Medication	No. of Years of Follow-up	Fracture Risk (95% CI)
Case–control design						
Scane et al (1999)[49]	Referrals to bone clinic	Case: 91; control: 91	Vertebral	Any anticonvulsant	–	6.1 (1.3–28.4)
Vestergaard et al (1999)50	Noninstitutionalized patients with epilepsy	Case: 999; control: 654	All	Any anticonvulsant	–	Overall: 2.0 (1.6–2.5); phenytoin: 2.4 (1.1–5.4)
van Staa et al (2002)[51]	UK General Practice Research Database (GPRD)	Case: 231,778; control: 231,778	All	Any anticonvulsant	–	2.1 (2.0–2.2)
Vestergaard et al (2004)[33]	National Hospital Discharge Register (Denmark)	Case: 124,655; control: 373,962	All	Carbamazepine, oxcarbazepine, clonazepam, phenobarbital, valproate, ethosuximide, lamotrigine, phenytoin, primidone, tiagabine, topiramate, vigabatrin	–	Carbamazepine: 1.18 (1.10–1.26); oxcarbazepine: 1.14 (1.03–1.26); clonazepam: 1.27 (1.15–1.41); phenobarbital: 1.79 (1.64–1.95); valproate: 1.15 (1.05–1.26); ethosuximide: 0.75 (0.37–1.52); lamotrigine: 1.04 (0.91–1.19); phenytoin: 1.20 (1.00–1.43); primidone: 1.18 (0.95–1.48); tiagabine: 0.75 (0.40–1.41); topiramate: 1.39 (0.99–1.96); vigabatrin: 0.93 (0.70–1.22)
Souverein et al (2006)[52]	Epilepsy patients from UK GPRD	Case: 1018; control: 1842	All	Carbamazepine, valproate, phenytoin, phenobarbital, lamotrigine, other	–	Carbamazepine: 1.88 (1.33–2.65); valproate: 1.57 (1.08–2.29); phenytoin: 1.67 (1.19–2.36); phenobarbital: 1.84 (1.18–2.87); >1 AED: 2.82 (2.05–3.89)
Perreault et al (2008)[53]	Prescription and medical-services database for Quebec province	Case: 1824; control: 18,240	All	Any anticonvulsant	–	1.41 (1.09–1.81)
Tsiropoulos et al (2008)[54]	Admissions to county hospitals with hip fracture (1996–2004)	Case: 7557; control: 27,575	Hip	Any anticonvulsant	–	Any anticonvulsant: 1.31 (1.16–1.48); enzyme inducers: 1.31 (1.14–1.51); non-enzyme inducers: 1.03 (0.77–1.37)
Prospective cohort design						
Cummings et al (1995)[55]	Community-dwelling women	9516	Hip	Any anticonvulsant	4.1	RR: 2.0 (0.8–4.9)
Ensrud et al (2003)[56]	Community-dwelling women	8127	Nonspine	Any anticonvulsant	4.8	HR: 1.68 (1.16–2.43)
Spector et al (2007)[57]	Nursing homes–Medical Expenditure Panel Survey	2711	Any	Any anticonvulsant	1	2.17 (1.37–3.45)
Retrospective cohort design						
Persson et al (2002)[58]	Epilepsy clinic	177	Extremity fracture	Any anticonvulsant	4.7	SMR: 2.39 (1.52–3.59)
Koppel et al (2005)[59]	Epilepsy clinic, women	50	Any	Any anticonvulsant	–	No. of fractures: 29 in 20 subjects

Study (Year)	Population	No. of Participants	Fracture Type	Medication	No. of Years of Follow-up	Fracture Risk (95% CI)
Chevrel et al (2007)[60]	Ambulatory epilepsy patients	52	Any	Phenobarbital	–	No. of fractures: phenobarbital, 23 in 9 patients; no phenobarbital: 8 in 5 patients

AED = antiepileptic drug; RR = risk ratio; HR = hazard ratio; SMR = standardized morbidity ratio.