THE IMPACT OF LONG-TERM ANTIEPILEPTIC DRUG USE ON BONE HEALTH*

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ABSTRACT

A growing amount of scientific literature describing long-term follow-up in patients taking antiepileptic drugs (AEDs) indicates a probable relationship between osteoporosis and the long-term use of these drugs. However, the exact influence on fracture risk is not yet clear. Osteoporosis in patients with epilepsy is a serious problem. Detriments in bone health can be measured as radiographic, pathologic, and biochemical abnormalities. Most of the data showing bone disease and increased fractures with AED use are in patients taking the older drugs. Several new AEDs have become available in the past decade, but the data for them in this regard is limited. Multiple treatments are available for bone disease, including calcium and vitamin D supplementation, bisphosphonates, hormone replacement, calcitonin, and parathyroid hormone. The efficacy and safety of these treatments in the general population are established but there are few studies of these treatments involving patients taking AEDs. Clinicians might consider a monitoring schedule for patients taking phenytoin and phenobarbital, particularly if these patients have other risk factors that contribute to bone disease. Clinicians should discuss a regimen of recommended daily allowances of calcium and vitamin D with all patients taking AEDs, regardless of the patient’s age or sex.

(Adv Stud Med. 2005;5(6C):S567-S571)

Osteoporosis is typically considered to be a disease of postmenopausal women and is not often considered by neurologists during routine patient management. However, a growing amount of scientific literature describing long-term follow-up in patients taking antiepileptic drugs (AEDs) indicates a probable relationship between osteoporosis and the long-term use of these drugs. Although the exact influence on fracture risk is not yet clear, epilepsy and AEDs have been associated with an increased risk of fractures. Osteoporosis in patients with epilepsy is a serious problem: patients with epilepsy already are at an increased risk of fractures because of falls during seizures; epilepsy can be a lifelong disorder requiring lifelong treatment; women constitute a significant portion of patients with epilepsy and are at an increased risk of osteoporosis simply because of their hormonal changes; there is a paucity of studies examining bone health with many of the newer AEDs, thus those patients’ risks are not yet known; and a recent study indicates that a minority of neurologists (40% of pediatric neurologists and 28% of neurologists treating adult patients) screen for bone disease in their patients taking AEDs.

MANIFESTATION OF BONE DISEASE

Bone health is a dynamic process, a coupling of bone resorption by osteoclasts and bone formation by osteoblasts. Poor bone health can manifest as osteopenia, osteoporosis, osteomalacia, and fractures. Osteopenia is a precursor to osteoporosis and is marked by decreased calcification, decreased bone density, or reduced bone mass. These conditions result from accelerated bone resorption so that the rate of bone formation lags behind and bone mass overall decreases. The standard for assessing bone density is through dual x-ray absorptiometry. Several studies have
documented decreased bone mass in several body sites in patients taking AEDs, in cohorts ranging in age from children to the elderly. At Columbia University, we performed a retrospective study to measure bone mineral density in an adult outpatient population (n = 153) who were receiving AEDs (specifically, those drugs that induce hepatic cytochrome P450 enzymes). Study results showed significantly increased osteoporosis and osteopenia in younger men and women (<50 years). In fact, the rate of osteoporosis was 10 times greater in the study group than the expected rate for the general population (Figure).14

Osteomalacia describes softening of the bone as a result of increased osteoid or unmineralized bone, thus it increases risk of fracture. Osteomalacia was originally described in the 1960s and '70s in institutionalized patients, but it has not been frequently reported since then. The apparent decrease in prevalence is most likely explained by the inadequate diet, poor sunlight exposure, and limited exercise of institutionalized patients versus community-dwelling patients with epilepsy.

Fractures are the most important manifestation of bone-mineral density decline. Patients with epilepsy are at an increased risk of injury and fractures as a result of their seizures; however, fractures have been described at multiple sites (ie, hip, radius, ankle, and vertebrae) in patients taking AEDs.15-19 Results in some studies did not suggest a relationship between AED use and increased fracture risk; however, some studies found that the increase in fractures was independent of seizure frequency, suggesting that AED use increases the risk of fracture.2,3,16,18

Biochemical abnormalities, in addition to radiographic and pathologic abnormalities, have been described in patients taking AEDs. As summarized in Table 1, calcium, phosphate, and vitamin D metabolites are decreased in patients taking AEDs. However, markers of bone formation and resorption, in addition to parathyroid hormone (which is involved in homeostasis of calcium levels), are increased compared to normal levels.20-23

**ANTIEPILEPTIC DRUGS ASSOCIATED WITH BONE DISEASE**

Most of the data showing bone disease and increased fractures with AED use are in patients taking the older drugs. However, several new AEDs have become available in the past decade, but data in this regard are limited. Phenytoin, phenobarbital, and primidone are the most commonly reported agents associated with adverse effects on bone health. These agents are all potent inducers of the hepatic cytochrome P450 enzyme system. Studies of patients taking these medications reveal decreased bone density; reduced serum calcium, phosphate, and vitamin D levels; and increased bone turnover.3,15,20

Carbamazepine is also an inducer of the cytochrome P450 enzyme system; however, the data regarding indices of bone and mineral metabolism and bone turnover and bone mineral density are conflicting. Some studies find no changes in measures of bone health, whereas other studies find significant changes in patients taking this drug.10,20,22-28 One study using

![Figure. Comparison of Bone Mineral Density Between Antiepileptic Drug Users and the General Population](image-url)

Percentages of normal density, osteopenia, and osteoporosis at the femoral neck of the hip in 50-year-old men and women receiving antiepileptic drugs compared to expected percentages from a healthy population of white postmenopausal women. Reprinted with permission from Pack et al. Epilepsy Behav. 2003;4:169-174.14
ultrasonography revealed decreased cortical bone mass with carbamazepine use, whereas a recent study showed limited increase in fracture risk.\textsuperscript{2,25} Of note, the study showing limited increase in fracture risk is the only study to examine individual AEDs; the other studies tended to analyze AED use as a group. Another study evaluated markers of bone turnover before treatment with carbamazepine in adolescent girls and boys and repeated these measurements after 1 and then 2 years of initiating treatment. The findings were compared to a control population matched by age, sex, and pubertal status.\textsuperscript{22,23} The results showed significantly elevated markers of bone turnover in the group treated with carbamazepine compared to the control group.\textsuperscript{2} These results are important for their insights into the bone effects of a single AED and a comparison to bone health before treatment initiation and because bone density increases during the first 20 to 30 years of life to obtain peak bone mineral density. The increased turnover during these years suggests that the peak bone mineral density will be affected by treatment with carbamazepine. Adolescents taking AEDs may not be able to build the same bone mineral density as other healthy children and young adults. A leading theory to explain the effects of enzyme-inducing AEDs on bone health is that hepatic induction of the cytochrome P450 enzyme system leads to increased catabolism of vitamin D, secondary hyperparathyroidism, and increased bone turnover.\textsuperscript{29} Valproate, by contrast, inhibits the cytochrome P450 enzymes. Interestingly, a study comparing valproate with carbamazepine use in children showed bone loss with valproate only. Another study involving adults also found decreased bone mineral density and elevated markers of bone turnover when compared to a control group without epilepsy who were not taking AEDs.\textsuperscript{21}

There are few studies assessing bone health with the newer AEDs (eg, lamotrigine, topiramate, and zonisamide). One study of a pediatric population found bone loss with lamotrigine use, but the authors suggest that the short stature, low bone mineral density, and reduced bone formation may have been caused by limited activity rather than the AEDs because the measures of bone density correlated with activity level.\textsuperscript{9} At Columbia University, we studied bone mineral density and indices of bone and mineral metabolism, including markers of bone turnover, in normally cycling premenopausal women taking phenytoin, carbamazepine, valproate, and lamotrigine. Those women taking lamotrigine had significantly higher calcium levels when compared to the other women. Bone-specific alkaline phosphatase (a marker of bone resorption) was significantly elevated in women taking phenytoin compared to lamotrigine, suggesting that lamotrigine has less effect on bone than phenytoin.\textsuperscript{30} To date, there are no published data regarding the effects of carbonic anhydrase inhibitors (topiramate and zonisamide) on bone health. One study showed a bone-sparing effect of acetazolamide in patients with glaucoma.\textsuperscript{31}

**RISK FACTORS**

Several other risk factors for osteoporosis are well defined: age, small body frame, white or Asian ethnicity, family history of osteoporosis, alcohol use, and smoking history. Therefore, patients who are taking AEDs—even the newer agents—who also have these risk factors should be considered for prophylactic treatment for osteoporosis and monitoring of bone mineral density.

**TREATMENT**

As described earlier in this article, results from a survey of neurologists’ practice patterns regarding bone and mineral effects of AEDs indicated that most neurologists do not screen for bone disease. Of those neurologists who screen and find evidence, approximately 40% administer calcium and vitamin D as treatment and approximately 55% refer these patients to a specialist (Table 2). Although only approximately

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**Table 1. Biochemical Abnormalities of Bone Metabolism Associated with Antiepileptic Drug Use**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>↓ Serum</td>
</tr>
<tr>
<td>Phosphate</td>
<td>↓ Serum</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>↑ Serum</td>
</tr>
<tr>
<td>Vitamin D metabolite levels</td>
<td>↓ Serum</td>
</tr>
<tr>
<td>Markers of bone formation</td>
<td>↑ Serum</td>
</tr>
<tr>
<td>Markers of bone resorption</td>
<td>↑ Serum/urine</td>
</tr>
</tbody>
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Data from Valimaki et al\textsuperscript{20}; Sato et al\textsuperscript{21}; Vernotti et al\textsuperscript{22,23}
5% of the neurologists neither treat nor refer, fewer than 10% of neurologists talk to their patients about prophylactic calcium and vitamin D during AED use. These results suggest that most neurologists are not aware of the effects of AEDs on bone health, and the appropriate treatment options are not routinely used when there is evidence of bone disease.6

Multiple treatments are available for bone disease, including calcium and vitamin D supplementation, bisphosphonates, hormone replacement, calcitonin, and parathyroid hormone. The efficacy and safety of these treatments in the general population are established, but there are few studies of these treatments in patients taking AEDs. For example, the only studies of vitamin D use in patients taking AEDs used broad ranges of high doses. Bone mineral density increased with vitamin D supplementation, but a safe recommended dose based on this study is unclear.25 Clinicians should counsel all patients taking AEDs about taking the recommended daily allowance of calcium and vitamin D. The recommended daily allowance of calcium ranges between 1000 to 1500 mg/day, depending on age, sex, and reproductive status (Table 3).32,33 Daily vitamin D intake for prophylaxis of bone mineral depletion is 400 to 2000 IU/day, and the endocrinology community recommends higher doses for the treatment of osteopenia and osteoporosis (2000–4000 IU/day), and even higher doses for the treatment of osteomalacia (5000–15000 IU/day).34

CONCLUSIONS

Antiepileptic drugs appear to negatively influence bone health, especially in patients with risk factors that also may contribute to the disease. The exact relationship between AED use and bone mineral density is not yet described completely. The most compelling evidence of a deleterious effect on bone health is with the use of phenytoin and phenobarbital. Patients taking these 2 drugs should have their bone mineral density monitored regularly. For patients taking carbamazepine and valproate, in addition to the newer medications, the recommendations are less clear. Clinicians should also consider a monitoring schedule for patients taking these drugs, particularly if they have other risk factors that contribute to bone disease. Physicians should discuss the recommended daily allowances of calcium and vitamin D with all patients taking AEDs, regardless of their age or sex. This conversation is a simple initiative that can create a long-term beneficial health outcome for patients.
REFERENCES