Antiepileptic drugs have long been linked to metabolic bone disease. The earliest studies reported an increased risk of osteomalacia and rickets in institutionalized patients receiving AEDs. Unfortunately, this patient population was plagued by inadequate diet, a lack of physical activity, and poor sunlight exposure, thus it is hard to extrapolate such findings to the outpatient setting. However, studies in ambulatory patients have found evidence of metabolic bone disorders such as osteomalacia, osteopenia, osteoporosis and fractures associated with AED use.

These medications not only cause a variety of bone diseases, they can affect several at-risk groups. Older men taking AEDs have been found to be at increased risk for bone disease, with significantly reduced Bone Mineral Density (BMD) at the lumbar spine and femur. Post-menopausal women, a group already prone to bone disease due to a lack of estrogen, are also at higher risk for hip fractures if they are on AEDs. The same study also found a twofold increased risk of fractures for patients on AEDs vs. controls, with the fractures being unrelated to seizure activity. Another study found patients on chronic phenytoin had a 1.7-fold greater mean bone loss vs. controls. Others have also confirmed a significantly decreased bone mineral density (BMD) in adults receiving AEDs. Thus the data have consistently shown AEDs are linked to bone disease, therefore maintaining proper bone health is vital in these patients.

### AED-Induced Bone Disease

Although the evidence reveals AED use leads to bone disease, the exact mechanism remains unclear. Several theories exist as to how AEDs lead to bone disease, however, the most plausible explanation is that AEDs cause low levels of vitamin D. The mechanism is thought to be through the cytochrome p450 enzyme system, which is induced by several AEDs. The activation of the p450 enzymes results in degradation of vitamin D levels and many studies have confirmed that patients on AEDs have lower levels of 25(OH)D. Although this is the most popular theory, it has been challenged, since some patient on AEDs have had normal vitamin D levels, yet still have decreased bone mineral density (BMD).

For this reason, other explanations have emerged. One theory suggests AEDs cause bone disease by directly inhibiting intestinal absorption of calcium. The resulting hypocalcemia leads to weaker bone and a state of secondary hyperparathyroidism. Others have speculated that AEDs lead to a calcitonin deficiency. Calcitonin is secreted by the thyroid gland and inhibits osteoclast-mediated bone resorption (bone break down). A calcitonin deficiency will lead to increased osteoclast activity, resulting in excessive bone turnover. Although there are many plausible theories, there is no single mechanism which is widely accepted as to how AEDs induce bone disease.

Patients on AEDs may suffer from hypocalcemia, vitamin D deficiency and secondary hyperparathyroidism all of which contribute to poor bone quality and increased risk of fractures. Calcium and vitamin D are important for bone remodeling which occurs on a daily basis. Parathyroid hormone (PTH), secreted by the parathyroid glands, plays a crucial role in regulating serum calcium and vitamin D levels.

When calcium and/or vitamin D levels are low, PTH appropriately increases in an attempt to correct these deficiencies. PTH acts directly on the bones to mobilize calcium, and on the kidneys to increase production of the active form of vitamin D, calcitriol. Calcitriol not only increases calcium absorption from the gut, but also stimulates osteoclasts to release calcium from the bones. This mechanism is termed secondary hyperparathyroidism, and although it may correct the underlying deficiencies, it is obviously occurring at the expense of the bone. Once the hypocalcemia and/or vitamin D levels have normalized, PTH levels return to normal via a negative feedback loop.

### Table 1. Osteoporosis Risk Factors

- Increasing age
- Caucasian/Asian race
- Menopause
- Tobacco use
- Alcohol use
- Family history of osteoporosis
- Small frame
- Chronic medications (glucocorticoids, antiepileptics)
- Hyperparathyroidism
- Hyperthyroidism
Many patients on AEDs suffer from hypocalcemia—up to 30 percent reported in one study—which can have a significant impact on bone health. Calcium, a major component of bones, is essential to the process of bone formation and resorption (bone break down). Thus, adequate stores are needed to maintain proper bone health and hypocalcemia in these patients must be corrected. Otherwise, the resulting secondary hyperparathyroidism will further weaken the bones and predispose these patients to fractures.

Specific AEDs have been linked to vitamin D deficiency, which also contributes to bone disease. Recent research shows that 44.5 percent of patients with epilepsy have vitamin D deficiency, with men being slightly more affected than women, 45.3 percent of men vs. 43.7 percent of women. Vitamin D is a hormone needed for skeletal development and proper bone mineralization with appropriate levels are maintained through diet and adequate sunlight exposure. Adequate stores are determined by serum measurements of 25(OH) vitamin D, which should be greater than 30ng/ml. If vitamin D levels are low, bone mineralization will not be sufficient, and the subsequent secondary hyperparathyroidism will lead to further bone disease. Thus, appropriate vitamin D levels are also essential in maintaining bone health.

**Specific AEDs and Bone Disease**

Not all AEDs are linked to bone disease. However, those which induce the cytochrome p450 system are closely associated with altered bone metabolism. These include phenobarbital, phenytoin, and carbamazepine. Valproic acid, is also an inducer of the p450 system, however, studies have been inconclusive regarding its effects on bone disease. Multiple new AEDs have recently become available such as lamotrigine, topiramate, vigabatrin, and gabapentin. Although there have been only a few studies examining the newer AEDs with bone disease, no significant adverse effects have been found with regards to bone health.

**Monotherapy vs. Polytherapy**

Therapy with multiple AEDs has been linked to higher risk of bone disease versus monotherapy. Biochemical evidence of patients on multiple AEDs reveal lower levels of calcium and vitamin D, along with elevated levels of alkaline phosphatase, which is a marker of bone turnover. Although there is no specific combination which has been linked to more severe bone disease, they all include at least one AED that is a P450 inducer.

Some studies have linked duration of therapy with worsening BMD, while others contradicted these findings. Thus, there is no clear answer if duration of therapy has an effect on bone disease.

**Clinical Manifestations**

Unfortunately, many patients with mild hypocalcemia, vitamin D deficiency and secondary hyperparathyroidism remain asymptomatic. These biochemical abnormalities are usually discovered after the work-up for bone disease has been initiated. Symptoms of severe hypocalcemia may manifest as parathesias of the hands and feet, or periorbital numbness. Severe vitamin D deficiency may cause diffuse proximal muscle weakness. However, these symptoms reflect cases of severe deficiencies, with the majority of patients being asymptomatic.

**Screening**

Currently, there are no formal guidelines to dictate screening for bone disease in patients on AEDs. Screening for bone disease such as osteoporosis is done via dual energy X-ray absorptiometry, (DEXA). Some practitioners recommend screening with a DEXA for patients on AEDs greater than five years or prior to initiating AED treatment in postmenopausal women. Others suggest all patients on AEDs should have a baseline DEXA. Some authors recommend only routine biochemical screening, with calcium, and vitamin D levels. If these are abnormal, further testing with a DEXA should be initiated.

For further evidence based medicine is available it is difficult to suggest a standardized screening program for these patients. However, most authors agree that adequate calcium and vitamin D levels should be maintained in all patients on AEDs and thus appropriate surveillance with periodic serum calcium and 25-hydroxyvitamin D measurements.

**Treatment**

Treatment guidelines are lacking in this patient population. Although various options are available for treating bone disease such as osteoporosis and osteomalacia, few studies have focused on treating bone disease associated with AEDs. The only regimen that has been studies in this patient population is vitamin D supplementation. One study found normalization of vitamin D levels did lead to

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**Table 2. Nonpharmacologic Interventions**

- Avoiding tobacco and excessive alcohol
- Adequate calcium and vitamin D intake
- Weight bearing exercise and muscle strengthening
- Falls prevention
- Balanced diet

**Table 3. World Health Organization Definition of Osteoporosis**

- Normal BMD: T score >-1
- Osteopenia: T score between -1 and -2.5
- Osteoporosis: T score less than -2.5
improvements in BMD and biochemical parameters of bone disease in patients on AEDs. If BMD measurements reflect osteoporosis (Table 3) then standard guidelines should be implemented for pharmacological treatment. Patients who do not meet these criteria, should focus on nonpharmacologic interventions such as lifestyle modifications, maintaining adequate levels of calcium (1000-1200mg/day) and vitamin D (200-400 IU/day), falls prevention strategies and good seizure control to optimize bone health.

Vitamin D and Cardiovascular Disease

Vitamin D deficiency is well known to cause bone disease; however, recent studies have linked vitamin D deficiency to an increased risk of cardiovascular disease as well. Low levels of vitamin D have been associated with congestive heart failure, and increased levels of inflammatory markers such as C-reactive protein. A recent study also found patients with vitamin D levels below 15ng/ml with a history of hypertension have a significantly higher risk of developing a cardiovascular event as compared to those with levels greater than 15ng/ml. This highlights the need to maintaining adequate vitamin D levels not only for proper bone health, but perhaps for cardiovascular protection as well. PN

10. Dietary Reference Index (DRIs). Food and Nutrition Board, Institute of Medicine, National Academies.

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