



## What You May Not Know about Antiseizure Medications and Bone Health

**Routine bone scans and patient education about diet and exercise are vital but often overlooked components of epilepsy management.**

**O**steopenia or osteoporosis affects men and women. However, the hormonal changes that occur in women after menopause increase the risk of poor bone health. In addition to hormones, there are many factors that contribute to bone health. A well-rounded diet that contains calcium, vitamins (especially vitamin D), and a routine of regular exercise are needed to maintain strong bones. Medical illnesses, such as primary hyperpara-thyroidism, may deplete bones of calcium. Finally, long-term use of antiseizure medications is known to contribute to osteopenia and osteoporosis.

### Background

Our bones are constantly being broken down and reformed through a process known as bone remodeling. Osteoblasts secrete and mineralize new bone while osteoblasts resorb old or worn out bone. There is a balance between the two. Our bodies are very efficient: if we exercise more, placing greater stress on our muscles and bones, our bodies respond by increasing the size of the muscle fibers and the density of bone.

Similarly, if we exercise infrequently, our bodies respond by resorbing “un-needed” bone matrix. In order for the mineralization process to take place, we need to take in the appropriate amount of calcium. Vitamin D, which is converted to its active form by sunlight, is needed as well. In other words, in order to optimize our bone health, we need to eat right (vitamin D and calcium), exercise regularly and be exposed to sunlight (a little).

Since the 1960s, antiseizure medica-

tions have been associated with osteomalacia. These observations were made in people who were taking the hepatic enzyme inducing agents (phenytoin, carbamazepine and phenobarbital). However, the hepatic enzyme inhibitor valproate has also been reported to cause bone loss.

One of the problems with these early observations is that many were performed in people who were institutionalized. Many factors were uncontrolled in these observational studies: diet, calcium intake and vitamin intake were not quantified. In addition, many people had little, if any, exercise, further contributing to bone problems. What has been needed for a long time is a study that controls for these factors.

### How AEDs Affect Bones

With regards to the issues that surround the long-term effects of AEDs on bone health, there are many questions that remain unanswered. For instance, the mechanism through which AEDs affect bones is unclear. Several theories have been proposed, including the induction of the hepatic enzyme P450 system by many

AEDs. This would cause increased catabolism of vitamin D, which is needed in order to absorb calcium from the intestines. This would therefore lower the serum calcium, and therefore impair bone formation.

This has been researched: some studies have shown that vitamin D levels are lower in people taking enzyme-inducing AEDs. However, other studies have not identified this deficiency. In addition, valproate, which is an enzyme inhibitor (and therefore should not lower vitamin D levels), has been shown to cause osteopenia. In other words, the enzyme theory may only be part of the answer.

A second hypothesis is that AEDs directly affect calcium absorption or calcium utilization, leading to hypocalcemia. The absorption of calcium depends on intestinal transportation of the ion to the bloodstream. In rats, one of the AEDs, phenytoin, has been shown to impair calcium absorption. Medicines like phenytoin and carbamazepine have been shown to reduce the proliferation of bone-forming cells (osteoblasts) at concentrations similar to the serum levels that would be

**Table 1. Interpreting the Results of DEXA Scans**

T-Score	Recommendations
Greater than -1	<ul style="list-style-type: none"> <li>Encourage calcium and vitamin D supplementation</li> <li>Encourage weight-bearing exercise</li> </ul>
Between -1 and -2.0	<ul style="list-style-type: none"> <li>Same as above</li> <li>Repeat DEXA scan in 1-2 years and consider referral for additional treatment</li> </ul>
Less than -2.0	<ul style="list-style-type: none"> <li>Refer for intervention</li> </ul>

*Source: Alison Pack, MD, Assistant Clinical Professor of Neurology, Columbia Comprehensive Epilepsy Center, New York City.*



# EPILEPSY ESSENTIALS

By Steven Karceski, MD

considered “normal” or within the reference range that has been established for these medications.

Third, the AEDs may induce a situation similar to hyperparathyroidism. It may be that the AED affects the cellular response to parathyroid hormone (PTH). Parathyroid hormone acts to increase bone resorption, and therefore to increase serum calcium levels. If true, the mechanism requires additional investigation as some studies have shown increased bone turnover in the presence of normal PTH levels.

Finally, the link between AEDs and bone loss may be due to changes in calcitonin levels. Calcitonin is a hormone that is released by the thyroid gland, inhibiting bone resorption. Phenytoin and primidone have been shown to lower serum calcitonin levels, thereby increasing bone resorption rates.

## Recent Research

Alison Pack, MD, Assistant Clinical Professor of Neurology at the Columbia Comprehensive Epilepsy Center, has been studying this problem for several years. She recently completed a study on the effects of the older AEDs (phenytoin, carbamazepine, and valproate), comparing their effects to one of the newer agents (lamotrigine) when used in monotherapy in a group of 93 adult women with epilepsy. She controlled for factors such as diet (calcium intake), exercise, and sunlight exposure.

In addition, all of the women were premenopausal, controlling for the effect of hormones on bone health. Several serum markers were followed in this prospective study, including vitamin D levels, PTH, serum calcium, and bone specific alkaline phosphatase (BSAP, a marker of bone turnover). Bone mineral density measures were determined using the standard DEXA (dual emission X-ray absorptiometry) scan.

Although the study has not yet been published (it will be published later this year), Dr. Pack’s findings support previous

reports that the older AEDs contribute to bone loss. Phenytoin, carbamazepine and valproate were associated with decreased serum calcium levels ( $p < 0.03$ ). Phenytoin was associated with a statistically significantly higher level of BSAP ( $p < 0.007$ ), a marker of bone resorption. Lamotrigine, in contrast, did not affect serum markers such as calcium levels.

## What Should Physicians Do?

The recommendations about bone health and AED use are unclear. Most experts agree that bone density testing should be done. However, the interval between tests varies: some recommend DEXA scans every six months, while others say that every two years is sufficient. If bone mineral loss is identified on testing, how often should testing be performed? Again, the recommendations are vague, although a shorter interval between tests seems indicated (six to 12 months). Table 1 provides a few guidelines for interpreting DEXA scans.

Counseling for patients is needed, both in regards to this side effect as well as calcium supplementation. The recommended range of calcium intake is between 1000mg to 1500mg each day. People who are at highest risk for bone loss, such as postmenopausal women not taking estrogen, should probably take the higher amount. Adolescents and young adults, who require more calcium for bone formation, also need higher amounts (between 1200mg to 1500mg each day). Obviously, the intake of calcium must be paired with vitamin D (at least 40 IU/day, the amount contained in an over-the-counter multivitamin) and, ideally, a good exercise regimen. Vitamin K has also been shown to mitigate bone loss in patients taking AEDs.

Hormone replacement therapy is quite controversial, due to its potential increase

in risk of breast cancer, cardiovascular disease and possibly cognitive changes or even increased seizure frequency.

Most of these are hotly debated, however, many practitioners still advocate HRT for most post-menopausal women after thorough patient education about the risks.

## Conclusion

Although the effects of long-term use of AEDs on bone health have been described for decades, we are just beginning to understand which AEDs are most problematic. Considering the fact that most people with epilepsy who take AEDs will be committed to long-term use, this problem is not insignificant. In addition, the use of AEDs has grown considerably as a treatment for mood: bipolar disorder is an excellent example where carbamazepine, valproate and now lamotrigine are commonly prescribed.

The same issues apply to both specialties: neurologists and psychiatrists must be aware of these side effects, and follow patients carefully for bone loss. Patients will need counseling regarding these issues, and will need to take vitamins and calcium regularly. Hopefully, as research continues, we will better understand the long-term effects of other newer AEDs on the bone health of both adults and children. **PN**

1. Pack AM. “Bone Disease in Epilepsy.” *Current Neurology and Neuroscience Reports* 2004;4:329-334.

**Steven Karceski, MD** is Assistant Clinical Professor of Neurology at the College of Physicians & Surgeons of Columbia University and Director of the Columbia Epilepsy Center at the Atlantic Neuroscience Institute.