



Exploring the Links Between Epilepsy, AEDs and Bone Fractures

Epilepsy patients are at increased risk for fractures. Here's a look at the most likely causes and strategies for prevention.

Given the increased vulnerability posed by seizures, injuries commonly occur in children and adults with epilepsy.^{1,2} Of all injuries, skeletal fractures are perhaps the most serious, and are estimated to be two to seven times higher than in controls.^{1,3} The exact cause of fractures is unclear: are they due to seizures, falling because of a seizure, or does the injury occur as a result of medication side effects such as dizziness or imbalance? New evidence has linked long-term antiepileptic drug (AED) use with bone disease such as osteopenia and osteoporosis in adults. This suggests another possible cause of the observed increased rate of fractures in people with epilepsy. Finally, the increased rate of fractures may be due to a combination of any of these factors. Optimal treatment of seizures is one way to prevent injuries related to seizures. Measures directed to preventing bone loss may also be of benefit; however, it is not yet known whether these therapies are effective in reducing the rate of fractures in people with epilepsy.

Incidence and Relative Risk of Fractures

Most studies that address the rate of fractures in people with epilepsy are retrospective reviews. The most quoted numbers are in the range of a two- to sevenfold increase in the rate of fractures compared to controls.^{1,3} The rates vary widely, likely reflecting the variability between the populations studied: the two-fold increase was reported in non-institutionalized individuals, while the seven-fold increase was reported in institutionalized patients.³ Vestergaard reported in 1999 a relative risk of 2.0 for

the development of extremity fractures, and noted that the risk increased with advancing age. In 1999, Scane calculated a relative risk of 6.1 for vertebral body fractures, a rate comparable to persons who chronically take steroids.³

In these studies, several risk factors for the development of fractures have been identified. First, it seems clear that fractures occur more often in individuals who experience specific seizure types: generalized tonic-clonic, tonic and atonic. The risk was higher when there was a higher seizure frequency. AED use has also been associated with increased fracture rates, especially use of phenytoin or polytherapy. Finally, those with intellectual disability were more likely to experience skeletal fractures. However, as we have seen in previous columns, people with intellectual disability are more likely to have generalized seizures, and often have refractory, or difficult-to-manage, epilepsy. In other words, the intellectual disability may not be an independent risk factor, but simply reflect the type and severity of the underlying seizure disorder.

Mechanism of Fracture

In people with seizures, both extremity fractures and vertebral body compression fractures are reported. It has been postulated that the extreme muscular contraction that occurs during generalized seizures is the

cause of the fracture. Of the various types of fractures, shoulder dislocation and fracture, especially when it is bilateral, has been touted highly indicative of the occurrence of a seizure.⁴ In one study 25 percent, the fracture was directly related to the seizure.¹ In another, the estimate of seizure-related fracture was 34 to 43 percent.

Seizures cause falls. Falls cause fractures. Antiseizure medications cause side effects such as dizziness and imbalance. Side effects can lead to falls, and therefore fractures. If 25 to 43 percent of fractures are directly due to seizures, the remainder may be in part due to these other factors.

The extent to which poor bone health leads to fractures epilepsy patients remains unclear. However, the link is clear: poor bone health increases the susceptibility to fracture. AEDs may cause "weakening" of bones. In a population that is already at risk for falls (whether due to seizures or not), this presents a particular concern.

Recent literature has shown that long-standing use of certain AEDs increases the risk of developing bone loss such as osteopenia and osteoporosis. Of the AEDs studied, phenytoin, phenobarbital, and primidone are the agents that are most often associated with bone loss. The results of studies with carbamazepine and valproate vary: some reports suggest that there is an association between these medications

Table 1. Commonly Reported Injuries in People with Seizures³

Injury	Percentage
Contusion	6%
Abrasion	3%
Fracture	3%
Concussion	2%
Sprain	2%

Table 2. Risk Factors for Poor Bone Health

- Poor diet
 - Poor vitamin intake
 - Inadequate calcium intake
- Poor regimen of exercise
- Family history of bone disease
- Postmenopausal
- Advancing age

Table 3. Recommendations for Calcium and Vitamin D

Profile.....	Recommended Daily Intake
Age 9-18 years.....	1300mg calcium
Age 19-50 years.....	1000mg calcium
Age >= 51 years.....	1200mg calcium
Pregnant and lactating mothers.....	1000mg calcium
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For osteoporosis prophylaxis.....	400-800 IU vitamin D
Established osteopenia or prophylaxis.....	2000-4000 IU vitamin D

and bone disease, while other studies show no link. The relationship between the newer AEDs and bone health is unknown. Of the newer agents, the one that has been most studied is lamotrigine. In one study, lamotrigine had no effect on bone turnover markers in a population of premenopausal women with epilepsy.⁵

The mechanism in which certain AEDs cause bone loss is unclear. In people with epilepsy (taking AEDs), it has been observed that calcium and phosphate levels are low. Vitamin D levels appear to be lower than the levels found in controls. Elevated levels of alkaline phosphatase have been reported: because the majority of the total level of alkaline phosphatase is derived from bone, when elevated, this can serve as a non-specific marker of increased bone turnover. Osteoblasts make bone, while osteoclasts resorb bone. Less is known about how AEDs affect the balance between these cell populations.

The most often cited cause of these serum abnormalities is the use of hepatic enzyme inducing antiseizure medications such as phenytoin or phenobarbital. Vitamin D is needed in order for calcium to be absorbed. Vitamin D is metabolized by the hepatic enzyme P450 system. Enzyme inducing agents may therefore cause increased breakdown of vitamin D, resulting in low serum levels of this vitamin, and therefore reduced calcium and phosphate absorption. Of course, this

would result in low serum levels of calcium and phosphate. Although an attractive hypothesis, the story must be more complex. Valproate, a hepatic enzyme inhibitor, has also been reported to cause the same changes in serum markers. If the mechanism is solely related to enzyme induction, how do we explain the same effect when using an enzyme inhibitor?

One mechanism of action in several of the newer AEDs is carbonic anhydrase inhibition. Acetazolamide (Diamox), a commonly used diuretic, works by this mechanism. Acetazolamide has been shown to inhibit osteoclast (bone resorbing cell) function. Women taking Diamox have been reported to have increased bone mineral density. However, people taking the anti-seizure medications that work through this mechanism have also been shown to have mild asymptomatic metabolic acidosis. Acidosis draws calcium from bones (and alkalosis promotes calcium deposition in bones). Do these newer medicines cause increased or decreased bone mineral density? At present, the answer is unknown.

Bone density can be easily measured using dual energy X-ray absorptiometry (DEXA). Persons who are at risk for bone loss (see Table 2) should be evaluated for osteopenia or osteoporosis. For persons taking AEDs, there are as yet no guidelines which indicate how often these tests should be performed. When bone loss is established, it is unclear whether “bone-

strengthening agents” such as bisphosphonates, calcitonin, or parathyroid hormone should be started. It is also unclear whether persons with complete seizure freedom, who also have bone loss, should switch their antiseizure medication. In switching medicines, do we place the person at risk for seizures and therefore fractures?

Conclusions

Although many questions need to be answered with carefully planned studies, neurologists have a very clear question: “What should I do now?” Since some fractures occur as a direct result of seizures, the neurologist should strive to control the seizures completely, if possible. The use of medication must be judiciously weighed against possible side effects such as dizziness and imbalance: seizure control must be established without causing these side effects. Counseling patients about the use of multivitamins and daily calcium supplementation (see Table 3) may help to prevent or minimize bone loss. Careful monitoring of bone health must be performed at regular intervals. Finally, if bone loss is established, whether to add a bisphosphonate (or other agent) versus switching the antiseizure medication must be weighed against the risk of worsening of seizures during such a switch. Unfortunately, no guidelines currently exist to help the neurologist: as in many situations, the physician must rely on his good clinical judgment in these instances. **PN**

1. Mattson RH, and Cidal BE. Fractures, epilepsy, and antiepileptic drugs. *Epilepsy & Behavior* 2004;S36-S40.
2. Wirrell EC, Camfield PR, Camfield CS, Dooley JM, Gordon KE. Accidental injury is a serious risk in children with typical absence epilepsy. *Archives of Neurology* 1997;54(9):1063.
3. Tomson T, Beghi E, Sundqvist A, Johannessen SI. Medical risks in epilepsy: a review with focus on physical injuries, mortality, traffic accidents, and their prevention. *Epilepsy Research* 2004;60:1-16.
4. Gosens T, Poels PJE, and Rondhuis JJ. Posterior dislocation of the shoulders in seizure disorders – two case reports and a review of the literature. *Seizure* 2000;9:446-448.
5. Pack 2005. Personal communication.

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