The Importance of Screening for Osteoporosis in Mental Health Settings

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Abstract

Antiepileptic/anticonvulsant medications are used for the effective treatment of mood disorders. However, these medications have the potential to adversely affect bone health. While most research in the area of antiepileptics and osteoporosis has been done in patients being treated for seizure disorders, it is appropriate to apply these findings to patients being treated for mood disorders. The need to begin to study the prevalence of bone loss in routine care, to initiate screening for bone loss, and to develop protocols for monitoring is evident.

Key Words: Anticonvulsants, Osteoporosis, Mental Health

Introduction

Many of the anticonvulsant or antiepileptic medications have been associated with decreased bone mass (1-8). Most studies done to assess the risk of osteoporosis in patients taking antiepileptic medications have been done in patients being treated for epilepsy, but many of these medications are also used to improve mood stabilization in psychiatric conditions, such as bipolar disorder (9-11). The use of antiepileptic medication is considered to be a secondary cause of osteoporosis, as are many other medications, cigarette smoking, and excessive use of alcohol (12). Very little has been written about attending to bone health in the mental health setting, but in a meta-analysis of studies of patients being treated with numerous psychotropic medications, including anticonvulsants, the overall risk of fracture was found to be moderate (13). Some studies in the epilepsy literature do address the problem of bone health and the findings appear to be appropriate for consideration by mental health clinicians as well. The purpose of this paper is to summarize previous studies that indicate that bone health is compromised in the presence of anticonvulsant medications and to underscore the need to evaluate bone mass in patients being treated with anticonvulsant medications in the mental health setting.

Anticonvulsant medications may be categorized as those that induce the hepatic cytochrome P-450 system and those that do not. Some of those that do induce the hepatic cytochrome P-450 system include phenytoin, phenobarbital, carbamazepine, primidone, and oxcarbazepine. Some of those that do not induce the hepatic cytochrome P-450 system include valproic acid, lamotrigine, gabapentin, azetazolomide, clonazepam, and topiramate. The differentiation between enzyme-inducing and nonenzyme-inducing anticonvulsants is important because a differentiation is often made in studies to determine whether either class is associated with greater bone loss.

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Submitted: January 31, 2009; Revised: March 27, 2009;
Accepted: April 27, 2009

Clinical Implications

While more study in the area of bone health and use of antiepileptic medications in mentally ill patients is needed, there is evidence available that points to the need to begin to pay closer attention to the prevention and treatment of bone loss in this population. Bone health is one of several metabolic parameters that merit monitoring in patients receiving anticonvulsant medications (26). Research in the area of the effect of anticonvulsants and other psychotropic medications on bone health and the development of more definitive guidelines for prevention, screening, and treatment of bone loss will aid prescribing clinicians in the delivery of improved care to patients receiving antiepileptic/anticonvulsant treatment.

Literature Review

Studies have used different methods to evaluate bone health. In a study including seizure patients ages 6.5 to 19 years, who were receiving treatment with carbamazepine for two years and had no prior history of treatment with anticonvulsants, serum markers of bone formation (bone alkaline phosphatase, osteocalcin, carboxy-terminal propeptide of type I procollagen, amino-terminal propeptide of type III procollagen) and bone resorption (carboxy-terminal telopeptide of type I collagen, urinary cross-linked N-telopeptides of type I collagen) were measured. Markers of both formation and resorption were found to be elevated in those receiving carbamazepine regardless of their stage of sexual development indicating an increase in bone turnover (1).

In a case-control study, fracture risk was found to be higher in patients receiving treatment with both enzyme-inducing and nonenzyme-inducing antiepileptic medications including carbamazepine, ethosuximide, gabapentin, lamotrigine, primidone, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate, vigabatrin, tiogabine, clonazepam, clobazam, piracetam, and acetazolamide. Increased fracture risk was found with increased length of treatment and was higher in women (2). However, in this study there was no comparison group unexposed to antiepileptic medications, and anticonvulsant exposure prior to the study period was unknown.

In patients receiving various antiepileptic medications (both enzyme inducing including phenytoin, phenobarbital, carbamazepine, and primidone and nonenzyme inducing including valproic acid, lamotrigine, clonazepam, gabapentin, topiramate, and ethosuximide) both bone density and 25-hydroxy vitamin D levels were found to be significantly decreased, but there was no correlation between bone density and 25-hydroxy vitamin D levels in adults.

There was a correlation between longer therapy, treatment with more than one antiepileptic drug, and lower bone density in adults (3). Children in the study also had significantly lower 25-hydroxy vitamin D levels, but no decrease in bone density. There was also no correlation between hydroxy-vitamin D levels and bone density in children. The authors speculate that the lack of decrease in bone density in children might be due to the shorter duration of treatment in the children and the small sample size. In a study comparing adult epilepsy patients on long-term (>1 year) valproic acid therapy to those on phenytoin and a control group, 60% of the patients on valproic acid had reduced bone mineral density (using a computer-linked x-ray densitometer, which measured bone density in the second right metacarpal). The patients on valproic acid had serum calcium levels significantly higher than either the control or phenytoin groups. In the valproic acid patients, there was a negative correlation between bone mineral density and both calcium and the bone resorption marker ICTP, and a positive correlation between calcium and ICTP. The authors suggest that long-term treatment with valproic acid may increase bone resorption with a resultant decrease in bone density. The authors recommend monitoring of ionized calcium and bone resorption markers during long-standing treatment with valproic acid (4).

In a large cross-sectional study using dual-energy x-ray absorptiometry to assess hip bone mineral density, bone density was significantly lower in those treated with anticonvulsants (carbamazepine, clonazepam, divalproex, ethosuximide, mephobarbital, methsuximide, phenobarbital, phenytoin, primidone, and valproic acid) even after adjusting for age, sex, and other potential confounders. Bone density was found to decrease as treatment duration increased (5).

In matched female twin and siblings pairs (one pair member with a history of treatment with antiepileptic medication and the other with no history of receiving treatment) dual-energy x-ray absorptiometry was used to measure bone mineral density at the lumbar spine, total hip, femoral neck, total forearm, and total body. In the group as a whole there were no significant differences in bone mineral density within pairs. However, there were significant within pair differences with lower bone density in the forearm with antiepileptic drug use for greater than two years and lower bone density in both the forearm and the lumbar spine in those older than forty years. Bone density in the forearm was lower for those treated with enzyme-inducing antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone) compared to non-users. Bone density was lower in the fore-

arm, lumbar spine, and femoral neck in those treated with an enzyme inducer for more than two years, and bone density was lower in the forearm, lumbar spine, and total hip in those older than forty years taking an enzyme inducer for more than two years (6).

Patients in Brazil being treated for epilepsy with a variety of antiepileptic medications, either alone or in combination (carbamazepine, phenobarbitone, phenytoin, sodium valproate, lamotrigine, clobazan, and clonazepam), showed decreased bone mineral density, as measured by dual-energy x-ray absorptiometry, in both the lumbar spine and femur when compared to controls. Levels of 25-hydroxy vitamin D were also lower in those treated with antiepileptics, but no correlation was found between low vitamin D and low bone mineral density (7). The researchers did assess other risk factors for osteoporosis (smoking, caffeine intake, age, sex, alcohol use, physical activity, calcium intake, and family history) and found only increased smoking related to osteoporosis. The study was small, however, with only 58 patients and 29 matched controls.

Fewer studies have been conducted including newer antiepileptic medications, such as lamotrigine. A small study comparing bone mineral density in the right calcaneus and markers of bone metabolism in Korean patients (who were drug-naive and newly diagnosed with epilepsy) receiving monotherapy with carbamazepine, valproic acid, and lamotrigine, both six months before the initiation of therapy and six months after the initiation of therapy, demonstrated decreased bone mineral density after six months of medication in those patients receiving carbamazepine, but not in those receiving either valproic acid or lamotrigine. Vitamin D levels were decreased in users of carbamazepine, but not in users of either valproic acid or lamotrigine. Osteocalcin, a bone formation marker, was increased in users of valproic acid and lamotrigine, parathyroid hormone increased in users of any of the three antiepileptic medications, and the measure of bone resorption, urinary Pyralinks, was not changed in any of the antiepileptic medications users. Based on their findings, the researchers conclude that use of carbamazepine leads to decreased bone mineral density (8). They also suggest that patients at high risk for the development of bone abnormalities, related to treatment with antiepileptic drugs, have bone density testing within the first six months of treatment with an antiepileptic medication.

In the studies reviewed, bone loss related to longer treatment is a consistent finding (2-6). Decreased bone density (8) and an increase in both bone resorption and formation markers, indicative of bone turnover (1), were found with carbamazepine, an enzyme-inducing anticonvulsant. A decrease in bone density was also found in patients being treated with various enzyme-inducing anticonvulsants, including carbamazepine (6). While decreased bone density was found with valproic acid after treatment longer than one year (4), it was not found after six months (8), indicating again the importance of the length of treatment with anticonvulsants in the development of bone loss. The findings of the anticonvulsant studies reviewed are summarized in Table 1.

In the studies reviewed, bone loss related to longer treatment is a consistent finding (2-6).

While it is difficult to compare these studies in light of the differences in methodology and measurement, it does become clear that it is important to assess bone health in patients receiving antiepileptic treatment in order to ideally prevent, and if necessary, treat bone loss.

However, awareness of the problem may be limited. When neurologists were surveyed to identify their practices in the prevention, diagnosis, and treatment of bone disease induced by antiepileptic medications, of the respondents it was found that 7% of adult and 9% of pediatric neurologists prescribed calcium and vitamin D for prophylaxis. Adult neurologists screened for bone disease 28% of the time and pediatric neurologists 41% of the time. Of those who screened for and identified bone disease, the adult neurologists treated with calcium or vitamin D 37% of the time, referred to a specialist 57% of the time, and did not treat or refer 7% of the time, while the pediatric neurologists treated with calcium or vitamin D 40% of the time, referred to a specialist 54% of the time, and did not treat or refer 5% of the time (14). This study indicates the need for further dissemination of information regarding bone health and antiepileptic/anticonvulsant medications to prescribers of these medications in all settings.

Definition of Osteoporosis

The World Health Association defines osteoporosis in terms of bone mineral density. An individual's score on bone mineral density testing is compared to that of a normal young adult and reported in terms of a T score. A normal result is a bone mineral density that is within one standard deviation of a normal young adult or a T score of -1.0 or higher. A bone mineral density result that is between 1.0 and 2.5 standard deviations lower than that of a normal young adult, or a T score between -1.0 and -2.5, indicates low bone mass or osteopoenia. A bone mineral density that is 2.5 standard deviations or more lower than that of a normal young adult, or a T score of -2.5 or below, indicates osteoporosis (15).

Table 1 Summary of Studies of Anticonvulsant Treatment and Bone Health

Author	Sample	Rx Duration	Medication	Measures	Results
Verrotti et al.	6.5–19 years	2 years	Carbamazepine	Bone markers	▲formation, and resorption markers
Souverin et al.	<20–≥80 years	Varied	Both enzyme and nonenzyme inducing	Fracture after cohort entry	▲fracture risk with▲length of treatment
Farhat et al.	Adults and children	At least 6 months	Both enzyme and nonenzyme inducing	Bone density: Adults—lumbar spine, total hip, femoral neck, trochanter, total body; Children—lumbar spine and total body	▼bone density in adults with more than one drug and ▲length of Rx
Sato et al.	Adults	>1 year	Valproic acid, phenytoin	Bone density: right metacarpal, calcium, bone formation and resorption markers	▼bone density with valproic acid with negative correlation between bone mineral density and both calcium and bone resorption and positive correlation between calcium and bone resorption
Kinjo et al.	Adults	Varied	Both enzyme and nonenzyme inducing	Bone density: hip	▼ bone density with ▲duration of treatment
Petty et al.	Female twin and sibling pairs age 21–75 years	>1 year	Both enzyme and nonenzyme inducing	Bone density: lumbar spine, total hip, femoral neck, total forearm, total body	Within pair differences of ▼ bone density forearm with treatment >2 years, ▼ bone density with enzyme inducers, ▼ bone density forearm and lumbar spine >40 years
Kulak et al.	Brazilian adults	2–38 years	Both enzyme and nonenzyme inducing	Bone density: lumbar spine, proximal femur, forearm	▼bone density lumbar spine and femur compared to controls, no correlation between▼vit. D and ▼bone density
Kim et al.	Korean adults 18–50 years	6 months	Valproic acid, lamotrigine, carbamazepine	Bone density: right calcaneus, bone formation and resorption markers	▼bone density and vit. D with carbamazepine, ▲ osteocalcin with valproic acid and lamotrigine, ▲parathyroid hormone all medications

Screening for Osteoporosis

It is important to review general screening guidelines for osteoporosis, because patients being treated in a mental health setting with anticonvulsants may also have other risk factors that impact on their need for additional evaluation and/or monitoring for bone loss. The National Osteoporosis Foundation (16) identifies indications for bone mineral density testing which include the following:

1. Women 65 years or older and men 70 years or older with or without clinical risk factors.
2. Younger postmenopausal women and men ages 50–70 if clinical risk factors are a concern.
3. Women experiencing menopausal transition in the presence of risk factors associated with increased fracture risk, such as thinness, a previous fracture due to low trauma, or medication related to decreased bone mass.
4. Any adult who has a fracture after age 50 years.
5. Adults who have a medical condition or are taking medication associated with bone loss or low bone mass.
6. Anyone for whom treatment for osteoporosis is being considered.
7. Anyone being treated for osteoporosis for the purpose of monitoring treatment effect.
8. Anyone not currently receiving treatment for osteoporosis when evidence of low bone mass would prompt treatment.
9. Postmenopausal women who are discontinuing use of estrogen.

There has recently been more interest in screening for osteoporosis in men. A literature review of osteoporosis in men (17) was conducted and used in the development of a

clinical practice guideline by the American College of Physicians for screening for osteoporosis in men (18). Because the majority of the studies included men older than 50 years who were from either Europe or the United States the guideline may not be generalizable to other groups (18). In its summary, the guideline states that:

> High-quality evidence shows that age, low body weight, physical inactivity, and weight loss are strong predictors of an increased risk for osteoporosis in men. There is also moderate-quality evidence that previous fragility fracture, systemic corticosteroid therapy, androgen deprivation therapy and spinal cord injury are predictors of an increased risk for osteoporosis in men. Cigarette smoking and low dietary intake of calcium predict low bone mass (18).

The guidelines include three recommendations: 1) that risk factors for the development of osteoporosis be periodically assessed in older men on an individual basis; 2) that a DEXA scan be obtained for men at increased risk for osteoporosis who are also candidates for drug treatment; and, 3) that further research be conducted to evaluate tests to screen for osteoporosis in men. While the guidelines do not call for any specific age at which to initiate screening, it is suggested that assessment of risk factors before age 65 may be indicated (18).

Recommendations

There is a lack of broad-based recommendations regarding screening for bone health in patients receiving anticonvulsant medications. It has been suggested that postmenopausal patients be screened with DEXA testing before treatment and all others be screened with DEXA testing after five years of anticonvulsant medication treatment. Those with results showing a T score higher than -1 should receive calcium and vitamin D supplementation and participate in weight-bearing exercise. If the T score is between -1 and -2, both calcium and vitamin D supplementation along with weight-bearing exercise should be continued and the DEXA scan repeated in 1–2 years. Those with a DEXA score less than -2 may be referred to an internist or endocrinologist for further evaluation (19, 20).

In the absence of the availability of solid guidelines to follow for patients on antiepileptic medications, some general measures have been suggested in patients who do not have a diagnosis of osteoporosis but have been receiving antiepileptic medications for more than six months. These measures include increasing both weight-bearing and non-weight-bearing physical activity as tolerated, maintaining a balanced diet, smoking cessation, moderation in use of both alcohol and caffeine, and treatment with 1,000–1,500 mg of calcium along with 400 IU of vitamin D daily. For those at higher risk of the development of osteoporosis, the measurement of serum calcium, alkaline phosphatase, and 25-hydroxy vitamin D may be obtained after 6–12 months of antiepileptic medication and reassessed annually if within normal limits. Baseline DEXA is also suggested. The authors recommend consultation with, or referral to, an endocrinologist in the presence of abnormalities of calcium and vitamin D, fracture, or DEXA scan results indicative of bone loss (21). Higher vitamin D doses of 800–1,000 IU daily have also been recommended as preventive therapy (22).

This study indicates the need for further dissemination of information regarding bone health and antiepileptic/anticonvulsant medications to prescribers of these medications in all settings.

While this paper focused on the risk of osteoporosis related to treatment with anticonvulsant medications, there are certainly other risks to which psychiatric patients are exposed. Some antipsychotic medications may cause hyperprolactinemia, which has been related to bone loss (23). However, in male patients with schizophrenia, decreased bone mineral density has also been found in men unrelated to prolactin-increasing antipsychotics (24), pointing to the need for increased attention to the assessment of bone health in all men. Certainly the new guidelines for screening for osteoporosis in men (18) make clear the need to assess for osteoporosis in males, as well as females.

Conclusions

Patients in mental health settings may be treated with anticonvulsant medications for a variety of conditions including mood stabilization, seizure disorder, or as part of a pain management regimen. Part of a comprehensive treatment plan should include attention to bone health. The barriers to prevention, diagnosis, and treatment of bone loss in epilepsy patients being treated in an epilepsy clinic have been studied (25) and could well be considered for patients being treated with antiepileptic medications for mood stabilization. The researchers identified six barriers to diagnosis including: 1) cognitive or neurologic impairment; 2) results not sent to referring clinic; 3) physical impairments that interfered with DEXA testing; 4) lack of follow-up with the primary care provider; 5) being lost to clinic follow-up; and, 6) pregnancy. The researchers also identified four barriers to the prevention of bone loss related to compliance including: 1) cost; 2) forgetfulness; 3) language barriers; and, 4) other compliance issues such as supplements being discontinued

by primary care provider, difficulty swallowing pills, and refusal of supplements or belief that supplements increase appetite. The researchers also identified two barriers to treatment: compliance and cost. While this study was small and retrospective, the results do provide an initial view of some areas to focus upon in improving bone health in all patients on antiepileptic medications.

However, in male patients with schizophrenia, decreased bone mineral density has also been found in men unrelated to prolactin-increasing antipsychotics (24), pointing to the need for increased attention to the assessment of bone health in all men.

While more study in the area of bone health and use of antiepileptic medications in mentally ill patients is needed, there is evidence available that points to the need to begin to pay closer attention to the prevention and treatment of bone loss in this population. Bone health is one of several metabolic parameters that merit monitoring in patients receiving anticonvulsant medications (26). Research in the area of the effect of anticonvulsants and other psychotropic medications on bone health and the development of more definitive guidelines for prevention, screening, and treatment of bone loss will aid prescribing clinicians in the delivery of improved care to patients receiving antiepileptic/anticonvulsant treatment.

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