Practice Patterns of Neurologists Regarding Bone and Mineral Effects of Antiepileptic Drug Therapy

Cassandra Valmadrid, MD; Carolyn Voorhees, PhD; Brian Litt, MD; Christine R. Schneyer, MD

Background: Antiepileptic drug (AED) therapy has been linked to bone disease that can be treated and prevented with calcium and vitamin D. However, because there have been no definitive studies on this subject, many physicians might not be aware of this association.

Objective: To determine the approaches of neurologists to skeletal disorders in patients taking AEDs.

Design: A self-administered mail survey.

Participants: United States board-certified or board-eligible pediatric (n = 404) and adult (n = 624) neurologists.

Main Outcome Measures: Practice patterns of neurologists regarding methods of screening for bone disorders and recommendations for treatment and prophylaxis.

Results: Few pediatric (41%) and adult (28%) neurologists routinely evaluate AED-treated patients for bone and mineral disease. Of physicians who detect bone disease through diagnostic testing, 40% of pediatric and 37% of adult neurologists prescribe calcium or vitamin D, and about half (54% of pediatric and 57% of adult neurologists) refer patients to specialists. Few neurologists (9% of pediatric and 7% of adult neurologists) prescribe prophylactic calcium or vitamin D for patients taking AEDs.

Conclusions: There is a lack of consensus among neurologists concerning the impact of AED therapy on bone. Because considerable evidence suggests that much of the bone pathology caused by AED therapy can be treated or prevented by administration of calcium and vitamin D, raising physician awareness of this problem could significantly improve the skeletal health of AED-treated individuals.

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TIEPLEPTIC drug (AED) use has been implicated as a cause of bone disease for more than 30 years.1,2 These disorders range from subclinical disease5-7 to short stature and abnormal dentition6 to rickets or osteomalacia.7-9 Prevalence rates of 50% or more have been reported for AED-induced skeletal disorders.3,7,9-12 Subclinical disease typically occurs in ambulatory individuals and is characterized by biochemical abnormalities (decreased serum calcium and 25-hydroxyvitamin D [25-OHD] levels and elevated serum para-thyroid hormone [PTH] levels), reduced bone density, and abnormal bone biopsy findings (increased osteoid).3,5,10,11,13-17 These subtle effects of AEDs can occur early in therapy.18 In contrast, the full-blown clinical syndromes of rickets and osteomalacia are usually restricted to non-ambulatory patients,7,9,12 presumably because of coexistent risk factors (eg, poor intake of calcium and vitamin D, infrequent sunlight exposure, and inadequate physical activity). There are several reviews on this subject.20-22

The most severe skeletal consequence of long-term AED therapy is increased risk of fractures, especially of the hip. This is certainly the case in institutionalized or nonambulatory patients,12,23-25 and it has been found in most studies of community-dwelling ambulatory individuals.14,26-29 Striking reversal of radiographic and biochemical abnormalities and improvement of bone mass occurs in AED-treated individuals given calcium and vitamin D (cholecalciferol or ergocalciferol).19,30-34

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Several mechanisms have been proposed for the skeletal effects of AED therapy. Vitamin D deficiency has been attributed to accelerated vitamin D catabolism by hepatic enzyme-inducing AEDs (eg, phenobarbital, phenytoin, and carbamazepine)35 and inhibition of 25-hydroxylation of vitamin D.36 A second mechanism involves a form of high-turnover bone disease, with hypocalcemia and secondary hyperparathyroidism, that might occur despite normal

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PARTICIPANTS AND METHODS

DATA SOURCE

Questionnaires were sent to 2226 pediatric and adult neurologists listed as fellow, active, or associate members in the directory of the American Academy of Neurology. To be eligible for participation, physicians had to be board certified or board eligible in neurology and to prescribe AEDs. Adult and pediatric neurologists were sampled separately. A sample size of 1500 for each group was based on a 95% level of confidence and adjusted for a 60% expected response rate and a 90% proportion of eligible participants. Adult neurologists were randomly selected from the American Academy of Neurology membership list using StatPac IV Gold (StatPac Inc, Minneapolis, Minn). All pediatric neurologists in the American Academy of Neurology (n = 726) were sampled. The methods used in this survey are described elsewhere.43

SURVEY CONTENT

The self-administered survey addressed demographic characteristics of physicians and their patients; experience of physicians in use of AEDs; and practice patterns concerning evaluation, treatment, and prophylaxis of patients for AED-induced bone disease. Respondents were asked whether they evaluate common risk factors for skeletal disorders and whether they screen for bone disease. Physicians who screen for bone disease were asked how often they (1) assess risk factors (eg, fracture history, calcium and vitamin D intake, and sun exposure) and (2) order diagnostic tests (eg, serum calcium, phosphate, and 25-OH-D levels and bone density measurements). Response options were “frequently” (>50% of the time), “sometimes” (25%-50% of the time), and “almost never” (<25% of the time).

To assess treatment practices, respondents were asked if they recommend calcium and vitamin D for prophylactic therapy and how they treat patients with established bone disease (eg, treat with calcium and vitamin D or refer to a specialist). We asked neurologists who prescribe calcium and vitamin D to select their usual recommendations for prophylaxis and treatment from a listing of 5 dosage ranges (for calcium, ≤300 to >1300 mg daily; for vitamin D, <800 IU daily to >50000 IU weekly).

SURVEY ADMINISTRATION

The questionnaire and procedures were approved by the institutional review board of Sinai Hospital of Baltimore and the Joint Commission on Clinical Investigation, The Johns Hopkins Hospital, Baltimore, Md. The survey was preevaluated by approximately 15 neurologists. In late 1995 we mailed questionnaires with cover letters and postage-paid return envelopes. There was no financial incentive for returning the survey, which required approximately 10 minutes to complete. After 8 weeks, we sent nonresponders a second questionnaire with a return postcard for those declining participation. After 16 weeks, we telephoned nonresponders to request return of questionnaires by mail or facsimile. In some cases, we completed the survey by telephone. To evaluate differences between nonresponders and responders, we obtained demographic information by telephone from the offices of 30 randomly selected nonresponders.

DATA ANALYSIS

Double data entry was used to prevent input errors. Bivariate analyses were performed to assess associations of physician practice patterns with their AED preferences and with physician and patient demographic characteristics. Multiple logistic regression models were used to determine the independent association of these characteristics with practice patterns. Neurologists who treat bone disease are reported as a subgroup of neurologists who screen for bone disease. Data were analyzed using SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

RESPONSE TO SURVEY

Of 726 pediatric and 1500 adult neurologists sent surveys, 662 and 1315, respectively, received them. Of the 413 pediatric (62%) and 693 adult (33%) neurologists who completed questionnaires, 404 pediatric and 624 adult neurologists were eligible for the study. Among responders, 60% answered the first mailing, 22% the second, and 18% the telephone/facsimile survey. Comparison of eligible respondents with a random sample of 30 nonrespondents showed that the 2 groups were similar in all characteristics except ethnic distribution. Whites composed 87% of eligible respondents and 63% of nonrespondents (P<.001).

CHARACTERISTICS OF RESPONDING PHYSICIANS AND THEIR PATIENTS

Most physicians were white men aged 40 years or older (Table 1). Approximately 90% of pediatric and adult neurologists were board certified in the practice of neurology, and 95% in both groups listed clinical work as their primary responsibility. Pediatric neurologists were more likely than adult neurologists to be women, to specialize in epilepsy, to practice in urban academic centers, and to see more than 10 AED-treated patients weekly.
Pediatric neurologists most often prescribe carbamazepine and valproate sodium and, compared with adult neurologists, more frequently administer phenobarbital and “other” AEDs (not specified). In contrast, adult neurologists commonly prescribe phenytoin as well as carbamazepine and valproate. As for patient demographic characteristics (Table 1), compared with adult neurologists, patients of pediatric neurologists were more often not white, of equal sex distribution, and somewhat less likely to pay for physician services through private insurance.

### Table 2. Practice Patterns of Neurologists Regarding Detection, Treatment, and Prevention of Bone Disease in Patients Taking Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Neurologists, No. (%)</th>
<th>Pediatric (n = 604)</th>
<th>Adult (n = 624)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen for bone disease*</td>
<td>160 (41)</td>
<td>174 (28)</td>
</tr>
<tr>
<td>Of those who screen and find evidence of bone disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treat with calcium or vitamin D</td>
<td>62 (40)</td>
<td>61 (37)</td>
</tr>
<tr>
<td>Refer to specialist</td>
<td>83 (54)</td>
<td>94 (57)</td>
</tr>
<tr>
<td>Neither treat nor refer</td>
<td>8 (5)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Prescribe prophylactic calcium or vitamin D</td>
<td>35 (9)</td>
<td>46 (7)</td>
</tr>
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</table>

*P = .001 for the difference between pediatric and adult neurologists using the Mantel-Haenszel $\chi^2$ test.

Our most significant findings are shown in Table 2. Only one third of neurologists evaluate AED-treated patients for bone disease, with more pediatric (41%) than adult (28%) neurologists performing investigative studies. Of physicians in both groups who screen and find evidence of bone disease, approximately 40% administer calcium or vitamin D, slightly more than half refer patients to a specialist, and 5% to 7% neither treat nor refer. Last, only 7% to 9% of pediatric and adult neurologists prescribe prophylactic calcium and vitamin D.

Of 160 pediatric and 174 adult neurologists who screen for bone disease in patients receiving AEDs, only 14% to 22% frequently (>50% of the time) inquire about intake of calcium and vitamin D and about sunlight exposure. One third to one half of neurologists frequently elicit information about fracture history and involvement in physical activity, and 28% to 40% frequently test their patients for serum total calcium, phosphate, and alkaline phosphatase levels. The percentage of neurologists who frequently order other diagnostic tests was 7% for serum ionized calcium, 3% for serum PTH or 25-OHD (the metabolite most indicative of tissue vitamin D stores), 6% for bone density studies, and 2% for plain radiographs. As for therapy, varying doses of calcium and vitamin D were recommended for treatment of bone disease detected through screening (62 pediatric and 61 adult neurologists) and for prophylaxis of bone disease (35 pediatric and 46 adult neurologists).

Multiple logistic regression analysis highlighted several characteristics of neurologists who regularly evaluate and treat patients for AED-induced bone disease and

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*HMO indicates health maintenance organization; AED, antiepileptic drug. Data were missing for all characteristics.

†P < .001 for differences between pediatric and adult neurologists using the Mantel-Haenszel $\chi^2$ test or the Fisher exact test (2-tailed) for cells with counts less than 5.

‡P < .003 for differences between pediatric and adult neurologists using the Mantel-Haenszel $\chi^2$ test or the Fisher exact test (2-tailed) for cells with counts less than 5.

§P < .02 for differences between pediatric and adult neurologists using the Mantel-Haenszel $\chi^2$ test or the Fisher exact test (2-tailed) for cells with counts less than 5.
who prescribe prophylactic therapy (Table 3). As expected, neurologists who screen AED-treated patients for bone disease were likely to be the same physicians who prescribe treatment with calcium and vitamin D if bone disease is diagnosed and who recommend calcium and vitamin D as prophylactic therapy. Adult neurologists who screen and treat bone disease tend to be subspecialists in epileptology. Furthermore, adult neurologists who screen for bone disease prescribe phenobarbital preferentially (unlike most adult neurologists [Table 1]) and more often refer patients with bone disorders to specialists for consultations. Pediatric neurologists who recommend calcium and vitamin D for patients with established bone disease tend to be more experienced (in practice for ≥10 years) and to prescribe carbamazepine frequently.

Our most important conclusion (Table 2) is that most neurologists do not consider the problem of AED-related bone disease to be of clinical importance, and they rarely administer prophylactic calcium and vitamin D to their AED-treated patients. However, of the few physicians who screen patients and find bone disease, most either treat patients or refer them to specialists. The few physicians who prescribe prophylactic therapy are typically members of the subgroup that screens (Table 3).

There are other significant findings. For example, a higher proportion of pediatric (approximately 41%) than adult (approximately 28%) neurologists screen for AED-induced bone disease (Table 2). This difference might reflect greater experience in the treatment of epilepsy because we found that pediatric neurologists treat more patients with seizures and more often subspecialize in epileptology (Table 1). We also found that pediatric and adult neurologists differ in AED-prescribing practices. Adult neurologists commonly prescribe phenytoin, whereas pediatric neurologists tend to avoid administration of this drug (Table 1). Although the motivation for this practice was not addressed, it could be related more to apprehension about adverse cosmetic effects in children (eg, distortion of craniofacial features) with long-term use of phenytoin than to concern about skeletal effects.

There are factors that could limit interpretation of our conclusions. In a self-report survey, some respondents might give inaccurate answers, especially if they suspect that their practice patterns are unsatisfactory. Another is the lower response rate of adult neurologists (53%) compared with pediatric neurologists (62%). However, if most nonresponding adult neurologists were less familiar with the effects of AED therapy on bone, our results would underestimate the magnitude of this problem. Conversely, even if all nonresponding pediatric and adult neurologists actually screen for bone disease, there still would be approximately 40% in each group who do not. Our findings are so striking that any inherent bias generated by self-reporting could not significantly affect our conclusions.

We propose 2 reasons why some neurologists might not focus on AED-induced bone disease: lack of familiarity with the relevant literature and uncertainty as to whether skeletal effects of AEDs are clinically important. Analysis of the literature reveals little basis for this ambivalence. Most studies, including recent ones, and especially that of Weinstein and coworkers, support the hypothesis that AEDs do not affect bone mineral density. However, the recommendations of neurologists are not consistent with this view. Pediatric neurologists who recommend calcium and vitamin D as prophylactic therapy are more likely to screen for bone disease and treat patients with established bone disease (Table 2).

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### Table 3. Multiple Logistic Regression Analysis of Neurologists Who Screen for Bone Disease and Administer Calcium and Vitamin D for Treatment and Prevention of AED-induced Bone Disease*

<table>
<thead>
<tr>
<th></th>
<th>Pediatric Neurologists (n = 404)</th>
<th>Adult Neurologists (n = 624)</th>
</tr>
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<tbody>
<tr>
<td>Screen and treat if bone disease is detected (vs those who screen but do not treat)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribe prophylactic therapy</td>
<td>13.7 (3.1-60.5)†</td>
<td>3.2 (1.4-7.2)‡</td>
</tr>
<tr>
<td>Treat bone disease</td>
<td>2.0 (1.1-3.6)§</td>
<td>3.3 (2.0-5.5)†</td>
</tr>
<tr>
<td>Refer to specialist</td>
<td>...</td>
<td>2.3 (1.3-4.2)†</td>
</tr>
<tr>
<td>Epileptologist</td>
<td>...</td>
<td>2.1 (1.1-4.0)§</td>
</tr>
<tr>
<td>Prescribe phenobarbital &gt;50% of the time</td>
<td>...</td>
<td>2.2 (1.3-3.5)‡</td>
</tr>
<tr>
<td>Prescribe other AEDs ≤50% of the time</td>
<td>2.1 (1.2-3.5)‡</td>
<td></td>
</tr>
<tr>
<td>Screen and treat if bone disease is detected (vs those who screen but do not treat)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribe prophylactic calcium or vitamin D (vs those who do not prescribe)</td>
<td>15.6 (3.6-68.0)§</td>
<td>3.6 (1.6-7.8)§</td>
</tr>
<tr>
<td>Treat</td>
<td>6.5 (2.6-16.3)§</td>
<td>6.4 (2.9-13.9)§</td>
</tr>
</tbody>
</table>

*AED indicates antiepileptic drug; CI, confidence interval; and ellipses, the odds ratios did not differ significantly from 1.
†P < .001 for an increase in the odds ratio of screening.
‡P < .05 for an increase in the odds ratio of screening.
§P < .01 for an increase in the odds ratio of screening.
||P < .001 for an increase in the odds ratio of treating.
¶P < .05 for an increase in the odds ratio of treating.
#P < .01 for an increase in the odds ratio of treating.
**P < .001 for an increase in the odds ratio of giving prophylaxis.
pothesis that AEDs affect serum calcium, 25-OHD, and PTH levels; reduce bone mass; and induce histomorphometric changes. The few studies\textsuperscript{18-20} that do not favor this contention can be mostly explained from the vantage point of contemporary knowledge, as described in the following paragraphs.

One issue is the use of insensitive variables to detect skeletal disorders. For example, Livingston et al\textsuperscript{46} reported no convincing evidence of bone disease during 36 years of experience with 15000 ambulatory patients receiving long-term AED therapy. Their conclusions were based on biochemical tests (serum total calcium, phosphate, and alkaline phosphatase levels) and radiographic studies (skull radiographs) now recognized as too insensitive to detect subtle bone and mineral alterations expected in ambulatory individuals. Similarly, Akin et al\textsuperscript{50} concluded that AEDs do not affect bone mass because they could discern no differences in the lumbar spine (ie, trabecular) bone density of AED-treated children. This conclusion is unreasonable because AEDs affect chiefly cortical and not trabecular bone.\textsuperscript{3}

Another problem is the failure in some studies to control for variables with potent skeletal effects, such as calcium and vitamin D intake, lack of weight bearing, nutrition, and sun exposure. Other confounding factors are that serum 25-OHD assays from different laboratories might not be comparable\textsuperscript{31,32} and that the definition of vitamin D deficiency (ie, laboratory reference values) is apparently incorrect. For example, the lower limit of normal for serum 25-OHD levels in most reference laboratories is approximately 25 nmol/L; yet, we know that serum 25-OHD levels below approximately 50 nmol/L stimulate compensatory increases in PTH secretion.\textsuperscript{23,24} Such confusion about serum 25-OHD levels could explain why Ala-Houhala et al\textsuperscript{49} reported winter serum 25-OHD levels of 25 to 42 nmol/L in AED-treated ambulatory adolescents as normal rather than as low.

Despite inherent difficulties in interpreting these data, results of many studies indicate that individuals who take AEDs have reduced bone mass\textsuperscript{5,10,14} and that children\textsuperscript{10} and adults\textsuperscript{14,17,34,53,56} who take some hepatic enzyme-inducing AEDs have substantially increased vitamin D requirements (up to 4000 IU/d). Although valproate and carbamazepine were thought to be relatively “bone sparing” compared with phenytoin and phenobarbital,\textsuperscript{11,12} results of recent studies\textsuperscript{5,13,47} indicate that use of these agents too might lower bone mass. Even use of some of the newer AEDs (eg, gabapentin, topiramate, and lamotrigine, included in the category of “other” in our survey) can reduce bone density.\textsuperscript{14} Because low bone mass\textsuperscript{57} and vitamin D deficiency\textsuperscript{58,59} constitute independent risk factors for fracture, it is probable that all AEDs increase fracture risk to some degree. Long-term AED therapy in general accentuates bone density loss, and hepatic enzyme-inducing agents in particular impose an additional demand for vitamin D on people who might already have occult vitamin D deficiency.\textsuperscript{4,14,54,55} Nonambulatory (hence, sun-deprived) patients are most vulnerable to bone disease, and it rises to 1.5% in the eighth decade. Therefore, the elderly (already at high risk for osteoporosis) compose the fastest growing group with epilepsy.\textsuperscript{61} If we assume that most people with epilepsy receive AEDs and that the prevalence of AED-induced bone disease is approximately 50%, then this is a sizable population at increased fracture risk. Not included in these statistics is the large population taking AEDs for other purposes (eg, management of neuropathic pain or psychiatric disorders). We postulate that close attention to the daily calcium and vitamin D intake of AED-treated patients would provide a cost-effective and safe therapeutic intervention to decrease fractures. Emphasis of these facts to physicians who care for patients taking AEDs should have considerable impact on the skeletal health of these individuals. Finally, a well-controlled prospective study is needed to determine the precise effects of AEDs on bone, the benefits of screening, and the effects of prophylaxis with calcium and vitamin D.

Notwithstanding the information available on adverse effects of AED therapy on bone metabolism, questions remain regarding whether screening is valuable, what constitutes reasonable treatment, and whether prophylaxis with calcium and vitamin D should be administered. Is screening valuable? Although a cost-benefit analysis of screening has not been done, for nonambulatory patients at greatest risk for vitamin D deficiency, we advocate measurement of serum 25-OHD levels. Despite assay differences, this remains the most sensitive and specific test (short of a bone biopsy) to diagnose osteomalacia due to vitamin D deficiency. This approach would identify patients with serious vitamin D deficiencies requiring treatment with pharmacologic doses of vitamin D. On the other hand, for ambulatory individuals without a history of fractures or other risk factors, a reasonable strategy would be to omit screening and empirically administer prophylactic calcium and vitamin D.

Because there are no official recommendations for calcium and vitamin D therapy in AED-treated individuals, it would be prudent for now to follow recommendations issued by the Institute of Medicine for daily calcium and vitamin D intake in the general population. For example, adults aged 51 to 70 years would be treated with 1200 mg of calcium and 400 IU of vitamin D daily.\textsuperscript{50} Given that calcium could inhibit AED absorption, these agents should be taken separately. Because most studies indicate that AED-treated patients are at risk for bone loss, we recommend monitoring bone density to ensure that it remains stable during AED treatment.

Detection and treatment of AED-induced bone disease and prevention of its development has important implications for public health. The prevalence of epilepsy in the United States is 0.6% to 0.9% up to age 60 years, and it rises to 1.5% in the eighth decade. Therefore, the elderly (already at high risk for osteoporosis) compose the fastest growing group with epilepsy.\textsuperscript{61} If we assume that most people with epilepsy receive AEDs and that the prevalence of AED-induced bone disease is approximately 50%, then this is a sizable population at increased fracture risk. Not included in these statistics is the large population taking AEDs for other purposes (eg, management of neuropathic pain or psychiatric disorders). We postulate that close attention to the daily calcium and vitamin D intake of AED-treated patients would provide a cost-effective and safe therapeutic intervention to decrease fractures. Emphasis of these facts to physicians who care for patients taking AEDs should have considerable impact on the skeletal health of these individuals. Finally, a well-controlled prospective study is needed to determine the precise effects of AEDs on bone, the benefits of screening, and the effects of prophylaxis with calcium and vitamin D.

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