Published in final edited form as:
Ann Neurol. 2005 February ; 57(2): 252–257. doi:10.1002/ana.20378.

Bone Mass and Turnover in Women with Epilepsy on Antiepileptic Drug Monotherapy

Alison M. Pack, MD[1], **Martha J. Morrell, MD**[1], **Robert Marcus, MD**[2], **Leah Holloway, MS**[3], **Edith Flaster, MS**[1], **Silvia Doñe, BA**[1], **Alison Randall, BA**[1], **Cairn Seale, MS**[2], and **Elizabeth Shane, MD**[4]

[1]Department of Neurology, Columbia University, New York, NY

[2]Stanford University School of Medicine, Stanford

[3]Palo Alto Veterans Administration Health Care System, Palo Alto, CA

[4]Department of Medicine, Columbia University, New York, NY

Abstract

Antiepileptic drugs, particularly cytochrome P450 enzyme inducers, are associated with disorders of bone metabolism. We studied premenopausal women with epilepsy receiving antiepileptic drug monotherapy (phenytoin, carbamazepine, valproate, and lamotrigine). Subjects completed exercise and nutrition questionnaires and bone mineral density studies. Serum was analyzed for indices of bone metabolism including calcium, 25-hydroxyvitamin D, parathyroid hormone, insulin growth factor I, insulin binding protein III, and bone formation markers, bone-specific alkaline phosphatase, and osteocalcin. Urine was analyzed for cross-linked N-telopeptide of type I collagen, a bone resorption marker. Calcium concentrations were significantly less in subjects receiving carbamazepine, phenytoin, and valproate than in those receiving lamotrigine ($p = 0.008$). Insulin growth factor-I was significantly reduced in subjects receiving phenytoin compared with those receiving lamotrigine ($p = 0.017$). Subjects receiving phenytoin had significantly greater levels of bone-specific alkaline phosphatase ($p = 0.007$). Our results demonstrate that phenytoin is associated with changes in bone metabolism and increased bone turnover. The lower calcium concentrations in subjects taking carbamazepine or valproate compared with those taking other antiepileptic drugs suggest that these antiepileptic drugs may have long-term effects. Subjects receiving lamotrigine had no significant reductions in calcium or increases in markers of bone turnover, suggesting this agent is less likely to have long-term adverse effects on bone.

Antiepileptic drugs (AEDs) are associated with osteoporosis[1,2] and other disorders of bone and mineral metabolism including hypocalcemia,[3–5] hypophosphatemia,[6,7] reduced serum concentrations of vitamin D metabolites,[3,5,8] and secondary hyperparathyroidism.[4,9,10] In addition, increased biochemical markers of bone formation and resorption have been reported.[11–14] These biochemical changes may place people treated with AEDs at increased risk for low bone mineral density (BMD), osteoporosis, osteomalacia, and fractures.[15]

Address correspondence to Dr Pack, Department of Neurology, Columbia University, 710 W. 168th St., 7th Floor, New York, NY 10032. ap390@columbia.edu.

The AEDs traditionally associated with abnormal bone and mineral metabolism are those that induce the cytochrome P450 enzyme (carbamazepine, phenobarbital, and phenytoin).[5,6,8,11,12,14] However, there is increasing evidence in children and adults that valproate, a cytochrome P450 enzyme inhibitor, can also affect bone metabolism.[13,16,17] Limited information is available regarding newer AEDs, such as lamotrigine.

Osteoporosis is more common in women than men, and women may be particularly vulnerable to the effects of AEDs on bone health, particularly after meno-pause. Moreover, women with substantial premenopausal bone loss may be at even greater risk for bone loss when entering menopause. Understanding the effects of individual AEDs on bone and early identification of women with abnormalities of bone and mineral metabolism are important in determining the optimal management of women with epilepsy. We therefore studied premenopausal women with epilepsy receiving AED monotherapy to determine the effect of individual drugs on markers of bone and mineral metabolism and to determine whether premenopausal use of AEDs has an adverse impact on bone mass.

Subjects and Methods

Subjects

Ninety-three premenopausal, normally cycling women with epilepsy between 18 and 40 years of age participated in the study. They were enrolled at either Stanford University (n = 83) or Columbia University (n = 10) between September 1997 and December 2000. All women were receiving a single AED (carbamazepine, lamotrigine, phenytoin, or valproate), and they had been taking that AED for at least 6 months before enrollment. Women with impaired motor function were excluded; women with medical illnesses that affect the skeleton (such as primary hyperparathyroidism, Paget's disease, or multiple myeloma) and women who were taking other medications or excessive doses of vitamins known to affect bone and mineral metabolism also were excluded. In addition, neither pregnant nor postmenopausal (spontaneous or surgical) women were enrolled.

Study Design and Analytical Methods

After informed consent was obtained, each subject completed detailed, standardized, and validated questionnaires regarding nutrition and exercise. The nutrition questionnaire is a food frequency questionnaire created by the National Cancer Institute[18] that includes questions on daily diet, vitamin intake, smoking habits, and alcohol use. The exercise questionnaire includes questions on specific exercises and the frequency of the exercises.[19] In addition, detailed clinical histories were taken, height and weight were measured, and body mass index (BMI) was calculated.

Serum samples were drawn for analysis of indices of bone and mineral metabolism and markers of bone formation. Serum measurements included total calcium, 25-hydroxy (25-OH) vitamin D, parathyroid hormone (PTH), insulin growth factor I (IGF-I), insulin binding protein 3 (IGFBP-3), and markers of bone formation. The first voided urine of the day was collected for analysis of cross-linked N-telopeptide of type I bone collagen (NTX), a marker of bone resorption. Serum and urine were stored at −20°C until analysis. All laboratory

measurements were conducted at the Veterans Administration Palo Alto Health Care System.

Serum calcium concentrations were measured in the clinical laboratories of the Veterans Administration Palo Alto Health Care System. Measurement of all other biochemical analyses were conducted in the Research Laboratory of the Clinical Studies Unit, Veterans Administration Palo Alto Health Care System by methods that have been validated previously.[20–22] The reference range for serum calcium in this laboratory is 8.5 to 10.5mg/dl. Serum 25-OH vitamin D was measured by a commercially available radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA) with an intra-assay coefficient of variation (CV) of 7.9, interassay CV of 9.6, and reference range of 9 to 52ng/ml. PTH was measured using a two-site immunoradiometric assay (Diagnostic Systems Laboratory, Webster, TX) with intra-assay and interassay CVs of 3.5 and 5.7, respectively, and a reference range of 9 to 55pg/ ml. Circulating IGF-I and IGFBP-3 were also measured by two-site immunoradiometric assays (Diagnostics Systems Laboratory). The intra-assay and interassay CVs were 8.5 and 9.5, respectively, for IGF-I; they were 4.9 and 3.9, respectively, for IGFBP-3. The reference ranges for IGF-I and IGFBP-3 were not applicable because they vary by age.

Serum bone-specific alkaline phosphatase was measured by competitive enzyme immunoassay (Metra Biosystems, Mountain View, CA) with an intra-assay CV of 4.2, interassay CV of 7.2, and reference range of 8 to 16U/L. Osteocalcin was measured using a two-site immunoradiometric assay (Diagnostic Systems Laboratory). The intra-assay and interassay CVs were 9.8 and 9.4, respectively. The reported mean for women younger than 40 years was 12.6ng/ml. Urinary N-telopeptide excretion was measured by an enzyme-linked immunosorbent assay (Ostex international, Seattle, WA) and corrected for creatinine excretion. The intra-assay CV was 7.6 and the interassay CV was 4.0 for this assay, and the reference range was 5 to 65nM/nM creatinine.

BMD was measured using Hologic (1000 and 4500) densitometers (Hologic, Waltham, MA) at either Stanford University or Columbia University. Lumbar spine results were expressed as *Z*-scores, which compare subjects with age-, race- and sex-matched normative data provided by the manufacturer. Proximal femur results were compared with data from the National Health and Nutrition Examination Survey (NHANES) of adults in the United States. *t* scores were not used because women younger than 25 to 30 years might not have attained peak bone mass.

Statistical Analysis

Analyses of variance were used to establish significant differences in markers of bone mineral metabolism among AEDs with Tukey's Studentized Range post hoc test. Each bone marker variable was analyzed versus AED, age, and the natural logarithm of BMI. The most parsimonious model was chosen. When age or BMI was statistically significant, means for AEDs were statistically adjusted for the significant variables in the model. All of the bone marker variables, except total calcium, were log normally distributed and were analyzed using natural logarithms. Therefore, we report in Table 2 the adjusted geometric (antilogged) means and 95% confidence limits on the means. These means are most

representative of the central values of the distributions for each AED. Food frequencies were analyzed as reported in the food frequency questionnaires. Exercise varied widely, was not normally distributed, and was analyzed in two ways: (1) using a χ^2 test for those who exercised versus those who did not; and (2) using a nonparametric Wilcoxon test of total hours per week spent exercising, in those who exercised versus AEDs. All analyses were done using SAS software (SAS Institute, Cary, NC).

Results

Characteristics of the Study Population

Of the 93 women (age range, 18–40 years) enrolled, 37 were taking carbamazepine, 19 were taking lamotrigine, 19 were taking phenytoin, and 18 were taking valproate as monotherapy (Table 1). Of these women, 79% were white with no differences among groups. The women had long-term epilepsy, the average total duration of treatment was 8 to 13 years, and there was no significant difference in treatment duration among the groups. The length of time receiving AED mono-therapy was significantly shorter for the women using lamotrigine than for the other groups ($p = 0.001$). However, the average length of time receiving this AED was 21 months, which is sufficient to affect the indices of mineral metabolism and markers of bone turnover.[23] BMI and BMD *Z*-scores did not differ among the groups. The average amount of exercise (11–17hr/wk) and calcium intake (635–798mg/day) did not differ among the groups.

Biochemical Indices of Bone and Mineral Metabolism and Bone Turnover

There were no significant differences in serum 25-OH vitamin D and PTH concentrations among the AED monotherapy groups (Table 2). In addition, there were no significant differences in the proportion of women in each group who had 25-OH vitamin D levels in the insufficient range (<20ng/ml).[24] Notably, however, no woman treated with lamotrigine had serum 25-OH vitamin D levels in the insufficient range. A correlation analysis between 25-OH vitamin D and PTH did not indicate any significant relationship. Serum calcium concentrations were significantly less in subjects receiving carbamazepine, phenytoin, and valproate than in those receiving lamotrigine ($p = 0.008$). A correlation analysis did not indicate any relationship between calcium concentrations and duration of treatment for the women treated with lamotrigine.

Serum IGF-1 levels were significantly reduced in subjects receiving phenytoin compared with those receiving lamotrigine ($p = 0.017$). There were overall no significant differences ($p = 0.06$) in IGFBP-3 concentrations among the AED monotherapy groups. However, when the concentration of bioavailable IGF was estimated by an IGF-I/IGFBP3 ratio, statistical significance was lost.

Osteocalcin did not differ significantly among the four treated groups. In contrast, subjects receiving phenytoin had significantly greater bone-specific alkaline phosphatase concentrations than those receiving carbamazepine, lamotrigine, and valproate ($p = 0.007$).

Urinary NTX was not significantly different among the treated groups. However, it tended to be greater in the phenytoin ($p = 0.06$) group than in the other AED-treated groups.

Discussion

The results of this study of premenopausal women with epilepsy receiving AED monotherapy confirm that certain AEDs are associated with altered bone and mineral metabolism. Carbamazepine, phenytoin, and valproate were associated with significant reductions in serum calcium concentrations compared with lamotrigine, although serum PTH and 25-OH vitamin D levels did not differ among AED monotherapy groups. Bone-specific alkaline phosphatase, a marker of bone formation and turnover, was significantly greater in subjects taking phenytoin compared with the other groups. In addition, NTX, a urinary marker of bone resorption, was greater in subjects receiving phenytoin, although the difference was not statistically significant. Significant reductions in serum IGF-I, a skeletal growth factor, were detected in subjects taking phenytoin compared with those taking lamotrigine. However, because the IGF-1/IGFBP-3 ratio did not show any significant differences, the physiological significance of this finding is uncertain. Despite these biochemical differences, BMD was normal and did not differ significantly among the groups. However, the biochemical data do suggest that bone turnover is greater in women taking phenytoin than in those taking other AEDs, which raises concern that these women may experience premature bone loss, and therefore enter menopause with substantially reduced bone mass.

Bone turnover is a dynamic process of remodeling in which osteoclasts erode old “worn-out” bone and osteoblasts secrete and mineralize new bone matrix or osteoid to replace the resorbed mineral and matrix, processes that are essential to maintaining bone health. Biochemical markers of bone turnover, measured in serum and urine, provide estimates of the rate of bone formation and resorption. Over time, disturbances in formation, resorption, or both can lead to accelerated bone loss that may result in osteopenia or osteoporosis, and that may result ultimately in fragility fractures. Moreover, for postmenopausal women, increased bone turnover has been shown to be a risk factor for fracture that is independent of BMD.[25,26] Thus, the results of this study raise the concern that phenytoin therapy, in particular, may have subclinical adverse effects on the skeleton over the long-term. Moreover, these adverse effects may be exacerbated after menopause, when the protective effects of estrogen on the skeleton have dissipated.

Early studies of patients taking AEDs found several abnormalities in indices of bone and mineral metabolism, including low serum concentrations of calcium and vitamin D metabolites and increased PTH levels.[3–5,8,9] All of the patients in these early studies were treated with cytochrome P450 enzyme-inducing AEDs, which increase conversion of vitamin D to inactive metabolites. The serum concentration of 25-OH vitamin D reflects body stores of vitamin D and is commonly measured as an index of vitamin D repletion. Vitamin D deficiency or insufficiency may be associated with lower serum calcium concentrations, secondary hyperparathyroidism, and increased markers of bone resorption and turnover. Abnormalities reported in early studies were consistent with this pathogenesis.[3,5,8] However, most subjects in these reports were institutionalized and had poor diets, inadequate sunlight exposure, and limited exercise, or lived in northern latitudes, all of which are risk factors for vitamin D deficiency and secondary hyperparathyroidism. Thus, this interpretation of the biochemical abnormalities can be questioned.

Interestingly, more recent studies do not consistently find significantly reduced serum vitamin D levels, and findings regarding serum calcium and PTH levels also are not consistent. Although one study of 120 adults treated with AEDs found significantly reduced calcium concentrations and increased PTH compared with control subjects,[9] serum 25-OH vitamin D levels did not differ between subjects and controls. Histomorphometric analyses of bone biopsy specimens indicated increased osteoid surface and volume, accelerated mineralization rate, and decreased mineralization lag time.[27] These studies established AED bone disease as a disorder of increased remodeling (turnover), rather than decreased mineralization.[9] In a Finnish study, women, but not men, were found to have reduced serum levels of 25-OH vitamin D and 1,25 $(OH)_2$ vitamin D.[11] However, bone turnover in these subjects was increased independent of vitamin D status. Similarly, a study of children with epilepsy showed no reductions in vitamin D metabolites, calcium, or PTH after 1 year of treatment with carbamazepine when compared with control subjects.[12] However, markers of bone formation and bone resorption were significantly greater in the carbamazepine-treated children than in control subjects.[12,14] In summary, studies in both adults and children have found increased markers of bone turnover independent of serum levels of vitamin D metabolites and other indices of bone and mineral metabolism.

The results of our study of community dwelling premenopausal women were consistent with the majority of recent studies. Despite equivalent daily calcium in-takes, women taking carbamazepine, phenytoin, or valproate had significantly reduced serum calcium concentrations when compared with women taking lamotrigine. Although the women were treated with lamotrigine for a significantly shorter period, a correlation analysis did not find a relation between calcium concentrations and duration of exposure to lamotrigine, suggesting that the shorter period of treatment is not significant. Serum 25-OH vitamin D levels did not differ among the AED-treated groups, nor did the prevalence of levels in the insufficient range. Notably, however, no woman taking lamotrigine had 25-OH vitamin D levels less than 20ng/ml. In our study, markers of bone turnover were increased in women taking phenytoin, as also observed in most recent studies. These findings suggest that accelerated bone turnover independent of vitamin D status may be responsible for the bone abnormalities in patients treated with AEDs. Phenytoin emerges as the AED with the greatest impact on bone mineral metabolism, whereas women taking lamotrigine did not demonstrate abnormalities in any index of bone and mineral metabolism.

The mechanism that is most commonly postulated to explain abnormalities in biochemical indices of bone mineral metabolism is induction of the cytochrome P450 enzyme system. However, our subjects treated with valproate, a cytochrome P450 enzyme inhibitor, also had significantly reduced serum calcium concentrations, suggesting that calcium concentrations do not solely reflect cytochrome P450 metabolism. Other postulated mechanisms for AED-associated bone disease include impaired absorption of calcium,[28] direct increases of bone resorption,[29] inhibition of response to PTH,[11] vitamin K deficiency,[30] hyperparathyroidism,[11,31] and calcitonin deficiency.[32,33] No single mechanism fully explains all the biochemical abnormalities found in our study or in other recent studies. Further studies are necessary to clarify mechanisms by which AEDs affect the skeleton.

This study is unique, because no other study has compared the effect of individual AEDs on bone health in premenopausal women. Other studies have included subjects receiving AED polytherapy[34] or have evaluated only a single drug.[12–14] Thus, our results permit a comparison of four commonly used AEDs. However, the study does have several limitations. Both the cross-sectional design and the inclusion criteria (only premenopausal women) limit interpretation of the results. Longitudinal studies of markers of bone and mineral metabolism and BMD are necessary to assess whether the observed increases in bone turnover translate into more rapid rates of bone loss. Including only premenopausal women limits generalization of our findings, particularly because estrogen-deficient, postmenopausal women may be more likely to respond to the increase in turnover with a decline in BMD. Another limitation is the lack of a control group of similar premenopausal women who were not taking AEDs. Finally, the women who participated in the study, as demonstrated by their daily exercise regimen, were typically highly motivated and health conscious and might not be representative of other women receiving AEDs. Despite these limitations, however, we believe the results are of interest and contribute to the body of knowledge on the effects of AEDs on the skeleton.

In summary, our results demonstrate that AED monotherapy with phenytoin is associated with significant differences in mineral metabolism and increased bone turnover in premenopausal women compared with women receiving other AEDs. In addition, the lower serum calcium concentrations observed in subjects treated with carbamazepine or valproate raise the concern that these AEDs also could have long-term adverse effects on the skeleton. Subjects treated with lamotrigine had no statistically significant reductions in serum calcium concentrations or increases in markers of bone turnover, suggesting that it is less likely to have long-term adverse effects on bone health. Longitudinal studies are necessary to determine whether the observed abnormalities translate into increased rates of bone loss. Similar studies in postmenopausal women are urgently needed, because the effects of estrogen deficiency might be expected to exacerbate the adverse effects of AEDs on the skeleton.

Acknowledgments

This study was supported by a research grant from GlaxoSmith-Kline (7–79210, A.M.P., M.J.M.).

References

1. Marcus, R. Secondary forms of osteoporosis.. In: Coe, FL.; Favus, MJ., editors. Disorders of bone and mineral metabolism. Raven Press; New York: 1992. p. 889-904.
2. Pack AM, Olarte LS, Morrell MJ, et al. Bone mineral density in an outpatient population receiving enzyme-inducing antiepileptic drugs. Epilepsy Behav. 2003; 4:169–174. [PubMed: 12697142]
3. Hahn TJ, Hendin BA, Scharp CR, Haddad JG Jr. Effect of chronic anticonvulsant therapy on serum 25-hydroxycalciferol levels in adults. N Engl J Med. 1972; 287:900–904. [PubMed: 4561667]
4. Bouillon R, Reynaert J, Claes JH, et al. The effect of anticonvulsant therapy on serum levels of 25-hydroxy-vitamin D, calcium, and parathyroid hormone. J Clin Endocrinol Metab. 1975; 41:1130–1135. [PubMed: 1206098]
5. Gough H, Goggin T, Bissessar A, et al. A comparative study of the relative influence of different anticonvulsant drugs, UV exposure and diet on vitamin D and calcium metabolism in out-patients with epilepsy. Q J Med. 1986; 59:569–577. [PubMed: 3092278]

6. O'Hare JA, Duggan B, O'Driscoll D, Callaghan N. Biochemical evidence for osteomalacia with carbamazepine therapy. Acta Neurol Scand. 1980; 62:282–286. [PubMed: 7468150]
7. Bogliun G, Beghi E, Crespi V, et al. Anticonvulsant drugs and bone metabolism. Acta Neurol Scand. 1986; 74:284–288. [PubMed: 3811834]
8. Hoikka V, Savolainen K, Esko M, Alhava EM. Osteomalacia in institutionalized epileptic patients on long-term anticonvulsant therapy. Acta Neurol Scand. 1981; 64:122–131. [PubMed: 7324878]
9. Weinstein RS, Bryce GF, Sappington LJ, et al. Decreased serum ionized calcium and normal vitamin D metabolite levels with anticonvulsant drug treatment. J Clin Endocrinol Metab. 1984; 58:1003–1009. [PubMed: 6725504]
10. Andress DL, Ozuna J, Tirschwell D, et al. Antiepileptic drug-induced bone loss in young male patients who have seizures. Arch Neurol. 2002; 59:781–786. [PubMed: 12020260]
11. Valimaki MJ, Tiihonen M, Laitinen K, et al. Bone mineral density measured by dual-energy x-ray absorptiometry and novel markers of bone formation and resorption in patients on anti-epileptic drugs. J Bone Miner Res. 1994; 9:631–637. [PubMed: 8053391]
12. Verrotti A, Greco R, Morgese G, Chiarelli F. Increased bone turnover in epileptic patients treated with carbamazepine. Ann Neurol. 2000; 47:385–388. [PubMed: 10716262]
13. Sato Y, Kondo I, Ishida S, et al. Decreased bone mass and increased bone turnover with valproate therapy in adults with epilepsy. Neurology. 2001; 57:445–449. [PubMed: 11502911]
14. Verrotti A, Greco R, Latini G, et al. Increased bone turnover in prepubertal, pubertal, and postpubertal patients receiving carbamazepine. Epilepsia. 2002; 43:1488–1492. [PubMed: 12460249]
15. Schneider, A.; Shane, E. Osteoporosis due to illness and medications.. In: Marcus, R.; Feldman, D.; Kelsey, J., editors. Osteoporosis. Vol. 2. Academic Press; San Diego: 2001. p. 303-326.
16. Sheth RD, Wesolowski CA, Jacob JC, et al. Effect of carbamazepine and valproate on bone mineral density. J Pediatr. 1995; 127:256–262. [PubMed: 7636651]
17. Guo C-Y, Ronen GM, Atkinson SA. Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. Epilepsia. 2001; 42:1141–1147. [PubMed: 11580761]
18. Block G, Hartman AM, Dresser CM, et al. A data-based approach to diet questionnaire design and testing. Am J Epidemiol. 1986; 124:453–469. [PubMed: 3740045]
19. Katzman DK, Bachrach LK, Carter DR, Marcus R. Clinical and anthropometric correlates of bone mineral acquisition in healthy adolescent girls. J Clin Endocrinol Metab. 1991; 73:1332–1339. [PubMed: 1955516]
20. Marcus R, Holloway L, Wells B, et al. The relationship of biochemical markers of bone turnover to bone density changes in postmenopausal women: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. J Bone Miner Res. 1999; 14:1583–1595. [PubMed: 10469288]
21. Ghiron LJ, Thompson JL, Holloway L, et al. Effects of recombinant insulin-like growth factor-I and growth hormone on bone turnover in elderly women. J Bone Miner Res. 1995; 10:1844–1852. [PubMed: 8619364]
22. Holloway L, Butterfield G, Hintz RL, et al. Effects of recombinant growth hormone on metabolic indices, body composition, and bone turnover in healthy elderly women. J Clin Endocrinol Metab. 1994; 79:470–479. [PubMed: 7519191]
23. Delmas PD, Eastell R, Garnero P, et al. The use of biochemical markers of bone turnover in osteoporosis. Osteoporosis Int. 2000; 11(suppl 6):S2–S17.
24. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Committee of Scientific Advisors of the International Osteoporosis Foundation. Lancet. 1998; 351:805–806. [PubMed: 9519960]
25. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. J Bone Miner Res. 2000; 15:1526–1536. [PubMed: 10934651]
26. Hannon RA, Eastell R. Biochemical markers of bone turnover and fracture prediction. J Br Menopause Soc. 2003; 9:10–15. [PubMed: 12804307]

27. Mosekilde L, Melsen F. Dynamic differences in trabecular bone remodeling between patients after jejuno-ileal bypass for obesity and epileptic patients receiving anticonvulsant therapy. Metab Bone Dis Relat Res. 1980; 2:77–82.

28. Koch HV, Kraft D, von Herrath D, Schaefer K. Influence of diphenylhydantoin and phenobarbital on intestinal calcium transport in the rat. Epilepsia. 1972; 13:829–841. [PubMed: 4509174]

29. Takahashi A, Onodera K, Shinoda H, Mayanagi H. Phenytoin and its metabolite, 5-(4-hydroxyphenyl)-5-phenylhydantoin, show bone resorption in cultured neonatal mouse calvaria. Jpn J Pharmacol. 2000; 82:82–84. [PubMed: 10874595]

30. Onodera K, Takahashi A, Sakurada S, Okano Y. Effects of phenytoin and/or vitamin K2 (menatetrenone) on bone mineral density in the tibiae of growing rats. Life Sci. 2002; 70:1533–1542. [PubMed: 11895104]

31. Hahn TJ, Scharp CR, Richardson CA. Interaction of diphenylhydantoin (phenytoin) and phenobarbital with hormonal mediation of fetal rat bone resorption in vitro. J Clin Invest. 1978; 62:406–414. [PubMed: 209062]

32. Vernillo AT, Rifkin BR, Hauschka PV. Phenytoin affects osteocalcin secretion from osteoblastic rat osteosarcoma 17/2.8 cells in culture. Bone. 1990; 11:309–312. [PubMed: 2252808]

33. Hahn TJ, Hendin BA, Scharp CR, et al. Serum 25-hydroxy calciferol levels and bone mass in children on chronic anti-epileptic therapy. N Engl J Med. 1975; 292:550–554.

34. Stephen LJ, McLellan AR, Harrison JH, et al. Bone density and epileptic drugs: a case-controlled study. Seizure. 1999; 8:339–342. [PubMed: 10512774]

Table 1

Characteristics of Premenopausal Women with Epilepsy Grouped by Antiepileptic Drug Treatment

Characteristic	PHT	CBZ	VPA	LTG
No. of women	19	37	18	19
Age (mean ± SD), range	33 ± 6.1 (21–40)	33 ± 5.5 (20–40)	30 ± 6.4 (18–40)	29 ± 6.1 (18–41)
BMI (kg/m^2)	26.0 ± 7.4	26.0 ± 6.1	25.8 ± 6.8	27.5 ± 5.7
Spine *Z*-score	0.09 ± 1.39	–0.21 ± 0.96	0.15 ± 1.64	0.27 ± 0.96
Total hip *Z*-score	–0.09 ± 1.25	–0.37 ± 0.95	0.12 ± 1.59	–0.08 ± 0.80
Femoral neck *Z*-score	0.15 ± 1.50	–0.15 ± 0.95	0.23 ± 1.57	0.07 ± 0.99
Length of studied AED Rx (mon),[a] range	97 ± 83 (6–241)	66 ± 49 (8–204)	66 ± 55 (7–168)	21 ± 26 (6–132)

PHT = phenytoin; CBZ = carbamazepine; VPA = valproate LTG = lamotrigine; BMI = body mass index; AED = antiepileptic drug.

[a] Time taking LTG significantly less than others ($p = 0.001$).

Table 2

Indices of Bone and Mineral Metabolism and Markers of Formation and Resorption in Women with Epilepsy on AED Monotherapy Grouped by AED Treatment

	PHT	CBZ	VPA	LTG
Calcium (mg/dl)	8.9[a] (8.8–9.1)	8.9[a] (8.8–9.0)	8.9[a] (8.7–9.1)	9.2 (9.0–9.3)
25(OH)D (ng/ml)	20 (14–29)	21 (18–25)	25 (18–35)	30 (24–37)
PTH (pg/ml)	35 (21–60)	31 (26–36)	30 (21–43)	31 (22–43)
BSAP[b] (U/L)	20.2 (17.2–23.8)	16.2 (14.8–17.6)	14.8 (13.0–16.9)	15.0 (12.9–17.4)
Osteocalcin (ng/ml)	10.3 (6.7–15.6)	5.3 (3.6–7.8)	8.8 (5.1–14.9)	6.7 (4.1–10.7)
NTX[c] (nM/mM creatinine)	46.4 (30.5–70)	36.1 (29.4–44.4)	31.8 (23.1–43.7)	28.4 (22.7–35.3)
IGF-1[d] (ng/ml)	142 (75–271)	266 (214–329)	179 (107–298)	357 (251–508)
IGFBP-3 (ng/ml)	2,483 (1,358–4,540)	3,631 (3,205–4,114)	3,682 (2,950–4,596)	4,212 (3,746–4,735)
IGF-1/IGFBP-3	0.062	0.083	0.071	0.094

[e] $p = 0.060$; LTG highest, PHT lowest.

AED = antiepileptic drug; BSAP = bone specific alkaline phosphatase; CBZ = carbamazepine; VPA = valproate; LTG = lamotrigine; PTH = parathyroid hormone; NTX = N-telopeptide of type I bone collagen; IGF = insulin growth factor I; IGFBP = IGF binding protein.

[a] $p = 0.03$; PHT CBZ VPA lower than LTG.

[b] $p = 0.007$; PHT highest, LTG and VPA low.

[c] $p = 0.064$; AEDs indistinguishable.

[d] $p = 0.012$; LTG highest, PHT lowest.