Bone Health and Antiepileptic Drugs

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Fracture

• Epilepsy associated with at least twofold elevation in fracture risk.
• The most common fractures involve the spine and hip.
• Etiology
  - seizure itself
  - falls due to ataxia or weakness from coexisting neurological deficits
  - falls due to short-term AED side effects: sedation, dizziness
  - reduction in bone mineral density associated with long-term use of AEDs
• Epilepsy significantly shifts the expected age effect on fractures associated with osteopathies to younger than would be expected in the general population.
Epilepsy, osteoporosis and fracture risk – a meta-analysis

- A total of 11 studies on fracture risk and 12 studies on BMD
- The relative risk of any fracture was increased (2.2, 95% CI: 1.9–2.5), as was the risk of hip (5.3, 3.2–8.8), forearm (1.7, 1.2–2.3), and spine fractures (6.2, 2.5–15.5).
- A large proportion of fractures (35%) seemed related to seizures.
- Spine and hip BMD Z-scores were significantly decreased, hip more than spine (2P < 0.05). The expected increases in relative risk of any fracture from BMD Z-scores were 1.2–1.3, and significantly lower than observed. The deficit in BMD is too small to explain the observed increase in fracture risk. The remainder of the increase in fracture risk may be linked to seizures. (and unmeasured adverse effect of AEDs on bone quality or additional, extraskeletal mechanisms)

Use of antiepileptic drugs and risk of fractures: case–control study

- 1,018 cases and 1,842 matched controls.
- The risk of fractures increased with cumulative duration of exposure, with the strongest association for greater than 12 years of use: adjusted OR 4.15 (95% CI 2.71 to 6.34).
- Risk estimates were higher in women than in men.
- No difference between users of EI-AEDs and NEI-AEDs

* Long-term use of AEDs was associated with an increased risk of fractures, especially in women.

Fracture risk associated with use of antiepileptic drugs: case–control study

- 124,655 fracture cases and 373,962 controls
- All AEDs were associated with an increased fracture risk in an unadjusted analysis.
- CBZ (OR, 1.18; 95% CI, 1.10-1.26), OXC (1.14, 1.03-1.26), CZP (1.27, 1.15-1.41), PB (1.79, 1.64-1.95), and VPA (1.15, 1.05-1.26) were statistically significantly associated with risk of any fracture.
- ESM (0.75, 0.37-1.52), LTG (1.04, 0.91-1.19), PHT (1.20, 1.00-1.43), PRM (1.18, 0.95-1.48), TGB (0.75, 0.40-1.41), TPM (1.39, 0.99-1.96), and VGB (0.93, 0.70-1.22) were not statistically significantly.
- CBZ, PB, OXC, and VPA displayed a dose-response relation.
- Fracture risk was more increased by liver-inducing AEDs (OR, 1.38; 95% CI, 1.31-1.45) than by noninducing AEDs (1.19; 95% CI, 1.11-1.27).
- A very limited increased fracture risk is present in users of CBZ, CZP, OXC, PB, and VPA. A limited significant increase cannot be excluded for the other AEDs because of the statistical power.

Regulation of Bone Metabolism

• Bone is a metabolically active tissue
  – 25% of trabecular bone and 3% of cortical bone is replaced annually

• Vitamin D
  – Vitamin D$_2$ in diet and vitamin D$_3$ in skin after sun exposure
  – Hydroxylated in the liver to 25(OH)D: the commonly used index
  – Hydroxylated in the kidney to 1,25(OH)$_2$D by 1α-hydroxylase: the most active metabolite

• Functions of 1,25(OH)$_2$D:
  – ↑ intestinal Ca absorption
  – ↑ osteoclast formation
  – ↑ mineralization of osteoid
Regulation of Bone Metabolism

• Parathyroid hormone (PTH)
  * release stimulated by fall in ionized calcium
  * functions of PTH
    ↑ Ca reabsorption by distal tubule
    ↑ Ca release from bone (osteoclast-mediated resorption)
    ↑ 1α-hydroxylase
    ↓ 24-hydroxylase

• Markers of bone formation
  bone-specific alkaline phosphatase, osteocalcin (intact bone Gla protein), carboxy-terminal propeptide of type I procollagen (PICP)

• Markers of bone resorption
  carboxy-terminal telopeptide of type I collagen (ICTP, β-crossLaps, CTX) in serum; N-telopeptide of type 1 bone collagen (NTX) in urine
Osteoblasts = bone forming cell
osteoid synthesis (type I collagen)
mineralization with P & Ca

Osteoclasts = bone resorbing cell
multinucleated cells
resorption of bone
Changes in the bone mass result from an imbalance between the amount of bone resorbed and the amount of bone formed.

Riggs et al. *JBMR* 2005;20:177
Bone Mineral Density

- Routine X-ray insensitive
  - X-ray can detect bone loss only after 30% of the skeleton has been depleted; the presence of osteoporosis may be missed.

- Dual-energy X-ray absorption (DXA) at the spine and hip
  - High and low energies of X rays absorbed differently by soft tissue and bone.
  - A BMD value relative to the mean for young adults (T-score) below -2.5 SD is diagnostic of osteoporosis, whereas a T-score between -1 and -2.5 SD is diagnostic of osteopenia, according to the diagnostic criteria of the WHO. (Z score is the number of S.D. values above or below the average of age- and sex-matched control subjects BMD)
  - Gold standard: correlates well with bone strength and excellent predictor of fracture risk.
  - For each SD reduction in BMD, fracture risk doubles.

*Bone strength is characterized by both bone density and bone quality.
Some risk factors for developing osteoporosis

Risk Factors
- Increased age
- Race/ethnicity (white or Asian)
- Family history of osteoporosis
- Small frame
- Menopause (female)
- Poor nutrition
- Physical inactivity
- Smoking

- Low sun exposure
- Excess intake: caffeine, alcohol
- Eating disorder
- Hyperthyroidism
- Hyperparathyroidism
- Liver disease…
- Medication use: glucocorticoids…
- Low levels of sex hormones, high levels of homocysteine
Reduced Bone Mineral Density in patients with epilepsy

- Risk Factors
  - Institutionalization
    - reduced sunlight exposure
    - reduced physical activity
    - nutritional factors
  - Chronic metabolic acidosis
    - ketogenic diet
    - acetazolamide
  - AEDs
Mechanisms linked with bone disease

- Decreased intestinal absorption of calcium
- **Accelerated vitamin D hydroxylation to inactive forms:** EI-AEDs
- Impairment of PTH-induced calcium mobilization
- Interference with vitamin K metabolism (PHT)
- Inhibition of calcitonin
- Increased urinary loss of calcium and phosphorus due to renal tubular dysfunction
- **Direct effect on bone cells**
- **Increased bone turnover**
- Inhibition of carbonic anhydrase
- Folate deficiency and hyperhomocysteinemia
- Carnitine deficiency (VPA)
- Hormonal changes (hypogonadism, EI-AEDs)
- **Physical and environmental factors (epilepsy and underlying condition)**
**Biochemical Abnormalities of Bone Metabolism Associated with AEDs**

<table>
<thead>
<tr>
<th>Calcium</th>
<th>25(OH)D</th>
<th>1,25(OH)₂D</th>
<th>PTH</th>
<th>Markers of bone formation</th>
<th>Markers of bone resorption</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>serum</td>
<td>serum</td>
<td>serum</td>
<td>serum/urine</td>
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<td>serum</td>
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Studies comparing 25-hydroxyvitamin D levels in patients treated with carbamazepine relative to controls (untreated or lamotrigine-treated)

<table>
<thead>
<tr>
<th>Study</th>
<th>CBZ patients</th>
<th>Control patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>%Δ from ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pack et al. (2008)</td>
<td>23.4</td>
<td>25.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-7%</td>
</tr>
<tr>
<td>Kim et al. (2007)</td>
<td>23.0</td>
<td>33.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-32%</td>
</tr>
<tr>
<td>Mintzer et al. (2005)</td>
<td>20.4</td>
<td>27.5</td>
<td>-26%</td>
</tr>
<tr>
<td>Pack et al. (2005)</td>
<td>21.0</td>
<td>30.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-33%</td>
</tr>
<tr>
<td>Verrotti et al. (2002)</td>
<td>26.2</td>
<td>27.0</td>
<td>-3%</td>
</tr>
<tr>
<td>Verrotti et al. (2000)</td>
<td>38.7</td>
<td>39.0</td>
<td>-1%</td>
</tr>
<tr>
<td>Lamberg-Allardt et al. (1990)</td>
<td>22.8</td>
<td>27.5</td>
<td>-17%</td>
</tr>
<tr>
<td>Gough et al. (1986)</td>
<td>22.9</td>
<td>39.2</td>
<td>-42%</td>
</tr>
<tr>
<td>Hoikka et al. (1984)</td>
<td>11.1</td>
<td>17.6</td>
<td>-37%</td>
</tr>
<tr>
<td>Tjellesen &amp; Christiansen (1982)</td>
<td>22.9</td>
<td>26.2</td>
<td>-13%</td>
</tr>
</tbody>
</table>

% Δ from ctrl, Percentage difference between carbamazepine-treated and control patients. All values in ng/ml. <sup>a</sup>Lamotrigine-treated controls.

*Mintzer & Mattson, 2009*
Increased bone turnover

- Bone biopsies in patients receiving AEDs reveal increased osteoid formation with normal calcification, accelerated mineralization, and decreased mineralization lag time indicative of increased bone turnover (Mosedike & Melsen, 1980).

- Other indirect evidence: elevated alkaline phosphatase and increased osteocalcin, PICP (carboxy-terminal propeptide of type I procollagen), and ICTP (carboxy-terminal telopeptide of type I collagen) levels

- Verrotti et al. reported increases in bone turnover markers in children and adolescents treated with CBZ (Verrotti et al., 2000, 2002); significant increases in turnover markers and not calcium, PTH, or vitamin D metabolites were found after 1 and 2 years after treatment.
Bone density and antiepileptic drugs: a case control study

- 78 patients either enzyme-inducing (n = 52) or non-inducing (n=26) AEDs (single or multiple) including newer AEDs
- Male patients had lower BMD than controls at the lumbar spine and neck of the femur. Female patients had significantly reduced bone density at the femoral neck only.
- Duration of treatment and type of AED were not independent factors for reduction in BMD.

Long-term anticonvulsant therapy leads to low BMD- evidence for direct drug effects of PHT and CBZ on human osteoblast-like cells

• 59 patients (with PHT and/or CBZ for at least 3 years) compared to age- and sex-matched controls

(Direct effects of PHT and CBZ on human osteoblast-like cells)

• BMD in the lumbar spine region was significantly lower in the patient group as compared to controls (p<0.0004). At femoral sites BMD was lower in patients (not statistically significant).

• The decrease in BMD at both sites was dependent on the duration of therapy. Excretion of pyridinoline crosslinks was markedly increased and 25-hydroxy-vitamin D$_3$ and 1,25-dihydroxy-vitamin D$_3$ were significantly decreased in patients.

• Both PHT and CBZ inhibited osteoblast-like cell growth at concentrations equivalent to therapeutic doses for the treatment of epileptic diseases.

Decreased bone mass and increased bone turnover on VPA

- 40 adults with epilepsy on long-term VPA monotherapy compared with PHT or control (n=40, respectively)
- Compared with controls, BMD decreased by 14% on VPA and 13% on PHT (more in women)
- On VPA, 23% had T-score below -2.5 SD, suggesting osteoporosis
  37% had T-score between -1 and -2.5 SD, suggesting osteopenia
- On PHT, 12% had T-score below -2.5 SD, suggesting osteoporosis
  48% had T-score between -1 and -2.5 SD, suggesting osteopenia
- Significant rise in calcium with VPA than PHT or controls
- Higher calcium (V), lower calcium (P), lower 25-OHD (P), higher 1,25 (OH)_{2}D (P), lower 1,25 (OH)_{2}D (V), secondary hyperparathyroidism (P), higher calcitonin and ICTP (P & V)
- Long-term VPA treatment decreases BMD by increased bone resorption

Effect of AEDs on BMD in ambulatory patients

• 71 patients on AED (single or multiple) for at least 6 months
• Over 50% of adults and children had low 25-OHD levels (but this finding did not correlate with BMD)
• AED treatment decreased BMD in adults
• Significant determinants of BMD: generalized seizures, longer duration of epilepsy and polypharmacy
• PHT, PB, CBZ, PRM (E-I) tended to lower BMD compared to VPA, LTG, CZP, GBP, TPM, ESM (NE-I)

Bone mineral density in an outpatient population receiving enzyme-inducing antiepileptic drugs

Percentages of normal density, osteopenia, and osteoporosis at the femoral neck of the hip in patients receiving enzyme-inducing AEDs as compared with the expected percentages (medically normal population of white postmenopausal women)

Antiepileptic drug use increases rates of bone loss in older women: a prospective study

- Calcaneal and hip BMD were measured in 9704 elderly community-dwelling women; most of the continuous users were taking PHT or PB.
- The average rate of decline in total hip BMD steadily increased from -0.70%/year in nonusers to -0.87%/year in partial AED users to -1.16%/year in continuous AED users (p value for trend 0.015).
- Higher rates of bone loss among continuous AED users at subregions of the hip and at the calcaneus.
- Continuous PHT users had an adjusted 1.8-fold greater at the calcaneus (-2.68 vs -1.46%/year; p 0.001) and an adjusted 1.7-fold greater mean rate of loss at the total hip compared with nonusers of AED (-1.16 vs -0.70%/year; p 0.069).
- If unabated, the rate of hip bone loss among continuous AED users is sufficient to increase the risk of hip fracture by 29% over 5 years among women age 65 years and older.

Effect of antiepileptic medication on bone mineral measures

- 31 female twin (15 monozygous and 16 dizygous) and four sibling pairs (< 3 years age difference) aged 21 to 75 years, in which one member had > 12 months of AED treatment.

- For all pairs, no significant within-pair differences in any Areal bone mineral density measure: however, subgroup analysis
  * use for >2 years; within-pair difference at the FA
  * use of enzyme-inducing AEDs; within-pair difference at the FA
  * age older than 40 years; within-pair differences at the FA and LS

- Patients using AEDs for >2 years, in particular those taking enzyme-inducing AEDs and those older than 40 years, have significantly lower bone mineral density at clinically relevant fracture risk sites.

Antiepileptic drug use and rates of hip bone loss in older men

- At baseline and an average of 4.6 years later in a cohort of 4,222 older community-dwelling men enrolled.
- After adjustment for multiple potential confounders, the average rate of decline in total hip BMD was 0.35%/year among nonusers compared with 0.53%/year among NEIAED users ($p = 0.04$) and 0.46%/year among EIAED users ($p = 0.31$).
  Multivariable adjusted rate of loss was 0.60%/year among men taking NEIAED at both examinations, 0.51%/year among men taking NEIAED at one examination only, and 0.35%/year among nonusers ($p$ for trend = 0.03). Findings were similar at hip subregions.
- Use of non–enzyme-inducing antiepileptic drugs was independently associated with increased rates of hip bone loss in this cohort of older community-dwelling men.

Ensrud et al. Neurology 2008;71:723–730
A 6-month longitudinal study of bone mineral density with antiepileptic drug monotherapy

- Subjects included 33 drug-naïve, newly diagnosed patients with epilepsy aged between 18 and 50.
- BMD at right calcaneus and various markers for bone metabolism were measured before and after 6 months of AED monotherapy including CBZ, VPA, and LTG.
- CBZ caused a significant decrease in BMD, which was accompanied by a decrease in the level of vitamin D (25-OHD$_3$). BMD and vitamin D were not affected by 6 months of VPA or LTG therapy. Interestingly, VPA and LTG, but not CBZ, significantly increased osteocalcin, a marker of bone formation.
- All AEDs almost doubled the parathyroid hormone level, whereas urinary Pyrilinks, a marker of bone resorption, was not affected by those AEDs.
- These findings suggest that CBZ, a hepatic enzyme-inducing drug, decreases BMD.

Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine

- Epilepsy patients taking CBZ (n=21) or OXC (n=24) in monotherapy compared with normal controls (n=24); CBZ patients were subsequently switched to OXC monotherapy.
- 25-OHD levels were lower in each drug-treated group than in the controls; significant for the OXC group (p<0.05).
- PTH, BAP, and NTX did not differ significantly among groups.
- Osteocalcin levels were somewhat elevated in the OXC group and more clearly and significantly elevated in the CBZ group.
- The combined drug-treatment group had significantly higher BAP (p=0.02) and lower 25-OHD (p=0.015).
- No significant differences after CBZ were switched to OXC.

Mintzer et al. Epilepsia 2006;47:510-5
Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy

- Premenopausal 93 women with epilepsy receiving AED monotherapy (PHT, CBZ, VPA, and LTG).
- Lower calcium concentrations in subjects receiving CBZ, PHT, and VPA than in those receiving LTG.
- Reduced Insulin growth factor-I in subjects receiving PHT compared with those receiving LTG.
- Greater levels of bone-specific alkaline phosphatase in subjects receiving PHT.
- No difference in BMD among the groups.
- Subjects receiving LTG 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.

Bone health in young women with epilepsy after one year of antiepileptic drug monotherapy

• Ninety-three premenopausal women with epilepsy receiving a single AED (PHT, CBZ, VPA, and LTG).

• Significant loss (2.6%) was seen at the femoral neck in PHT group. BMD remained stable in the other AED groups. Bone turnover markers and calcitropic hormones were unchanged after 1 year in all groups except for a significant decline in urine N-telopeptide in the phenytoin group. In women receiving PHT, lower serum 25-hydroxyvitamin D concentrations were associated with higher parathyroid hormone, bone alkaline phosphatase, and urine N-telopeptide levels, a biochemical pattern consistent with secondary hyperparathyroidism and increased remodeling.

• Young women treated with PHT had significant femoral neck bone loss over 1 year.

Pack et al. Neurology 2008;70:1586–1593
Which AEDs are linked with bone disease?

- All types of AEDs are potentially implicated and the mechanisms are multifactorial and are probably augmented by individual risk factors that promote susceptibility to a specific mechanism responsible for bone loss.
- Significant differences in BMD between those taking anticonvulsants and controls.
- Cytochrome P450 inducers: PB, PHT, PRM and CBZ. Most of the published studies and evidence (CBZ still under discussion).
- VPA (cytochrome P450 inhibitor)? Some studies have suggested that it has a negative effect on bone health, such as low BMD (Sheth et al., 1995; Sato et al., 2001), low serum calcium level (Pack et al., 2005), or increased osteocalcin (Kim et al., 2007). (still under discussion)
- Higher risk of bone metabolism abnormalities with polytherapy than monotherapy.
- Stronger adverse effect of AEDs on bone health in patients with old age (especially women) or reduced activity.
- Longer duration of AED therapy.
One recent study of elderly men found that bone loss was not associated with enzyme-inducing AED use, and in fact seemed to be higher among those taking noninducing AEDs (Ensrud et al., 2008); most of these patients were taking GBP (85/100).

Unknown in most new AEDs except LTG & OXC
- LTG does not appear to affect bone health (Pack et al., 2005; Sheth & Hermann, 2007; Pack et al., 2008).
- OXC: no significant differences in vitamin D levels and markers of bone turnover after CBZ were switched to OXC (Mintzer et al., 2006); 18 months follow-up of 34 newly diagnosed pediatric patients (18 prepubertal, and 16 pubertal) – decreased 25-hydroxyvitamin D and increased osteocalcin, and drug-induced osteopenia in 3 patients with z scores of BMD less than 2.0 (these patients had z scores of less than 1.5 before treatment) (Cansu et al., 2008)
- ZNS? LEV? PGB? LCM?.... How about TPM?
Effect of topiramate on bone health

Heo et al. Epilepsia 2011;52:1884–1889

• 36 premenopausal women on long-term (at least 1 year) TPM were compared with 36 women taking CBZ, 32 women taking VPA, and 36 controls.

• BMD Z-scores, and serum 25-hydroxyvitamin D and 1alpha,25-dihydroxyvitamin D₃ concentrations did not differ among the groups. Serum calcium concentrations were significantly lower in patients receiving TPM than in those receiving VPA, and in patients receiving CBZ than in those receiving VPA and controls. Patients taking TPM had lower levels of PTH compared with controls and those taking CBZ or VPA. Patients receiving TPM had higher levels of bone-specific alkaline phosphatase and osteocalcin when compared with controls and higher levels of C-terminal telopeptide of type 1 collagen when compared with those taking CBZ or VPA. Patients receiving CBZ had higher levels of bone-specific alkaline phosphatase compared with controls and those receiving VPA. Serum bicarbonate concentrations were significantly lower in patients receiving TPM than in the other groups.

• Our results demonstrate that use of TPM is associated with lower PTH and bicarbonate concentrations along with mild hypocalcemia and increased bone turnover, which suggest that TPM may have long-term effects.
## Indices of bone and mineral metabolism and markers of bone formation and resorption

<table>
<thead>
<tr>
<th></th>
<th>TPM</th>
<th>CBZ</th>
<th>VPA</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>Calcium (mg/dl) (mean ± SD)</td>
<td>9.26 ± 0.37</td>
<td>9.19 ± 0.29</td>
<td>9.56 ± 0.34</td>
<td>9.42 ± 0.38</td>
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<tr>
<td>25(OH)D (ng/ml) (mean ± SD)</td>
<td>25.65 ± 11.64</td>
<td>27.94 ± 12.62</td>
<td>27.30 ± 9.87</td>
<td>25.61 ± 11.98</td>
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<tr>
<td>1,25(OH)₂D (pg/ml) (mean ± SD)</td>
<td>49.94 ± 12.85</td>
<td>41.71 ± 11.88</td>
<td>43.18 ± 18.68</td>
<td>46.91 ± 14.33</td>
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<tr>
<td>PTH (pg/ml) (mean ± SD)</td>
<td>25.30 ± 9.85</td>
<td>38.99 ± 11.00</td>
<td>32.79 ± 12.91</td>
<td>35.70 ± 11.95</td>
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<tr>
<td>BSAP (U/L) (mean ± SD)</td>
<td>25.14 ± 7.48</td>
<td>26.81 ± 7.19</td>
<td>21.76 ± 5.47</td>
<td>19.00 ± 4.68</td>
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<tr>
<td>Osteocalcin (ng/ml) (mean ± SD)</td>
<td>15.82 ± 6.26</td>
<td>12.35 ± 4.46</td>
<td>14.50 ± 4.04</td>
<td>12.61 ± 3.22</td>
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<td>CTx (ng/ml) (mean ± SD)</td>
<td>0.31 ± 0.12</td>
<td>0.20 ± 0.10</td>
<td>0.20 ± 0.09</td>
<td>0.25 ± 0.11</td>
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<td>IGF-1 (ng/ml) (mean ± SD)</td>
<td>327.77 ± 114.48</td>
<td>257.38 ± 77.76</td>
<td>276.34 ± 86.78</td>
<td>294.91 ± 116.78</td>
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<td>Bicarbonate (mEq/L) (mean ± SD)</td>
<td>18.78 ± 1.68</td>
<td>21.72 ± 3.16</td>
<td>23.50 ± 2.60</td>
<td>21.69 ± 2.47</td>
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<td>Urine excretion of calcium</td>
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<tr>
<td>Random urine (mg/dl) (mean ± SD)</td>
<td>13.69 ± 7.74</td>
<td>5.09 ± 2.97</td>
<td>5.97 ± 4.33</td>
<td>11.17 ± 7.06</td>
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<td>24-hour urine (mg/day) (mean ± SD)</td>
<td>146.60 ± 81.26</td>
<td>87.74 ± 46.38</td>
<td>107.29 ± 63.69</td>
<td>136.27 ± 60.29</td>
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</table>
LEV reduces bone strength and bone formation without altering bone mass (the uncoupling of bone strength and bone mass).

**Levetiracetam, Phenytoin, and Valproate Act Differently on Rat Bone Mass, Structure and Metabolism**

*Lise Sofie H. Nissen-Meyer, Sigrid Svalheim, Erik Taubøll, Sjur Reppe, Tove Lekva, Lene B. Solberg, Gunhild Melhus, Finn P. Reinholdt, Leif Gjerstad, and Rune Jemtland*

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**Summary: Purpose:** Long-term treatment with antiepileptic drugs (AEDs) is associated with increased risk of fractures. Phenytoin (PHT) and valproate (VPA) have both been suggested to influence bone health, whereas levetiracetam (LEV) is scarcely studied. The present study compares the effect of these AEDs on bone mass, biomechanical strength, and bone turnover in rats.

**Methods:** Female rats received PHT (50mg/kg), VPA (300mg/kg), or LEV (50 and 150mg/kg) for 90 days. Dissected femurs were analyzed using dual energy x-ray absorptiometry (DXA), three-point cantilever bending, and histomorphological evaluation. Serum levels of biochemical bone turnover markers were monitored using immunoassay quantification.

**Results:** PHT and VPA reduced bone mineral density (BMD) and content (BMC) in one or more bone compartments, whereas LEV did not. VPA induced increased bone turnover, whereas modest changes were observed for PHT. Interestingly, low-dose LEV was associated with reduced biomechanical strength of the femoral neck (mainly trabecular bone). In addition, low-dose LEV treatment resulted in significantly reduced levels of serum osteocalcin, a marker of bone formation. Histomorphological analyses indicated increased retention of cartilage remnants at the growth plate metaphysis of rats treated with low-dose LEV vs. controls.

**Conclusions:** PHT, VPA, and LEV exert differential effects on bone mass and strength, suggesting different mechanisms of action. The weakening effect of low-dose LEV on the femoral neck, despite a constant BMD, suggests a primary effect on bone quality. These findings warrant further human studies of possible adverse effects of LEV on bone development and growth, particularly in children and adolescents. Key Words: Levetiracetam—Phenytoin—Valproate—Bone mineral content—Biomechanical strength.
Physician awareness of AED-associated bone disease

Valmadrid et al. (2001)

- One-third of the neurologists surveyed routinely evaluated AED-treated patients for bone disease.
- Of those who did evaluate patients and found evidence of bone disease, fewer than 50% prescribed calcium and vitamin D supplementation, and approximately 50% referred patients with disease to a specialist.
- Fewer than 10% of the neurologists prescribed prophylactic calcium and vitamin D supplementation to patients treated with AEDs.
Management recommendations

• Optimal control of seizures, environmental modification to minimize risk, avoidance of overtreatment with AEDs
• Have patient optimize sunlight exposure and weight-bearing.
• Have patient maintain a balanced diet.
• Advise patient to stop smoking.
• Advise moderation in alcohol and caffeine.
• All patients: adequate intake of dietary vitamin D and Ca

*serum 25(OH)D levels of 30 ng/ml or greater may be needed for optimal health benefits although the lower limit of reference range is much less.
- Institutionalized patients and postmenopausal women: supplement of vitamin D (800 IU) and Ca (1000 mg)
- Patients with additional increased risk: supplement of vitamin D (1000-4000 IU) and Ca (1500 mg)
- Dual-energy X-ray absorptiometry (DXA) scan 5 years after initiation of AED treatment
- DXA scan at initiation of AED treatment in postmenopausal women
- DXA scan every 2–3 years in high-risk patients (eg. users of enzyme inducers or VPA?, OXC?, TPM?)
- T-scores < -1: supplement of vitamin D (800 IU) and Ca (1000 mg) and weight-bearing exercise
- T-scores between -1 and -2.5: supplement of vitamin D (800 IU) and Ca (1000 mg), weight-bearing exercise, new DXA scan repeated after 1–2 years
- T-scores < -2.5: referral for the treatment of bone disease, usually with the addition of bisphophonates – refer to endocrinologist

Svalheim et al., 2011, modified
Medical Treatment

- Conservative management: cornerstones in the treatment of bone loss with epilepsy
  - Calcium and vitamin D
- Vertebral fractures or DXA T scores < -2.5.
  - Bisphosphonates: antiresorptive compounds
  - Hormone and non-hormonal therapies: selective estrogen receptor modulator, estrogen-like, calcitonin, parathyroid hormone, lab-produced mAb, antibodies against RANKL
  - Hormonal and non-hormonal therapy of men with hypogonadism and osteoporosis
- Folic acid, vitamin B\textsubscript{12}, carnitine
- Change the AED? *(enzyme inducing drugs should be avoided as the first choice of drug, especially patients with risk factor, if possible)*
Vitamin D in ambulatory patients on anticonvulsants

- Two parallel, randomized, controlled trials in 72 adults and 78 children and adolescents on long-term AED therapy.
- Either low-dose vitamin D 400 IU/day or high-dose vitamin D 4,000 IU/day (adults) and 2,000 IU/day (children/adolescents).
- In adults, baseline BMD was lower than that of controls. After 1 year, there were significant increases in BMD at all skeletal sites compared to baseline in the high-, but not in the low-dose treatment group. However, BMD at 1 year remained below normal.
- In children, baseline BMD was normal vs controls and showed significant and comparable increases in both treatment groups.
- In ambulatory adults on AEDs, high-dose vitamin D therapy substantially increased bone mineral density at several skeletal sites. In children, both doses resulted in comparable increases in bone mass.

Up to 95% of total bone development is completed by the age of 18 years and the peak BMD is obtained between ages 20 and 30. In the ensuing years, there is typically a gradual loss of bone. Throughout life, there are some periods that are associated with an increased susceptibility to bone loss, for instance in the perimenopausal years and in puberty. Puberty is a vulnerable stage in skeletal health as linear height increases the rapid bone remodeling; adequate calcium intake in adolescence can result in a 5 - 10% difference in peak bone mass which may reduce the risk of hip fracture in old age by 50%.