Levetiracetam Treatment Does Not Result in Broken Bones

**Effects of Levetiracetam as a Monotherapy on Bone Mineral Density and Biochemical Markers of Bone Metabolism in Patients With Epilepsy.**

Koo DL, Joo EY, Kim D, Hong SB. [Published online ahead of print September 30, 2012, Epilepsy Res. doi:xxxxxx.]

PURPOSE: Antiepileptic drugs (AEDs) may have adverse effects on bone metabolism and bone mineral density (BMD). The aim of this study is to determine the changes of bone metabolism and BMD in epilepsy patients who are undergoing levetiracetam (LEV) monotherapy. METHODS: Drug-naive, sixty-one patients with recent onset epilepsy were recruited (24 female, 37 males; mean age: 31.0±13.1 years) in this study. We measured calcium, phosphate, bone alkaline phosphatase, parathyroid hormone, osteocalcin, insulin-like growth factor (IGF)-1, C-telopeptide, vitamin D3 levels and bone density measurements with DEXA method before and after LEV administration of mean duration 14.16±3.36 months. RESULTS: T score in lumbar spine (L1-L4) was significantly increased with the correction of multiple T tests using Bonferroni's test across LEV monotherapy (p=0.0401). However, no significant change was observed in other parameters for BMD and T score. Repeated measures ANOVA with Bonferroni’s correction of confounders such as sex, age, and treatment duration revealed significant increase in T score in lumbar spine (p=0.0164). The level of average LEV dosage itself did not reveal any significant association with BMD and bone metabolism. CONCLUSIONS: We suggest that LEV monotherapy may have no harmful effect on bone strength and metabolism for 1 year.

Commentary

Persons with epilepsy have a two- to six-fold increased risk of fracture (1). Antiepileptic drug (AED) exposure independently increases the risk (2, 3). Therefore, when choosing an AED, it is important to understand its potential secondary effects on bone. AEDs most commonly associated with adverse effects on bone include phenytoin and phenobarbital (1). Levetiracetam is a broad-spectrum AED used for the treatment of partial and generalized epilepsy syndromes. Whether levetiracetam affects bone has received limited study and is not well understood.

The impact of levetiracetam on bone was previously evaluated in an animal study (4). Rats were treated with low-dose (50 mg/kg) and high-dose (150 mg/kg) levetiracetam. Levetiracetam did not affect bone mass. Low-dose levetiracetam was associated with reduced biochemical strength of the femoral neck, which is predominantly trabecular bone. Trabecular bone is metabolically active bone and contains relatively more cartilage. The femoral diaphysis, which is predominantly cortical bone was not significantly altered. In addition, osteocalcin, a marker of bone formation, was increased in low-dose levetiracetam–treated animals. Increased osteocalcin reflects increased bone turnover resulting in bone loss over time.

An abstract presentation of 16 subjects showed a favorable effect of levetiracetam on bone mineral density (BMD) and vitamin D concentrations (5). Subjects ranging in age from 20 to 66 had BMD measurements using dual energy x-ray absorptiometry (DXA) and serologic vitamin D concentrations as well as osteocalcin measurements after a minimum of 6 months levetiracetam exposure. DXA is the most commonly used tool to assess BMD. No subject had evidence of low bone mass (osteopenia or osteoporosis). Osteopenia is defined by the World Health Organization as T-scores between −1.0 and −2.5. Osteoporosis is defined as −2.5 or lower. All subjects had vitamin D concentrations in the normal range. Four subjects had elevated osteocalcin. In the absence of other bone turnover markers, and normal BMD, this finding is of unclear significance. Unfortunately, these results were never published as a peer-reviewed paper.

In contrast, a retrospective cross-sectional study, published as a short communication, found that the incidence of low BMD (either osteopenia or osteoporosis) was higher among levetiracetam monotherapy users compared with users of other AEDs including topiramate, lamotrigine, carbamazepine, and valproate (6). Among 17 subjects treated with levetiracetam, 70% had low BMD. This study is limited by the sample size and lack of evaluation of potential confounders such as diet and exercise.

In order to better understand the effects of levetiracetam on bone, Koo and colleagues designed a prospective study evaluating BMD and bone metabolism among drug-naïve subjects (average age 31.0 ± 13.1 years) with recent onset epilepsy treated with levetiracetam monotherapy (mean duration 14.16 ± 3.36 months) (7). Subjects were recruited from a Korean outpatient epilepsy clinic; among the original 107
recruited subjects, 46 (43%) were excluded. Common reasons for exclusion included loss of follow-up, evidence of osteoporosis, and mental retardation. All subjects initially received either 500 or 1,000 mg per day and were increased to 3,000 mg per day if clinically indicated. The effect of the dose was evaluated. Subjects were grouped into either low-dose (<1,000 mg per day) or high-dose groups (≥1000 mg per day). Physical activity and dietary habits were assessed at baseline and every 3 months after levetiracetam administration. Subjects had baseline and repeat DXA scans as well as serologic biochemical bone markers (vitamin D3, calcium, phosphate, bone alkaline phosphatase, parathyroid hormone, osteocalcin, insulin-like growth factor, C-telopeptide). The mean duration of follow-up was 14.16 ± 3.36 months. The average dose of levetiracetam at the last visit was 1398 ± 616 mg per day. There were no significant decreases in BMD at either the lumbar spine or proximal femur. Of interest, there was an increase in BMD at the lumbar spine. This finding is likely related to the age range in this group as opposed to a direct effect of levetiracetam. BMD typically increases until approximately age 30. The age range in this study was 13–55 and therefore included individuals who were continuing to increase BMD. No changes were found in any of the measured biochemical bone markers. The level of levetiracetam dosage (low or high) was not associated with BMD or bone metabolism. The results of this study suggest that levetiracetam monotherapy does not adversely affect bone health.

The currently available data do not support a negative association between levetiracetam and bone health. Two studies suggest there may be an effect on bone strength and BMD. However, one of these studies was an animal study and one was a retrospective study, which had a limited sample size and did not control for potential confounders. The recently published report by Koo and colleagues adds to the literature as this was a well-designed longitudinal study in drug-naïve persons. Subjects were, however, followed for only a limited time. Well-powered prospective studies in individuals on levetiracetam monotherapy followed for more prolonged periods should be conducted.

by Alison Pack, MD

References

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. **Identifying information.**
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. **The work under consideration for publication.**
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. **Relevant financial activities outside the submitted work.**
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFGR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFGR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. **Other relationships**
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
## Disclosure of Potential Conflicts of Interest

### Section #1 Identifying Information

1. Today’s Date: May 7, 2012

2. First Name  Alison  Last Name Pack  Degree MD, MPH

3. Are you the Main Assigned Author?  ☒ Yes  ☐ No

   If no, enter your name as co-author:

4. Manuscript/Article Title: Levetiracetam Treatment Does Not Result in Broken Bones

5. Journal Issue you are submitting for:  13.2

### Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grant</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consulting fee or honorarium</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Support for travel to meetings for the study or other purposes</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Payment for writing or reviewing the manuscript</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Provision of writing assistance, medicines, equipment, or administrative support.</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Other</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.
Section #3  Relevant financial activities outside the submitted work.
Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type of relationship (in alphabetical order)</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Board membership</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consultancy</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Employment</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td>☐</td>
<td></td>
<td>NIH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Payment for manuscript preparation.</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Patents (planned, pending or issued)</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Royalties</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Payment for development of educational presentations</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Stock/stock options</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
<td>☐</td>
<td>X</td>
<td>Vivus</td>
<td>Paid for flight and hotel to meeting</td>
<td></td>
</tr>
<tr>
<td>13. Other (err on the side of full disclosure)</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☑ No other relationships/conditions/circumstances that present a potential conflict of interest.
☐ Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.
_Epilepsy Currents_ Editorial Board