Use of Antidepressants and Rates of Hip Bone Loss in Older Women

The Study of Osteoporotic Fractures

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Background: Serotonin transporters have recently been described in bone, raising the possibility that medications that block serotonin reuptake could affect bone metabolism.

Methods: We assessed current use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) and obtained serial bone mineral density (BMD) measurements in a cohort of 2722 older women (mean age, 78.5 years) participating in the Study of Osteoporotic Fractures, a prospective cohort study of community-dwelling women. Hip BMD was measured at the sixth examination and an average of 4.9 years later at the eighth examination. We categorized women as nonusers (used no SSRIs or TCAs at either examination; n=2406), SSRI users (used SSRIs but no TCAs at either examination; n=198), or TCA users (used TCAs but no SSRIs at either examination; n=118). Depressive symptoms were identified using a cutoff score of at least 6 on the Geriatric Depression Scale.

Results: After adjustment for potential confounders, including the Geriatric Depression Scale score, mean total hip BMD decreased 0.47% per year in nonusers compared with 0.82% in SSRI users (P<.001) and 0.47% in TCA users (P=.99). Higher rates of bone loss were also observed at the 2 hip subregions for SSRI users. Results were not substantially altered when women who scored at least 6 on the Geriatric Depression Scale were excluded from the analysis.

Conclusion: Use of SSRIs but not TCAs is associated with an increased rate of bone loss at the hip in this cohort of older women.

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ANTIDEPRESSANTS ARE ONE of the most commonly prescribed classes of pharmacologic agents in the United States; in 2002, 8.5% of Americans used antidepressants.1 With the development of the selective serotonin reuptake inhibitors (SSRIs), prescriptions for antidepressants for the elderly have increased substantially during the past 2 decades.2

SELECTIVE SEROTONIN REUPTAKE INHIBITORS function by inhibiting the serotonin transporter.3 An older class of antidepressants, the tricyclic antidepressants (TCAs), inhibit uptake of norepinephrine and serotonin to varying degrees.3 The recent description of functional serotonin transporters in osteoblasts, osteoclasts, and osteocytes4,5 raises the possibility that serotonin transporters may play a role in bone metabolism and that medications that affect these transporter systems may also affect bone metabolism.

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To determine whether SSRI and TCA use among older women is associated with increased rates of hip bone loss, we ascertained use of antidepressants, assessed evidence of depressive symptoms, and performed hip bone mineral density (BMD) measurements at 2 examinations in a cohort of 2722 women 65 years and older who were enrolled in the Study of Osteoporotic Fractures.

METHODS

PARTICIPANTS

From September 10, 1986, through January 5, 1989, 9704 women 65 years or older were recruited for participation in the prospective...
Study of Osteoporotic Fractures. Women were recruited from population-based listings in Baltimore County, Maryland; Minneapolis, Minn; Portland, Ore; and the Monongahela Valley, Pennsylvania. We initially excluded African American women because of their low incidence of hip fracture, women who were unable to walk without help, and women with a history of bilateral hip replacement.

From January 3, 1997, through February 8, 1999, 7008 of the original cohort (91.6% of survivors) and an additional 662 African American women attended a sixth clinic examination (visit 6). From January 15, 2002, through April 30, 2004, 4727 women (74.4% of survivors) completed at least the questionnaire component of the eighth clinic examination (visit 8). Of these, 2844 women completed a medication inventory at both visits, completed the Geriatric Depression Scale (GDS) at visit 6, and had technically adequate hip BMD measurements at both visits. We excluded 122 women from our analysis who were taking antidepressants other than SSRIs or TCAs (n = 91) or who reported use of both an SSRI and a TCA (n = 31). The remaining 2722 women are included in these analyses of SSRI use, TCA use, and rate of change in hip BMD.

Because depression is associated with lower BMD in some studies, we also performed a secondary analysis in which we excluded 336 women who had a GDS score of at least 6 at visit 6 or 8.

The appropriate institutional review boards approved the study, and written informed consent was obtained from all participants.

**SSRI AND TCA USE**

Participants attending visits 6 and 8 were asked to bring all current (any use within past 2 weeks) prescription and nonprescription medications. Interviewers completed a medication history for each participant, including the name of the medication and frequency of use. A computerized dictionary was used to categorize the type of medication from product brand and generic names obtained from containers. Subsequently, a physician (S.J.D.) blinded to outcome status reviewed the computerized drug data for SSRI use, TCA use, and verified classification of medications.

Nonusers were defined as women not taking an SSRI, a TCA, or any other type of antidepressant at visit 6 or 8. The SSRI users were defined as women reporting SSRI use but not TCA use at either visit; TCA users, those reporting TCA use but not SSRI use at either visit. Women reporting SSRI or TCA use at only 1 of these visits were classified as partial users of that medication; women reporting use at both visits were classified as continuous users.

**MEASUREMENT OF BMD**

Bone mineral density of the total hip and 2 subregions (femoral neck and trochanter) were measured at visits 6 and 8 (mean ± SD, 4.9 ± 0.6 years between examinations) using dual-energy x-ray absorptiometry with bone densitometry scanners (QDR-1000 or QDR-2000; Hologic, Bedford, Mass). The second measurements of hip BMD were performed using the same instruments as used for the initial measurements. Further details of the measurement method, densitometry quality control procedures, and precision of the measurements in our cohort have been published elsewhere. 12-13 For the primary analysis, the rate of change in BMD was expressed as an annualized percentage of the difference between the follow-up BMD and the initial BMD divided by the initial BMD. Secondary analyses were performed with absolute rate of change in BMD (reported as grams per square centimeter) as the outcome measure.

**DEPRESSIVE SYMPTOMS**

Depressive symptoms were evaluated at visit 6 using the 15-item GDS, a self-report scale consisting of 15 yes/no questions regarding symptoms of depression. A standard cutoff of 6 or more symptoms was used to define evidence of depression; the cutoff of 6 or more symptoms has a sensitivity of 88% and a specificity of 62% compared with a structured clinical interview for depression. 12

**OTHER MEASUREMENTS**

Participants completed a questionnaire and were interviewed at visits 6 and 8 about self-reported health, physical activity, and smoking status. Current use of oral estrogen, thiazides, bisphosphonates, vitamin D supplements, and calcium supplements were determined using the method described for ascertainment of antidepressant use. Dietary calcium intake was estimated by using the validated 60-item Block semiquantitative food frequency questionnaire, which was developed from the Second National Health and Nutrition Examination Survey. 16 To assess function, women were asked whether they had difficulty performing any of 6 independent activities of daily living. 17-18 A composite functional impairment score (range, 0-6) expressed the total number of activities that a participant reported difficulty performing. Cognitive function was assessed with the Mini-Mental State Examination (maximum score, 30). 20 Body weight and height were measured by using a balance beam scale and wall-mounted Harpenden stadiometer (Holtain Ltd, Crymych, Wales). 21 Body mass index was calculated as weight in kilograms divided by height in meters squared. Neuromuscular function was assessed by measuring the time in seconds needed to walk 12 m and by determining whether the participant could rise up from a chair (without using the chair’s arms) 5 times. 22

**STATISTICAL ANALYSIS**

We used χ² tests for categorical variables; unpaired, 2-tailed t tests for normally distributed continuous data; and Wilcoxon rank sum tests for skewed continuous data to compare characteristics at visit 6 by category of antidepressant use (nonusers vs SSRI users and nonusers vs TCA users). To examine the association between SSRI use and the rate of change in BMD at the total hip, femoral neck, and trochanter, we calculated the annualized mean change in BMD and its 95% confidence interval (CI) at these sites for nonusers and SSRI users using the least squares method. Similar analyses were performed to examine the association between TCA use and the rate of change of hip BMD. Known risk factors for bone loss in our cohort and characteristics related to antidepressant use were examined for inclusion in multivariable models for the associations between SSRI and TCA use and the rate of change in BMD. We included in our multivariable models age and those variables (race, health status, number of independent activities of daily living impairments, walking speed, ability to rise from a chair, Mini-Mental State Examination score, smoking status, calcium supplement use, vitamin D supplement use, estrogen use, thiazide use, bisphosphonate use, body mass index, weight change, total hip BMD at visit 6, and GDS score) that were related to SSRI or TCA use at P ≤ .10 or a rate of change in BMD at P ≤ .10 independent of age.

Because depression is associated with lower BMD in some studies, we performed secondary analyses in which we excluded women who had a GDS score of at least 6 at visit 6 or 8.

We also performed secondary analyses that examined the as-
Table 1. Use of Antidepressants*

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>No. (%) of Subjects Using Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 6</td>
</tr>
<tr>
<td>SSRIs</td>
<td>65 (2.4)</td>
</tr>
<tr>
<td>Fluoxetine hydrochloride</td>
<td>9 (0.3)</td>
</tr>
<tr>
<td>Paroxetine hydrochloride</td>
<td>25 (0.9)</td>
</tr>
<tr>
<td>Sertraline hydrochloride</td>
<td>30 (1.1)</td>
</tr>
<tr>
<td>Citalopram hydrobromide</td>
<td>0</td>
</tr>
<tr>
<td>Escitalopram oxalate</td>
<td>0</td>
</tr>
<tr>
<td>Fluvoxamine maleate</td>
<td>0 (0.04)</td>
</tr>
<tr>
<td>TCAs</td>
<td>86 (3.2)</td>
</tr>
<tr>
<td>Amitriptyline hydrochloride</td>
<td>55 (2.0)</td>
</tr>
<tr>
<td>Nortriptyline hydrochloride</td>
<td>10 (0.4)</td>
</tr>
<tr>
<td>Imipramine hydrochloride</td>
<td>12 (0.4)</td>
</tr>
<tr>
<td>Desipramine hydrochloride</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>Doxepin hydrochloride</td>
<td>8 (0.3)</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>0</td>
</tr>
<tr>
<td>Protriptyline hydrochloride</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

*Use of antidepressants among the 2722 subjects in the primary analysis.

Forty-three participants were taking an SSRI at visits 6 and 8. One participant was taking 2 SSRIs at visit 6; another participant was taking 2 SSRIs at visit 8. Forty-two participants were taking a TCA at visits 6 and 8. Forty-three participants were taking an SSRI at visits 6 and 8. One participant was taking 2 SSRIs at visit 6; another participant was taking 2 SSRIs at visit 8.

Association between antidepressant (SSRI or TCA) use at visit 6 and change in BMD. To explore whether there was an effect of duration of treatment, we also calculated the annualized mean change in BMD and its 95% CI for nonusers, partial SSRI users, and continuous SSRI users.

All analyses were performed using SAS statistical software (version 9.1, SAS Institute Inc., Cary, NC).

### RESULTS

**CHARACTERISTICS OF THE STUDY POPULATION**

The cohort included 2722 women, of whom 198 (7.3%) were SSRI users and 118 (4.3%) were TCA users. The remaining 2406 women (88.4%) reported no use of an SSRI, a TCA, or other antidepressant at either visit. Specific drug use among women taking SSRIs and TCAs is listed in Table 1.

Characteristics of the 2722 participants at visit 6 according to use of an antidepressant are shown in Table 2. Compared with nonusers, SSRI users were more likely to have a GDS score of at least 6 (13.1% vs 5.2%; P < .001); similar proportions of TCA users and nonusers of antidepressants had a GDS score of at least 6. The SSRI and TCA users had more impairment of independent activities of daily living than did nonusers. The TCA users had evidence of poorer physical functioning, as reflected by slower walking speeds (P < .01) and more difficulty arising from a chair (P = .002).

### SSRI USE AND RATE OF HIP BONE LOSS

Mean rates of bone loss at the total hip, femoral neck, and trochanter, according to category of antidepressant use, are shown in Table 3. On average, women taking SSRIs experienced a higher age-adjusted rate of bone loss at the total hip than nonusers (−0.77% vs −0.49% per year; P = .005). Results were not substantially altered after adjusting for multiple potential confounding factors including age, race, health status, functional status, walking speed, ability to rise from a chair, Mini-Mental State Examination score, smoking status, calcium supplement use, vitamin D supplement use, estrogen use, thiazide use, bisphosphonate use, body mass index, weight change, total hip BMD at visit 6, and GDS score (−0.82% vs −0.47% per year; P < .001). At any of the sites, the adjusted rate of loss among SSRI users was at least 1.6-fold higher than that among nonusers of antidepressants.

In secondary analyses that examined rates of change in BMD for nonusers (n = 2406), partial SSRI users (n = 155), and continuous SSRI users (n = 43), there was no difference in the rate of bone loss between partial and continuous SSRI users.
TCA USE AND RATE OF HIP BONE LOSS

Average rates of hip bone loss among TCA users and antidepressant nonusers were similar in age- and multivariable-adjusted analyses (Table 3). Findings were similar at the femoral neck and trochanter.

SUBJECTS WITH GDS SCORE LESS THAN 6

When 336 women with a GDS score of at least 6 at visit 6 or 8 were excluded, the mean rate of hip bone loss for SSRI users remained higher than that for nonusers, although the magnitude of the difference between the groups was less pronounced. In the multivariable model, the mean rate of bone loss at the total hip among SSRI users was −0.62% (95% CI, −0.93% to −0.31%) per year for SSRI users compared with −0.48% (95% CI, −0.53% to −0.43%) per year for nonusers (P = .36). For TCAs, results of this secondary analysis were unchanged from those of the primary analysis.

USE OF SSRIs AND TCAS AT VISIT 6

We also performed analyses limited to subjects who were taking an SSRI or a TCA at visit 6 compared with nonusers. Use of an SSRI was less common at visit 6 than at visit 8. In this analysis, the association between SSRI use and the rate of change in hip BMD was weaker and did not reach significance. In the multivariable model, the mean rate of bone loss at the total hip was −0.62% (95% CI, −0.54% to −0.43%) per year for continuous users. The mean adjusted rate of total hip bone loss was −0.47% (95% CI, −0.54% to −0.43%) per year for continuous users. The mean adjusted rate of total hip bone loss was −0.47% (95% CI, −0.54% to −0.43%) per year among nonusers, −0.83% (95% CI, −1.03% to −0.63%) per year for partial users, and −0.76% (95% CI, −1.14% to −0.38%) per year for continuous users.

COMMENT

We found that use of SSRIs in our cohort of older women was independently associated with an increased rate of hip bone loss. Use of a TCA was not similarly associated with increased rates of hip bone loss in our cohort.

One potential explanation for our findings is that SSRI use may have a direct deleterious effect on bone. This theory is supported by findings of in vitro and in vivo laboratory investigations. Functional receptors for serotonin and serotonin transporter systems have been identified in osteoblasts, osteoclasts, and osteocytes.23,24 Serotonin has been shown to induce murine osteoblast proliferation and human osteoclast differentiation in vitro.24 Other in vitro data suggest that fluoxetine hydrochloride inhibits osteoblast formation23 and reduces osteoclast differentiation.2,24 These findings suggest that a reduction in osteoblast activity or a reduction in coupled osteoclast/osteoblast activity owing to serotonin transporter inhibition could be a potential mechanism by which SSRIs may influence BMD.

In vivo, both young and adult mice with a null mutation in the gene encoding for the serotonin transporter had reduced bone mass, altered skeletal architecture, and inferior mechanical properties,23 suggesting a role for the serotonin transporter in bone metabolism. Growing mice treated with an SSRI demonstrated reduced bone mineral accrual.25 In both models (genetic disruption of the serotonin transporter and pharmacologic inhibition of it), bone formation rates were reduced, indicating that osteoblast function is significantly reduced in vivo, with inhibition of serotonin transporter function.

Table 3. Mean Annualized Rate of Bone Loss at Total Hip, Femoral Neck, and Trochanter by Category of Antidepressant Use

<table>
<thead>
<tr>
<th>Antidepressant Use Category</th>
<th>Nonusers (n = 2406)</th>
<th>TCA Users (n = 118)</th>
<th>SSRI Users (n = 198)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total hip</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted model</td>
<td>−0.49 (−0.54 to −0.43)</td>
<td>−0.44 (−0.68 to −0.20)</td>
<td>−0.77 (−0.96 to −0.58)†</td>
</tr>
<tr>
<td>Multivariable model*</td>
<td>−0.47 (−0.53 to −0.42)</td>
<td>−0.47 (−0.70 to −0.24)</td>
<td>−0.82 (−1.00 to −0.64)‡</td>
</tr>
<tr>
<td><strong>Femoral neck</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted model</td>
<td>−0.24 (−0.31 to −0.17)</td>
<td>−0.31 (−0.62 to −0.01)</td>
<td>−0.57 (−0.82 to −0.03)†</td>
</tr>
<tr>
<td>Multivariable model*</td>
<td>−0.23 (−0.29 to −0.16)</td>
<td>−0.32 (−0.62 to −0.02)</td>
<td>−0.60 (−0.84 to −0.36)†</td>
</tr>
<tr>
<td><strong>Trochanter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted model</td>
<td>−0.49 (−0.57 to −0.42)</td>
<td>−0.47 (−0.80 to −0.14)</td>
<td>−0.89 (−1.16 to −0.63)†</td>
</tr>
<tr>
<td>Multivariable model*</td>
<td>−0.48 (−0.55 to −0.41)</td>
<td>−0.47 (−0.79 to −0.15)</td>
<td>−0.93 (−1.18 to −0.68)‡</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

*Adjusted for age, race, health status, functional status, walking speed, ability to rise from a chair, Mini-Mental State Examination score, smoking status, calcium supplement use, vitamin D supplement use, estrogen use, thiazide use, bisphosphonate use, body mass index, change in weight, total hip bone mineral density at visit 6 examination, and Geriatric Depression Scale score.

†P < .01 for comparison between SSRI users and nonusers.

‡P < .001 for comparison between SSRI users and nonusers.
On the other hand, evidence in humans that blockade of serotonin reuptake has a negative effect on bone metabolism is limited. Recently, Haney et al.20 reported an association between SSRI use and decreased BMD in older men. In other cross-sectional analyses,8,9,27,28 use of antidepressants has not been associated with reduced BMD, although these other analyses have generally not separated TCA use from SSRI use. Use of antidepressants has been linked to an increased risk of fractures,27,29,30 although the mechanisms underlying this association remain unclear. Owing to their limitations, cross-sectional studies might underestimate or overestimate any association between antidepressant use and bone density.

Observational studies examining possible associations among antidepressant use, bone density, and fractures are subject to confounding, which may also explain our findings. In particular, confounding by indication may be an important issue. Antidepressants are often prescribed for depressive symptoms, and depression itself has been associated with a lower BMD.8-10 Depression has been postulated to have a direct effect on bone density, through such pathways as alterations in the hypothalamic-pituitary-adrenal system and up-regulation of the proinflammatory cytokines interleukin 6 and tumor necrosis factor α.9,31,32 In our study, when women with a GDS score of at least 6 were excluded, the magnitude of the difference in rates of hip bone loss between SSRI users and nonusers was attenuated, suggesting that confounding by indication at least partially explains our findings. The GDS measurement was only available at the clinic examinations; thus, we cannot account for depressive symptoms that may have been present between visits. In addition, although the GDS is a useful screening tool for depression, it cannot substitute for a clinical diagnosis of depression based on established diagnostic criteria.

Medical conditions associated with increased loss of bone density, such as chronic obstructive pulmonary disease, liver disease, and diabetes mellitus,33 may also predispose to depression; thus, patients with these conditions may be more likely to be prescribed antidepressants. In addition, depression is associated with decreased mobility and weight loss, both of which have effects on bone. Owing to concerns about the adverse effects of TCAs, SSRIs may be preferentially prescribed to participants perceived to be at higher risk for falls because of comorbidities; these comorbidities may also predispose them to higher rates of bone loss, another potential source of confounding. To address these potential confounders, we adjusted for health status, functional status, and weight change, although unmeasured factors might explain our results.

Because our cohort consists of elderly women, we cannot extrapolate our findings to other populations. Because we have limited information on dose and duration of use of antidepressants in the cohort, we were limited in our ability to look for evidence of a dose effect of antidepressants on the rate of change of BMD. We did not find evidence that continuous users had higher rates of bone loss than partial users. In addition, the small number of SSRI users at visit 6 was insufficient to determine whether SSRI use was prospectively associated with subsequent rates of bone loss. We observed an increase in the prevalence of SSRI use in our cohort between visit 6, which occurred in 1997 through 1998, and visit 8, which occurred in 2002 through 2004, consistent with other data.1 Future research with larger numbers of SSRI users will be important to determine whether SSRI use is prospectively associated with increased rates of bone loss.

We did not find that use of TCAs, which also have an effect on serotonin reuptake, was associated with an increased rate of hip bone loss. There are several potential explanations for this finding. Tricyclic antidepressants are often prescribed for reasons other than depression, such as sleep disorders or chronic pain. As a result, fewer subjects receiving TCAs than the number receiving SSRIs may have underlying depression. When prescribed for treatment of insomnia or chronic pain, TCAs are often prescribed at lower doses than those used to treat depression; as a result, the degree of serotonin blockade may be lower than that associated with SSRI use. Alternatively, we may not have observed an association between TCA use and rates of bone loss because the degree of serotonin transporter inhibition differs among the many TCAs; for example, desipramine’s potency at the serotonin transporter is lower than that of fluoxetine in osteoblasts.3

Our findings suggest that, in this cohort, use of SSRIs is associated with increased rates of hip bone loss. Although some of this association is likely due to confounding by indication, further investigation of SSRI use and rates of change in BMD in other populations with longer follow-up is warranted given the recent description of serotonin transporters in bone.

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Author Contributions: Dr Diem had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Diem, Stone, and Ensrud. Acquisition of data: Diem, Stone, and Ensrud. Analysis and interpretation of data: Diem, Blackwell, Stone, Yaffe, Haney, Bliziotes, and Ensrud. Drafting of the manuscript: Diem. Critical revision of the manuscript for important intellectual content: Blackwell, Stone, Yaffe, Haney, Bliziotes, and Ensrud. Statistical analysis: Blackwell, Stone, and Yaffe. Obtained funding: Stone and Ensrud. Study supervision: Stone.

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