Central Nervous System Active Medications and Risk for Fractures in Older Women

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Background: Use of central nervous system (CNS) active medications may increase the risk for fractures. Prior studies are limited by incomplete control of confounders.

Methods: To determine whether use of CNS active medications, including benzodiazepines, antidepressants, anticonvulsants, and narcotics, increases fracture risk in elderly, community-dwelling women, we examined use of these 4 categories of medications in a cohort of 8127 older women and followed the participants prospectively for incident nonspine fractures, including hip fractures. Current use of CNS active medications was assessed by interview with verification of use from containers between 1992 and 1994 and between 1995 and 1996. Use was coded as a time-dependent variable. Incident nonspine fractures occurring after the initial medication assessment until May 31, 1999, were confirmed by radiographic reports.

Results: During an average follow-up of 4.8 years, 1256 women (15%) experienced at least one nonspine fracture, including 288 (4%) with first hip fractures. Compared with nonusers, women taking narcotics (multivariate hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.06-1.83) and those taking antidepressants (multivariate HR, 1.25; 95% CI, 0.99-1.58) had increases in the risks for any nonspine fractures. Women taking tricyclic antidepressants and those using selective serotonin reuptake inhibitors (SSRIs) had similar fracture rates. There were no independent associations between benzodiazepine use or anticonvulsant use and risk for nonspine fracture. Women taking antidepressants compared with nonusers had a 1.7-fold increase in the risk for hip fracture (multivariate HR, 1.65; 95% CI, 1.05-2.57). We did not observe independent associations between use of any of the other 3 classes of CNS active medications and risk of hip fracture.

Conclusions: Community-dwelling older women taking narcotics have an increased risk for any nonspine fracture, and those taking antidepressants have a greater risk for nonspine fractures, including hip fracture. Rates of fracture were similar in women taking tricyclic antidepressants and those using SSRIs. Benzodiazepine use and anticonvulsant use were not independently associated with an increased risk of nonspine fractures, including hip fracture.

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zodiazepines, whereas the risk in users of short-acting preparations is similar to that in nonusers. However, other investigations\textsuperscript{10,11} have reported an increase in risk with use of specific types of short-acting preparations but not with use of long-acting preparations. The association between use of newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and hip fracture risk is also uncertain. Often, SSRIs are preferentially prescribed in elderly people instead of tricyclic antidepressants because of a reduction in the potential for adverse effects.\textsuperscript{12,13} However, a population-based case-control study that linked data on diagnoses and medication prescriptions in large computerized files\textsuperscript{5} reported that exposure to either class of antidepressant was associated with an increase in the odds of hip fracture. To test the hypothesis that current use of certain CNS active medications, including benzodiazepines, antidepressants, anticonvulsants, and narcotics, increases the risks for fractures in older, community-dwelling women, we examined the use of these 4 categories of medications in a cohort of 8127 elderly women and followed up the participants prospectively for incident nonspine fractures, including hip fractures.

**METHODS**

**PARTICIPANTS**

From September 10, 1986, to October 31, 1988, 9704 women at least 65 years old were recruited for participation in the baseline examination of the prospective Study of Osteoporotic Fractures. Women were recruited from population-based listings in 4 areas of the United States: Baltimore County, Maryland; Minneapolis, Minn; Portland, Ore; and the Monongahela Valley, Pennsylvania.\textsuperscript{14} We excluded black 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.

Beginning on August 4, 1992, all surviving participants (93% of the original cohort) were invited to participate in a fourth examination completed on July 31, 1994. Of these participants, 8127 women (93% of survivors as of July 31, 1994) completed at least the questionnaire component of the fourth examination and are the subject of this analysis. A total of 6330 women (78%) attended a fourth clinic visit, 488 (6%) had a home visit, and 1309 (16%) completed the questionnaire but did not have a clinic or home visit. A fifth clinic examination was conducted between January 3, 1995, and August 31, 1996. Of the 8127 women completing the fourth examination, 7278 women (93% of survivors as of August 31, 1996) completed at least the questionnaire component of the fifth examination. These included 5674 women (78%) who attended a fifth clinic visit, 571 (8%) who had a home visit, and 1033 (14%) who completed a questionnaire but did not have a home or clinic visit. After the fourth examination, we contacted participants every 4 months for incident nonspine fractures until May 31, 1999. The appropriate institutional review boards approved the study. Written informed consent was obtained from all participants.

**USE OF CNS ACTIVE MEDICATIONS**

Participants who attended a clinic visit during the fourth and fifth examinations were asked to bring all current (any use within the past 2 weeks) prescription and nonprescription medications with them to the clinic. Interviewers completed a medication history for each participant, including type of medication and frequency of use. Women who completed home visits during either examination had their medication history performed by an interviewer at the participant’s residence. For participants who did not complete a visit during either examination, the medication history was obtained during a telephone interview.

A computerized dictionary was used to initially categorize type of medication from product brand and generic names obtained from containers or from participant report. Subsequently, a physician (K.E.E.) and doctor of pharmacy (J.T.H.) blinded to outcome status reviewed the computerized drug data and classified medications using the Veterans Affairs Medication Classification System.\textsuperscript{13} Four mutually exclusive categories of CNS active medications, benzodiazepines, antidepressants, anticonvulsants, and narcotics, were considered in this analysis. Benzodiazepines were further classified as long acting (elimination half-life of at least 24 hours) or short acting (elimination half-life of less than 24 hours). Long-acting benzodiazepines included flurazepam, chlordiazepoxide, clorazepate, diazepam, clonazepam, halazepam, and prazepam. Short-acting preparations included alprazolam, estazolam, lorazepam, oxazepam, temazepam, and triazolam. Antidepressants were further classified as tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, trimipramine, desipramine, nortriptyline, and protriptyline) and SSRIs (fluoxetine, paroxetine, and sertraline). No participant reported taking either citalopram or fluvoxamine at the fourth or fifth examination. Women who reported current use of opioid-containing antidiarrheal medications or cough syrups were classified as nonusers of narcotics.

**ASCERTAINMENT OF FRACTURES**

After the fourth examination, we contacted participants about fractures every 4 months by postcard or telephone and were able to complete 98% of these follow-up contacts. All fractures were confirmed by radiographic reports; hip fractures were also validated by reviewing preoperative radiographs.\textsuperscript{16} We excluded fractures that occurred because of major trauma. Self-reported vertebral fractures were also excluded, since most vertebral fractures do not come to medical attention.\textsuperscript{17} The category “all nonspine fractures” included all nontraumatic, nonvertebral fractures. Follow-up for fractures after the fourth examination ranged from 1 day to 6.7 years; average follow-up was 4.4 years for any nonspine fracture and 4.8 years for hip fracture.

**OTHER MEASUREMENTS**

Participants completed a questionnaire and were interviewed at the fourth examination and asked about self-reported health, physical activity, smoking, trouble with dizziness, and falls during the previous year. A selected medical history was obtained, including a history of stroke, diabetes, Parkinson disease, dementia, chronic obstructive lung disease, osteoarthritis, and nonskin cancer. Current use of oral estrogen was determined using the method described for ascertainment of use of other medications. To assess function, women were asked whether they had difficulty performing any of 5 independent activities of daily living.\textsuperscript{18} These activities included walking 2 to 3 blocks on level ground, climbing up to 10 steps, preparing meals, doing heavy housework, and shopping for groceries or clothing. A composite functional impairment score expressed the total number of activities (ranging from 0 to 5) that a participant reported difficulty performing. Cognitive function was assessed with a modified version of the Mini-Mental State Examination,\textsuperscript{18} with a maximum score of 26.

Depressive
symptoms were evaluated using the 15-item Geriatric Depression Scale; the standard cutoff of 6 or more symptoms was used to define depression.

Body weight was measured with a standard balance beam scale at the baseline and fourth examinations. Weight change was calculated by subtracting weight at the baseline examination from weight at the fourth examination. Tests of neuromuscular function included gait speed assessed by measuring the time in seconds needed to walk 12 m and ability to rise from a chair assessed by determining whether the participant could rise from a chair (without using her arms) 5 times. Bone mineral density (in grams per square centimeters) of the proximal femur was measured using dual x-ray absorptiometry (QDR 1000; Hologic Inc, Waltham, Mass).

**STATISTICAL ANALYSIS**

Differences in characteristics at the fourth examination between women who were current users of drugs in each of the 4 categories of CNS medications and those women who were nonusers of medications in any of the 4 categories were compared using χ² tests for dichotomous variables, t tests for continuous variables with normal distributions, and Wilcoxon tests for categorical variables with skewed distributions.

We used Cox proportional hazards models to analyze the association between current use of drugs in each of the 4 categories of CNS medications and risk of subsequent fracture, including any nonspine and hip fractures. Current use of drugs in each of the 4 categories of CNS active medications was expressed as a time-dependent predictor variable. For women who experienced fractures between the fourth and fifth examination, the coding of CNS active medication use was based on data from the fourth examination. For women experiencing fractures after the fifth examination, the coding of CNS active medication use was based on data from the fifth examination.

For all primary analyses, the risk of the outcome in women who were current users of drugs in each of the 4 categories of CNS medications was compared with the risk in those women who were nonusers of medications in any of the 4 categories. Based on our medication use data at the fourth and fifth examinations, we had 80% power to detect hazard ratios (HRs) of 1.41 (benzodiazepines), 1.40 (antidepressants), 1.94 (anticonvulsants), and 1.48 (narcotics) for the outcome of any nonspine fracture.

Secondary analyses were performed comparing the risk of the outcome in women who were current users of medications in a given category of CNS medications with the risk in those women who were not taking medications in that specific drug category. The risk of each outcome in women who were daily users of drugs in each of the 4 categories of CNS medications was also compared with the risk in those women who were nonusers of medications in any of the 4 categories. Finally, we excluded from the analyses women taking 2 or more CNS active medications categorized in different classes (eg, benzodiazepine and narcotic). Since the findings from these secondary analyses were similar to those from our primary analyses, we present the results from our primary analyses.

To obtain adjusted risk estimates for each fracture outcome, we added covariates individually one at a time and simultaneously to models that included current use and age as predictors. Potential covariates examined included known risk factors for fractures in our cohort and characteristics related to use of CNS active medications. All potential covariates were measured at the fourth examination. Covariates for a given multivariate model included those factors that were related to both current use of a specific category of CNS active medications at P≤.10 and risk of a given fracture outcome at P≤.10 independent of age and specific medication category. Multivariate mod-

**RESULTS**

**CHARACTERISTICS OF THE STUDY POPULATION**

At the time of the fourth examination, the cohort included 8127 elderly women, of whom 626 (8%) were current users of benzodiazepines, 501 (6%) were current users of anticonvulsants, 123 (2%) were current users of anticonvulsants, and 437 (5%) were current users of narcotics (Table 1). Of the women taking benzodiazepines, 358 (57%) were daily users and 238 (38%) took long-acting preparations. Among the women taking antidepressants, 452 women (90%) were daily users, 353 (70%) took tricyclic antidepressants, and 103 (21%) were using SSRIs. Of the women taking anticonvulsants, 117 (95%) were daily users and 62 (50%) reported a history of a physician-diagnosed seizure disorder. Among the women taking narcotics, 241 (55%) were daily users. There were 253 women in the cohort (3%) at the time of the fourth examination who reported taking 2 or more CNS active medications categorized in different classes. These included 68 women taking a benzodiazepine and narcotic, 74 taking a benzodiazepine and antidepressant, 64 taking an antidepressant and narcotic, and 17 taking a benzodiazepine, narcotic, and antidepressant.

At the time of the fifth examination, 7278 participants in the original cohort of 8127 women reported data on medication use. Of these, 518 (7%) were current users of benzodiazepines, 534 (8%) were current users of anticonvulsants, 116 (2%) were current users of anticonvulsants, and 409 (6%) were current users of narcotics.
Among women taking benzodiazepines at the fifth examination, 192 (37%) used long-acting preparations. Of the women taking antidepressants at the time of the fifth examination, 316 (57%) took tricyclic antidepressants and 194 (35%) reported use of SSRIs.

Characteristics of the 8127 participants at the fourth examination according to use of CNS active medications are shown in Table 2. Compared with current users in each of the 4 categories of CNS active medications, nonusers were more likely to report excellent or good health status and walking for exercise and less likely to report a history of chronic medical conditions, dizziness, falling in the past year, and depressive symptoms. In addition, nonusers had less functional impairment and weight loss and better physical performance as measured by gait speed and ability to rise from a chair. During an average follow-up of 4.4 years after the fourth examination, 1256 women (15%) experienced at least one nonspine fracture, including 288 women (4%) who had a first hip fracture.

After adjustment for age alone, current benzodiazepine users compared with nonusers had a 28% increased risk of any nonspine fracture (HR, 1.28; 95% confidence interval [CI], 1.05-1.57) and a 54% increased risk of first hip fracture (HR, 1.54; 95% CI, 1.04-2.28) (Table 3 and Table 4). However, the relationships were reduced in magnitude and not significant after adjustment for multiple factors related to benzodiazepine use and risk of fracture (multivariate HR, 1.12; 95% CI, 0.88-1.42; for nonspine fracture; and multivariate HR, 1.20; 95% CI, 0.72-2.00; for hip fracture). In particular, the association between benzodiazepine use and risk for hip fracture seemed to be largely explained by lower femoral neck bone density among older women taking benzodiazepines (HR adjusted for age and bone density, 1.24; 95% CI, 0.75-2.05). We found no evidence of independent associations between either use of long-acting preparations or use of short-acting agents and risk for fracture, including hip fracture (Figure 1).

**ANTICONVULSANT USE AND RISK FOR FRACTURES**

After adjustment for multiple potential confounders, women taking anticonvulsants had a 1.7-fold increase in the risk for subsequent hip fracture (multivariate HR, 1.65; 95% CI, 1.05-2.57) (Table 4). Antidepressant users also had a 1.3-fold increase in the risk for any nonspine fracture (multivariate HR, 1.25; 95% CI, 0.99-1.58; \( P = .07 \)), although the CIs slightly overlapped 1.0 (Table 3).

The presence of depressive symptoms appeared to increase the risk for fracture to a similar degree as use of antidepressants in models adjusted for age, antidepressant use, and depressive symptoms (results not shown). However, after adjustment for additional confounders, depression was not independently related to the risk of fracture (multivariate HR, 1.08; 95% CI, 0.83-1.41; for any nonspine fracture; and multivariate HR, 1.36; 95% CI, 0.85-2.18; for hip fracture).

Compared with nonusers, women using tricyclic antidepressants and those using SSRIs appeared to be at increased risk of fracture, especially hip fracture (Figure 2). However, the association between medication use and hip fracture reached significance only in the case of women taking tricyclic antidepressants (multivariate HR for hip fracture, 1.83; 95% CI, 1.08-3.09; for tricyclic antidepressant users; and multivariate HR for hip fracture, 1.54; 95% CI, 0.62-3.82; for users of SSRIs).

**ANTIDEPRESSANT USE AND RISK FOR FRACTURES**

After adjustment for age alone, women currently taking antidepressants had a 1.7-fold increase in the risk for subsequent hip fracture (multivariate HR, 1.65; 95% CI, 1.05-2.57) (Table 4). Antidepressant users also had a 1.3-fold increase in the risk for any nonspine fracture (multivariate HR, 1.25; 95% CI, 0.99-1.58; \( P = .07 \)), although the CIs slightly overlapped 1.0 (Table 3).

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**BENZODIAZEPINE USE AND RISKS FOR FRACTURES**

After adjustment for age alone, current benzodiazepine users compared with nonusers had a 28% increased risk of any nonspine fracture (HR, 1.28; 95% confidence interval [CI], 1.05-1.57) and a 54% increased risk of first hip fracture (HR, 1.54; 95% CI, 1.04-2.28) (Table 3 and Table 4). However, the relationships were reduced in magnitude and not significant after adjustment for multiple factors related to benzodiazepine use and risk of fracture (multivariate HR, 1.12; 95% CI, 0.88-1.42; for nonspine fracture; and multivariate HR, 1.20; 95% CI, 0.72-2.00; for hip fracture). In particular, the association between benzodiazepine use and risk for hip fracture seemed to be largely explained by lower femoral neck bone density among older women taking benzodiazepines (HR adjusted for age and bone density, 1.24; 95% CI, 0.75-2.05). We found no evidence of independent associations between either use of long-acting preparations or use of short-acting agents and risk for fracture, including hip fracture (Figure 1).
Table 2. Characteristics of Participants According to Current Use of Central Nervous System Active Medications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonusers of 4 Drug Classes (n = 6720)</th>
<th>Benzodiazepine Users (n = 626)</th>
<th>Antidepressant Users (n = 501)</th>
<th>Anticonvulsant Users (n = 123)</th>
<th>Narcotics Users (n = 437)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>76.9 ± 5.0</td>
<td>77.0 ± 4.7</td>
<td>77.1 ± 4.8</td>
<td>77.6 ± 5.1</td>
<td>78.0 ± 5.4†</td>
</tr>
<tr>
<td>Self-reported health status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent or good</td>
<td>82</td>
<td>66†</td>
<td>63†</td>
<td>62†</td>
<td>53†</td>
</tr>
<tr>
<td>Fair</td>
<td>16</td>
<td>28</td>
<td>31</td>
<td>27</td>
<td>38</td>
</tr>
<tr>
<td>Poor or very poor</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Current oral estrogen user, %</td>
<td>16</td>
<td>18</td>
<td>27†</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>≥1 Selected medical conditions, %‡</td>
<td>45</td>
<td>60†</td>
<td>61†</td>
<td>66†</td>
<td>68†</td>
</tr>
<tr>
<td>Walks for exercise, %</td>
<td>49</td>
<td>42†</td>
<td>38†</td>
<td>41§</td>
<td>27†</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>6</td>
<td>6§</td>
<td>8§</td>
<td>10§</td>
<td>6</td>
</tr>
<tr>
<td>Mean number of IADL difficulties, ±SD</td>
<td>0.6 ± 1.2</td>
<td>1.2 ± 1.6†</td>
<td>1.5 ± 1.7†</td>
<td>1.6 ± 1.9†</td>
<td>2.0 ± 1.7†</td>
</tr>
<tr>
<td>Trouble with dizziness, %</td>
<td>25</td>
<td>35†</td>
<td>36†</td>
<td>34†</td>
<td>38‡</td>
</tr>
<tr>
<td>Fall in previous year, %</td>
<td>29</td>
<td>37†</td>
<td>40†</td>
<td>45†</td>
<td>40†</td>
</tr>
<tr>
<td>Mini-Mental State Examination score, mean ± SD</td>
<td>24.5 ± 1.9</td>
<td>24.2 ± 2.1</td>
<td></td>
<td></td>
<td>24.0 ± 2.3†</td>
</tr>
<tr>
<td>Depression, %</td>
<td>6</td>
<td>18†</td>
<td>21†</td>
<td>20†</td>
<td>20†</td>
</tr>
<tr>
<td>Weight change, mean ± SD, kg</td>
<td>-0.9 ± 5.2</td>
<td>-1.8 ± 6.1</td>
<td></td>
<td></td>
<td>-1.7 ± 6.5</td>
</tr>
<tr>
<td>Gait speed, mean ± SD, m/s</td>
<td>1.0 ± 0.2</td>
<td>0.9 ± 0.2†</td>
<td>0.9 ± 0.2†</td>
<td>0.9 ± 0.3†</td>
<td>0.8 ± 0.3†</td>
</tr>
<tr>
<td>Inability to rise from chair, %</td>
<td>10</td>
<td>18†</td>
<td>23†</td>
<td>25†</td>
<td>37†</td>
</tr>
<tr>
<td>Femoral neck bone density, mean ± SD, g/cm²</td>
<td>0.634 ± 0.116</td>
<td>0.619 ± 0.123¶</td>
<td>0.629 ± 0.126</td>
<td>0.596 ± 0.101¶</td>
<td>0.613 ± 0.122¶</td>
</tr>
</tbody>
</table>

Abbreviation: IADL, independent activities of daily living.
*All characteristics were measured at the fourth examination; change in weight was the difference between baseline and fourth examinations.
†P<.001 compared with nonusers.
‡One or more selected medical conditions, including stroke, diabetes, Parkinson disease, dementia, chronic obstructive lung disease, osteoarthritis, and nonskin cancer.
§P<.10 compared with nonusers.
¶P<.05 compared with nonusers.
†P<.01 compared with nonusers.

Table 3. Association Between Current Use of Central Nervous System Active Medications and Risk of Any Nonspine Fracture

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age-Adjusted RR (95% CI)</th>
<th>Multivariate RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>1.28 (1.05-1.57)</td>
<td>1.12 (0.88-1.42)†</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1.48 (1.21-1.80)</td>
<td>1.25 (0.99-1.58)‡</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>1.68 (1.16-2.43)</td>
<td>1.26 (0.79-1.98)§</td>
</tr>
<tr>
<td>Narcotics</td>
<td>1.76 (1.44-2.16)</td>
<td>1.40 (1.06-1.83)§</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
*Relative risk of any nonspine fracture for current users compared with nonusers of central nervous system active medications expressed as hazard ratios.
†Adjusted for age, health status, 1 or more medical conditions, walking for exercise, functional impairment, cognitive function, depression, weight change, gait speed, inability to rise from chair, and femoral neck bone density (base model).
‡Base model plus smoking and depression minus femoral neck bone density.
§Base model plus cognitive function and depression.

Table 4. Association Between Current Use of Central Nervous System Active Medications and Risk of Hip Fracture

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age-Adjusted RR (95% CI)</th>
<th>Multivariate RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>1.54 (1.04-2.28)</td>
<td>1.20 (0.72-2.00)†</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>2.03 (1.40-2.93)</td>
<td>1.65 (1.05-2.57)‡</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>2.00 (0.94-4.25)</td>
<td>1.37 (0.51-3.73)§</td>
</tr>
<tr>
<td>Narcotics</td>
<td>2.12 (1.46-3.09)</td>
<td>1.22 (0.69-2.15)§</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
*Relative risk of hip fracture for current users compared with nonusers of central nervous system active medications expressed as hazard ratios.
†Adjusted for age, health status, walking for exercise, smoking, functional impairment, cognitive function, depression, weight change, gait speed, inability to rise from chair, and femoral neck bone density (base model).
‡Base model minus health status, walking for exercise and femoral neck bone density.
§Base model minus cognitive function and depression.

...with a history of a seizure disorder from the analyses did not alter these results.

NARCOTIC USE AND RISK FOR FRACTURES

After adjustment for age, women taking narcotics were at increased risk for subsequent fractures (Tables 3 and 4). Compared with nonusers, current users of narcotics had an approximate 2-fold increase in the risks of any nonspine fracture and hip fracture (age-adjusted HR, 1.76;
95% CI, 1.44-2.16; for nonspine fracture; and age-adjusted HR, 2.12; 95% CI, 1.46-3.09; for hip fracture). After adjustment for multiple factors related to narcotic use and risk of fracture, women taking narcotics still had a moderate increase in the risk for any nonspine fracture (multivariate HR, 1.40; 95% CI, 1.06-1.83). However, the association between narcotic use and risk of hip fracture was considerably reduced in magnitude and no longer significant after adjustment for gait speed (HR adjusted for age and gait speed, 1.44; 95% CI, 0.89-2.32). Additional adjustment for other potential confounders further diminished the strength of the association (multivariate HR, 1.22; 95% CI, 0.69-2.15).

We found an increased risk for nonspine fractures among community-dwelling, older women taking antidepressants and those taking narcotics. In particular, elderly women taking antidepressants had a 1.7-fold increased risk of hip fracture. We did not observe independent associations between use of benzodiazepines or anticonvulsants and risk for fracture. Our findings suggest that the higher risk of hip fracture observed among older women taking benzodiazepines in previous studies might be due to lower hip bone density in women using benzodiazepines. Our results also indicate that preferential use of SSRIs instead of tricyclic antidepressants is unlikely to decrease fracture risk among older women taking antidepressants.

Our results suggest that elderly women taking antidepressants have a small increase in the risk of any nonspine fracture and a moderate increase in the risk of hip fracture. These results are in agreement with those of prior analyses of administrative databases. In addition, we found that hip fracture risk was similar among women taking SSRIs and those taking tricyclic antidepressants. Similarly, Liu and colleagues' reported that exposure to either SSRIs or tricyclic antidepressants was associated with an increase in the odds of hip fracture. An increased risk for hip fracture among women taking antidepressants may be related to medication adverse effects, such as sedation and postural hypotension, or may be due to confounding by indication. Since the increased risk of hip fracture in antidepressant users in our cohort was not explained by controlling for a variety of potential confounders, including functional impairment, cognitive function, depressive symptoms, weight change, and neuromuscular performance, confounding by indication is unlikely to account for our findings.

Clinical depression or depressive symptoms have been associated with lower bone density in prior studies, including a small case-control study of younger women and a cross-sectional study of 1566 men and women aged 65 years and older. However, a previous analysis of our large cohort of elderly women indicated that women with depressive symptoms had an average bone density similar to that among women without symptoms. In addition, findings from our present analysis suggest that average bone density in elderly women taking antidepressants is similar to that of nonusers. Irrespective of whether depression or antidepressant use is or is not related to lower bone density, the association we observed between antidepressant use and risk of hip fracture in our cohort was not substantially
reduced after additional adjustment for hip bone density. In our current analysis with its comprehensive assessment of medication use at the fourth and fifth examinations, antidepressant use appeared to be a more robust predictor of subsequent fracture risk than presence of depressive symptoms. In contrast, a previous analysis from our cohort reported that the association between depressive symptoms at the second examination and risk of subsequent nonspine fracture was independent of psychotropic medication use. However, use of psychotropic medications was assessed at the second examination with a general question asking about use of any medications for anxiety, nerves, or relaxation during the past 12 months.

Our findings indicate that older women taking narcotics have an increased risk for fracture. The apparent increase in risk for hip fracture among narcotic users in our cohort appeared to be largely explained by slower gait speed. However, narcotic use was independently associated with the risk of any nonspine fracture despite adjustment for several potential confounders, including age, health status, estrogen use, comorbid medical conditions, physical activity, functional impairment, dizziness, fall history, depressive symptoms, weight change, neuromuscular performance, and hip bone density. Narcotic use may increase the risk of fracture by increasing propensity to fall due to CNS effects, such as sedation and dizziness. It is also plausible that narcotics use directly results in neuromuscular impairments that increase the risk of falls. However, the women taking narcotics in our cohort had multiple reasons for impaired neuromuscular function apart from narcotic use, including a higher prevalence of comorbid medical conditions such as osteoarthritis. A prior case-control study reported a 1.6-fold increase in the risk of hip fracture among current users of opioid analgesics, and a prospective cohort study of 1608 elderly men and women found a 2-fold risk of hip fracture in users of opioid analgesics (97% took propoxyphene). However, neither of these studies adjusted for characteristics such as low bone density, poor health status, weight loss, and impairments in neuromuscular function, which are more common in narcotics users and strongly related to risk of hip fracture.

Benzodiazepine use may directly increase the risk of fracture in elderly individuals by increasing susceptibility to falls. On the other hand, benzodiazepine use among older people may be a marker of conditions that substantially increase fracture risk, such as poor health, frailty, impaired cognition, weight loss, and low bone density. After adjustment for these and other potential confounding factors in our cohort of elderly women, we did not find evidence of an independent association between use of benzodiazepines and risk for fracture. In particular, we observed that the increased risk for hip fracture among elderly women taking benzodiazepines was largely explained by their lower hip bone density.

Our results suggest that neither use of short-acting preparations nor use of long-acting preparations is independently associated with an increased risk of nonspine fracture, including hip fracture. Some prior studies have reported increases in hip fracture risk with use of long-acting but not short-acting benzodiazepines. On the other hand, other investigations have reported increases in hip fracture risk only with use of certain types of short-acting benzodiazepines, whereas still others have not found an increase in risk with benzodiazepine use irrespective of drug elimination half-life. Doseage among users of either short or long half-life benzodiazepines has been associated with hip fracture risk in a prior study. However, Pierfitte and colleagues did not find the presence of benzodiazepines in plasma to be associated with an increased risk of hip fracture, except for lorazepam, in a recent case-control study. None of these previous studies that evaluated the association between benzodiazepine use and hip fracture controlled for characteristics such as low hip bone density and recent weight loss, including a previous analysis from our cohort that reported an association between use of long-acting benzodiazepines and hip fracture. Benzodiazepine use may increase the risk of hip fracture by directly impairing neuromuscular function and increasing susceptibility to falls. However, our current findings indicate that the relationship observed between benzodiazepine use and hip fracture is largely because benzodiazepine use is a marker of low hip bone density.

Anticonvulsant use may increase the risk of fracture for several reasons. First, effects of anticonvulsant use on the CNS, such as sedation and impairments in balance, may increase the risk of falls. Second, anticonvulsant use may be directly detrimental to bone by resulting in osteomalacia or secondary hyperparathyroidism. Finally, anticonvulsant use may be a marker of conditions such as poor health and weight loss that increase fracture risk. Our findings support the viability of all these pathways linking anticonvulsant use and fracture. Deficits in neuromuscular function and a fall history were common among older women in our cohort taking anticonvulsants. In addition, our results indicate that average bone density is decreased among anticonvulsant users, and this lower bone density among users explained a substantial portion of the increased fracture risk attributable to anticonvulsant use. After adjustment for these factors and markers of frailty, such as poor health status, functional impairment, depressive symptoms, and weight change, our associations between anticonvulsant use and fracture were no longer significant. However, given the magnitude of the HRs and wide CIs, our findings suggest the presence of an association between anticonvulsant use and increased risk of fracture but indicate that our statistical power was inadequate to detect this relationship. In general, our findings are in agreement with prior studies of anticonvulsant use and fracture risk that included less comprehensive measures of potential confounders, including an earlier analysis from our cohort. It may be that specific types, various doses, or certain combinations of anticonvulsant drugs have different effects on the risk of bone loss and fractures. For example, antiepileptic drugs that induce hepatic microsomal enzymes, thereby increasing vitamin D metabolism, might be expected to increase the risk of bone loss and...
fracture to a greater extent than drugs without hepatic enzyme–inducing effects. Our study has insufficient power to evaluate the risk of fracture with use of specific anticonvulsant medications or combinations of antiepileptic drugs.

Our study has several strengths. We verified medication use using detailed interviews at 2 different examinations and coded medication use as a time-dependent variable in our analyses. Although we were not able to completely control for all confounders of the associations between medication use and risk of fracture, we made adjustments where appropriate for several factors, including health status, estrogen use, comorbid medical conditions, physical activity, smoking, functional impairment, dizziness, fall history, cognitive performance, depressive symptoms, weight change, neuromuscular function, and hip bone density. Finally, fractures were confirmed with radiographic reports, and all measurements were blinded to fracture outcome.

However, our study also has several limitations. Because the participants were elderly, white women living in the community, our findings may not apply to other population groups. Adjusting our analyses for factors such as fall history, dizziness, cognition, and neuromuscular function in our multivariate analyses may also have biased our estimates of the associations between medication use and fractures toward the null hypotheses. On the other hand, since these factors may be simultaneously intermediate and confounding variables, failure to adjust for them would have resulted in incomplete control of confounding. Although medication use was assessed at 2 points and coded as a time-dependent variable, unmeasured changes in medication use likely occurred during follow-up. In addition, information regarding the medication dosage was not readily available, although we did find that substitution of daily users for current users in our analyses had no impact on our results. Finally, we had limited power to detect small differences in fracture risk between users and non-users, especially in the case of anticonvulsants.

We conclude that antidepressant use and narcotic use are independent risk factors for nonspine fractures in community-dwelling, elderly women and that older women taking antidepressants are at increased risk for hip fracture. Our findings suggest that preferential prescription of SSRIs instead of tricyclic antidepressants will not likely reduce the risk of fracture associated with antidepressant use in elderly people. In addition, our results indicate that the relationship between benzodiazepine use and increased risk for hip fracture previously observed in elderly women may be largely explained by lower bone density among users of benzodiazepines. To provide more definitive data on the relationship between use of CNS active medications and risk for fracture in elderly people, randomized clinical trials of these medications in elderly patients to test possible long-term benefits should also include fractures as secondary outcomes.

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