Clinical and Practical **Psychopharmacology**

Antidepressant Drugs and the Risk of Hip Fracture in the Elderly: Is There More to It Than Confounding by Indication?

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

The risk of bone fracture is increased in the elderly, in persons with depression, and in those who receive antidepressant drugs. Plausible mechanisms explain these risks. It is not clear whether the risk in depression is related to the disorder alone or to its treatment with antidepressant drugs as well; this is because observational studies of the fracture risk associated with antidepressant exposure may adjust analyses for confounding variables but cannot eliminate residual confounding by inadequately measured, unmeasured, and unknown confounds. A recent observational study examined hip fracture in the context of depression and antidepressant treatment using a resourceful method to address confounding by indication. The authors studied the risk of fracture not only in the year after antidepressant initiation but also in the year before antidepressant initiation. They found a significantly increased risk of fracture in all of 10 time windows during the 2 years; the highest risks, in fact, lay in the weeks to months *before* antidepressant initiation. These findings suggest that unremitted depression and persistence of depression-related mechanisms in remitted depression may together drive the risk of hip fracture in observational studies of antidepressant-treated patients; however, there is evidence from other sources to suggest that a contribution from antidepressant-related mechanisms cannot be ruled out. An additional message is that investigators need to use resourceful methods to address confounding by indication, as is now being done in several fields of research. Finally, readers who evaluate the findings of studies that relate exposures to outcomes must consider how the investigators addressed confounding and must draw conclusions based not merely on the findings but also on issues related to research design.

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Elderly persons, especially women, are vulnerable to osteoporosis and to fragility fractures.[1] Elderly persons are also vulnerable to falls,[2] and to fractures after falls, the risk of which is mitigated by exercise.[3] Finally, depression is common in the elderly,[4] and depression in the elderly is itself associated with reduced bone mineral density[5] and an increased risk of fractures. For example, in an updated meta-analysis of prospective studies, Wu et al[6] found that depression was associated with an increased risk (risk ratio [RR], 1.39; 95% confidence interval [CI], 1.19–1.62; 7 studies, N = 64,975) as well as hazard (hazard ratio [HR], 1.26; 95% CI, 1.10–1.43; 9 studies; N = 309,862) of fractures.

There are many reasons why depression may increase the risk of incident fracture[7]: depression is associated with poor diet, smoking, alcohol intake, sedentariness, poor adherence to medical advice, and other health-related behaviors that may predispose to osteopenia and osteoporosis; depression is associated with low vitamin D levels, hypercortisolemia, and other hormonal changes that affect bone resorption and/or formation; depression is associated with elevated levels of inflammatory cytokines that are linked to decreased bone mineral density; depression is associated with a variety of medical comorbidities that can independently increase the risk of fractures; last but not least, depression is associated with cognitive slowing, psychomotor retardation, impaired judgement, and other changes that may affect gait, balance, and precautionary behavior against falls.

In a systematic review and meta-analysis of 13 published data sets (N = 375,438), Shi et al[7] reported that depression was associated with a small but significantly increased risk of fracture (HR, 1.21; 95% CI, 1.11–1.31) across a median follow-up duration of 12.5 years. Importantly, drugs that treat depression may be associated with sedation and impaired psychomotor reflexes and may thereby themselves predispose to falls and fractures. In the same meta-analysis,[7] depression was significantly associated with fracture risk in studies that adjusted for antidepressant use ($k = 5$; HR, 1.12; 95% CI, 1.01–1.25) as well as in studies that did not adjust for antidepressant use ($k = 8$; HR, 1.32; 95% CI, 1.17–1.50). The attenuation of the HR in the studies that adjusted for antidepressant use suggests that antidepressants might contribute to the risk.

Antidepressant Drugs and Fracture Risk

In a systematic review and meta-analysis, Rabenda et al[8] identified 34 case-control and cohort studies that examined the relationship between the use of antidepressants and the risk of fractures. They found that, relative to nonusers, the risk of fractures of all types was elevated in antidepressant users (RR, 1.39; 95% CI, 1.32–1.47).

A general problem with the literature is that studies on antidepressants may have been confounded by the presence

Table 1. Important Findings From the Study by Brännström et al[10]

1. In the year after initiating antidepressants, the risk of hip fracture was more than doubled in antidepressant users as compared with nonusers (3.5% vs 1.3%, respectively). The risk was significantly elevated in all of 5 time windows examined during the year.
2. In the year *before* initiating antidepressants, also, the risk of hip fracture was more than doubled in antidepressant users as compared with nonusers (2.8% vs 1.1%, respectively). Here, as well, the risk was significantly elevated in all of 5 time windows examined during the year.
3. The risk was high in the first fortnight after antidepressant initiation (OR, 3.36; 95% CI, 2.76–4.09). However, the risks were highest during days 16–30 (OR, 5.76; 95% CI, 4.73–7.01) and days 31–91 (OR, 4.14; 95% CI, 3.71–4.61) *before* antidepressant initiation.
4. In subgroup analyses, the risks both before and after antidepressant initiation were generally higher in men than in women.
5. The results were similar in different age bands (65–84 years and > 84 years) and for individual antidepressants (citalopram, mirtazapine, amitriptyline).
6. Higher doses of antidepressants were associated with higher risk of hip fracture in the 16–30 day time window after antidepressant initiation (OR, 1.31; 95% CI, 1.09–1.57). However, higher doses were also associated with higher risk in the 16–30 day window *before* antidepressant initiation (OR, 1.48; 95% CI, 1.27–1.72). In none of the other 8 time windows examined was higher antidepressant dose associated with significantly higher fracture risk. In fact, for citalopram, after day 91, higher doses were associated with significantly *decreased* risks.

Abbreviations: CI = confidence interval, OR = odds ratio.

of depression, and studies on depression may have been confounded by antidepressant use; adjustment for confounds in each context may have been inadequate, resulting in residual confounding. Here, confounds may not have been adequately measured in the available data; data may not have been available for all confounds; and unknown confounds would not have been adjusted for.

Psychiatrists who treat patients with antidepressant drugs would want to know the contribution of these drugs to the risk of fracture in elderly depressed persons. This issue is examined in the present article with specific reference to hip fracture, which is a common site at which fractures occur in the elderly.

Antidepressant Drugs and Hip Fracture

Antidepressant drugs have been associated with an increased risk of hip fracture in community-dwelling older persons with (HR, 1.61; 95% CI, 1.45–1.80) and without (HR, 2.71; 95% CI, 2.35–3.14) Alzheimer's disease.[9] A meta-analysis of case-control and cohort studies[8] found that antidepressants were associated with an increased risk of hip fracture (RR, 1.47; 95% CI, 1.36–1.58). Given the uncertainty about the role of depression and antidepressant drugs in this context, Brännström et al[10] examined the antidepressant-related risk of hip fracture in the elderly using a resourceful way to address confounding by indication.

These authors[10] described a Swedish register-based, nationwide cohort study of 204,072 subjects aged 65 years or older, all of whom had received a prescription for an antidepressant drug; this drug was a selective serotonin reuptake inhibitor in nearly two-thirds of the subjects. Each subject was age- and sex-matched with 1 control subject who had not been prescribed an antidepressant.

The mean age of the sample was 80 years. The sample was 63% female. The risk of hip fracture was compared between antidepressant users and nonusers in analyses that adjusted for a large number of confounding variables.

Important findings from the study[10] are presented in Table 1. In summary, antidepressant drugs were associated with an increased risk of hip fracture in the elderly. This risk was significantly elevated in all 5 time windows during the first year after antidepressant prescription. However, the risk was also significantly elevated in all 5 time windows during the first year *before* antidepressant prescription. The greatest density of risk was during the 3 months *before* antidepressant prescription. The implication, therefore, is that the indication for antidepressant use, most commonly depression, is probably the risk factor for hip fracture, and that the receipt of an antidepressant prescription is merely a marker of the risk.

Interpretations

There are 2 possible interpretations for these findings (Table 1). One is that antidepressants have no effect on the risk of hip fracture in the elderly; depression and its correlates are wholly responsible for the risk associated with antidepressants, before and after initiation of the antidepressant, and antidepressant prescription or use is merely a marker of risk. In support of this interpretation is the consideration that many of the depression-related mechanisms, outlined in an earlier section, affect the integrity of bone, and these mechanisms will not reverse as quickly as depression might after antidepressant initiation. Furthermore, not all patients who initiate antidepressants respond and remit with treatment; in these patients, ongoing biological and behavioral correlates of depression may contribute to continued depression-related vulnerability to hip fracture.

The other interpretation is that antidepressants reduce the depression-related risk by effectively treating depression but independently raise the risk through anticholinergic, hypotensive, sedative, or other effects; however, the net effect may be more favorable than unfavorable because the risks are (numerically) lower after antidepressant initiation than before. It is possible that both interpretations are right. The only way of knowing for certain is through the conduct of a randomized controlled trial (RCT). However, because the absolute risk is small, the sample size for such an RCT will need to be very large, and the RCT would therefore be challenging to conduct.

Comments on the Research Design

This study[10] found that the risk of hip fracture was significantly greater in antidepressant users relative to

nonusers during the entire year after antidepressant initiation. The study also found that higher antidepressant dose was associated with higher risk (Table 1). Taken in isolation, these findings suggest that antidepressants are associated with an increased risk of hip fracture and that these drugs should hence be used with caution in patients in whom the risk is of potential concern. However, the authors of this study[10] extended their analyses to also examine the risk in the year before antidepressant initiation. This allowed the discovery that depression may drive the risk of antidepressant-associated hip fracture.

Investigators who study exposure-related outcomes in observational research therefore need to do more than just adjust analyses for confounding variables. They need to use innovative methods to address confounding by indication, as done in this study[10] and in research in other fields, such as antidepressant-associated atrial fibrillation[11] and antidepressant exposure during pregnancy and the risk of autism spectrum disorder in the offspring.[12,13] It is also important for readers to base their interpretations of observational research upon how the investigators addressed the risk of confounding by indication.

The Possibility of Antidepressant-Driven Risk

In a large (N = 3,127) RCT[14] in which patients with acute stroke were randomized to receive fluoxetine (20 mg/d) or placebo for 6 months, those who received fluoxetine were less likely to develop new depression (risk difference, 3.78%; 95% CI, 1.26%–6.30%) but more likely to suffer bone fractures (risk difference, 1.41%; 95% CI, 0.38%–2.43%). On the one hand, these findings were obtained from an RCT and so suggest that fluoxetine does increase the risk of bone fracture and that depression is not necessarily a confound. On the other hand, these 2 findings were obtained in secondary analyses of 17 different outcomes, and so it is possible that one or both is a false-positive finding arising from multiple hypothesis testing.

Conclusions

Untreated depression appears to be associated with a significantly increased risk of hip fracture. The risk remains elevated during the year after antidepressant initiation; it is likely that this risk is driven by the persistence of depression-related mechanisms and by incompletely remitted depression, but a contribution from ongoing antidepressant exposure cannot be ruled out.

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