Central Nervous System Active Medications and the Risk of Fracture in Older Women


Study Overview

Objective. To investigate the association between psychotropic medication use and fractures in elderly women.

Design. Prospective cohort study.

Setting and participants. A cohort of 8127 white women aged 65 years and older was recruited from population-based listings from Baltimore, Minneapolis, Portland, OR, and Monongahela Valley, PA. Patients who were unable to walk at baseline evaluation or had a history of bilateral hip replacement were excluded.

Methods. Patients were interviewed between 1992 to 1994 and 1995 to 1996 to collect information on their use of central nervous system (CNS) active medications, including benzodiazepines, narcotics, antidepressants, and anticonvulsants. Reported use was verified by examination of pill bottles in the 86% of the cohort who were seen in the study clinic or at a home visit. Observation period began after first medication assessment and continued until 1999.

Main outcome measures. Incident nonspine and hip fractures as reported by participants every 4 months and confirmed by radiology reports.

Main results. After a mean 4.8 years of follow-up, 1256 (15%) of women experienced at least 1 nonspine fracture, including 288 (4%) with first hip fractures. When compared to medication nonusers, narcotics users were more likely to develop nonspine fractures with a multivariate hazard ratio (HR) of 1.40 (95% confidence interval [CI], 1.06–1.83). Antidepressant users also were more likely to develop nonspine fractures (multivariate HR, 1.25 [95% CI, 0.99–1.58]) and hip fracture (multivariate HR, 1.65 [95% CI, 1.05–2.57]). Women taking tricyclic antidepressants or using selective serotonin reuptake inhibitors had similar fracture rates. No independent relationship was detected between benzodiazepine and anticonvulsant use and fractures.

Conclusion. Narcotic and antidepressant use are associated with nonspine fractures, and antidepressant use also is associated with hip fractures in community-dwelling elderly women. Neither benzodiazepines nor anticonvulsants are associated with fractures.

Commentary

Psychotropic medications, particularly benzodiazepines, have been associated with both falls and fractures in multiple epidemiologic investigations [1]. The reported pooled odds ratio for use of any psychotropic drugs and falling is 1.7 [2], and this finding is reasonably consistent across psychotropic medication classes. However, few prospective studies have examined these associations, and most retrospective studies have not been able to adjust for differences in dosage or duration of therapy. Additionally, the narrow spectrum of data available in administrative databases used by previous studies does not allow adjustment for all confounders, particularly confounding by indication (ie, the conditions being treated by the medication also are responsible for the poor outcomes) or confounding by comorbid conditions. A gold standard randomized trial would likely be unethical or significantly limited by selection criteria and would not settle all issues of confounding and generalizability. Thus, a prospective cohort study with long follow-up, careful and thorough measurement of exposure and outcome, and little attrition is the most definitive study design to address adverse events related to psychotropic medications.

This latest report satisfies many of the above criteria: the data collection is prospective, participant reports of psychotropic use are confirmed by examination of pill bottles, and fractures are confirmed by radiology reports. Loss to follow-up is 7%, compared with an overall event rate of 15%, so it is unlikely that complete ascertainment of the data would change the conclusion. The finding that narcotics and antidepressant use are associated with nonspine fractures is consistent with previous research. However, the univariate relationship between benzodiazepines and hip fractures so often reported in other studies is no longer significant after

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adjustment for femoral neck bone density. This finding implies that women with osteoporosis are more often being prescribed benzodiazepines, and it is the osteoporosis rather than the benzodiazepine that is increasing the fracture risk. Is it possible that benzodiazepines are contributing to lower bone density by inhibiting weight-bearing activities that are known to ameliorate osteoporosis? The authors do not address this possibility. In fact, untangling the risk associated with medication use from the risk associated with comorbid conditions is still very difficult, even in a high-quality study such as this one. Ultimately, it is the responsibility of the treating physician to ensure the benefit of these medications outweighs the risk of a low-frequency but potentially devastating adverse drug event.

Applications for Clinical Practice
Opiates and antidepressants are associated with fractures in elderly women and should be avoided in the absence of clear indications for their use.

—Review by Josh F. Peterson, MD, MPH

References