See article by Wu et al

Do Antipsychotics Cause Hip Fractures?

Promise and Pitfalls of Big Data

John M. Davis, MD, and Christopher E. Ramsden, MD

Wu et al[1] report in this issue of the *Journal* that, on the basis of reimbursement claims, patients with schizophrenia who were currently on antipsychotic drug treatment had a higher risk of hip fractures than patients who were not currently on antipsychotics, based on reimbursement claims. Furthermore, more fractures occurred with typical antipsychotics than with atypical antipsychotics. This finding is consistent with a modest body of literature based on various registries.[2–4] Studies by Vestergaard et al,[2] Sørensen et al,[5] and Pouwels et al[4] showed more hip fractures in individuals receiving antipsychotics compared to controls. Vestergaard et al[2] concluded that there is a small increase in fracture risk with antipsychotics, anxiolytics, antidepressants, and sedatives. By contrast, lithium decreases the risk and may have a favorable effect on bone.[3]

Mechanisms that could help explain the relationship between hip fractures and antipsychotic use include prolactin elevation, extrapyramidal symptoms, sedative effects, and postural hypotension. Long-term exposure to prolactin-elevating antipsychotics leads to reduced bone mineral density (BMD),[6,7] and markers of bone reabsorption correlate with prolactin elevation, while discontinuation of antipsychotics can cause improvement in markers of bone resorption.[8] Hip fractures are more common with antipsychotics that elevate prolactin than prolactin-sparing antipsychotics. Selective serotonin reuptake inhibitors are also associated with hip fractures and low BMD[9] through a different mechanism. Since Parkinson's disease is associated with fractures, the pronounced extrapyramidal symptoms produced by some typical antipsychotics may also play a role. Since sedatives are associated with falls, antipsychotic-induced sedation may also play a role. Last, some antipsychotics cause postural hypotension, which can cause falls. Schizophrenic patients have more medical comorbid conditions, such as alcohol and substance abuse, than controls. Fractures are also associated with comorbid alcoholism and substance abuse. Schizophrenic patients on medications are sicker than those not on medications. The excess in falls may be partly attributed to the schizophrenia, not the medication.

When weighing this finding of a small increase in fractures based on choice of drugs, clinicians should be mindful that studies of cognitive biases have shown that uncommon events are often ignored (underweighted), but knowledge of a patient experiencing a dramatic occurrence of a rare side effect can result in the finding being overweighed.

We are entering the era of big data providing an opportunity for epidemiologic studies to detect rare drug-related side effects that are not likely to be demonstrated in randomized clinical trials, which are powered to detect the main study end points rather than rare events, and, in any case, trials large enough to detect a rare event would be so expensive that they could not be done. These events should be reported, including zero events, in clinical trials and analyzed in meta-analyses just in case this information could be helpful. The quality of epidemiologic investigations is enhanced when observational findings are integrated with extensive knowledge about the drugs investigated and the mechanisms of the observed side effects. In the present study,[1] the investigators used potency in receptor binding in test systems as a marker for mechanism. However, these mechanistic assessments are only an approximate marker of the actual occurrence in patients on clinical doses, and much more accurate quantitative data exist in randomized, blinded controlled trials. Similarly, the general classification of typical or atypical antipsychotics is only approximately correlated to side effects. For example, although amisulpride and risperidone are classified as atypical antipsychotics, both produce marked prolactin elevation compared to that of typical antipsychotics.[10]

Epidemiologic investigations have resulted in many important discoveries. However, one cannot infer cause from correlation, and many epidemiologic findings are not replicated in randomized controlled trials (RCTs). On rare occasions, drugs that were associated with reduced risk of disease in observational studies were subsequently found to increase risk in an RCT.[11] Therefore, statistical associations reported in observational studies should not be interpreted as demonstrating causality.

Despite these limitations, big data offers an opportunity to detect rare side effects that may otherwise be missed in RCTs. The considerable resources required to complete RCTs often result in smaller sample sizes and relatively shorter duration of follow-up. For many conditions in which relapse occurs rapidly in placebo patients, long-term studies are not possible because most patients relapse so early that not enough unrelapsed patients are left to have an adequate placebo comparison group. Sometimes researchers cannot ethically withhold active drugs when patients deteriorate on placebo. Thus, while some side effects take years to develop, clinical trials often only gather

Submitted: September 26, 2014; accepted September 30, 2014.

Corresponding author: John M. Davis, MD, The University of Illinois at Chicago, The Psychiatric Institute (M/C 912), 1601 W. Taylor St, Chicago, IL 60612 (jdavis@psych.uic.edu).

J Clin Psychiatry 2015;76(9):e1155–e1156
dx.doi.org/10.4088/JCP.14com09551

evidence of acute and subacute side effects. Big data can help fill this gap by identifying longer term side effects.

Hip fractures, which can lead to substantial disability and death, are an important side effect. Psychiatrists should be mindful of the general medical needs of their patients, including bone mineral density testing, medical management of osteoporosis, and exercise.

Author affiliations: Department of Psychiatry, University of Illinois at Chicago (Dr Davis); and National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland (Dr Ramsden).

Potential conflicts of interest: None reported.

Funding/support: None reported.

REFERENCES

1. Wu C-S, Chang C-M, Tsai Y-T, et al. Antipsychotic treatment and the risk of hip fracture in subjects with schizophrenia: a 10-year population-based case-control study. *J Clin Psychiatry*. 2015;76(9):1216–1223.
2. Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. *Osteoporos Int*. 2006;17(6):807–816.
3. Vestergaard P, Rejnmark L, Mosekilde L. Reduced relative risk of fractures among users of lithium. *Calcif Tissue Int*. 2005;77(1):1–8.
4. Pouwels S, van Staa TP, Egberts AC, et al. Antipsychotic use and the risk of hip/femur fracture: a population-based case-control study. *Osteoporos Int*. 2009;20(9):1499–1506.
5. Sørensen HJ, Jensen SO, Nielsen J. Schizophrenia, antipsychotics and risk of hip fracture: a population-based analysis. *Eur Neuropsychopharmacol*. 2013;23(8):872–878.
6. Wang M, Hou R, Jian J, et al. Effects of antipsychotics on bone mineral density and prolactin levels in patients with schizophrenia: a 12-month prospective study. *Hum Psychopharmacol*. 2014;29(2):183–189.
7. Takahashi T, Uchida H, John M, et al. The impact of prolactin-raising antipsychotics on bone mineral density in patients with schizophrenia: findings from a longitudinal observational cohort. *Schizophr Res*. 2013;147(2–3):383–386.
8. de Kuijper G, Evenhuis H, Minderaa RB, et al. Effects of controlled discontinuation of long-term used antipsychotics for behavioural symptoms in individuals with intellectual disability. *J Intellect Disabil Res*. 2014;58(1):71–83.
9. Okita K, Kanahara N, Nishimura M, et al. Second-generation antipsychotics and bone turnover in schizophrenia. *Schizophr Res*. 2014;157(1–3):137–141.
10. Bushe C, Shaw M, Peveler RC. A review of the association between antipsychotic use and hyperprolactinaemia. *J Psychopharmacol*. 2008;22(suppl):46–55.
11. Ramsden CE, Zamora D, Leelarthaepin B, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *BMJ*. 2013;346(3):e8707.