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Do Long-Term Side Effects Matter? Evaluating the Risk of Hip Fracture in Subjects With Schizophrenia Over a Decade

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Antipsychotic drugs remain the mainstay of treatment in schizophrenia, having shown their ability to reduce psychotic symptoms and relapse rates.¹ Treatment selection based on efficacy has been difficult since head-to-head studies have not shown significant differences, with the exception of clozapine for treatment-resistant cases.² Often the choice of antipsychotic lies with the potential or history of an adverse effect in individual patients. Side effects such as sedation, weight gain, orthostatic hypotension, and prolactin effects can influence a clinician's treatment choice.

In this month's issue, Wu et al³ present a study of antipsychotic treatment and the risk of hip fracture in patients with schizophrenia. The study replicates and expands on previous work by other investigators⁴⁻⁶ showing exposure to antipsychotics increases risk of hip fractures in exposed patients. This study³ retrospectively mines a decade of information from a large national database to study an outcome that is not robustly apparent in smaller, short-term studies. Health care is moving toward a model of assessing outcomes no longer solely based on short-term individual trial data but rather including broader, primary prevention-based patient care. Specialties such as psychiatry have been slower to implement this movement, perhaps because of a paucity of data regarding overall best practices. Assuming that antipsychotics are effective for the symptoms of schizophrenia and a growing number of other psychiatric illnesses, the long-term side effect potential has treatment implications that providers should be aware of. For years, psychiatrists have known of the long-term potential risk of tardive dyskinesia, that it can be disfiguring and debilitating and, therefore, when possible, have tried to identify early cases and mitigate its progression. No antipsychotic is entirely free of a tardive dyskinesia risk, but studies have shown that first-generation antipsychotics (FGAs) have a greater incidence than second-generation antipsychotics (SGAs).⁷ This unequal prevalence has, in part, guided treatment selection toward SGAs over FGAs. There has been less urgency and treatment selection based on other factors, including weight gain, or metabolic and endocrine effects and even less attention to long-term adverse consequences. This article highlights that risks like hip fracture, which may be years in the making, can lead to considerable morbidity and mortality.

The authors of the study³ explore various aspects of the increased risk and find several noteworthy results. First, they found that current, not past, users of antipsychotics appear to be at greater risk and that FGAs pose a greater increased risk of hip fracture than SGAs. Let's look at the implications of both of these findings. If hip fracture risk was solely caused by long-term exposure to antipsychotics, most likely via osteoporosis, the risk should be there regardless of current use. What may be occurring is a "two-hit" model. The long-term antipsychotic bone effects are present, but they must be coupled with the short-term effects of current use. In other words, a patient with brittle bones is also vulnerable to the potential acute sedative, extrapyramidal, or hypotensive effects of the medication they are receiving. The increased risk of hip fracture by FGAs and not SGAs is perplexing. We know that several SGAs elevate prolactin, even more than FGAs, and there has been a long-standing concern for osteoporosis in patients, especially women, taking the newer prolactin-elevating antipsychotics. The study authors³ postulate that in SGAs there may be some protective effect of serotonin blockade, attenuating serotonin's negative effect on bone formation. With regard to the two-hit model, the FGAs have a greater propensity for EPS that can impart postural instability as compared to the SGAs. In addition, anticholinergic medications (eg, benzotropine mesylate and trihexyphenidyl) used to counter EPS, may also increase the risk of fall.⁸

Does a study such as this one by Wu and colleagues³ lead us to improve our practice? It is a bit hard to say. The axiom still tends to hold, that effect trumps side effect. In other words, first find an efficacious antipsychotic and deal with the side effects second. Clozapine is the prime example of this practice. For patients meeting the criteria for treatment resistance, clozapine is the only proven effective medication. This efficacy comes at the price of a variety of side effects, ranging from discomforting to life threatening. However, in the majority of cases, a first-line antipsychotic (first or second generation) can be found that is effective. Choosing a specific antipsychotic medication is still a "hit or miss" approach. Trying something that has worked in the past or was effective with one of the patient's family members are reasonable choices. Side effects may also determine medication selection, with clinicians opting to either avoid or utilize certain medications on the basis of these effects. For example, a clinician may avoid an antipsychotic that causes weight gain in obese patients or use a sedating antipsychotic for patients who cannot sleep. The Wu article³ suggests that the risk of hip fracture could be treated as an avoidable side effect. Assuming that current antipsychotic use is the "second

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hit⁸ in patients with hip fractures, clinicians treating patients at high risk for fracture might tailor treatment away from prolactin-elevating antipsychotics and the first-generation compounds. However, complete abandon of these important classes of drugs may not always be clinically prudent since the benefits of these antipsychotics may outweigh the potential risk in some cases. In these cases, identifying high risk patients and considering mitigation therapy (eg, calcium and vitamin D replacement) might be considered. This practice has been the mainstay of management of fracture risk in patients with Parkinson's disease.⁹

With the adoption of electronic medical records, including electronic medication ordering, selection based on side effects, and periodic monitoring of parameters such as prolactin levels, glycosylated hemoglobin, and bone health could be operationalized. Given no overriding efficacy bias (eg, prior good response), a simple checklist of side effect risks versus benefits could be created and antipsychotic selection could be based on periodic assessments.

Finally, there is another issue that this article raises, albeit indirectly. It specifically studied adult individuals with the diagnosis of schizophrenia. Antipsychotics now have a growing number of diagnostic indications such as for mood disorders. Similar studies of side effects need to be done for antipsychotic use in mood disorders, namely, bipolar disorder and major depression, as well as in child and adolescent populations. The approach utilized by Wu and colleagues³ might be applicable to these illnesses. We can only guess if there is an increased risk of hip fractures

in patients taking antipsychotics for these diagnoses. Considering that the absolute number of individuals with these illnesses probably exceeds those with schizophrenia, these risk assessments would be warranted.

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REFERENCES

1. Citrome L. A systematic review of meta-analyses of the efficacy of oral atypical antipsychotics for the treatment of adult patients with schizophrenia. *Expert Opin Pharmacother*. 2012;13(11):1545–1573.
2. Leucht S, Cipriani A, Spinelli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962.
3. 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.
4. Hugenholtz GW, Heerdink ER, van Staa TP, et al. Risk of hip/femur fractures in patients using antipsychotics. *Bone*. 2005;37(6):864–870.
5. Liperoti R, Onder G, Lapane KL, et al. Conventional or atypical antipsychotics and the risk of femur fracture among elderly patients: results of a case-control study. *J Clin Psychiatry*. 2007;68(6):929–934.
6. 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.
7. Kane JM. Tardive dyskinesia rates with atypical antipsychotics in adults: prevalence and incidence. *J Clin Psychiatry*. 2004;65(suppl 9):16–20.
8. Cao Y-J, Mager DE, Simonsick EM, et al. Physical and cognitive performance and burden of anticholinergics, sedatives, and ACE inhibitors in older women. *Clin Pharmacol Ther*. 2008;83(3):422–429.
9. Lyell V, Henderson E, Devine M, et al. Assessment and management of fracture risk in patients with Parkinson's disease. *Age Ageing*. 2015;44(1):34–41.