Are selective serotonin reuptake inhibitors associated with fractures?

Sarah Drost, BScPharm; Anne Massicotte, BPharm, MSc

Case scenario

A woman in her mid-60s presents to your pharmacy with a new prescription for citalopram. She tells you that she's been tired and weepy lately and has been avoiding her usual activities. She has been diagnosed with a first episode of depression by her family physician. Your patient is hopeful that citalopram will help with her mood but is concerned about some of the long-term risks of using this class of medications. One of her friends told her to avoid this medication because it could increase her risk of breaking a bone. How do you address her concern?

Introduction

Antidepressant use in North America is on the rise. From 2007 to 2011, antidepressants were the most commonly used medication class by Canadian women aged 25 to 79 years and among the top 5 classes of drugs used by men aged 25 to 64 years.¹ Selective serotonin reuptake inhibitors (SSRIs; e.g., citalopram, paroxetine, sertraline) are one of the most widely used classes of antidepressants because of their efficacy, favourable side effect profile and broad indications for use.²

In the past decade, more attention has been paid to the adverse effects of medications on bone health. Glucocorticoids, aromatase inhibitors (e.g., anastrozole, letrozole, exemestane), thiazolidinediones or "glitazones" (e.g., pioglitazone) and proton pump inhibitors (e.g., pantoprazole, omeprazole), among others, are suspected contributors to fractures.³ There is evidence indicating that SSRIs may also be implicated.³ In patients aged 66 years and older, current exposure to SSRIs has been associated

with hip fractures compared with no antidepressant exposure (adjusted odds ratio [aOR]; 2.4; 95% CI: 2.0-2.7).⁴

One-third of women and one-fifth of men in Canada will experience an osteoporotic fracture during their lifetime. In 2010, osteoporosis and fractures cost the Canadian health care system upwards of 2.3 billion dollars.⁵ Fractures can cause a loss of long-term mobility and increase the risk of institutionalization. A prospective observational cohort of older adults showed that 12 months after a hip fracture, only half of patients regained their prefracture mobility level and only one-third of those who were previously mobile without an aid regained full mobility.⁶ A Canadian cohort (2001-2006) revealed that 12 months after a hip fracture, 24% of adults aged 75 years and older who were previously living in the community required institutionalization.⁷ However, that risk was much lower in patients aged 60 to 74 years, in whom only 14% of men and 4% of women required a transfer to a long-term care institution.⁷ Fractures are also associated with mortality, with 28% of women and 37% of men who experience a hip fracture dying within a year.⁵ It is therefore increasingly important to quantify the association between SSRIs and bone health. This review will discuss the current evidence that explores their association with an increased fracture risk.

Search strategy

A literature search was conducted using MEDLINE, PubMed and the Cochrane library on August 14, 2015. The terms searched, either as MESH words or keywords, were *serotonin uptake*

inhibitors, antidepressant or anti-depressive agents* in combination with *osteoporosis, fracture* or bone**. Searches were limited to clinical studies (encompassing clinical trials and observational studies), reviews, systematic reviews and meta-analyses in humans. After removing duplicates, irrelevant articles, trials already included in meta-analyses and articles focusing on antidepressants but not SSRIs specifically, 5 articles were chosen as best available evidence.

Proposed mechanism of effect

The mechanism by which SSRIs are associated with osteoporotic fractures has not been fully elucidated. One proposed mechanism is through an increased fall risk. Originally, it was hypothesized that SSRIs would decrease the risk of falls in elderly patients compared with tricyclic antidepressants (TCAs) and therefore be a better option in this population. However, research did not confirm this hypothesis. SSRIs increased fall risk in nursing home residents when compared with TCAs (TCA adjusted rate ratio [aRR]: 2.0; 95% confidence interval [CI]: 1.8-2.2; SSRI aRR: 1.8; 95% CI: 1.6-2.0).⁸ In another study, primary care patients older than 65 years taking SSRIs had a significant increase in fall risk compared with nonusers of antidepressants (adjusted hazard ratio [aHR]: 1.66; 95% CI: 1.58-1.73).⁹

Another proposed mechanism is that the increased fracture risk with SSRI use is mediated through the 5-hydroxy-tryptamine transporter (5HTT), which SSRIs inhibit in the presynaptic membrane, blocking serotonin reuptake.¹⁰ The 5HTT is also present in various bone cell types, such as osteoblasts, osteocytes and osteoclasts, which build up, maintain and break down bone, respectively.¹⁰ However, the role of serotonin in bone tissue regulation is still unclear.¹¹

Of note, there is a potential indication bias when researching the association between SSRIs and fracture risk, as depression itself is a risk factor for fractures through an increased frequency of falls and possibly a lowering of bone mineral density (BMD).¹²⁻¹⁴

The evidence

Meta-analyses. Two meta-analyses published in 2012 evaluated the risk of fractures in patients using SSRIs. Wu et al.¹⁵ pooled the results of 13 observational studies, including 7 cohort studies and 6 case-control studies. Studies published up to February 2010 were included in the

analysis. The authors determined that SSRI use significantly increased the fracture risk (relative risk [RR]: 1.72; 95% CI: 1.51-1.95; $p < 0.001$). The association between SSRI use and fracture risk remained similar when various subgroups were analyzed separately (e.g., sex, race/ethnicity, age, study design, study location and whether the studies controlled for depression or BMD). The relative risk remained statistically significant when publication bias was accounted for (RR: 1.40; 95% CI: 1.22-1.61; $p < 0.001$). Wu et al.¹⁵ self-identified several limitations to their meta-analysis, including the small number of studies available, undetermined heterogeneity in SSRI use (dosage, duration of use, indications) and unknown or unreported confounding variables (such as other medications contributing to fracture risk).

The second meta-analysis by Eom et al.¹⁶ pooled the results of 12 studies (7 case-control and 5 cohort studies) and included studies published up to October 2010. Eom et al.¹⁶ evaluated similar literature as Wu et al.¹⁵; however, the former included 1 additional case-control study and the latter 2 additional cohort studies. Eom et al.¹⁶ found a significant association between SSRI use and fracture risk (aOR: 1.69; 95% CI: 1.51-1.90; $I^2 = 89.9\%$). Subgroup analyses, comprising the type of study (case-control vs cohort), geographic latitude, number of clinical risk factors used for statistical adjustment by the study, anatomical fracture site, study quality (high vs low), medication dose (high vs usual), age, sex and exposure duration, also found a significant association between SSRI use and fracture risk. However, a subgroup analysis of exposure duration found that the risk of fractures was greater within the first 6 weeks of SSRI exposure and then decreased over time (aOR: 3.83, 95% CI: 1.96-7.49 for <6 weeks exposure; aOR: 1.60, 95% CI: 0.93-2.73 for ≥ 6 weeks). Similar to Wu et al.,¹⁵ limitations of the meta-analysis were the presence of known and unknown confounding variables and the small number of observational studies. Eom et al.¹⁶ pointed out that their study might lack external validity in certain populations, as most studies were performed in Western countries.

Recent observational studies. A 2012 retrospective, population-based cohort study examined the association between SSRIs and bone loss-related events. Data were drawn from a large health

organization in Israel and collected from January 2004 to April 2010.¹⁷ The cohort comprised 10,621 women aged 40 years and older who started SSRIs within the data collection time frame; they were followed up for a mean duration of 3 years. Adherence was classified as low (proportion of days covered [PDC] $\leq 20\%$), intermediate (PDC 21%-79%) or high (PDC $\geq 80\%$) and was assessed based on automated health plan data that accounted for prescription dispensing in the community and hospital discharge data. The study outcome of bone loss-related events was defined as a fracture or initiation of bisphosphonate therapy. To minimize surveillance bias and events related to postural adverse effects, events occurring within the first 180 days of follow-up were excluded. Results were also adjusted for age, primary care visits and body mass index. In patients with intermediate and high adherence, the aHR for bone loss-related events was 1.15 (95% CI: 0.97-1.37) and 1.40 (95% CI: 1.14-1.73), respectively, when compared with those with poor adherence, showing that higher SSRI adherence was associated with an increase in bone loss-related events. Compared with the meta-analyses above, the lower aHR may be attributable to a younger study population. In addition, using initiation of bisphosphonate therapy as an outcome could be problematic, as bisphosphonate therapy may be initiated in women with osteopenia as opposed to a fragility fracture.

In 2014, the Canadian Multicentre Osteoporosis Study (CaMoS) published data from a 10-year prospective, population-based community cohort in adults aged 50 years and older (mean age of 65 years at enrollment).¹⁸ This study assessed the fracture risk related to SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI; e.g., venlafaxine) use. The study used information gathered from an interviewer-administered questionnaire that focused on the patient's medical history, fracture risk factors and medication use and was administered at 0, 5 and 10 years. The main outcome was clinical fragility fractures (i.e., fractures caused by minimal trauma and confirmed by medical or radiographic reports). Of 6645 subjects, 192 were using an SSRI or SNRI at the study's outset and 333 were using an SSRI or SNRI at year 10. After adjustments for age, sex, education level, Charlson score (the Charlson Comorbidity Index is a scoring tool designed to predict mortality by

weighting comorbidities), smoking, falls in the previous month, BMD (hip and lumbar), thiazolidinedione use, vitamin D level and previous deformity, the aHR was 1.68 (95% CI: 1.32-2.14). This aHR assumes that SSRI/SNRI use was constant between interviews. The results of a further analysis that used a more conservative definition (assuming SSRI/SNRI use for only 1 year if not reported at subsequent interviews) were also significant (aHR: 1.47; 95% CI: 1.09-1.99). In addition, the analysis demonstrated a dose-effect relationship.

In a nested case-control study published in 2016, Wang et al.¹⁹ analyzed the association between SSRI/SNRI use and fracture risk. Data were drawn from the Taiwan National Health Insurance Research Database from 2002 to 2011. The cohort consisted of patients 20 years of age and older (mean age of 46 years at enrollment) who had received at least 3 antidepressant prescriptions (at least 1 of which was an SSRI or SNRI) during the specified time period. A total of 8250 cases who had a first admission for fracture and 33,000 matched controls were identified. After adjusting for comorbidities and comedications, the aOR was 1.16 (95% CI: 1.07-1.25, $p < 0.001$) among the current SSRI/SNRI users. The lower reported aOR compared with previous meta-analyses may be explained by a younger studied population.

Discussion

Recent meta-analyses of observational studies estimate an approximate 1.7-fold increase in the risk of fracture in SSRIs users. Newer observational studies have also shown an association between SSRIs and fracture risk, although the demonstrated relative risk is lower than the meta-analyses described, possibly because of the inclusion of younger populations. In the CaMoS study, 978 of the 6645 (14.7%) patients (mean age of 65 years at enrollment) experienced at least 1 fragility fracture over 10 years, translating to a baseline event rate of 1.47% per year. This implies that the absolute increase in fracture risk for patients taking SSRIs would be relatively small.

However, all studies discussed are limited by the large potential for bias inherent to observational studies as well as a number of confounding variables. Additional research into the long-term safety of SSRIs is needed to further quantify this association. In the meantime,

Canadian product monographs for SSRIs now warn of an increased risk of bone fracture. Patients initiated on an SSRI should be assessed for appropriateness of medication use and general bone health and may benefit from risk management strategies, including adequate calcium intake, vitamin D supplementation and weight-bearing exercise.

Conclusion: Back to the case

You reassure the patient, first stating how important it is to treat depression, and review the efficacy of her prescribed antidepressant in

overcoming her depressed state and increasing her quality of life. As with any other drugs, citalopram can cause side effects, one of them possibly being a small increase in annual risk of fractures. However, one might help prevent fractures by doing weight-bearing exercise and ensuring adequate intake of vitamin D and calcium. You also tell the patient to be diligent about preventing falls, especially in the first few weeks of treatment. You add that the use of citalopram will be reassessed periodically by her physician and may be gradually stopped based on the improvement and resolution of her depressive symptoms. ■

From The Ottawa Hospital (Civic Campus) Pharmacy Department, Ottawa, Ontario. Contact sdrost@toh.ca.

Acknowledgment: The authors wish to thank Mirella Giudice, Drug Information Pharmacist at The Ottawa Valley Regional Drug Information Service, for her valuable comments during the preparation of the article.

Author Contributions: S. Drost initiated the project, conducted the literature search and drafted the manuscript. A. Massicotte initiated the project, edited the manuscript drafts and revised the final manuscript prior to submission. Both authors approved the final version of the manuscript.

Declaration of Conflicting Interests: The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding: The authors received no financial support for the research, authorship and/or publication of this article.

References

1. Rotermann M, Sanmartin C, Hennessy D, et al. Prescription medication use by Canadians aged 6 to 79. Health reports. June 2014. Available: <http://www.statcan.gc.ca/pub/82-003-x/2014006/article/14032-eng.pdf> (accessed Aug. 25, 2015).
2. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. *Primary Care Companion J Clin Psychiatry* 2001;3:22-7.
3. Pitts CJ, Kearns AE. Update on medications with adverse skeletal effects. *Mayo Clin Proc* 2011;86(4):338-43.
4. Liu B, Anderson G, Mittmann N, et al. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. *Lancet* 1998;351:1303-7.
5. Osteoporosis Canada. Osteoporosis facts and statistics. Available: www.osteoporosis.ca/osteoporosis-and-you/osteoporosis-facts-and-statistics/ (accessed Aug. 25, 2015).
6. Vochteloo AJH, Moerman S, Tuinebreijer WE, et al. More than half of hip fracture patients do not regain mobility in the first postoperative year. *Geriatr Gerontol Int* 2013;13:334-41.
7. Morin S, Lix LM, Azimae M, et al. Institutionalization following incident non-traumatic fractures in community-dwelling men and women. *Osteoporos Int* 2012;23:2381-6.
8. Thapa PB, Gideon P, Cost TW, et al. Antidepressants and the risk of falls among nursing home residents. *N Engl J Med* 1998;339(13):875-82.
9. Coupland C, Dhiman P, Morris R, et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011;343:d4551.
10. Warden SJ, Robling AG, Sanders MS, et al. Inhibition of the serotonin (5-hydroxytryptamine) transporter reduces bone accrual during growth. *Endocrinology* 2005;146(2):685-93.
11. Schwan S, Hallberg P. SSRIs, bone mineral density and risk of fractures—a review. *Eur Neuropsychopharmacol* 2009;19(10):683-92.
12. Chen F, Hahn TJ, Weintraub NT. Do SSRIs play a role in decreasing bone mineral density? *J Am Med Dir Assoc* 2012;13(5):413-7.
13. Whooley MA, Kip KE, Cauley JA, et al. Depression, falls and risk of fracture in older women. *Arch Intern Med* 1999;159:484-90.
14. Mezuk B, Eaton WW, Golden SH, et al. Depression, antidepressants and bone mineral density in a population-based cohort. *J Gerontol A Biol Sci Med Sci* 2008;63(12):1410-5.

15. Wu Q, Bencaz AF, Hentz JG, et al. Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. *Osteoporos Int* 2012;23(1):365-75.
16. Eom CS, Lee HK, Ye S, et al. Use of selective serotonin reuptake inhibitors and risk of fracture: a systematic review and meta-analysis. *J Bone Miner Res* 2012;27(5):1186-95.
17. Zucker I, Chodick G, Grunhaus L, et al. Adherence to treatment with selective serotonin reuptake inhibitors and the risk for fractures and bone loss. *CNS Drugs* 2012;26(6):537-47.
18. Moura C, Bernatsky S, Abrahamowicz M, et al. Anti-depressant use and 10-year incident fracture risk: the population-based Canadian Multicentre Osteoporosis Study (CaMoS). *Osteoporos Int* 2014;25(5):1473-81.
19. Wang CY, Fu SH, Wang CL, et al. Serotonergic antidepressant use and the risk of fracture: a population-based nested case-control study. *Osteoporos Int* 2016;27(1):57-63.