SSRI use in middle-aged women with no mental issues linked to increased bone fracture risk

Findings show association continued over time, suggest shorter treatment duration when used for vasomotor symptoms


Summary. The selective serotonin reuptake inhibitor (SSRI) paroxetine 7.5 mg was FDA approved in 2013 for treatment of vasomotor symptoms associated with menopause. SSRIs have previously been shown to be associated with increased fracture risk in psychiatric patients. Because the number of women who may be prescribed SSRIs for their menopause symptoms will likely increase, researchers undertook a study to see whether women who did not have psychiatric disorders and took SSRIs had an increased risk of fracture.

Using data from the PharMetrics Claims Database, researchers compared 137,031 women aged 40 to 64 years without mental illness who took SSRIs from 1998 to 2010 with a cohort of 236,294 women of the same age who were prescribed H₂ antagonists (H₂As) or proton pump inhibitors (PPIs), usually prescribed for gastric disorders, during this same time period.

Fracture rates in those who took SSRIs were 76% higher after 1 year of treatment, 73% higher after 2 years of treatment, and 67% higher after 3 years of treatment compared with the H₂/PPI cohort.

Researchers concluded that SSRIs appear to increase fracture risk in midlife women who do not have psychiatric disorders and that the effect is sustained over time.

Editor’s Note. We are witnessing a transformational change in how therapeutic modalities are investigated for risks, benefits, and costs. The traditional gold standard for drug testing has been the randomized, controlled trial, despite its deficiency in being applied to highly selective populations, with strict inclusion and exclusion criteria, and then extrapolating the results to a general and often quite different population. The secondary standard has been the different types of observational studies

The paradigm change has come in the use of gigantic healthcare databases made available through modern computer technology and as used in the study that is the focus of this issue of First to Know. We are now able to search for
utilization and outcomes of therapies in real world populations and over lengthy time periods.

Although none of these modalities is perfect, use of large databases will become a significant mechanism for detecting the risks and benefits of drugs and procedures. The paper under review here illustrates the use of a large healthcare database and exposes some of the benefits and difficulties involved in extracting meaningful data that can direct future clinical practice.

Wulf Utian, MD, PhD, DSc(Med)
Editor, First to Know

Comment. In this paper using data from a pharmacy claims database covering 61 million unique patients, the authors show that SSRIs increase fractures. Patients (n=137,031) prescribed SSRIs were compared to patients (n=236,294) prescribed PPIs or H2As. Fracture rates, expressed as hazard ratios (HR), were significantly higher by 76% with SSRIs in year 1 (HR, 1.76; 95% confidence interval (CI), 1.33-2.32) and persisted in year 5 (HR, 1.67; 95% CI, 1.30-2.14). Because of the widespread use of SSRIs, we must recognize that this adverse event is now a significant clinical problem.

Of particular note in this paper is that patients with depression were excluded from analysis. In a recent paper, antidepressant use is noted to be the third most commonly prescribed medication. However, between 1996 and 2007, the proportion of antidepressant prescriptions for depression had remained fairly constant over 10 years, but the proportion of antidepressant prescriptions for nonpsychiatric diagnoses (off-label) is now 4 times higher than for depression in primary care offices.

Because of this newer and definitive data on fractures, there needs to be more careful prescribing of SSRIs. In recent years, there has been increased use of SSRIs in menopausal women for vasomotor symptoms because of the negative reports about hormone therapy use from the Women’s Health Initiative study. For menopause practitioners, this data is yet another concern. The recent approval of low-dose paroxetine 7.5 mg was not included in this fracture analysis, but closer attention will now have to be given to the potential problem of fractures, even on lower doses. There was no measure on bone density in this paper.

In a Canadian osteoporosis study, there was a significant increase in fractures with SSRIs (HR, 2.1; 95% CI, 1.3-2.4) starting in the second year. That was attributed in part to an increase in falls and 4% lower hip density; however, after controlling for these variables, there was still an increase in fractures, and an effect of SSRIs on bone quality is another possibility.

Because SSRIs are invaluable for depression, how can we manage this problem?

Understanding all the possible mechanisms by which SSRIs affect bone metabolism is essential. Serotonin (5-hydroxytryptamine [5-HT]) has major effects on the brain and on cardiovascular and gastrointestinal systems. In the brain, 5-HT is released into the synaptic gap and binds to the 5-HT receptors, influencing mood, behavior, and cognitive behaviors. However, serotonin does not cross the blood-brain barrier. There is some evidence that central hypothalamic signaling of 5-HT modulates an inhibitory sympathetic effect on bone formation.

All bone cells have receptors for 5-HT, so what is the origin of serotonin that acts on these cells if serotonin does not cross the blood-brain barrier? Circulating serotonin has two sources: In the gut, serotonin is synthesized by the enterochromaffin cells in the duodenum and acts locally on peristalsis. The other major reserve source is in platelets, and its release stimulates vasoconstriction and vasodilatation of blood vessels.
It has been suggested that the gut is the major source of circulating serotonin that acts on bone and that higher serotonin levels are a negative regulator of bone formation. From previous work, we know that the coreceptor LRP5 is important in Wnt signaling in bone remodeling.

For example, in humans, a gain of function mutation in the gene *LRP5* is associated with high bone mass (t-scores +7) and loss of function with osteoporosis (t-scores −4). In fascinating studies on mice, it has been shown that LRP5 inhibits the enzyme Tph1 in the enterochromaffin cells in the gut that regulates serotonin production. If the enzyme Tph1 is inhibited or there is specific activation in the gut of LRP5, then serotonin levels decrease, bone formation is normalized, and bone mass is increased. The idea several years ago that duodenum-derived serotonin might regulate bone mass and bone remodeling would have seemed far-fetched.

At this point in time, central serotonergic control and duodenum-derived serotonin regulation of bone mass could explain the causes of low bone mass and fractures in people taking SSRIs. Perhaps by targeting duodenal control of serotonin, we can open up a new way to treat osteoporosis and fractures in these people.

Chris Gallagher, MD
Professor of Medicine
Director, Bone Metabolism Unit
Division of Endocrinology
Creighton University School of Medicine
Omaha, NE

References