

Serotonergic antidepressants' effects on bone health

Autumn Walkerly, PharmD, BCPS, and Chris Paxos, PharmD, BCPP, BCPS, BCGP

Mrs. D, age 67, has a history of major depressive disorder. She has had adequate treatment trials with duloxetine, mirtazapine, and sertraline; each failed to produce remission. She is currently prescribed paroxetine, 40 mg/d, and aripiprazole, 10 mg/d, with good efficacy. She also has a history of hypertension and seasonal allergies, for which she receives amlodipine, 10 mg/d, and loratadine, 10 mg/d, respectively.

Mrs. D's depressive symptoms were well controlled until 2 months ago, when she fell and fractured her hip. With encouragement from her prescriber, she enrolled in a partial hospitalization program for more intensive psychotherapy. During a medication education session, she is surprised to learn that antidepressants may affect bone health.

During a medication management meeting with her prescriber, Mrs. D asks about the risk of osteoporosis, and whether her antidepressant could have contributed to her hip fracture.

Bone is a dynamic tissue that undergoes a continuous process of remodeling. Osteoblasts are responsible for bone formation, whereas osteoclasts are responsible for bone resorption. Osteocytes—the

predominant cell type in bone—along with cytokines, hormones, and growth factors help to orchestrate these actions.¹ Serotonin is increasingly recognized as a factor in bone homeostasis. Bone synthesizes serotonin, expresses serotonin transporters, and contains a variety of serotonin receptors.²

Serotonin serves many physiologic functions outside of the CNS, and it appears to have opposing actions on bone metabolism (*Table 1*,^{1,3} *page 46*). Peripheral (gut-derived) serotonin inhibits bone formation through its effects on osteoblasts, whereas the actions of serotonin in the CNS promote bone growth through inhibitory effects on sympathetic output.² Selective serotonin reuptake inhibitor (SSRI) enhancement of



Vicki L. Ellingrod,
PharmD, FCCP
Department Editor

Practice Points

- **Central and peripheral actions of serotonin on bone result in positive and negative effects on bone formation, respectively.**
- **The risk of fracture is likely multifactorial, and includes risk from serotonergic antidepressant use and from depression. The extent to which selective serotonin reuptake inhibitors (SSRIs) are responsible for fracture risk is unknown.**
- **In vitro SSRI data suggest sertraline may adversely affect bone the most, followed by fluoxetine, paroxetine, fluvoxamine, and citalopram; however, the implications for clinical care are unclear and require more investigation.**
- **Educate patients on modifiable risk factors and discuss calcium and vitamin D requirements, diet, and exercise.**

Dr. Walkerly is a PGY-2 Psychiatric Pharmacy Resident, Michigan Medicine, Ann Arbor, Michigan. Dr. Paxos is Professor, College of Pharmacy, and Associate Professor, College of Medicine, Northeast Ohio Medical University, Rootstown, Ohio.

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Table 1

Range of physiological function of serotonin and selected receptor locations

System	Effect	Select implicated receptors
Central nervous system	Behavior Mood Reward Memory	5HT-1A 5HT-2A 5HT-2C
Skeletal	Inhibit osteoclast and osteoblast function	5HT-1A 5HT-2A 5HT-2B
Gastrointestinal	Motility Pancreatic enzyme secretion Vomiting	5HT-3 5HT-4
Hematologic	Platelet activation and aggregation	5HT-2A 5HT reuptake transporter
Vascular	Vasodilation Vasoconstriction	5HT-1B

Source: References 1,3

Clinical Point

Central and peripheral actions of serotonin on bone result in positive and negative effects on bone formation, respectively

peripheral serotonin and its negative effect on bone may outweigh the benefits caused by SSRI enhancement of central serotonin neurotransmission.¹ In vitro data suggest SSRIs inhibit osteoblast and osteoclast function, theoretically decreasing bone turnover and increasing fracture risk.⁴ Other data indicate SSRI treatment may decrease procollagen type 1 N-terminal propeptide, a peripheral marker of bone formation.⁵ Both SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been associated with lower cortical bone mineral density (BMD).⁶ Table 2^{7,8} (page 47) details the relative affinity of select antidepressants for the serotonin transporter.

Both serotonergic antidepressants and depression have been associated with decreased BMD and increased fracture risk.^{1,9} Behavioral aspects of depression, such as inadequate nutrition or physical inactivity, overlap with risk factors for poor bone health. In addition, elevated levels of circulating cortisol and proinflammatory cytokines in patients with depressive symptoms may contribute to decreased bone mass.^{10,11} Modifiable risk factors for osteoporosis and

fractures include low calcium and vitamin D intake, low body weight, and a sedentary lifestyle. Nonmodifiable risk factors include advancing age, female sex, Asian or White ethnicity, malabsorptive conditions, and chronic corticosteroid use.¹²

What the evidence says

Evidence for the correlation between fractures and serotonergic antidepressant use is mixed. One meta-analysis found a significant association between SSRIs and fractures, suggesting a 1.62-fold increased risk.¹³ Another meta-analysis investigated SSRIs and SNRIs and the risk of fracture.¹⁴ The SSRIs had a 1.67-fold increased risk; however, a lack of studies prohibited making conclusions about SNRIs. The number needed to harm was calculated at 85, 46, and 19 with 1, 2, and 5 years of SSRI exposure, respectively. A third meta-analysis found increased fracture risk related to depression and reported a hazard ratio of 1.26 after adjusting for confounders.⁹ This analysis suggests depression affects fracture risk and may limit the interpretation of causation from SSRI use. Studies



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Table 2

Affinity for serotonin and norepinephrine transporters by select antidepressants

Antidepressant	Serotonin transporter	Norepinephrine transporter
Selective serotonin reuptake inhibitors		
Citalopram	+++	–
Escitalopram	+++	–
Fluoxetine	+++	–
Fluvoxamine	+++	–
Paroxetine	+++	+
Sertraline	+++	–
Serotonin-norepinephrine reuptake inhibitors		
Duloxetine	++	++
Levomilnacipran	++	++
Venlafaxine	++	+
Tricyclic antidepressants		
Amitriptyline	++	+
Clomipramine	+++	+
Desipramine	+	+++
Doxepin	+	+
Imipramine	++	+
Nortriptyline	+	++
Other antidepressants		
Bupropion	–	–/ +
Trazodone	+	–
Vortioxetine	+++	+
+++: high affinity ++: moderate affinity +: mild affinity –: minimal to no affinity Source: References 7,8		

Clinical Point

Both SSRIs and SNRIs have been associated with lower cortical bone mineral density

included in these meta-analyses had significant heterogeneity.

The effect of SSRIs vs non-SSRIs on BMD also has been studied. The SSRIs were associated with significantly reduced BMD of the lumbar spine but not the total hip or femoral neck as compared to non-SSRIs; however, this BMD loss was not examined in relation to the presence of fractures. Older patients had more pronounced bone loss.¹⁵ Conversely, another meta-analysis examined BMD in women receiving SSRIs or tricyclic antidepressants.¹⁰ Neither medication class was associated with lower BMD at measured locations, including lumbar

spine, femoral neck, and total hip. This analysis was limited by the lack of available trials; only 4 were included.

Other recent research has continued to explore the relationship between antidepressants and fracture in various patient populations. In a study of patients receiving maintenance dialysis treatment, short- and long-term SSRI use increased hip fracture risk. The authors speculated that short-term risk may be mediated by adverse effects that increase fall risk (eg, hyponatremia, orthostasis), whereas long-term risk may be influenced by changes in bone homeostasis.¹⁶ In two 6-month analyses of fluoxetine

Clinical Point

The risk of fracture is likely multifactorial, and includes risk from serotonergic antidepressant use and from depression

Related Resources

- Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25(10):2359-2581.
- Dodd S, Mitchell PB, Bauer M, et al. Monitoring for antidepressant-associated adverse events in the treatment of patients with major depressive disorder: an international consensus statement. *World J Biol Psychiatry*. 2018;19(5):330-348.
- Fernandes BS, Hodge JM, Pasco JA, et al. Effects of depression and serotonergic antidepressants on bone: mechanisms and implications for the treatment of depression. *Drugs Aging*. 2016;33(1):21-25.
- US National Library of Medicine. DailyMed. <https://dailymed.nlm.nih.gov/dailymed>

Drug Brand Names

Amitriptyline • Elavil	Imipramine • Tofranil
Amlodipine • Norvasc	Levomilnacipran • Fetzima
Aripiprazole • Abilify	Loratadine • Claritin
Bupropion • Wellbutrin	Mirtazapine • Remeron
Citalopram • Celexa	Nortriptyline • Pamelor
Clomipramine • Anafranil	Paroxetine • Paxil
Desipramine • Norpramin	Risedronate • Actonel
Doxepin • Silenor, Sinequan	Sertraline • Zoloft
Duloxetine • Cymbalta	Teriparatide • Forteo
Escitalopram • Lexapro	Trazodone • Desyrel
Fluoxetine • Prozac	Venlafaxine • Effexor
Fluvoxamine • Luvox	Vortioxetine • Trintellix

treatment in patients following an acute stroke, fluoxetine increased the risk of bone fractures.^{17,18} Finally, in women with osteoporosis receiving risedronate or teriparatide, in both groups a higher fracture risk was observed for patients who were also receiving an SSRI or SNRI.¹⁹

Monitor BMD and educate patients about bone health

Available literature has not identified any clear risk factors for fracture with SSRI use. Guidelines suggest monitoring BMD in patients with risk factors for osteoporosis, if clinically indicated, as well as monitoring BMD in those receiving long-term antidepressant treatment.²⁰⁻²² Educate patients on strategies that promote optimal bone health, such as consuming a balanced diet that meets the recommended dietary allowance of calcium, vitamin D, and limits soda consumption. Teach patients to avoid tobacco and excessive alcohol use because both adversely impact BMD. Maintaining

a healthy weight, physical activity, and adequate sleep also support bone health.¹¹ Instruct patients receiving antidepressants to report unexplained bone pain, tenderness, swelling, or bruising because these symptoms may be indicative of fracture.

CASE CONTINUED

Mrs. D's age, sex, and depression place her at higher risk of fracture. Paroxetine is the only SSRI that has bone fracture listed as a precaution in its labeling.²³ In addition, it is the most anticholinergic SSRI and may have contributed to her fall. Switching to bupropion by cross titration may benefit Mrs. D because bupropion is not serotonergic. Little data exist regarding the effects of bupropion on bone. Her prescriber monitors Mrs. D's BMD periodically, and educates her on dietary considerations. He also recommends calcium, 1,200 mg/d, and vitamin D, 800 IU/d, to help prevent fractures,²⁴ and that she continue physical therapy exercises and increase physical activity as tolerated.

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Clinical Point

Educate patients on modifiable risk factors and discuss calcium and vitamin D requirements, diet, and exercise