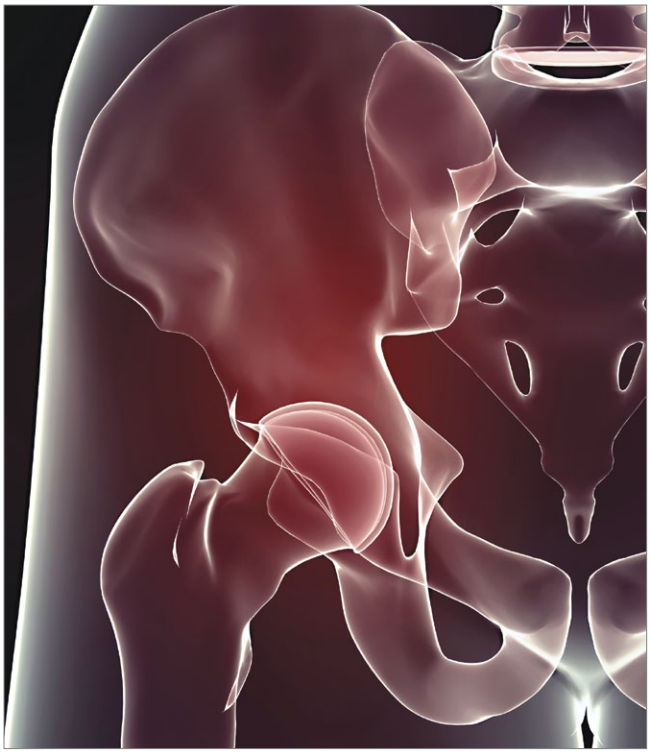
Current PSYCHIATRY

Osteoporosis in depression: Which patients are at risk?

Psychotropics increase fracture risk; depression compounds poor bone health

Ms. P, age 44, is concerned about her risk of osteoporosis after her 70-year-old mother is hospitalized for a hip fracture. Ms. P has been taking fluoxetine, 40 mg/d, for 10 years to treat recurrent major depressive episodes that began at age 25. She was diagnosed with anorexia nervosa as a teenager, but recovered after 2 years of psychotherapy. She is lactose intolerant, has mild asthma that does not require steroids, and has no history of thyroid disease or bone fracture. Ms. P smokes 10 cigarettes a day but denies using alcohol or illicit drugs. She does not exercise, and her menses occur every 28 to 30 days.



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Osteoporosis is a skeletal disease characterized by low bone mineralization and deteriorating bone architecture that results in increased susceptibility to fracture. Approximately 1 in 2 women and 1 in 5 men in the United States will have an osteoporosis-related fracture.[1] Proximal femur and vertebral fractures are most common—1.5 million per year—but other bones may be involved.[2]

Osteoporosis-related fractures are associated with substantial morbidity and mortality. After a hip fracture, osteoporosis patients have a 10% to 20% risk of death within a year.[3] Those who recover from hip fracture have a 2.5-fold increased risk of recurrent fracture and often struggle with chronic pain, disability, and loss of self-esteem and independence.[1,3-5]

Evidence links osteoporosis and depression

Research has shown that patients with major depression are at higher risk of osteoporosis.[6] In one study,

Clinical Point

Depression is associated with lower estrogen and testosterone levels, which have been linked to decreased bone formation

Table 1

Psychotropic medications associated with osteoporosis risk

Medication/class	Odds ratio (95% confidence interval)
Selective serotonin reuptake inhibitors (SSRIs)	1.45 (1.32 to 1.59)
Carbamazepine	1.18 (1.10 to 1.26)
Non-SSRIs (eg, tricyclics, atypicals)	1.15 (1.07 to 1.24)
Valproate	1.15 (1.05 to 1.26)
Oxcarbazepine	1.14 (1.03 to 1.26)
Benzodiazepines	1.10 (1.04 to 1.16)
Lamotrigine	1.04 (0.91 to 1.19)
Typical antipsychotics	1.01 (0.86 to 1.19)
Atypical antipsychotics	0.96 (0.79 to 1.17)
Lithium	0.63 (0.43 to 0.93)

Source: References 17-22

bone mineral density among 70 depressed outpatients was 15% lower than among age-matched controls.[7] In a cross-sectional study, Michelson et al[8] found that compared with nondepressed controls, women with current or past major depression had a lower mean bone mineral density—6.5% lower at the spine and 13.6% lower at the femoral neck.

Fewer prospective studies exist; however, most found depression has some impact on bone health. Whooley et al[9] prospectively evaluated changes in bone mineral density among 7,414 Caucasian women age ≥65 for 6 years. Depressed women—those who scored ≥6 on the Geriatric Depression Scale—had a 40% higher risk of nonvertebral fracture after adjusting for history of fracture, weight, physical activity level, smoking, alcohol use, nutritional status, and cognitive function. The depressed cohort also had an increased risk of vertebral fracture. In a prospective study of 21,441 Norwegian female and male subjects, women who reported being depressed at 2 of 3 time points—from 1980 until 1995—had 2.5 times the risk of sustaining a nonvertebral fracture compared with those who did not report depression.[10]

Depressed women also have greater bone loss over time. Mean hip bone mineral density decreased by 0.69% per year in nondepressed women vs 0.96% in depressed women in a study of 4,177 women age ≥69.[11] These findings were significant after adjusting for age, functional status, cognitive function, smoking, calcium intake, vitamin D supplement use, weight, antidepressant use, and bisphosphonate use. These findings have been replicated.[12]

Behavioral factors such as tobacco use and physical inactivity play a role in the risk of osteoporosis; however, emerging findings suggest a pathophysiologic link between depression and poor bone health. Depression is associated with lower estrogen and testosterone levels, which have been linked to decreased bone formation.[6] Similarly, compared with matched controls, depressed women with low bone mineral density have higher urinary cortisol levels, suggesting that hypercortisolemia accelerates bone turnover.[6,9,13] Finally, evidence suggests that depression is a pro-inflammatory state associated with production of numerous cytokines. Interleukin-6 and tumor necrosis factor-alpha, for example, inhibit osteoclast apoptosis and accelerate bone turnover.[6]

Fracture risk and psychotropics

Many psychotropic medications—including anticonvulsants, barbiturates, narcotics, and neuroleptics[14-16]—are associated with increased risk of falls, fractures, and osteoporosis. In this article we focus on selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) because little data is available on other antidepressants (***Table 1***).[17-22]

SSRIs are associated with increased fracture risk. In a cohort of 5,995 men age ≥65, Haney et al[23] showed that men taking SSRIs have lower bone mineral density at the hip (3.9% lower) and spine (5.6% lower) compared with non-users after adjusting for age, weight, and race. Current SSRI use carries a greater risk than past use. In a prospective study of 7,983 men and women age ≥55, Ziere et al[24] reported that risk of nonvertebral fracture among current SSRI users was 28% higher than among past users

over a mean follow-up of 8.4 years. In the same study, the risk ratio of nonvertebral fracture was 2.10 for patients using SSRIs within the previous 6 months and 2.98 for use >6 months.

Increased fracture risk with SSRIs may be partially explained by the greater risk of osteoporosis in major depression.[25] SSRI use has been linked to higher risk of fracture in the absence of depressive symptoms, however.[26] Bolton et al[17] revealed a trend of increasing fracture risk with higher SSRI dose. In this study, SSRI users had 45% greater likelihood of fracture than controls after adjusting for a diagnosis of depression.

Researchers are studying the mechanism by which SSRIs affect bone mineralization. Serotonin receptors—including 5-HT2A, 5-HT2B, and 5-HT2C—are present in bone.[27] Preliminary investigations suggest SSRIs are concentrated in bone and impact fibroblast formation and osteoblast activity. High bone marrow concentrations of fluoxetine inhibit human osteoblast proliferation. Osteoblasts contribute to bone production.[28] Fluoxetine concentrations in bone marrow can be up to 100-fold higher than serum levels, and the drug can be detected in bone up to 3 months after discontinuation.[29]

TCAs. U.S. veterans with prior hip fracture are twice as likely to have received TCAs than age- and sex-matched controls.[14] In prospective studies, the risk of hip fracture among men and women age ≥65 is 50% higher in patients exposed to TCAs.[30] Other investigations have revealed a dose-response relationship between TCA use and risk of fracture.[31] A direct comparison of TCAs and SSRIs has found an equivalent increase in fracture risk in these 2 classes.[30]

A direct effect of TCAs on bone metabolism has not been elucidated. However, side effects of TCAs include orthostatic hypotension, impaired cognition, dizziness, and altered balance, all of which increase the risk of falls and fractures, particularly in elderly patients.[31] Most studies of TCAs, however, do not account for depression's role in fracture risk. Some patients in these studies may have received TCAs for disorders other than major depression, such as peripheral neuropathy or prophylaxis of migraine headaches.

Table 2

Risk factors for osteoporosis-related fracture*

Clinical factors
Age >50
Female sex
Amenorrhea
Cognitive impairment
Family history of osteoporosis-related fracture
Malnutrition
Poor visual acuity
Previous falls
Low body mass index
Glucocorticoid use (prednisone >5 mg/d for ≥3 months)
Secondary medical conditions
Hyperprolactinemia
Anorexia nervosa
Postmenopausal status
Adrenal insufficiency
Diabetes mellitus
Hyperparathyroidism
Celiac disease
Inflammatory bowel disease
Malabsorption syndromes
Multiple myeloma
End-stage renal disease
Behavioral factors
Low calcium intake
Tobacco abuse
Physical inactivity
Excessive alcohol intake (>3 drinks per day)
Vitamin D deficiency
Immobilization

*Italics indicate conditions commonly encountered in psychiatric patients
Source: Reference 1

Benzodiazepine use is associated with confusion, ataxia, and vertigo, which may increase the incidence of falls. Even low doses pose a risk. In one case-control study of 1,222 hip fracture patients age ≥65, use of >3 mg/d diazepam equivalents increased risk of hip fracture by 50% after adjusting for confounding factors.[30] Although the data are mixed, benzodiazepines with shorter half-lives (eg, lorazepam) might not be safer than those with longer half-lives (eg, clonazepam).[31,32]

Other psychotropics. Some anticonvulsants may lead to bone demineralization

Clinical Point

Investigations suggest that SSRIs are concentrated in bone and impact fibroblast formation and osteoblast activity

Depression and bone health

Clinical Point

The mechanism by which antipsychotics accelerate bone turnover has not been described, but hyperprolactinemia likely plays a role

Table 3

Reducing osteoporosis risk: Recommendations for patients age >50

Assess dietary calcium (at least 1,200 mg/d) and dietary vitamin D intake (800 to 1,000 IU/d)
Exercise regularly, especially weight-bearing and muscle-strengthening activities (eg, walking, jogging, stair climbing, weight-lifting)
Stop using tobacco
Avoid heavy alcohol use
Implement fall precautions such as rubber-soled shoes when walking, handrails for staircases, and removing tripping hazards, including loose rugs

Source: Reference 1

via induction of the cytochrome P450 hepatic enzyme system, which accelerates conversion of vitamin D to an inactive metabolite that cannot adequately facilitate absorption of ingested calcium. The subsequent release of parathyroid hormone causes bone resorption.[33] Patients taking anticonvulsants have nearly double the serum parathyroid hormone level of matched controls.[34] Carbamazepine, oxcarbazepine, and valproate have been associated with increased risk of fracture.[32] Although lamotrigine has not been widely studied, evidence suggests that its impact on bone metabolism is negligible.[35]

Many antipsychotics, including risperidone and haloperidol, have been associated with osteoporosis. The mechanism by which antipsychotics accelerate bone turnover has not been described; hyperprolactinemia likely plays a role.[36]

Screening and treatment

Effective pharmacotherapy for osteoporosis includes bisphosphonates (eg, alendronate), selective estrogen receptor modulators (eg, raloxifene), recombinant parathyroid hormone (eg, teriparatide), as well as calcium and vitamin D supplementation. Consider recommending bone density evaluation for depressed patients who have predisposing risk factors (***Table 2, page 11***)[1] and those with long-term exposure to psychotropic agents. Dual energy X-ray absorptiometry is the preferred screening method. Refer patients whose results indicate osteopenia or osteoporosis to primary care. Although pharmacotherapy for osteoporosis should be managed by primary care practitioners, psychiatrists can serve an important role by promoting healthy lifestyle behaviors—such as regular exercise and adequate dietary vitamin D and calcium intake (***Table 3***).[1]

CASE CONTINUED

High risk can be lowered

Ms. P's family history, antidepressant use, smoking, and low dietary calcium intake associated with lactose intolerance increase her risk for osteoporosis. Her history of anorexia nervosa also increases her risk if she experiences amenorrhea. You advise her that she can ameliorate some of these factors by quitting smoking, exercising regularly, and taking calcium and vitamin D supplements. You refer her to her primary care physician because she wishes to undergo bone mineral density screening.

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Related Resources

- National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. www.nof.org/professionals/Clinicians_Guide.htm.
- World Health Organization Fracture Risk Assessment Tool. Calculates a 10-year probability of hip fracture using demographic data, family history, comorbid medication and predisposing medical conditions. www.shef.ac.uk/FRAX.

Drug Brand Names

Alendronate • Fosamax
Carbamazepine • Tegretol
Clonazepam • Klonopin
Diazepam • Valium
Fluoxetine • Prozac
Haloperidol • Haldol
Lamotrigine • Lamictal
Lithium • Eskalith, Lithobid
Lorazepam • Ativan
Oxcarbazepine • Trileptal
Prednisone • Deltasone, Meticorten
Raloxifene • Evista
Risperidone • Risperdal
Teriparatide • Forteo
Valproate • Depakote

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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Bottom Line

Psychiatric patients often are at risk for low bone mineral density, falls, and fractures because of behavioral factors, physiologic mechanisms, and psychotropic use. Closely assess risk factors for fracture, recommend exercise, and discourage tobacco and alcohol use. Refer patients at high risk to a primary care physician.

Clinical Point

Recommend bone density testing for depressed patients with predisposing risk factors and long-term psychotropic use