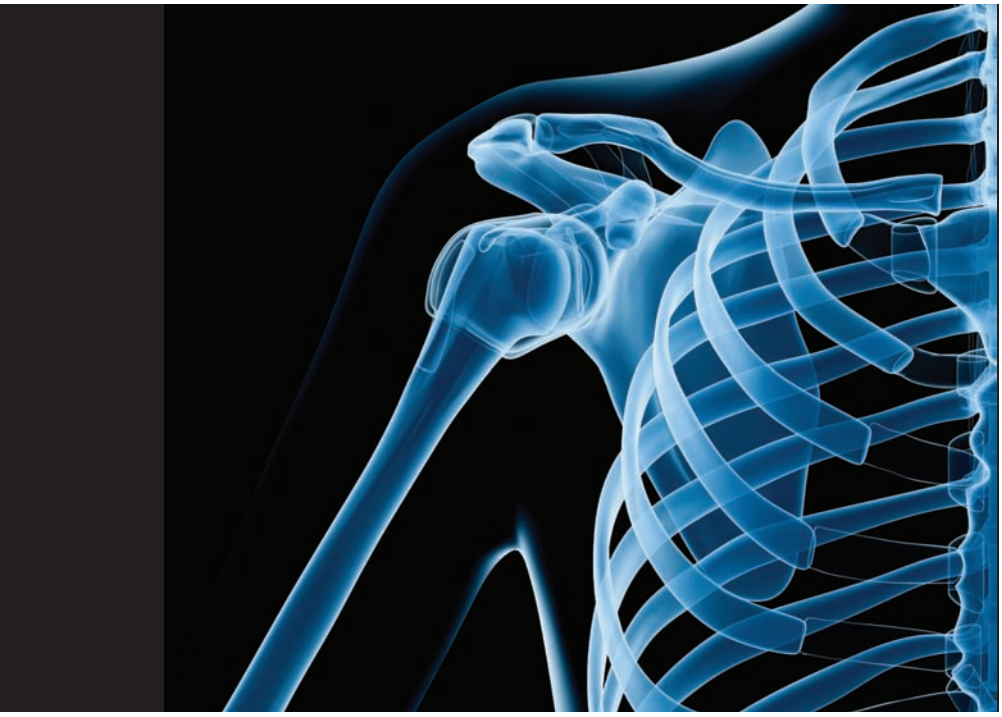
The Interface



SSRIs: BAD TO THE BONE?

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

ABSTRACT

Selective serotonin reuptake inhibitors are globally popular antidepressants with broad clinical indications. Despite an overall favorable side-effect profile, our examination of 19 studies, one review, and one meta-analysis indicates that these unique antidepressants appear to have negative effects on bone, particularly with regard to bone mineral density and fracture risk. These risks may be enhanced by more serotonergic agents and/or longer exposure to selective serotonin reuptake inhibitors. The magnitude of this relationship is difficult to determine due to the myriad of potential confounds in available studies, but all indicate risk. In additional support of these findings, serotonin receptors have been identified on osteoclasts, osteoblasts, and osteocyte cell lines, suggesting that serotonin may be an important regulatory agent in bone. While no formal recommendations regarding the use of selective serotonin reuptake inhibitors in risk populations are available, caution is advised in individuals with potential risk (i.e., those with osteoporosis or histories of osteoporotic fractures).

KEY WORDS

Bone, fractures, osteoporosis, selective serotonin reuptake inhibitors, SSRIs, skeleton

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are globally popular antidepressants. In addition to their generally favorable side-effect profiles compared with other classes of antidepressants, SSRIs currently have the broadest range of clinical indications approved by the United States Food and Drug Administration.[1] Depending on the individual SSRI, these indications include major depression, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, social anxiety disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and bulimia nervosa (Table 1).[1] Given their tolerability and broad clinical efficacy, however, continuing examination of risk is important. In this edition of The Interface, we examine one potential risk associated with SSRIs—their effects on bone, specifically decreased bone mineral density (BMD) and fractures.

A SAMPLING OF STUDIES

To collect data, we performed a search of the PubMed and PsycINFO databases, using the search terms *SSRI, bone, fractures* and *osteoporosis*. We eliminated one study in which the article was only available in Japanese,which left us with 21 studies[2–22] dating back to 1998 (Table 2). These studies consist of retrospective, cross-sectional, prospective, review, and

TABLE 1. Approved clinical indications by the Food and Drug Administration for selective serotonin reuptake inhibitors (SSRIs)[1]

SSRI	Major Depression	Generalized Anxiety Disorder	Panic Disorder	Obsessive-Compulsive Disorder	Social Anxiety Disorder	Posttraumatic Stress Disorder	Premenstrual Dysphoric Disorder	Bulimia Nervosa
Citalopram	X							
Escitalopram	X	X						
Fluoxetine	X		X	X			X	X
Fluvoxamine				X	X			
Paroxetine	X	X	X	X	X	X	X	
Sertraline	X		X	X	X	X	X	

meta-analytic designs. With the exclusion of the review and meta-analysis, the remaining 19 studies were from the United States (9 studies), Canada (3 studies), the Netherlands (3 studies), Denmark (2 studies), the United Kingdom (1 study), and Australia (1 study). Study populations included men, women, both men and women, and male children. Using different study variables, varying approaches to statistical analyses, and controlling for various potential confounds in a number of studies, each and every study indicates a risk of reduced BMD, fracture, or both. In other words, we could not find a study that disputed this clinical association.

Importantly, the explicit magnitude of the relationship between SSRI use and decreased BMD/fracture remains somewhat undefined. One reason for this is the potential for confounds in these studies, which we will discuss. Yet, in a recent meta-analytic examination of 13 studies by Wu et al,[22] researchers concluded that despite confounds, SSRI use was associated with a significantly increased risk of fracture.

According to limited data, bone risk may vary. For example, Vestergaard[13] found that paroxetine did not exhibit an increased risk of fracture when compared to the other SSRIs. This finding is somewhat unexpected given that Verdel et al[19] reported an association between fracture risk and a given antidepressant's affinity for serotonin, with more serotonergic compounds evidencing higher risk (i.e., paroxetine is the most serotonergic SSRI). Likewise, in a review, Ginzberg and Rosero[16] found that fracture risk appeared to slightly increase over time with exposure to an SSRI.

To summarize these findings, there appears to be a higher risk of negative effects on BMD and fracture among individuals taking SSRIs, although this risk is difficult to specifically quantify. Greater risk may be associated with more serotonergic antidepressants as well as longer exposure.

POTENTIAL CONFOUNDS

From a statistical perspective, there are always potential confounds that temper findings in any study. The relationship between SSRIs and their effects on bone are no different. For example, depression itself has been associated with adverse skeletal consequences through postulated effects on the hypothalamic-pituitary-adrenal axis as well as pro-inflammatory cytokines.[23] However, in examining various studies, the effects of depression on bone are statistically inconsistent.[24] In addition, several studies have controlled for other suspected confounds (nicely outlined by Wu et al[22]), such as potential bias in claims database studies,[5] the possibility of physical inactivity induced by antidepressants,[25] and estrogen deficiency[26]—all with unwavering conclusions that SSRIs continue to exert negative effects on bone.

SSRIs AND BONE: PATHOPHYSIOLOGICAL RELATIONSHIPS

While the pathophysiology of SSRI effects on bone is just beginning to be elucidated and is not totally clarified,[27] serotonin appears to have major functions outside of the central nervous system.[28] In this more peripheral role, serotonin may exert effects on the skeleton.[28] In support of this, serotonin receptors have been identified on osteoclasts, osteoblasts, and osteocyte cell lines,[29] suggesting that this neurotransmitter may be an important regulatory agent in bone.[30] While a number of studies have confirmed serotonergic influences on skeletal bone, they offer contrasting

TABLE 2. Sampling of studies examining skeletal effects of selective serotonin reuptake inhibitors (SSRIs)

FIRST AUTHOR/YEAR	SAMPLE/STUDY CHARACTERISTICS	FINDINGS
Liu/1998[2]	Canadian case-controlled study of 8,239 hospitalized patients, ages 66 years or older, matched to five controls per case	Adjusted odds ratio for hip fracture=2.4 (CI=2.0–2.7)
Ensrud/2003[3]	United States prospective study of 8,127 women, ages 65 years or older, in which 6% were current users of antidepressants and of these, 21% were on SSRIs	Over average follow-up of 4.8 years, multivariate hazard ratios for the risk of non-spine and hip fractures in current SSRI users=1.44 (CI=0.93–2.24) and 1.54 (CI=0.62–3.82), respectively
Hubbard/2003[4]	United Kingdom case-controlled study of 16,341 cases of hip fracture and 29,889 controls from the United Kingdom General Practice Research Database	Odds ratio for fracture within the first 15 days of prescription=6.30 (CI=2.65–14.97); incidence ratio=1.96 (CI=1.35–2.83)
Schneeweiss/2004[5]	United States examination of the Medicare Current Beneficiary Survey, consisting of 7,126 participants, ages 65 years or older	Relative risk for hip fractures among SSRI users=1.8 (CI=1.5–2.1)
Vestergaard/2006[6]	Danish case-controlled study comparing 124,655 cases of fracture with 373,962 controls	Fracture rate in SSRI cases=12.0% versus controls=7.2% (significant difference)
Diem/2007[7]	United States prospective controlled study of 2,722 community women, mean age 78.5 years, in the Study of Osteoporotic Fractures	After approximately 5 years, SSRI-users had a mean decrease of 0.82% in total hip BMD versus 0.47% for controls (significant difference)
Haney/2007[8]	United States cross-sectional controlled study of 5,995 men, ages 65 years or older, in the Osteoporotic Fractures of Men Study	In SSRI-users, mean total hip and lumbar spine BMD were 3.9% and 5.9% lower, respectively, than in men with no antidepressant exposure (significant difference)
Lewis/2007[9]	United States prospective study of 5,995 community men, ages 65 years or older	Over 4.1 years, the hazard ratio for a non-spine fracture=1.79 (CI=1.00–3.19)
Richards/2007[10]	Canadian prospective controlled cohort study of 5,008 community adults, ages 50 years or older	Over 5 years, daily SSRI users had a 2-fold risk of fragility fractures (hazard rate=2.1, CI=1.3–3.4)
Bolton/2008[11]	Canadian review of database examining individuals with osteoporotic fractures (N=15,792) with matched controls	Adjusted odds ratio for osteoporotic fractures with SSRI-use=1.45 (CI=1.32–1.59)

BMD: bone mineral density; CI: confidence interval at 95%

evidence as to its effects.[28] For our purposes, one postulated effect of serotonin is a role in bone-resorption pathways.[28] In addition, studies indicate that the inhibition of the serotonin transporter, which is the function of SSRIs, may have detrimental effects on bone mineral accrual.[31] Clearly, more research will be required before the explicit pathway is uncovered, but current evidence supports an overall negative serotonergic effect on bone regulation.

CONCLUSION

Our review of 19 studies on the effect of SSRIs on bone indicates negative effects on BMD and/or heightened fracture risk. The explicit magnitude of this effect remains unclear due to the tempering effects of various potential confounds. However, in support of this relationship, there are known negative pathophysiological effects of serotonin on bone regulation. While no recommendations are presently available, SSRI use in high-risk individuals (e.g., those with osteoporosis, history of osteoporotic fractures) is cautioned.

TABLE 2, CONTINUED. Sampling of studies examining skeletal effects of selective serotonin reuptake inhibitors (SSRIs)

FIRST AUTHOR/YEAR	SAMPLE/STUDY CHARACTERISTICS	FINDINGS
Spangler/2008[12]	United States prospective study of 82,410 women between the ages of 50 and 79 years	At average follow-up of 7.4 years, adjusted hazard ratios for clinical spine fracture or wrist fracture with SSRI use=1.25 (CI=0.96–1.63) and 1.29 (CI=1.07–1.56), respectively
Vestergaard/2008[13]	Danish cross-sectional case-controlled study of 124,655 fracture cases and 373,962 controls from the National Hospital Discharge Register, mean age of 43.4 years with 48.2% men	Citalopram, fluoxetine, and sertraline were associated with a dose-dependent increase in fracture risk; paroxetine was not
Williams/2008[14]	Australian cross-sectional study of community women, mean age 51.5 years, 128 on current SSRI treatment, versus nonusers	Compared with nonusers, participants on SSRIs demonstrated BMD measurements that were 5.6%, 6.2%, and 4.4% lower at the femoral neck, trochanter, and mid-forearm, respectively (significant differences)
Ziere/2008[15]	Dutch study of 7,983 adults, ages 55 years or older, in The Rotterdam Study	Current SSRI users demonstrated a risk of nonvertebral fractures of 2.35 (CI=1.32–4.18)
Ginzburg/2009[16]	Medline review of 13 studies	Possible correlation between SSRI use and risk of fracture that slightly increases over time
van den Brand/2009[17]	Dutch case-controlled study of the PHARMO-RLS health registry, comparing 6,763 cases, mean age of 75.7 years, to 26,341 controls	Odds ratio of a hip/femur fracture with SSRIs was 2.35 (CI=1.94–2.84)
Calarge/2010[18]	United States cross-sectional study of 83 male children and adolescents, ages 7–17 years, in an outpatient psychiatry clinic on risperidone and SSRI treatment	SSRI use was associated with a statistically significant lower BMD at the radius and lumbar spine
Verdel/2010[19]	Dutch case-controlled study using the PHARMO RLS health registry, comparing 16,717 fracture cases with 61,517 controls	Osteoporotic fracture risk was statistically significantly higher for antidepressants with a high affinity for serotonin (odds ratio=1.86, CI=1.63–2.13)
Diem/2011[20]	United States prospective 10-year study of 8,217 community women, ages 69 years or older	Women on SSRI therapy had a higher risk of nonspine fractures (hazard ratio=1.36, CI=1.11–1.67) and wrist fracture (hazard ratio=1.54, CI=1.01–2.36)
Gagne/2011[21]	United States study of Medicare database from two states, consisting of 56,941 individuals on SSRIs, with a mean age of 77.7 years	Among the antidepressants, SSRIs demonstrated the highest association with fracture rate (hazard ratio=1.30, CI=1.12–1.52)
Wu/2011[22]	Meta-analysis of 13 studies	SSRI use associated with a significantly increased risk of fracture (relative risk=1.72, CI=1.51–1.95), independent of depression and BMD

BMD=bone mineral density; CI=confidence interval at 95%

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