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Review

Antidepressant medications and osteoporosis

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ABSTRACT

Use of antidepressant medications that act on the serotonin system has been linked to detrimental impacts on bone mineral density (BMD), and to osteoporosis. This article reviews current evidence for such effects, and identifies themes for future research. Serotonin receptors are found in all major types of bone cell (osteoblasts, osteocytes, and osteoclasts), indicating an important role of the neuroendocrine system in bone. Observational studies indicate a complex relationship between depression, antidepressants, and fracture. First, the presence of depression itself increases fracture risk, in relation with decreased BMD and an increase in falls. A range of aspects of depression may operate, including behavioral factors (e.g., smoking and nutrition), biological changes, and confounders (e.g., comorbidities and concomitant medications). A substantial proportion of depressed patients receive antidepressants, mostly selective serotonin reuptake inhibitors (SSRIs). Some of these have been linked to decreased BMD (SSRIs) and increased fracture risk (SSRIs and tricyclic agents). Current use of SSRIs and tricyclics increases fracture risk by as much as twofold versus nonusers, even after adjustment for potential confounders. While there is a dose–response relationship for SSRIs, the effect does not appear to be homogeneous across the whole class of drugs and may be linked to affinity for the serotonin transporter system. The increase in risk is the greatest in the early stages of treatment, with a dramatic increase after initiation, reaching a peak within 1 month for tricyclics and 8 months for SSRIs. Treatment-associated increased risk diminishes towards baseline in the year following discontinuation. The body of evidence suggests that SSRIs should be considered in the list of medications that are risk factors for osteoporotic fractures.

Contents

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Introduction

Serotonin is well known as a regulator of mood. An increase in synaptic availability of serotonin is known to have an antidepressant effect, and is involved in all or part of the mechanism of action of some of the most widely used antidepressants. However, serotonin also plays an important role centrally in functions such as appetite, sleep, sex, and temperature, and acts peripherally in the cardiovascular and gastrointestinal systems. There is increasing evidence that serotonin may also be an important regulatory agent in bone metabolism [1], notably bone mass.

Antidepressant treatments that act on serotonin pathways may therefore be expected to have some impact on bone, bone mass, and fracture rates. The link between depression, antidepressant use, and osteoporosis is becoming more widely understood, and there is mounting evidence for an effect of depression and antidepressants on fracture rates. This article was prepared by a working group of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), which reviewed the evidence for an effect of antidepressants on bone mass and fracture, as well as the impact of various confounders, including depression itself.

Methods

Relevant articles, reviews, and abstracts were identified through a PubMed/MEDLINE search of English-language articles published between 1990 and September 2011. The search strategy included the terms antidepressant, serotonin, selective serotonin reuptake inhibitor (SSRIs, fluoxetine, paroxetine, citalopram, escitalopram, sertraline, and fluvoxamine), serotonin and noradrenaline reuptake inhibitor (SNRIs, venlafaxine and duloxetine), tricyclic antidepressants (amitriptyline, clomipramine, desipramine, and imipramine), mianserin, mirtazapine, moclobemide, nefazodone, osteoporosis, fracture, central nervous system, bone, and risk for fracture. Separate subsearches were also performed using a cross-search of the above terms combined, as well as the reference lists of the selected articles. Overall, 112 items were detected, 64 of which were selected by the authors according to their quality and pertinence for discussion by the ESCEO working group and inclusion in this review.

Serotonin and bone pathophysiology

Serotonin (5-hydroxytryptamine, 5-HT) is synthesized in the gut and the brain from tryptophan via the enzyme tryptophan hydroxylase (TPH) [1]. More than 95% of human serotonin is synthesized in the gut (i.e. the duodenum) by enterochromaffin cells via the *TPh1* isoform of the enzyme. Gut-derived serotonin is for the most part stored in platelets, and it plays a role in platelet aggregation and blood clotting after injury. The rest of human serotonin (<5%) is produced in the brainstem, also from tryptophan via the *TPh2* isoform of the TPH enzyme. Since serotonin does not cross the blood–brain barrier, the pools of peripheral and central serotonin function in relative isolation. Human studies directly linking serotonin levels to bone health have been difficult to perform because measuring free serotonin in the circulation is extremely challenging. Accordingly, a recent review of the methods used for measuring serotonin in platelet-poor plasma – which is necessary due to the abundance of serotonin within platelets – found results to be highly discrepant and called for a collaborative effort to develop a gold standard reference [2].

The impact of serotonin on bone has been explored in a variety of animal models. This action occurs via interaction with 5-HT receptors situated in all of the major types of bone cell (osteoblasts, osteocytes, and osteoclasts) [1,3,4]. There may also be a link with the effects of LRP5 (low-density lipoprotein receptor-related protein 5), which inhibits the expression of *TPh1* in the duodenum. This suggests that gut-derived serotonin acts as a downstream mediator of skeletal effects of LRP5, which was confirmed by experiments in *Lrp5*-deficient mice [5]. Indeed, *Lrp5*-deficient mice that also lack one copy of *TPh1* in the gut and have therefore normalized levels of gut-derived serotonin were found to have a high bone mass, which was demonstrated by increases in bone volume, osteoblast number, and rate of bone formation, with no impact on bone resorption [5]. Further evidence for these effects is provided by the observation that TPh1 inhibitors have an anabolic effect in ovariectomized mice and rats, as well as in *Lrp5*-deficient mice by correcting their low bone mass phenotype [6]. In contrast, recent research has pointed to other mechanisms, notably that LRP5 may also be locally involved in bone mass control, with mutations being associated with either low or high bone mass [7]. Yadav's and Cui's results on gastrointestinal serotonin and bone are different and cannot be reconciled, but any attempt to resolve these discrepancies [6,7] would be beyond the scope of this review.

Brain-derived serotonin appears to favor bone mass accrual, according to similar experiments in *TPh2*-knockout mice, which displayed decreases in bone volume, osteoblast number, and rate of bone formation, and an increase in osteoclast surface [8]. Whereas gut-derived serotonin acts directly on osteoblasts, the effect of brain-derived serotonin on bone mass is mediated by its ability to down-regulate sympathetic output, an inhibitor of bone mass accrual [5,8,9]. These data are consistent with the possible role of the adrenergic system in depression [10]. Although brain-derived serotonin constitutes only 5% of circulating serotonin, this finding may be relevant insofar as the majority of gut-derived serotonin is stored intracellularly in platelets [1].

Serotonin therefore appears to have opposite effects on bone mass according to its origin. Central serotonin acts by inhibiting sympathetic output, a negative regulator of bone mass accrual controlling both bone formation and bone resorption, and thereby enhances this process [8]. In contrast, gut-derived serotonin inhibits bone formation by directly decreasing osteoblast proliferation [5]. Yet, blocking the synthesis of both central and peripheral serotonin results in a low bone mass phenotype [8]. Based on these observations, decreasing levels of serotonin globally would be expected to reduce bone mass, while increasing serotonin levels should result in bone mass accrual. It follows that treatment with an antidepressant that increases serotonin signaling – such as an SSRI – should induce bone mass accrual. In this case, the results of experimental models do not fit the prediction. Accordingly, inactivation of the plasma membrane serotonin transporter (5-HTT) in mice causes a low bone mass phenotype [11], with reduced bone mass, altered architecture, and inferior bone mechanical properties; the effect of 5-HTT inactivation on circulating serotonin levels was not specified. Moreover, administration of the SSRI fluoxetine to mice (which antagonizes 5-HTT) reduced bone mineral density (BMD) and altered trabecular architecture, independently of the effects of estrogen deficiency [12]. The molecular basis for these phenotypes is poorly understood.

Together, these studies highlight the need for further research into the role of serotonin in bone. There are many confounding factors [1,4]. For example, the inactivation of 5-HTT in animal models is global and enhanced serotonin signaling could trigger negative feedback mechanisms. Moreover, these negative regulations could be site- or

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SSRI-specific. Finally, it is unknown whether the impact of fluoxetine varies across different skeletal sites, or whether other SSRIs could have different efficacies at different sites. Research to date suggests that the neuroendocrine system plays an important role in the regulation of bone, and that this should be considered in the management of depression with antidepressants that act on the serotonin system.

Depression and antidepressants

Depression is a major public health problem and a leading cause of disability. Epidemiological studies suggest that the prevalence of some form of depression is about 22% in the US population, with substantially higher rates in women (26%) than in men (18%) [13]. The lifetime prevalence of major depressive disorder (Diagnostic and Statistical Manual of Mental Disorders IV [DSM-IV] criteria) is estimated at 16% [14]. Similar rates of depression are reported in European populations [15].

According to a study from the National Health and Nutrition Examination Survey (NHANES), about half of patients with moderate or severe depressive symptoms have some form of treatment [13]. However, this figure reflects symptoms in a population cohort, many of whom will not have sought medical help or have a formal diagnosis of depression. In contrast, an analysis in the UK General Practice Research Database (GPRD) found that about 80% of patients diagnosed with depression received some form of pharmacological antidepressant treatment in the following 12 months [16]. Antidepressant prescribing was found to have almost doubled in the UK in the period from 1993 to 2005, and the majority of prescriptions, whether they were continuous or intermittent, were long-term, which is an indicator of the chronic nature of the illness.

There is a range of pharmacological antidepressant treatments available. Current newer generation antidepressant drugs include the SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) and the SNRIs (venlafaxine and duloxetine). Older agents include the tricyclics (amitriptyline, clomipramine, imipramine, maprotiline, and nortriptyline) and the monoamine oxidase inhibitors (isocarboxazide and moclobemide), which are still used in some patients, notably for treatment-resistant depression. The mechanisms of action of these agents all involve some impact on the serotonin system (Table 1), though the degree of inhibition of the 5-HTT system may differ between classes. The SSRIs inhibit serotonin reuptake by the presynaptic neuron, thereby maintaining higher levels of serotonin in the synapse and increasing postsynaptic neurotransmission. The SNRIs have a similar action on serotonin levels in the synapse, but also increase synaptic levels of noradrenaline. Tricyclic antidepressants block the 5-HTT and the equivalent noradrenaline transporter, and therefore act primarily as reuptake inhibitors for serotonin and noradrenaline. The individual tricyclics may also have antagonistic effects on the histamine and acetylcholine systems. The exact mode of action with respect to serotonin levels varies across the tricyclics, with tertiary amines (e.g., amitriptyline) inhibiting serotonin reuptake to a greater extent than that of noradrenaline, while the opposite is true for the secondary amines (e.g., nortriptyline). Finally, the monoamine oxidase inhibitors prevent the breakdown of monoamine neurotransmitters, including serotonin and noradrenaline, thereby indirectly increasing their availability; like the tricyclics, they also affect the histamine and acetylcholine systems.

Prescribing patterns for antidepressants in Europe were reported by the Factors Influencing Depression Endpoints Research (FINDER) observational study performed in 2004 and 2005 [17]. The most common prescription was reported to be one of the newer generation antidepressants, the SSRIs (63% of patients) and the SNRIs (14% of patients). However, the same authors also reported considerable variation between the countries, for example, prescribing patterns for SSRIs varied from 32% in Germany to 82% in France, and SNRIs from 6% in Austria to 26% in the Netherlands [17]. The choice of antidepressant was dictated by both patient- and physician-related issues, including severity of disease, clinical profile of the antidepressant, side effects, treatment history, and previous experience with the agent.

The side effects of antidepressants are related to the neurotransmitters they target (Table 1). The tricyclics have noradrenergic effects (e.g., cardiac arrhythmia) and impair adrenergic response (e.g., orthostatic hypotension), but may also have antihistaminergic (e.g., sedation and weight gain) and anticholinergic effects (e.g., dry mouth). Because of their selective nature, the SSRIs and SNRIs appear to be less likely associated with these types of side effect.

Depression and risk for fracture

Before considering the impact of any pharmacological modification of the serotonin system on bone, it is necessary to understand the

Table 1
Neurotransmitter targets and associated side effects for antidepressant agents.
Adapted from a table produced by the Danish College of General Practitioners and the Danish Psychiatric Society. Available at: http://pro.medicine.dk. Accessed 17 October 2011.

Agent	Neurotransmitter target		Side effects		
	Serotonin	Noradrenaline	Noradrenergic effects (orthostatic hypotension)	Histaminergic effects (sedation, weight gain)	Anticholinergic effects (dry mouth, impaired vision, constipation, confusion)
Selective serotonin reuptake inhibitors					
• Citalopram	++++				+
• Escitalopram	++++				+
• Fluoxetine	+++				+
• Fluvoxamine	+++				
• Paroxetine	+++				+
• Sertraline	++++		(+)		(+)
Serotonin and noradrenaline reuptake inhibitors					
• Duloxetine	++++	+++			
• Venlafaxine	+++	++			
Tricyclic antidepressants					
• Amitriptyline	++	+	+++	+++	+++
• Clomipramine	++++	+	++	++	+++
• Imipramine	+	+	++	++	++
• Nortriptyline	+	+++	+	+	+
• Maprotiline		+++	++	++	++
Monoamine oxidase inhibitors					
• Isocarboxazide			+++	+++	
• Moclobemide			+		

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Table 2
Features of depression that may reduce bone mass and increase fracture risk [23].

Behavioral factors	Biological factors	Confounders
Smoking	Hypercortisolemia	Comorbidities
Alcohol abuse	Inflammation	Other medications
Poor nutrition (lower calcium intake)	Increased catecholamines	Antidepressants
Weight loss	Decreased gonadal steroids	
Decreased physical activity (lower muscle strength)		
Less daylight (lower vitamin D)		
Falls		

impact of depression itself on bone health. The association between depression and fracture has been known since the late 1990s, and has been the subject of a number of studies. For instance, a prospective study in 7414 elderly white women with depression showed that the presence of depression increased the risk for nonvertebral fracture (adjusted hazard ratio [HR], 1.30, $P=0.008$) and vertebral fracture (adjusted odds ratio [OR], 2.10, $P<0.001$) [18]. This increase in risk appears to be partly explained by an increase in falls, and partly by a decrease in BMD [18–23]. Indeed, the greater the severity of depression, the lower the BMD [19]. These findings are further supported by a recent meta-analysis of 20 studies on the relationship between depression and osteoporosis,which found that depressed patients had lower BMD at all sites versus controls (spine, femoral neck, and total femur), which is likely to increase fracture risk [24].

There are a range of features of the depressed patient that could be associated with the reduction in BMD and increased rate of fracture (Table 2). Most of the behavioral factors that contribute to reduced bone mass are also known to be risk factors for osteoporosis [25]. These include increased rates of smoking and alcohol use; poor nutrition; weight loss and lower body mass index; immobilization or reduced physical activity leading to muscle weakness and increased risk for falls; and a sedentary lifestyle with less exposure to sunlight and lower vitamin D levels. The use of bone-active medications may confound the observation of an association between depression and BMD. However, it is currently impossible to evaluate this with the current dataset, since many of the studies were performed in younger (premenopausal) individuals [24] or in populations with very low rates of the use of osteoporosis treatments [18,19]. Bone mass may also be affected by a number of biological changes during the depressive episode, such as persistently elevated plasma cortisol levels due to stress (although not all studies could confirm this [26]), increased catecholamine levels, and a decrease in gonadal steroids [19]. Finally, there are a series of potentially confounding factors [23], including comorbid conditions known to affect the risk for depression and osteoporotic fracture, e.g., cardiovascular disease, Crohn's disease, and diabetes, as well as concomitant use of medications that reduce bone mass, such as glucocorticoids, estrogen, and loop diuretics [27]. Another group of confounders includes the use of antidepressants. Chronic disease may also be associated with depression induced by the disability stemming from the chronic disease in question.

Antidepressants and BMD

The impact of antidepressants on fracture may be linked to the effects on BMD [28,29]. There have been a number of cross-sectional and cohort studies exploring the relationship between the use of antidepressants and BMD (Table 3) [30–36]. A population-based cohort study in 5000 adults reported a significant reduction in hip BMD (−4%, 95% confidence interval [CI], −6.6% to −1.4%) in SSRI users versus nonusers, and a trend towards a reduction in spine BMD (−2.4%, 95% CI, −5.5% to +0.9%) [34]. These results have been confirmed in a cohort study including nearly 3000 women [31] divided into three categories: SSRI users (n=198), tricyclic users (n=118), or nonusers (n=2406). After 5 years, the women in the nonuser group had a 0.5%

Table 3
Studies exploring the relationship between the use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), and bone mineral density (BMD) [30–36].

Authors	Description of study	Population	Effect on BMD versus nonusers		Main conclusion of study
			SSRI	TCA	
Kinjo et al. [33]	Cross-sectional analysis in the NHANES population	14646 adults receiving CNS-active agents, including 154 patients on antidepressants	No association	No association	• No relationship between antidepressant use and BMD (but <1% of the NHANES population was using antidepressants)
Diem et al. [19]	Cohort study (USA)	2722 women, aged ≥65 years 5 years of follow-up	Hip BMD decreased by 0.8% in users versus 0.5% in nonusers ($P<0.001$)	Hip BMD decreased by 0.5% in users (same as in nonusers)	• SSRI use, but not TCA use, is associated with reduced BMD
Haney et al. [32]	Cross-sectional analysis (USA)	5995 men, aged ≥65 years	Hip BMD 4% lower ($P=0.002$) and spine BMD 6% lower in users versus nonusers ($P<0.001$)	No difference between users and nonusers	• BMD is lower among men reporting current SSRI use
Richards et al. [34]	Population-based cohort (Canada)	5008 adults, aged ≥50 years 5 years of follow-up	Hip BMD reduced by 4% (significant) and spine BMD by 2% (nonsignificant) versus nonusers	No information	• SSRI use lowers BMD at hip and spine
Spangler et al. [35]	Prospective cohort study (Women's Health Initiative, USA)	6441 women, mean age 64 years, with BMD evaluation 3 years of follow-up	No association	No information	• SSRI use not associated with a change in BMD
Williams et al. [36]	Cross-sectional analysis (Australia)	124 women	Reductions in femoral neck BMD (6%), trochanter BMD (6%), and forearm BMD (4%), all $P<0.05$ versus nonusers	No information	• SSRI use lowers BMD at certain sites
Calarge et al. [30]	Cross-sectional analysis (USA)	83 adolescent boys treated with risperidone, mean age 12 years 45 out of 83 on risperidone and SSRI	SSRI use associated with lower trabecular BMD at radius ($P=0.03$) and spine ($P<0.05$)	No information	• SSRI use reduces BMD in adolescents

CNS, central nervous system. NHANES, National Health and Nutrition Examination Survey.

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decrease in total hip BMD per year. In the patients in the cohort using antidepressants, the rate of bone loss was greater in SSRI users (0.8% reduction per year, $P<0.001$), but unchanged in tricyclic users (0.47% per year, $P=0.99$) [31]. These results were adjusted for potential confounders and, interestingly, there was no difference in the result for continuous users of SSRIs versus intermittent users (women who reported SSRI use at only one of the study visits). Similar results were reported in a cross-sectional analysis of a population of 5995 men, of whom 160 were classified as SSRI users [32]. In this population, SSRI use was associated with 4% lower total hip BMD ($P=0.002$) and 6% lower lumbar spine BMD ($P<0.001$). Cross-sectional studies in smaller populations are in line with these results [30,36]. On the other hand, the evidence for a relationship between the use of SSRIs and loss of BMD is not uniform. Analyses in the NHANES population [33] and the Women's Health Initiative (WHI) study [35] failed to detect an association, though this may be due to confounders such as the size of the sample (e.g. 154 patients, <1% of the NHANES study population, was using antidepressants).

None of the studies exploring tricyclic use could detect an effect of those agents on BMD (Table 3), with similar values of BMD in users and nonusers [31,32]. The number of users of TCAs was relatively small (around 100 in each study) [31,32], which somewhat reduces the power of this observation. Concerning other antidepressants, there are no studies on BMD and the use of monoamine oxidase inhibitors or SNRIs, though high-dose venlafaxine has been associated with an increased loss of alveolar bone in rats [37]. Similarly, the effect of the noradrenaline reuptake inhibitor reboxetine is unknown, though it has been reported that blockade of the beta-adrenergic receptors is associated with an impact on bone metabolism [38,39]. Finally, lithium may actually improve BMD. A cross-sectional study in 75 lithium-treated patients and 75 normal subjects indicated that lithium was associated with a 4.5% higher spine BMD, a 5.3% higher femoral neck BMD, and a 7.5% higher BMD at the trochanter (all $P<0.05$) [40].

Overall, the evidence suggests that current SSRI use is associated with a reduction in BMD and bone loss. It has even been suggested that SSRI use may be as detrimental as glucocorticoids on bone loss [32]. The evidence for an impact of the other antidepressant agents on bone loss and BMD is mixed, and further research is necessary.

Antidepressants and risk for fracture

The association between antidepressants and fracture has been the subject of a number of observational studies, generally with case–control or cohort designs (Table 4) [27,34,35,41–56]. The results indicate that current use of SSRIs and tricyclics increases the risk for fracture by as much as twofold versus nonusers. Although there is some variation between the studies, the ORs for increases in nonvertebral fracture risk associated with treatment (users versus nonusers) are between 1.3 and 2.4 for SSRIs and 1.2 and 2.4 for tricyclics; the associated increases in hip fracture risk are between 1.0 and 2.4 for SSRIs and 1.1 and 1.8 for tricyclics. A meta-analysis of 13 observational studies has further supported an increased fracture risk with SSRI use. Additionally, subanalysis of the three studies that adjusted for BMD revealed a similar association between SSRI use and fracture risk to that observed in the overall analysis. Since SSRIs might be prescribed for diagnoses other than depression (for example, anxiety or chronic pain), a further subanalysis was performed in the four studies that adjusted for depression; inclusion of this covariate did not appear to modify the association between SSRI use and fracture risk [44].

The largest study to date is a case–control analysis in Danish national registers, which compared 124 655 cases with fracture and 373 962 controls [48,50]. Use of SSRIs or tricyclics was associated with an increased risk for any fracture, hip fracture, and vertebral fracture compared with nonusers, though the effect was more pronounced with SSRIs than with tricyclics (Table 4). The results showed dose–response relationships for SSRIs and tricyclics at all the fracture sites studied (any fracture, hip fracture, Colles' fracture, and vertebral fracture). For instance, there was a higher risk for any fracture in patients who were receiving the maximum dosage of SSRI (≥0.75 recommended daily dose: OR, 1.40, 95% CI, 1.35–1.46) than in patients receiving lower dosages (<0.15 recommended daily dose: OR, 1.15, 95% CI, 1.11–1.19) [48].

The same study highlighted differences among the classes of antidepressants [50]. Use of the SSRIs citalopram, fluoxetine, and sertraline was associated with a significant dose-dependent increase in fracture risk, but the relationship did not reach significance for paroxetine. Similar differences were observed for the tricyclics, with greater increases in fracture risk with amitriptyline than with imipramine and nortriptyline [50]. These findings are in line with mounting evidence that the impact of antidepressants on fracture is linked to their affinity for the 5-HTT [47,49,50]. Classification of antidepressants according to degree of inhibition of 5-HTT (e.g., high 5-HTT inhibition: fluoxetine and sertraline; intermediate 5-HTT inhibition: imipramine and amitriptyline; and low 5-HTT inhibition: nortriptyline and mianserin) has enabled quantification of this effect, and the risk of nonvertebral fracture was found to rise from the agents with a low degree of 5-HTT inhibition (OR, 1.64, 95% CI, 1.14–2.35) to those with a high degree (OR, 2.31, 95% CI 1.94–2.76) [49]. On the other hand, not all studies agree on this, and a cohort study in 10 844 patients failed to detect any difference between patients receiving SSRIs, secondary amine tricyclics, tertiary amine tricyclics, and atypical antidepressants [56]. Those authors attributed this to impacts on neurotransmitters other than serotonin. To conclude, the association between antidepressants and fracture may be linked to an impact of the individual agents on the serotonin transporter system, but further research is necessary to confirm this.

There are few studies with agents other than SSRIs and tricyclics. The available data are in line with some form of relationship with fracture for other types of antidepressant, though the evidence is much weaker [41,48]. A Canadian case–control study (15 792 cases and 47 289 controls) reported moderate increases in risk for fragility fracture with monoamine oxidase inhibitors (OR, 1.15, 95% CI, 1.07–1.24) versus nonusers [41]. On the other hand, the same study provided clinical evidence that lithium was protective, with a lower risk for fracture (OR, 0.63, 95% CI, 0.43–0.93) [41]. To our knowledge, there are no studies on SNRIs.

A number of studies have addressed the timing of the effect. A case–control study in the GPRD database found that risk for hip fracture increased dramatically in the first 2 weeks after initiation of treatment by about 5-fold for SSRIs and 6-fold for tricyclics (Table 4) [51]. A substantial early increase in risk was also reported in a study from the Netherlands, which demonstrated that the risk of fracture reaches a peak within a month or so for tricyclics, and around 8 months for SSRIs [49]. Thereafter, risk declines, but remains elevated after about 18 months of continuous use. The same study explored the effect of discontinuation of treatment, which is associated with a gradual reduction in fracture risk. For instance, there was a 235% increase in risk for hip fracture with current use of SSRI versus nonusers [49], versus 148% in recent users (treated 1 to 3 months previously) and 123% in past users (treated more than 3 months previously) [49]. The difference in risk diminishes towards baseline a year of more after discontinuation [47]. These onset/offset effects may be due to a rapid effect (particularly for tricyclics) on postural stability or cardiovascular outcomes predisposing to falls in the short term, which stabilizes in the long term. On the other hand, the effect of SSRIs may be more linked to an effect on bone mass. An alternative interpretation is that the timecourse represents Berkson's bias (i.e. the simultaneous identification by health care practitioners of two independent disorders). The effect of SSRIs on fracture risk might also be mediated through an effect on falling.

There are a number of potential confounders, and most of the analyses in Table 4 are adjusted for a range of parameters. These include characteristics known to increase the risk for fracture [25], such as greater age, female sex, low body mass index, ethnicity, current smoking, low BMD, and previous fracture. General health status and comorbidities

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Table 4
Studies exploring the relationship between the use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) and fractures [27,34,35,41–56].

Authors	Description of study	Population	Adjusted odds ratio (95% confidence interval)		Main conclusion of study
			Fractures with SSRI versus nonusers	Fractures with TCA (tertiary amines) versus nonusers	
Liu et al. [45]	Case–control study (Canada)	8239 cases with hip fracture 41 195 controls	Hip: 2.4 (2.0–2.7)	Hip: 1.5 (1.3–1.7)	• SSRI and TCA use is associated with increased risk for hip fracture
Ensrud et al. [46]	Population-based cohort study (USA)	8127 women, aged ≥65 years 4.8 years of follow-up	Nonvertebral: 1.44 (0.93–2.24); hip: 1.54 (0.62–3.82)	Nonvertebral: 1.30 (0.98–1.73); hip: 1.83 (1.08–3.09)	• SSRI and TCA use associated with increased risk for nonvertebral fracture, including hip
Hubbard et al. [51]	Case–control study (UK)	16 341 cases with hip fracture 29 889 controls	In first 14 days of treatment, hip: 4.76 (3.06–7.41)	In first 14 days of treatment, hip: 6.30 (1.35–2.83)	• Elevated risk for hip fracture in first 14 days after initiation of SSRI or TCA
Schneeweiss and Wang [43]	Medicare claims data (USA)	7126 patients aged ≥65 years	Hip: 1.8 (1.5–2.1)	No information	• SSRI use increases risk for hip fracture, even after adjustment for confounders
French et al. [42]	Case–control study (USA)	2212 cases with hip fracture 2212 controls	SSRI use doubled risk for hip fracture	No information	• SSRI use is associated with increased risk for hip fracture
Vestergaard et al. [48,50]	Case–control study (Denmark)	124 655 cases with fracture 373 962 controls	At maximum dosage: any fracture: 1.40 (1.35–1.46); hip: 2.02 (1.85–2.20); vertebral: 1.56 (1.29–1.88)	At maximum dosage: any fracture: 1.27 (1.13–1.42); hip: 1.35 (0.99–1.84); vertebral: 1.98 (1.22–3.22)	• A dose–response relationship for SSRI • Sedating TCAs were associated with higher risk for fracture • Increase in risk may be linked to affinity of SSRI to 5-HTT system
Lewis et al. [54]	Prospective study in men (MrOS)	5995 men, aged ≥65 years 4.1 years of follow-up	Nonvertebral: 1.65 (0.92–2.94)	Nonvertebral: 2.39 (1.27–4.50)	• Use of TCA or SSRI is a determinant of non-vertebral fracture in men
Richards et al. [34]	Population-based cohort (Canada)	5008 adults, aged ≥50 5 years of follow-up	Clinical fragility: 2.1 (1.3–3.4)	No information	• SSRI use is associated with increased risk for clinical fragility fracture
Bolton et al. [41]	Case–control study (Canada)	15 792 cases with fracture 47 289 controls	Osteoporotic fracture: 1.45 (1.32–1.59)	No information	• SSRI use is associated with increased risk for osteoporotic fracture • Fracture risk was increased with MAOI, but reduced with lithium
Spangler et al. [35]	Prospective cohort study (Women's Health Initiative, USA)	82 410 women, mean age 64 years, 7.4 years of follow-up	Hip: 1.33 (0.95–1.86); vertebral: 1.25 (0.96–1.63)	No information	• SSRI use is associated with an increased risk for hip and vertebral fracture
Ziere et al. [55]	Prospective population-based cohort study (The Netherlands)	1219 patients with nonvertebral fracture	Nonvertebral: 2.35 (1.32–4.18)	Nonvertebral: 1.69 (0.97–2.93)	• SSRI and TCA use is associated with increased risk for nonvertebral fracture • Current users of SSRI are at greater risk than past users, and risk increases with treatment duration
Abrahamsen and Brixen [27]	Case–control study (Denmark)	15 716 men with fracture, aged ≥50, and 47 149 age- and sex-matched controls	Any fracture: 1.7 (1.6–1.9); hip: 2.0 (1.8–2.2); vertebral: 1.2 (1.0–1.5)	No association	• SSRI use is associated with increased risk for fracture • Population overlaps with Vestergaard et al.
van den Brand et al. [49]	Case–control study (The Netherlands)	6763 cases with hip fracture 26 341 controls	Hip: 2.35 (1.94–2.84)	Hip: 1.76 (1.45–2.15)	• Rapid changes in SSRI- and TCA-associated risk for fracture after initiation and cessation • Risk increases with 5-HTT affinity of agent
Verdel et al. [47]	Case–control study (The Netherlands)	16 717 cases with fracture 61 517 controls	Osteoporotic fracture: 1.95 (1.69–2.26)	Osteoporotic fracture: 1.37 (1.16–1.63)	• SSRI- and TCA-associated risk for fracture reduces with time after cessation of treatment • Risk increases with 5-HTT affinity of agent
Coupland et al. [52]	Cohort study (UK)	60 746 patients with depression, aged 65 to 100 years	Any fracture: 1.58 (1.48–1.68)	Any fracture: 1.26 (1.16–1.37)	• SSRI and TCA use is associated with increased risk for any fracture
Diem et al. [53]	Cohort study (USA)	8217 women, aged ≥69 years	Nonvertebral: 1.30 (1.04–1.62); hip: 1.01 (0.71–1.44)	Nonvertebral: 1.16 (0.95–1.41); hip: 1.21 (0.86–1.69)	• SSRI use is associated with increased risk for nonvertebral fracture, but not hip • No increase in risk with TCA
Gagne et al. [56]	Medicare data (USA)	2711 patients receiving SSRI and 2711 patients receiving TCA	Composite fracture: 1.30 (1.12–1.52); hip: 1.33 (1.06–1.66)	Composite fracture: 1.01 (0.87–1.18); hip: 1.05 (0.84–1.32)	• SSRI use, but not TCA use, was associated with increased risk for fracture • Association did not depend on 5-HTT affinity of agents
Wu et al. [44]	Meta-analysis	13 observational studies	Any fracture: 1.40 (1.22–1.61)	No information	• SSRI increases fracture risk independently of depression and bone mineral density

such as cardiovascular disease may also influence fracture risk, as does a history of falls. In this context, the use of antidepressants (particularly SSRIs) also appears to increase the risk for falls [57], possibly via an impact on postural stability [58]. This effect may be related to the sedating nature of some agents, which is illustrated by the observation that tricyclics with a greater impact on sedation are associated with greater increases in fracture risk than non-sedating tricyclic agents [50]. Other influences may include severity of the depressive episode, lack of exercise, functional impairment, and previous and concomitant drug exposure, particularly drugs acting on the central nervous system. Multivariate models suggest that the effect of tricyclics on fracture may be partly explained by the impact of confounders [53].

Discussion

There is a complex interaction between depression, the drugs used to treat depression, and osteoporosis. To summarize, patients with depression may have decreased BMD [20,22], though not all studies have agreed on this finding [21]. This decrease in BMD may be associated with an increased rate of fracture, though part of this elevated risk appears to be independent of BMD, perhaps through increased frequency of falls. The management of depression with antidepressant medications such as SSRIs and tricyclics is associated with a further increase in risk of falls and fractures, though the effects are not always easy to dissociate. While there is strong evidence for these effects with SSRIs and tricyclics, the impact of the other antidepressants is unclear. There is a biological precedent for the effects of SSRIs and tricyclics, linked to impact of serotonin on bone, though there are many confounders.

Our review has highlighted a number of themes for the research agenda. First, from an experimental point of view, further exploration of the molecular basis for the role of serotonin in bone is necessary. This should include research into the roles of gut-derived and brain-derived serotonin in bone. In connection with this, there is a clear need for more investigation into the effects of SSRIs in animal models, notably across a variety of bone sites and with a range of agents. The extension of the studies to other antidepressant medications is an important theme for future research, especially for the SNRIs, which are currently prescribed to a considerable proportion of depressed patients.

Second, none of this research would be complete without a better understanding of the role of confounders, notably targeting the separation of the effects of treatment from the effects of depression. Investigation of other confounders, such as lifestyle (exercise, smoking, nutrition, and vitamin D status), comorbidities (e.g., cardiovascular disease or primary osteoporosis) and concomitant treatments (e.g., sedatives or hypnotics) is an important aim. Other confounders that have been insufficiently studied are age, gender, and body weight, notably because many of the studies have been performed in older, more "osteoporotic", populations with a majority of women. Here it is important to recall that the increase in fracture risk may affect depressed patients of all ages and both sexes, and so studies in younger samples of both genders would be informative. Similarly, the severity of depression may also play a role, in that the increase in fracture risk may be lower in patients with milder depression. Another issue is the role of hyponatremia (a side effect of SSRI treatment) and hypercortisolemia (due to stress), which is associated with low BMD [59,60] and merit further investigation. One route may be to perform more case–control studies using propensity score matching to provide an unbiased estimation of treatment effects.

Third, although there has been much progress made in our understanding of the links between SSRIs and tricyclics and BMD and fracture, there remains a need for further clinical research into dose–response relationships and the time-course of the effect during chronic treatment. There is a need for more prospective studies in depressed patients, and for studies on the use of antidepressants in fracture patients. Meta-analysis of adverse event data from randomized controlled trials of antidepressant medications (i.e. fracture outcomes) may also prove to be insightful. Another area for research is the investigation of intra-class differences, based on observations that, for example, the SSRIs may not all have the same effect on orthostatic hypotension [61,62] and may therefore differ in their impact on falls. Finally, these studies should be extended to include exploration of the clinical effects of other antidepressant agents, notably the SNRIs.

In conclusion, it is clear that there is a link between the use of antidepressant medications and increased risk of fracture, even after adjustment for confounders. The body of evidence suggests that SSRIs should be added to the list of medications that contribute to osteoporosis, and there have been calls for consideration of BMD testing in patients receiving SSRIs [63]. Antidepressant use is not listed as a secondary cause of osteoporosis in the FRAX algorithm [64], though it may be useful to consider this possibility, particularly since the association may be independent of BMD.

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