

Skeletal effects of serotonin (5-hydroxytryptamine) transporter inhibition: Evidence from clinical studies

E.M. Haney¹ and S.J. Warden²

¹Department of Medicine, Oregon Health & Science University, Portland, OR, USA;

²Department of Physical Therapy, School of Health and Rehabilitation Sciences, Indiana University, Indianapolis, IN, USA

Abstract

The discovery of a functional serotonin (5-hydroxytryptamine; 5-HT) transporter (5-HTT) in bone has given rise to questions about the physiologic role of 5-HT in bone, and the possible clinical implications for humans. 5-HT is known to play a role in the pathophysiology of depression, and many antidepressant medications function by inhibiting the 5-HTT. Among the antidepressants, those that selectively block the 5-HTT (namely, selective serotonin reuptake inhibitors; SSRIs) appear to have skeletal effects. Several studies have demonstrated lower bone density, increased rates of bone loss at the hip, and increased rates of fracture among older individuals taking SSRIs. However, there remains uncertainty about whether it is the antidepressant medications themselves or the reason for their use (depression) that is responsible for these observed bone changes. This paper reviews the epidemiologic literature that explores the role of the 5-HTT in bone health, by looking at questions about how depression, antidepressant therapy and SSRIs impact bone health in humans. Further research will be important to better understand how these factors interact to influence skeletal status, and to characterize the biochemical mechanism through which 5-HT may mediate bone turnover and metabolism.

Keywords: Selective Serotonin Reuptake Inhibitors, Depression, Osteoporosis, Bone Density, Fracture

Introduction

Neuronal control of bone physiology is an area of recent attention and research focus. Bone tissue is innervated by sympathetic and sensory neurons. Several neuropeptides have been demonstrated in bone, many with corresponding receptors or transporters in osteoblasts, osteocytes and osteoclasts. Specifically, leptin, and neuropeptide Y regulate bone through central mechanisms¹⁻⁴. Other neurotransmitters and transporters (e.g., dopamine) have been demonstrated in bone cells, and associated with changes in bone metabolism⁵, but clinical effects have not been investigated. The discovery of functional serotonin (5-hydroxytryptamine; 5-HT) transporters (5-HTT) in bone has given rise to ques-

tions about the physiologic role of 5-HT in bone⁶, and the subsequent clinical implications for humans. These questions have been potentiated by preclinical *in vitro* and animal-based studies demonstrating the presence of functional pathways for responding to 5-HT in bone and the skeletal effects of pharmaceutical agents that selectively inhibit the 5-HTT-agents collectively known as selective serotonin reuptake inhibitors (SSRIs). The findings of these preclinical studies are discussed in an accompanying paper in this issue⁷.

5-HT is unique among the neurotransmitters that have potential impact in bone because it is tightly linked to another disease state: depression. 5-HT appears to play an important role in depression and 5-HTT is implicated in the pathophysiology of this disease⁸. Indeed, 5-HTT antagonists are the mainstay of antidepressant therapy. Many antidepressant medications block the 5-HTT as part of what is thought to be their mechanism of action and mode of treatment effectiveness⁹. SSRIs are a class of antidepressant medications that inhibit the 5-HTT as their primary effect (Figure 1). Although other classes of antidepressants also block the 5-HTT to lesser degrees, SSRIs are the most potent and spe-

The authors have no conflict of interest.

Corresponding author: Elizabeth M. Haney, M.D., Division of General Internal Medicine & Geriatrics, 3181 SW Sam Jackson Park Road, L-475, Portland, OR 97239, USA

E-mail: haneye@ohsu.edu

Accepted 20 March 2008

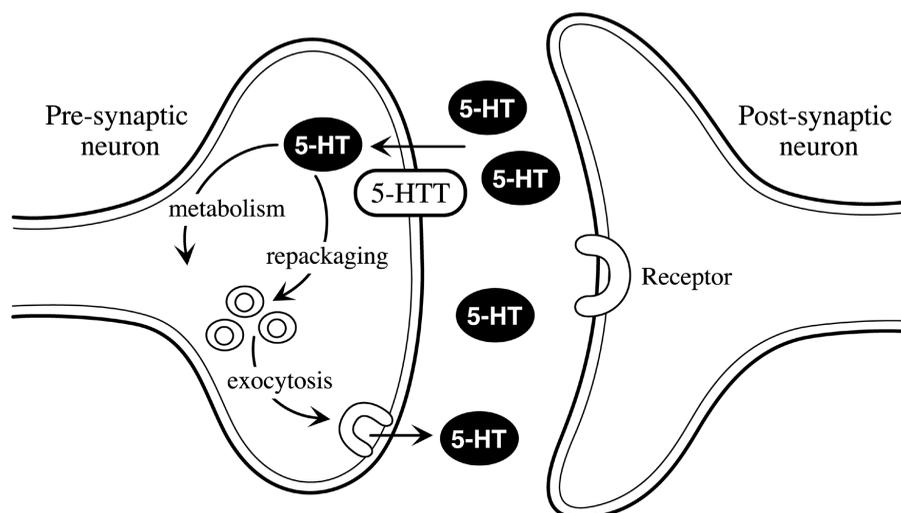


Figure 1. In the nervous system, 5-HTT is present in the pre-synaptic neuron. When 5-HT is released into the synaptic cleft, it can be taken up by receptors on the post-synaptic neuron or can undergo reuptake by the transporter into the pre-synaptic neuron. Blockade of the serotonin transporter increases serotonin concentrations within the synapse in the interneuronal (synaptic) space. [Reproduced from *Future Rheumatology* (2007);2(2):213-22 with permission of Future Medicine Ltd].

cific inhibitors of the transporter. SSRIs are widely used and are considered the first line therapy for depression because they have a more favorable side effect profile, and are safer in terms of overdose and drug-drug interactions than other classes of antidepressants¹⁰.

Because SSRIs selectively and potently inhibit the 5-HTT, they provide a model for studying 5-HTT blockade in humans. The widespread use of SSRIs creates an epidemiological platform for studying the effect of 5-HT in bone, but also makes understanding the role of the 5-HTT in bone an urgent clinical question. Depression is a clinical disease state that is associated with alterations in the 5-HT/5-HTT system, among changes in other neuroendocrine and related systems¹¹⁻¹³. SSRIs are typically prescribed for depressive symptoms. Therefore, any discussion of a possible effect of SSRIs on bone must also address the possible effect of depression on bone. To identify the literature that has explored the role of the 5-HTT in bone, we searched Medline - using the terms depression, antidepressant, osteoporosis and fracture. This paper reviews the epidemiologic literature that may help explain the role of the 5-HTT in bone health, by looking at questions about how depression, antidepressant therapy, and SSRIs impact bone health in humans.

Depression

While there have been reports of low BMD among depressed patients and several theories exist about mechanisms that might link low BMD and osteoporosis to depression, the expression of the 5-HTT in bone and the importance of the 5-HTT in treatment of depression makes under-

standing this relationship an urgent clinical question. Several studies have explored the possibility of a relationship between depression and osteoporosis, with varied results. Table 1 lists studies that used population-based recruitment strategies to evaluate depression and bone outcomes (BMD and fracture)^{14-18,19,20-27}.

Depression and bone density

Initial reports of an association between depression and lower bone mineral density (BMD) were case reports and case-control studies. Some of these²⁸⁻³⁵ but not all^{36,37}, demonstrated lower BMD among depressed patients. In most of these studies, participants were recruited from psychiatric clinics or wards and compared with non-depressed controls, such as hospital or clinic staff. Some studies evaluated psychiatric medication use among the patients²⁸⁻³⁰. Overall, the case-control study design can be less applicable to a general population because of bias in the selection of cases and controls. However, a number of these studies deserve mention. One well-designed case-control study used similar recruitment methods for both the cases and the controls, and demonstrated that depressed patients had 6.5% lower BMD at the spine and 13.6% lower BMD at the femoral neck compared with non-depressed controls (24 in each group)³⁰. Another prospective study initially recruited patients in a case-control fashion, and then followed them for 2 years. Depressed men and women had lower BMD than controls initially²⁹, and their bone loss per year during the time course of the study was greater after adjustment for age, gender and baseline BMD³⁸.

Table 1. Population-based analyses of depression, BMD and fracture.

Author, year	Study design, population	Depressive symptom assessment	BMD	Fracture	Medication assessment conducted?	Comments
Coelho, 1999 ³⁹	Cross-sectional analysis of 102 Portuguese white women (ages 40-80 yrs).	BDI and Hopkins SCL-90 R, Psychological GWB index.	Depression was associated with BMD after adjustment for confounders. Compared to women with normal BMD, those with osteoporosis (n=48) had higher mean depressive symptoms scores on BDI and higher odds of depression (OR=2.9, 95% CI 1.0-7.6).	NR	NR	
Forsen, 1999 ²¹	Longitudinal study of 18,612 Norwegian women age ≥ 50 yrs followed 3 yrs.	Composite measure of mental distress based on 7 items that were part of a county-wide health screening.	NR	Women with mental distress scores in the highest 10% had increased risk of hip fracture compared to those with scores in the lowest 10%, after adjustment for confounders (RR=1.95, 95% CI 1.15-3.29).	Yes. Daily medication use was associated with increased risk for fracture. Age-adjusted RR=2.11 (95% CI 1.55-2.86), multiple-adjusted RR=1.48 (95% CI 0.99-2.21).	
Reginster, 1999 ²³	Cross-sectional analysis of 121 postmenopausal women recruited from a health fair.	GHQ-28	No association between depressive symptoms and BMD at spine, total hip and femoral neck.	NR	No.	
Whooley, 1999 ¹⁵	Longitudinal analysis of 7,414 women age ≥ 65 yrs followed for an average of 3.8 yrs (SOF).	15-item GDS, (depression defined as a score ≥ 6).	No difference in mean BMD at the hip and lumbar spine for those with and without depression.	Women with depression had a 40% increased rate of non-vertebral fracture (adjusted HR 1.4, 95% CI 1.2-1.7).	Yes. No SSRI users. Adjustment for TCA use did not influence the association between depression and fracture.	Women with depression were more likely to fall than women without (70% of depressed, vs. 59% of non-depressed). This appears to explain part but not all of the relationship between depression and fracture.
Robbins, 2001 ¹⁶	Cross-sectional analysis of 1,566 men and women age ≥ 65 yrs (CHS).	CES-Dm (10 item scale)	Depression was associated with lower BMD overall, adjusted for covariates. After stratification by race and gender, the association remained significant only for white women (For each 1 unit increase in CES-Dm score, total hip BMD decreased by 0.3 mg/cm ²).	NR	Yes, 3% used antidepressants.	
Ensrud, 2003 ²²	Longitudinal analysis of 8,127 women age ≥ 65 yrs, followed for an average of 4.8 yrs (SOF).	15-item GDS (depression defined as a score ≥ 6).	NR	Presence of depressive symptoms appeared to increase risk for fracture in models adjusted for age, antidepressant use and depressive symptoms. However, no significant effect remained for either hip or non-spine fracture after adjustment for other confounders.	Yes, 6% of population reported antidepressant use.	

Table 1, cont.

Author, year	Study design, population	Depressive symptom assessment	BMD	Fracture	Medication assessment conducted?	Comments
Mussolino, 2004 ¹⁷	Cross-sectional analysis of 2,528 men and 2,643 women ages 20-39 (NHANES III).	DIS (15) structured psychiatric interview by trained lay interviewers according to DSM-III and DSM-III-R.	MDE was associated with lower BMD among men. For 1 SD reduction in BMD, OR=1.65 (95% CI 1.08-2.52) after adjustment for confounders. No association between MDE and BMD among women.	NR	No.	Dysthymia also associated with low BMD among men but not women. Evidence of a threshold effect: 3% lower BMD for men with 5-9 depressive symptoms vs. those with 0-4 symptoms.
Whooley, 2004 ¹⁴	Cross-sectional analysis of 515 men age ≥ 50 yrs from a Pittsburgh voter registration list and from a cohort from MrFIT; 100 randomly selected men were followed for 3.6 yrs on average	15-item GDS (depression defined as a score ≥ 6).	No difference in BMD for men with 5 or fewer symptoms compared to men who had 6 or more depressive symptoms controlling for confounders. No difference in mean percentage change in BMD per yr at hip and lumbar spine.	NR	Antidepressant use NR.	Prevalence of depressive symptoms by GDS ≥ 6 was 3.1%.
Wong, 2005 ¹⁸	Cross-sectional analysis of 1,999 men age ≥ 65 yrs (MrOS Hong Kong).	Chinese version of the GDS (depression defined as a score ≥ 8).	Depressed group had 2.1% lower BMD than controls after adjusting for confounders.	NR	0.5% of population reported antidepressant use. No significant difference in BMD for antidepressant users vs. non-users.	
Jacka, 2005 ²⁰	Cross-sectional analysis of 78 women age 45-60 yrs (Geelong Osteoporosis Study).	Self-report questionnaire based on DSM-IV criteria.	Adjusted BMD at the total hip was 7.8% lower for women with self-reported depression compared to non-depressed women, adjusting for age, weight and height.	NR	No.	14 women met criteria for depression according to the self-report questionnaire.
Mussolino, 2005 ²⁵	Longitudinal analysis of 6,195 men and women from ages 25-74 at baseline, followed for up to 22 yrs (NHANES I).	GWB-D	NR	Association between depression and hip fracture was significant in unadjusted, but not the final adjusted model (HR 1.70, 95% CI=0.99-2.91).	No.	95% of cohort completed the study.
Sogaard, 2005 ²⁴	Longitudinal analysis of 12,278 men and women age ≥ 20 yrs at enrollment (Tromso Study); 7,948 had BMD measurements.	Self-reported mental distress measured by questionnaire: feeling depressed, bothered with insomnia, and difficulty coping with problems.	No association between depressive symptoms and BMD at the distal radius for either men or women.	Women reporting depression at two time points had increased odds of non-vertebral fracture (OR 2.5, 95% CI 1.3-4.9; and OR 3.8, 95% CI 1.6-8.9). No association between symptom report and fracture for men.	Participants were asked about their use of medications for nerves and sleeping.	Mental distress assessed at 3 time points. BMD assessed at the final visit.
Tolea, 2007 ²⁶	Cross-sectional analysis of 1,350 Hispanic women, mean age 65 yrs (Hispanic EPESE).	CES-D score ≥ 16 at baseline categorized as high level of depressive symptoms.	NR	Women with high depressive symptoms had increased odds of self-reported new fracture (OR 1.43, 95% CI 1.03-1.99).	7.8% reported use of antidepressants. No association between antidepressant use and report of new fracture.	31% reported high level of depression; 18% reported a new diagnosis of depression. Depressed women had increased odds of self-reported new diagnosis of osteoporosis (OR 1.42, 95% CI=1.05-1.92).

Table 1, cont.

Author, year	Study design, population	Depressive symptom assessment	BMD	Fracture	Medication assessment conducted?	Comments
Diem, 2007 ²⁷	Longitudinal analysis of 4,177 women age ≥ 69 yrs followed for an average of 4.4 years (SOF).	15-item GDS (depression defined as a score ≥ 6).	Those with depressive symptoms had greater age-adjusted rates of bone loss at the hip compared to those without (0.96%/yr vs. 0.69%/yr, $p < 0.01$). Similar results in multivariate model.	NR	4.8% of the included participants reported antidepressant use (0.7% on SSRIs; 3.7% on TCAs; 0.5% other).	Results not altered by exclusion of those on antidepressants.
Eskandari, 2007 ³³	Nested case-control analysis of 89 premenopausal women with MDD and 44 non-depressed age- and BMI-matched controls (POWER Study, age 21-45 yrs).	DSM-IV Structured Clinical Interview for MDD, GAF for level of functioning, Hamilton Depression and Anxiety Scales for severity.	Overall prevalence of low BMD among women with MDD was 28% vs. 11% for controls. Specifically, BMD was lower at the femoral neck and total hip for controls.	NR	73 women with MDD were taking an antidepressant; 54 (61%) on SSRIs. Use of SSRI did not contribute to low BMD at the hip, spine or radius after adjustment for BMI.	MDD group had higher levels of bone-specific alkaline phosphatase than non-depressed controls. No differences in urinary-free cortisol, serum osteocalcin, N-telopeptide.
Silverman, 2007 ¹⁹	Cross-sectional analysis 3,798 women mean age 66.7 yrs (MORE).	15-item GDS (probable depression defined as a score ≥ 6).	Lumbar spine BMD was associated with higher number of depressive symptoms.	Prevalence of probable depression was higher for women with vertebral fracture compared to those without (6.6% vs. 4.1%, $p = 0.008$ in adjusted analyses).		MORE is an RCT of raloxifene.
Spangler, 2008 ⁴⁰	Longitudinal analysis of 93,676 women ages 50-79 yrs followed 3 yrs for change in BMD and average of 7.4 yrs for fracture (WHI).	Burnam's scale	No association between 3-year change in BMD at the hip or spine and depressive symptoms.	Depressive symptoms associated with risk of any fracture (HR 1.08, 95%CI 1.02-1.14) but not with hip, spine or wrist fracture.	Antidepressant use evaluated separately and analyses of depression conducted with and without those women using antidepressants (see Table 2).	

Abbreviations: AA=African American; BDI=Beck Depression Inventory; BMD=bone mineral density; BMI=body mass index; CES-Dm=Center for Epidemiologic Studies 10-item Depression scale; CHS=Cardiovascular Health Study; CI=confidence interval; DIS=Diagnostic Interview Schedule; DSM=Diagnostic & Statistical Manual (III=3rd edition; III-R=3rd edition, Revised; IV=4th edition); GAD=Generalized Anxiety Disorder; GAF= Global Assessment of Functioning; GDS=Geriatric Depression Scale; GHQ-28=General Health Questionnaire (28-item); **GWB index**= General Well-being index (GWB-D=General Well-being-Depression subscale); HR=hazard ratio; **Hispanic EPESE**= Hispanic Established Populations for Epidemiologic Studies of the Elderly; **Hopkins SCL-90**=Hopkins Symptom Checklist (90-item); **MDD**=Major Depressive Disorder; **MDE**=Major Depressive Episode; **MrFIT**=Multiple Risk Factor Intervention Trial; **MrOS**=Osteoporotic Fractures in Men; **MrOS Hong Kong**=Osteoporotic Fractures in Men, Hong Kong; **MORE**=Multiple Outcomes of Raloxifene Evaluation; **NHANES**=National Health Examination and Nutrition Study (NHANES I and III); **NR**=not reported; **OR**=odds ratio; **POWER**=Premenopausal, Osteoporosis Women, Alendronate, Depression Study; **SOF**=Study of Osteoporotic Fractures; **SSRI**=selective serotonin reuptake inhibitor; **TCA**=tricyclic antidepressants; **WHI**=Women's Health Initiative Observational Study; yrs=years.

Compared to case-control studies, studies that recruit a larger population-based cohort and use cross-sectional, nested case-control, or longitudinal analytic methods may be more widely applicable. However, even among population-based studies that evaluated depression and BMD, results have been mixed. Some studies of women have demonstrated a relationship between depressive symptoms and lower BMD^{19,20,27,33,39} while others have not^{15,23,40}. The literature for

men is likewise conflicting^{14,18}.

Two studies have used cohorts that included both men and women. Among 1,552 Medicare enrollees in the Cardiovascular Health Study, those with depression had an average BMD that was 40 mg/cm² lower than those without depressive symptoms. After stratification by race and gender, this association held for white women only, not for men or African American women¹⁶. Men recruited for the

National Health and Nutrition Examination III (NHANES III) who had dysthymia or depression had lower BMD compared to controls, but women did not¹⁷.

Recently, Eskandari et al. compared BMD for 89 depressed and 44 non-depressed young women, all of whom were recruited from within a population-based cohort study - the Premenopausal, Osteoporosis Women, Alendronate, Depression (POWER) Study³³. All of these women had structured interviews to diagnose major depressive disorder. After adjusting for BMI, BMD was lower at the spine and femoral neck for those with depression, but not at the total hip³³.

Two studies have prospectively evaluated depressive symptoms and bone loss, and have yielded conflicting results. Among women from the Study of Osteoporotic Fractures (SOF), those with depressive symptoms (measured by a GDS score ≥ 6) had greater rates of bone loss compared to those without after adjustment for confounders²⁷. Another recent study used data from 93,676 women ages 50-79 enrolled in Women's Health Initiative Observational Study (WHI); depressive symptoms were not associated with 3-year change in BMD. These results were unchanged after adjustment for confounders and exclusion of those women taking antidepressants⁴⁰.

Thus, an association between depression and BMD has been documented, but is inconsistent. The reasons for discrepant results may include population differences, differences in assessment of depressive symptoms, the lack of a true diagnostic assessment for depression, the effect of medications, or other non-measured confounders.

Depression and fracture

Depression has also been associated with fracture (Table 1). Whooley et al. demonstrated that women with depression were more likely to fall (70% vs. 59%, $p < 0.001$) and more likely to sustain non-vertebral (28% vs. 21%, $p < 0.001$) and vertebral (11% vs. 5%, $p < 0.001$) fractures than women without depression. The greater frequency of falls among women with depression appeared to explain part, but not all of the relationship between depression and fracture in this group. Adjustment for potential confounding variables including medications and BMD did not alter the relationship between depression and falls¹⁵.

In contrast, other studies have not shown an association between depression and fracture^{22,25}. For women in the WHI Observational Study, depressive symptoms were not associated with any increase in risk of hip, wrist, or self-reported spine fracture. There was a minimal increase in the risk of any fractures, which included other sites⁴⁰.

Depression and bone biomarkers

Studies have demonstrated elevated biomarkers among depressed patients^{34,41,42}. Among population-based cohort studies, Eskandari demonstrated higher levels of bone-spe-

cific alkaline phosphatase, intact parathyroid hormone, pro-inflammatory cytokines (IL-1 β , IL-2, IL-6, TNF- α), and lower levels of the anti-inflammatory cytokines IL-13 but no difference in levels of IL-10³³. A case-control study that compared hospitalized depressed premenopausal young women to healthy volunteers also demonstrated higher bone alkaline phosphatase and urine n-terminal telopeptide normalized to creatinine among the depressed women, but no difference between the two groups in cortisol, parathyroid hormone or estradiol³⁵.

Thus, depression has been associated with low BMD and fracture, but studies are conflicting. In some cases, elevations in biomarkers among depressed patients suggest increased bone turnover. There are several possible mechanisms, by which depression could be related to bone health, and the direction of a possible association is not clear. Depression could lead to declines in bone health because of direct effects on physiology: increased cortisol levels^{34,42-45}, cytokines³⁴, or changes in behavior such as reduced sunlight exposure (resulting in reduced vitamin D) and exercise^{46,47}. Depression itself may be associated with falls⁴⁸. Depression is shown to occur after hip fracture^{49,50}. Mechanisms for this effect may be cognitive or physiologic. A diagnosis of osteoporosis or hip fracture could also lead to depression based on having a new diagnosis of a chronic disease, immobility and reduced activity as a result of a fracture, or through other behaviors and medical conditions that are common to both osteoporosis and depression such as hypogonadism, smoking, and alcohol abuse⁴⁷. One proposal is that specific 5-HTT genotype variations increase the risk for post-hip fracture depression⁵¹.

Antidepressant medications

The question of whether antidepressant medications are associated with low BMD and fractures has also been investigated (Table 2)^{22,40,52-59}. CNS active medications such as antidepressants, opioids, antipsychotics, anticonvulsants, and benzodiazepines increase the risk of falls and fractures in the elderly^{22,60,61}. Separating the potential for these medications to increase fractures as a result of an increase in the risk of falls is a challenge. Recent studies have tried to distinguish the effect of SSRIs on fractures.

Selective serotonin reuptake inhibitors and bone density

Several recent studies have examined various aspects of bone health among SSRI users. An analysis aimed at understanding determinants of bone density among men identified SSRIs as one of several factors contributing to BMD using data from the Osteoporotic Fractures in Men (MrOS) study⁶². MrOS is a multicenter prospective cohort study of 5,995 men from six U.S. clinical sites. A separate analysis focused on understanding the relationship between SSRI use and BMD in that cohort, determined that SSRI use was associated with a 3.9% lower BMD at the hip and 5.9%

Table 2. Population-based analyses of antidepressant medications, BMD and fracture.

Study, year	Study design, n, population	n(%) on medication	BMD	Fracture	Comments
Ray, 1987 ⁵²	Case-control study using Michigan Medicaid data 1980-1982; 1,021 cases of hip fracture and 5,606 randomly selected controls without hip fracture (age ≥ 65 yrs).	SSRIs: none TCAs: 3.5% of cases, NR for controls.	NR	TCAs associated with increased odds of fracture (OR 1.9, 95% CI 1.3-2.8).	
Liu, 1998 ⁵³	Case-control analysis, using administrative data from 8,239 cases (age ≥ 60 yrs, hospitalized between April 1994 and March 1995 for hip fracture, with data available to link with Ontario Drug Benefit Programme) and 41,195 controls from the Registered Persons Database (Ontario Ministry of Health).	SSRIs: 6.6% of cases and 2.8% of controls. TCAs: 11.6% of cases (2.6% to secondary-amine TCAs and 9% to tertiary-amine TCAs) and 7.7% of controls (1.1% to secondary-amines and 6.6% to tertiary amines).	NR	Increased odds of hip fracture for current antidepressant users after adjustment for confounders. SSRIs: (OR=2.4, 95% CI 2.0-2.7), secondary-amine TCAs (OR=2.2, 95% CI 1.8-2.8) and tertiary-amine TCAs (OR=1.5, 95% CI 1.3-1.7).	OR for hip fracture for SSRIs >secondary-amine TCAs >tertiary-amine TCAs.
Hubbard, 2003 ⁵⁴	Case-control and case-series analyses using administrative dataset 1987-1999: 16,341 cases of hip fracture and 29,889 matched controls (UK GPRD).	SSRIs: 955 (5.8%) of cases; 892 (3.0%) of controls. TCA: 2908 (17.8%) of cases, 2,544 (11.9%) of controls.	NR	Case control: SSRIs and TCAs associated with increased rates of fracture. For SSRIs, adjusted OR= 1.42 (95% CI 1.28-1.58); For TCAs, adjusted OR=1.22, 95% CI 1.15-1.29. Case-series: TCA associated with marginally higher early risk of fracture than SSRIs.	In case-control analysis, the highest OR seen for first 14 days of the prescription for both SSRIs and TCAs.
Ensrud, 2003 ²²	Longitudinal analysis of 8,127 women age ≥ 65 yrs followed for 4.8 yrs on average (SOF).	SSRIs: 103 (1.3%) TCAs: 353 (4.3%) Trazodone: 57 (0.7%) Other: 7 (<0.1%).	NR	Risk for hip fracture was increased for all antidepressant users (SSRI and TCA combined, HR=1.65, 95% CI 1.05-2.57), after adjustment for confounders.	Individually, the associations between medication use and hip fracture reached significance only for TCAs.
Kinjo, 2005 ⁵⁵	Cross-sectional analysis of 14,646 adults age ≥ 17 yrs (NHANES III).	Antidepressants (either TCA or SSRI): 154 (1.1%).	No association between antidepressant use and femoral BMD.	NR	Data shown only for combined (SSRI and TCA) antidepressant users. Authors state that reduced BMD was not detected among either TCA or SSRI users.
Vestergaard, 2006 ⁶⁴	Case-control analysis of data from the Danish National Hospital Discharge Register. 124,655 cases and 373,962 controls, ages 0-100 yrs (mean age 43 yrs).	Any antidepressant: 14.8% of cases and 9.2% of controls. SSRIs: 12% of cases and 7.2% of controls. TCA: 3.8% of cases and 2.4% of controls.	NR	Increased risk of any fracture and hip fracture for antidepressant users. RR for hip fracture=2.02 (95% CI 1.85-2.20) for SSRI users at ≥ 0.75 DDD/day, after adjustment for covariates.	Dose-dependent increase in fracture risk seen for any fracture with all antidepressants, SSRIs and TCAs. Seen for hip and spine fracture with SSRIs.
Richards, 2007 ⁵⁶	Cross-sectional and longitudinal analyses 5,008 men and women \geq age 50 (CaMOS).	SSRIs: 137 (2.7%) TCA: 162 (3.2%);	SSRI use associated with 4% lower BMD at the hip, NS at the spine (baseline data, cross-sectional, adjusted for confounders).	SSRIs associated with increased rates of fracture (HR 2.1, 95% CI 1.3-3.4) after adjustment for confounders.	Depressive symptoms reported in 609 (12.2%). SSRIs associated with increased odds of falling (OR 2.2, 95% CI 1.4-3.5).
Diem, 2007 ⁵⁷	Longitudinal analysis of 2,722 women, mean age 78.5 yrs followed for 4.9 yrs (SOF)	SSRIs: 198 (7.2%) overall, 65(2%) at baseline and 178 (6.5%) at follow-up. TCAs: 118 (4.3%) overall, 86 (3.2%) at baseline and 74 (2.7%) at follow-up.	Greater rates of hip bone loss for SSRI users after adjustment for confounders (0.82% for SSRI users, 0.47% for TCA users and 0.47% for non-users).	NR	

Table 2, cont.

Study, year	Study design, n, population	n(%) on medication	BMD	Fracture	Comments
Haney, 2007 ⁵⁸	Cross-sectional analysis of 5,995 men ages ≥ 65 yrs (MrOS).	SSRIs: 160 (2.7%). TCAs: 99 (1.7%). Trazodone: 52 (0.9%).	Total hip BMD was 3.9% lower and lumbar spine BMD was 5.9% lower among users compared to non-users after adjustment for confounders.	NR	No significant differences in BMD between trazodone, TCA or non-users.
Williams, 2008 ⁵⁹	Cross-sectional analysis of 128 women with lifetime or current depression (Geelong Osteoporosis Study).	SSRIs: 26 (20%) TCAs: NR	BMD was 5.6% lower at the femoral neck among SSRI users compared to non-users after adjustment for confounders.	NR	
Spangler, 2008 ⁴⁰	Longitudinal analysis of 93,676 women ages 50-79 yrs (WHI). BMD analyses done with subset of 6,441 women.	Antidepressants: 7,212 (8%). SSRIs: 3,534 (4%). TCAs: NR.	No association between antidepressant use and 3 yr change in BMD after adjustment for confounders.	Antidepressants associated with increased risk of any fracture (HR 1.22, 95% CI 1.15-1.30) and clinical spine fracture (HR 1.36, 95% CI 1.14-1.63) but not hip or wrist fracture, after adjusting for depressive symptoms and other confounders.	SSRI use was associated with any fracture (OR=1.30, 95% CI 1.20-1.41), wrist fracture (OR=1.29, 95% CI 1.07-1.56) and fracture at other sites, but not hip or clinical spine fracture. In the BMD subset, 220 (3%) were on SSRIs and 1,877 (14%) had depressive symptoms.

Abbreviations: BMD=bone mineral density, CaMOS= Canadian Multicentre Osteoporosis Study, CI=confidence interval, DDD=defined daily dose, GPRD=UK General Practice Research Database, HR=hazard ratio, MrOS=Osteoporotic Fractures in Men, NHANES=National Health and Nutrition Examination, NR=not reported, OR=odds ratio, SOF=Study of Osteoporotic Fractures, SSRI=Selective serotonin reuptake inhibitor, TCA=tricyclic antidepressant, UK=United Kingdom, WHI=Women's Health Initiative Observational Study.

lower BMD at the spine compared to non-users⁵⁸. These results were adjusted for depressive symptoms as measured by the SF-12, an important factor considering that depression can lead to physiologic and behavioral changes (cortisol and physical activity) that might also affect bone density.

Importantly, one cross-sectional population-based study has used data from women who underwent Structured Diagnostic Interviews according to DSM-IV-TR for depression. Including only those who met criteria for lifetime or current depression, Williams et al. used data from the Geelong Osteoporosis Study to conduct an analysis of SSRI use and BMD. In this population, SSRI use was associated with 5.6% lower BMD at the femoral neck, with consistent results at the trochanter and mid-forearm. No differences were detected at the spine⁵⁹. While still cross-sectional in nature, this study contributes substantially to the support for a relationship between SSRIs and low BMD, independently of depression.

The Study of Osteoporotic Fractures (SOF) is a prospective cohort study of women that enrolled women beginning in

1986. Women who were using SSRIs at visit 6 had increased rates of bone loss over an average of 4.9 years. Specifically, SSRI use was associated with a 0.82% rate of bone loss at the total hip compared to 0.47% for TCA and 0.47% for non-users⁵⁷. Exclusion of women with depression (defined by GDS score ≥ 6) did not change these results. Also, the absence of a detrimental skeletal effect associated with the use of TCAs while controlling for depression in that study suggests that SSRIs may have unique effects on the skeleton.

The Canadian Multicentre Osteoporosis Study (CaMOS) is a large cohort study that enrolled both men and women aged 50 and older, and has reported on SSRI use as it affects bone health outcomes. This study evaluated SSRI use at two time points five years apart, and characterized participants as either users (at baseline), continuous users (both time points) or non-users (never). SSRI use was associated with a 4.0% lower BMD at the total hip and 2.4% lower BMD at the lumbar spine⁵⁶.

Spangler et al. found no association between antidepressants

sant use and change in 3-year BMD among 93,676 women ages 50 to 79 years enrolled in the WHI⁴⁰. This study excluded women who suffered from serious emotional issues and mental illness, making it likely that this population had fewer depressive symptoms than a general population might. Thus, studies from four of five separate cohorts consistently support a relationship between SSRI use and lower BMD/change in BMD both in cross-sectional and longitudinal analyses.

Selective serotonin reuptake inhibitors and fracture

Several large studies have demonstrated either similar or increased rates of hip fracture among SSRI users compared to TCA users^{22,53,54,56,63-65}. Among 8,239 cases of hip fracture in patients ages 66 years and older, those with exposure to SSRIs had an adjusted odds ratio for hip fracture of 2.4 compared to controls with no antidepressant exposure (vs. OR of 2.2 for exposure to tertiary-amine TCAs and 1.5 for secondary-amine TCAs)⁵³.

In an analysis using data from 1,256 women from SOF followed for 4.8 years, women using antidepressant medications had an increased risk of fracture, after adjustment for depressive symptoms. Based on point estimates, the risk appeared increased for both TCAs and SSRIs, however the association was statistically significant only for TCAs²².

An analysis of determinants of fracture among men using the MrOS cohort also found that SSRI use contributed to fracture risk⁶⁵. The CaMOS study demonstrated a higher risk of incident fragility fractures among SSRI users compared to non-users (HR 2.0, 95% CI 1.3-3.1)⁵⁶. The WHI analysis has also demonstrated an association between SSRI use and any fracture, clinical spine fracture, and wrist fracture, but no association with hip fracture⁴⁰.

Other database studies have also supported an association between SSRIs and fracture. A case-control study using national pharmacy and hospital discharge data from Denmark showed that SSRIs and TCAs had increased fracture risk compared to other antidepressants (RR of any fracture 1.27 for TCA, 95% CI 1.13-1.42; RR 1.40 for SSRI, 95% CI 1.35-1.46; RR for other antidepressants 1.09; 95% CI 1.01-1.18)⁶⁴. An analysis of the United Kingdom General Practice Research Database demonstrated increased rates of hip fracture for those using TCAs (OR 4.76, 95% CI 3.06, 7.41) and SSRIs (OR 6.30, 95% CI 2.65, 14.97)⁵⁴.

Administrative database studies have limited ability to adjust for certain unmeasured confounders such as cognitive and physical impairment and other risk factors for fracture. This can lead to overestimation of risk and can make it difficult to draw conclusions about complex pathways like those linking SSRIs, BMD, and fracture risk. One additional study modeled the association between SSRI use and hip fractures with U.S. Medicare Current Beneficiary Survey data, using estimates of adjustment for risk factors from survey data. After adjusting for confounders that included cognitive and physical impairment, and impairment in activities of daily

living (ADLs), there remained a significantly higher risk for hip fracture with SSRI use⁶³. This group also used their method to adjust results from other published studies evaluating SSRI use and fracture risk. They determined that even after adjustment for these unmeasured confounders, a significant association remained⁶³.

Causation and limitations of current literature

Epidemiologic associations favor a causal relationship when results are biologically plausible, consistent, strong, and when the outcome increases with dose⁶⁶. In the case of 5-HT and bone, biological plausibility is established by preclinical studies⁷. The 5-HTT has been demonstrated in human osteoclasts, osteoblasts and osteocytes⁶⁷⁻⁶⁹. Osteoblasts, osteoclasts and osteocytes express mRNA for tryptophan hydroxylase, the rate limiting step of 5-HT synthesis^{70, 71}. Mice with genetic disruption of the 5-HTT have a consistent skeletal phenotype of reduced mass, altered architecture, and inferior mechanical properties, whereas bone mineral accrual was impaired in growing mice treated with an SSRI⁷². Coinciding with these studies, three different cohort studies of older men and women have shown that SSRIs users have lower BMD^{56,58}, increased bone loss at the hip⁵⁷, and greater risk of fracture⁵⁷. There has not yet been a definitive demonstration of a dose response. The CaMOS study of fractures attempted to evaluate dose and did find a correlation between increasing SSRI dose reported at baseline, and increased risk of both falls and fractures⁵⁶.

Establishing a causal relationship also requires that the potential for erroneous conclusions due to chance, bias, and confounding are minimized. Confounding by indication continues to be a limitation of studies investigating SSRIs' effects on bone health, because depression itself has been associated with lower BMD. Most population-based studies have relied on measures of depressive symptoms rather than actual diagnoses of depression made with diagnostic interviews. Likewise, in these studies, there may be unmeasured or imperfectly assessed variables (e.g., cortisol, physical activity, age of menopause in women). Antidepressants have been associated with falls^{60,73,74}, but so has depression¹⁵. However, the otherwise favorable side effect profile of SSRIs compared to TCAs in terms of drug-drug interactions and their low risk in overdoses may contribute to preferential prescribing of SSRIs among older, frailer individuals who may be at increased risk for falls. These issues of measurement error and potential preferential prescribing further complicate the evaluation of a relationship between SSRIs and fractures²².

Conclusion

In summary, there is mounting evidence to suggest that serotonergic pathways may play an important role in bone. Depression and antidepressant medications may both influ-

ence bone health, either through 5-HT signaling or through some other mechanism. Indeed, there are emerging theories that relate depression, antidepressant therapy and bone outcomes through other physiologic (cytokine, cortisol) or behavioral mechanisms. However, SSRIs are unique among the classes of antidepressants because they potently and selectively inhibit the 5-HTT. Therefore, the 5-HTT provides a potential explanation for differences in bone outcomes seen between SSRI users and users of TCAs or other psychotropic medications⁶¹. It also suggests that relationships between bone outcomes and other CNS-active medications may be mediated by an alternative pathway (e.g., falls, physical inactivity, low sunlight exposure and subsequent vitamin D insufficiency, other hypothalamic dysfunction).

Whether the role of 5-HT in bone is demonstrated through depression or SSRIs or both remains unclear. Studies evaluating the association between depression and BMD are too mixed in their results to be definitive. Studies of SSRIs are more consistent, but have been limited by inability to completely adjust for confounding by the indication for treatment (depression). Providers treating patients requiring SSRIs who are also at risk for bone loss and fracture will need to use clinical judgment based on current knowledge about these potential risks for bone health and the benefits of SSRIs relative to non-pharmacologic treatment modalities, such as cognitive behavioral therapy, for treatment of depression. SSRI users may warrant special attention to promotion of bone health (calcium and vitamin D supplementation, exercise) and fall prevention. To aid clinicians in making these decisions, prospective studies evaluating bone loss and fractures for people taking SSRIs will be important. Likewise, it will be useful to have evaluations of the relationships between depression, bone loss and fracture in populations that have been rigorously assessed for depression. Description of the precise biochemical pathway for 5-HT action and down-stream signaling within bone cells may provide therapeutic insights for both osteoporosis and depression. Such studies should contribute to an understanding of why SSRIs may have a different effect on bone density and fractures than other antidepressants, and of the role of 5-HT and the 5-HTT in bone cells.

Acknowledgements

This publication was made possible by grants AR 051926 and AR 052018 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases. We would like to thank the reviewers for their helpful comments and suggestions for revisions of this manuscript.

References

1. Elefteriou F. Neuronal signaling and the regulation of bone remodeling. *Cell Mol Life Sci* 2005;62:2339-49.
2. Takeda S, Elefteriou F, Lévassieur R, Liu X, Zhao L, Parker KL. Leptin regulates bone formation via the sympathetic nervous system. *Cell* 2002;111:305-17.
3. Ducy P, Amling M, Takeda S, Priemel M, Schilling AF, Beil FT. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. *Cell* 2000;100:197-207.
4. Baldock PA, Sainsbury A, Couzens M, Enriquez RF, Thomas GP. Hypothalamic Y2 receptors regulate bone formation. *J Clin Invest* 2002;109:915-21.
5. Blizotes M, McLoughlin S, Gunness M, Fumagalli F, Jones SR, Caron MG. Bone histomorphometric and biomechanical abnormalities in mice homozygous for deletion of the dopamine transporter gene. *Bone* 2000;26:15-9.
6. Warden SJ, Blizotes MM, Wrenn KM, Eshleman AJ, Turner CH. Neural regulation of bone and the skeletal effects of serotonin (5-hydroxytryptamine). *Mol Cell Endocrinol* 2005;242:1-9.
7. Warden SJ, Haney EM. Skeletal effects of serotonin (5-hydroxytryptamine) transporter inhibition: evidence from in vitro and animal-based studies. *J Musculoskelet Neuronal Interact* 2008;8:126-37.
8. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med* 2008;358:55-68.
9. Meyer JH, Wilson AA, Ginovart N, Goulding V, Hussey K, Hood K, Houle S. Occupancy of serotonin transporters by paroxetine and citalopram during treatment of depression: A [11C]DASB PET imaging study. *Am J Psychiatry* 2001;158:1843-9.
10. Pirraglia PA, Stafford RS, Singer DE. Trends in prescribing of selective serotonin reuptake inhibitors and other newer antidepressant agents in adult primary care. *Prim Care Companion J Clin Psychiatry* 2003;5:153-7.
11. Parker KJ, Schatzberg AF, Lyons DM. Neuroendocrine aspects of hypercortisolism in major depression. *Horm Behav* 2003;43:60-6.
12. Bao A-M, Meynen G, Swaab DF. The stress system in depression and neurodegeneration: focus on the human hypothalamus. *Brain Res Rev* 2008;57:531-53.
13. Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. *Ann Intern Med* 1998;128:127-37.
14. Whooley MA, Cauley JA, Zmuda JM, Haney EM, Glynn NW. Depressive symptoms and bone mineral density in older men. *J Geriatr Psych Neurol* 2004;17:88-92.
15. Whooley MA, Kip KE, Cauley JA, Ensrud KE, Nevitt MC, Browner WS. Depression, falls, and risk of fracture in older women. *Arch Intern Med* 1999;159:484-90.
16. Robbins J, Hirsch C, Whitmer R, Cauley J, Harris T. The association of bone mineral density and depression in an older population. *J Am Geriatr Soc* 2001;49:732-6.
17. Mussolino ME, Jonas BS, Looker AC. Depression and bone mineral density in young adults: Results from

- NHANES III. *Psychosom Med* 2004;66:533-7.
18. Wong SY, Lau EMC, Lynn H, Leung PC, Woo J, Cummings SR, Orwoll E. Depression and bone mineral density: is there a relationship in elderly Asian men? Results from Mr. Os (Hong Kong). *Osteoporos Int* 2005;16:610-5.
 19. Silverman SL, Shen W, Minshall ME, Xie S, Moses KH. Prevalence of depressive symptoms in postmenopausal women with low bone mineral density and/or prevalent vertebral fracture: Results from the Multiple Outcomes of Raloxifene Evaluation (MORE) study. *J Rheumatol* 2007;34:140-4.
 20. Jacka FN, Pasco JA, Henry MJ, Kotowicz MA, Dood S, Nicholson GC, Berk M. Depression and bone mineral density in a community sample of perimenopausal women: Geelong Osteoporosis Study. *Menopause* 2005;12:88-91.
 21. Forsen L, Meyer HE, Sogaard AJ, Naess S, Schei B, Edna T-H. Mental distress and risk of hip fracture. Do broken hearts lead to broken bones? *J Epidemiol Community Health* 1999;53:343-7.
 22. Ensrud KE, Blackwell T, Mangione CM, Bowman PJ, Bauer DC, Schwartz A, Hanlon TJ, Nevitt MC, Whooley MA. Central nervous system active medications and risk for fractures in older women. *Arch Intern Med* 2003;163:949-57.
 23. Reginster JY, Deroisy R, Paul I, Hansenne M, Anseau M. Depressive vulnerability is not an independent risk factor for osteoporosis in postmenopausal women. *Maturitas* 1999;33:133-7.
 24. Sogaard AJ, Joakimsen RM, Tverdal A, Fonnebo V, Magnus JH, Berntsen GKR. Long-term mental distress, bone mineral density and non-vertebral fractures. The Tromso Study. *Osteoporos Int* 2005;16:887-97.
 25. Mussolino ME. Depression and hip fracture risk: the NHANES I Epidemiologic Follow-up Study. *Public Health Rep* 2005;120:71-5.
 26. Tolea MI, Black SA, Carter-Pokras OD, Kling MA. Depressive symptoms as a risk factor for osteoporosis and fractures in older Mexican American women. *Osteoporos Int* 2007;18:315-22.
 27. Diem SJ, Blackwell TL, Stone KL, Yaffe K, Cauley JA, Whooley MA, Ensrud KE. Depressive symptoms and rates of bone loss at the hip in older women. *J Am Geriatr Soc* 2007;55:824-31.
 28. Halbreich U, Rojansky N, Palter S, Hreshchyshyn M, Kreeger J, Bakhai Y, Rosan R. Decreased bone mineral density in medicated psychiatric patients. *Psychosom Med* 1995;57:485-91.
 29. Schweiger U, Ceuschle M, Korner A, Lammers C, Schmider J, Gotthardt U, Holsboer F, Heuser I. Low lumbar bone mineral density in patients with major depression. *Am J Psychiatry* 1994;151:1691-3.
 30. Michelson D, Stratakis C, Hill L, Reynolds J, Galliven E, Chrousos G, Gold P. Bone mineral density in women with depression. *N Engl J Med* 1996;335:1176-81.
 31. Yazici KM, Akinci A, Sutcu A, Ozcarar L. Bone mineral density in premenopausal women with major depressive disorder. *Psychiatry Res* 2003;117:271-5.
 32. Cizza G, Eskandari F, Martinez P, Torvik S, Kotila C, Mistry S, Sebring N, Drinkard B, Ronsaville D, Reynolds J, Gold PW. Twenty-one to 45-year-old premenopausal women suffering from major depression are at increased risk for osteoporosis. *J Bone Miner Res* 2003;18(Suppl.2):S87.
 33. Eskandari F, Martinez PE, Torvik S, Phillips TM, Sternberg EM, Mistry S, Ronsaville D, Wesley R, Toomey C, Sebring NG, Reynolds JC, Blackman MR, Calis KA, Gold PW, Cizza G. Low bone mass in premenopausal women with depression. *Arch Intern Med* 2007;167:2329-36.
 34. Kahl KG, Rudolf S, Stoeckelhuber BM, Dibbelt L, Gehl H-B, Markhof K, Hohagen F, Schwiger U. Bone mineral density, markers of bone turnover, and cytokines in young women with borderline personality disorder with and without comorbid major depressive disorder. *Am J Psychiatry* 2005;162:168-74.
 35. Petronijevic M, Petronijevic N, Ivkovic M, Stefanovic D, Radonjic N, Gilsic B, Risticv G, Damjanovic A, Paunovic V. Low bone mineral density and high bone metabolism turnover in pre-menopausal women with unipolar depression. *Bone* 2008;42:582-90.
 36. Amsterdam JD, Hooper MB. Bone density measurement in major depression. *Prog Neuro-Psychopharmacol Biol Psychiatry* 1998;22:267-77.
 37. Kavuncu V, Kulogu M, Kaya A, Sahin S, Atmaca M, Firidin B. Bone metabolism and bone mineral density in premenopausal women with mild depression. *Yonsei Med J* 2002;43:101-8.
 38. Schweiger U, Weber B, Deuschle M, Heuser I. Lumbar bone mineral density in patients with major depression: evidence of increased bone loss at follow-up. *Am J Psychiatry* 2000;157:118-20.
 39. Coelho R, Silva C, Maia A, Prata J, Barros H. Bone mineral density and depression: a community study in women. *J Psychosom Res* 1999;46:29-35.
 40. Spangler L, Scholes D, Brunner RL, Robbins J, Reed SD, Newton KM, Melville JL, Lacroix AZ. Depressive symptoms, bone loss, and fractures in postmenopausal women. *J Gen Intern Med* 2008;[Epub ahead of print].
 41. Herran A, Amado JA, Garcia-Unzueta MT, Vazquez-Barquero JL, Perera L, Gonzalez-Macias J. Increased bone remodeling in first-episode major depressive disorder. *Psychosom Med* 2000;62:779-82.
 42. Altindag O, Altindag A, Asoglu M, Gunes M, Soran N, Deveci Z. Relation of cortisol levels and bone mineral density among premenopausal women with major depression. *Int J Clin Pract* 2007;61:416-20.
 43. Furlan PM, Have TT, Cary M, Zemel B, Wehrli F, Katz IR, Gettes DR, Evans DL. The role of stress-induced

- cortisol in the relationship between depression and decreased bone mineral density. *Biol Psychiatry* 2005;57:911-7.
44. Cizza G, Ravn P, Chrousos G, Gold P. Depression: a major, unrecognized risk factor for osteoporosis? *Trends Endocrinol Metab* 2001;12:198-203.
 45. Greendale GA, Unger JB, Rowe JW, Seeman TE. The relation between cortisol excretion and fractures in healthy older people: results from the MacArthur Studies – Mac. *J Am Geriatr Soc* 1999;47:799-803.
 46. Haney EM, Bliziotis MM. Selective serotonin reuptake inhibitors and bone health. *Future Rheumatol* 2007;2:213-22.
 47. Mezuk B, Eaton WW, Golden SH. Depression and osteoporosis: epidemiology and potential mediating pathways. *Osteoporos Int* 2008;19:1-12.
 48. Rubenstein LZ, Josephson KR. The epidemiology of falls and syncope. *Clin Geriatr Med* 2002;18:141-58.
 49. Bruggemann L, Nixon RD, Cavenett T. Predicting acute anxiety and depression following hip fracture. *J Behav Med* 2007;30:97-105.
 50. Lenze EJ, Munin MC, Skidmore ER, Dew MA, Rogers JC, Whyte EM, Quear T, Begley A, Reynolds CFI. Onset of depression in elderly persons after hip fracture: implications for prevention and early intervention of late-life depression. *J Am Geriatr Soc* 2007;55:81-6.
 51. Lenze EJ, Munin Mc, Ferrell RE, Pollock BG, Skidmore E, Lotrich F, Rogers J, Quear T, Houck P, Reynolds CFI. Association of the serotonin transporter gene-linked polymorphism region (5-HTTLPR) genotype with depression in elderly persons after hip fracture. *Am J Geriatr Psychiatry* 2005;13:428-32.
 52. Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ III. Psychotropic drug use and the risk of hip fracture. *N Engl J Med* 1987;316:363-9.
 53. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. *Lancet* 1998;351:1303-7.
 54. Hubbard R, Farrington P, Smith C, Smeeth L, Tattersfield A. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. *Am J Epidemiol* 2003;158:77-84.
 55. Kinjo M, Setoguchi S, Schneeweiss S, Solomon DH. Bone mineral density in subjects using central nervous system – active medications. *Am J Med* 2005;118:1414.
 56. Richards JB, Papaioannou A, Adachi JD, Joseph L, Whitson HE, Prior JC, Goltzman D, CMOSRSG. The impact of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med* 2007;167:188-94.
 57. Diem S, Blackwell T, Stone KL, Haney EM, Bliziotis MM, Ensrud KE. Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. *Arch Intern Med* 2007;167:1240-5.
 58. Haney EM, Chan BKS, Diem S, Ensrud K, Cauley J, Barrett-Connor E, Orwoll E, Bliziotis MM. Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. *Arch Intern Med* 2007;167:1246-51.
 59. Williams LJ, Henry MJ, Berk M, Dodd S, Jacka FN, Kotowicz MA, Nicholson GC, Pasco JA. Selective serotonin reuptake inhibitor use and bone mineral density in women with a history of depression. *Int Clin Psychopharmacol* 2008;23:84-7.
 60. Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA. Antidepressants and the risk of falls among nursing home residents. *N Engl J Med* 1998;339:875-82.
 61. Takkouche B, Montes-Martinez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture. *Drug Safety* 2007;30:171-84.
 62. Cauley JA, Fullman RL, Stone KS, Zmuda JM, Bauer DC, Barrett-Connor E, Ensrud KE, Lau EMC, Orwoll E. Factors associated with the lumbar spine and proximal femur bone mineral density in older men. *Osteoporos Int* 2005;16:1525-37.
 63. Schneeweiss S, Wang PS. Association between SSRI use and hip fractures and the effect of residual confounding bias in claims database studies. *J Clin Psychopharmacol* 2004;24:632-8.
 64. Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. *Osteoporos Int* 2006;17:807.
 65. Lewis CE, Ewing SK, Taylor BC, Shikanv JM Fink HA, Ensrud KE, Barrett-Connor E, Cummings SR, Orwoll E. Predictors of non-spine fracture in elderly men: the MrOS Study. *J Bone Miner Res* 2007;22:211-9.
 66. Newman TB, Browner WS, Hulley SB. Enhancing causal inference in observational studies. In: Hulley SB, Cummings SR, Browner WS, Grady D, Hearst N, Newman TB, editors. *Designing Clinical Research*. 2 ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 125-142.
 67. Bliziotis M, Eshleman A, Zhang X, Wiren K. Neurotransmitter action in osteoblasts: expression of a functional system for serotonin receptor activation and reuptake. *Bone* 2001;29:477-86.
 68. Westbroek I, Plas Avd, Rooij Kd, Klein-Nulend J, Nijweide P. Expression of serotonin receptors in bone. *J Biol Chem* 2001;276:28961-8.
 69. Battaglini R, Fu J, Spate U, Ersoy U, Joe M, Sedaghat L, Stashenko P. Serotonin regulates osteoclast differentiation through its transporter. *J Bone Miner Res* 2004;19:1420-31.
 70. Bliziotis MM, Eshleman A, Burt-Pichat B, Zhang X-W, Hashimoto J, Wiren KM, Chenu C. Serotonin transporter and receptor expression in osteocytic MLO-Y4 cells. *Bone* 2006;39:1313-21.
 71. Gustafsson BI, Thommesen L, Stunes AK, Tommeras K, Westbroek I, Waldum HL, Slordahl K, Tamburstuen MV, Reseland JE, Syversen U. Serotonin and fluoxe-

- tine modulate bone cell function *in vitro*. J Cell Biochem 2006;98:139-51.
72. Warden SJ, Robling AG, Sanders MS, Bliziotes MM, Turner CH. Inhibition of the serotonin (5-hydroxytryptamine) transporter reduces bone accrual during growth. Endocrinology 2005;146:685-93.
73. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Dauer DC, Schwartz AV, Hanlon JT, Nevitt MC. Central nervous system – active medications and risk for falls in older women. J Am Geriatr Soc 2002;50:1629-37.
74. Hartikainen S, Lonroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. J Gerontol 2007;62A:1172-81.