Effects of Escitalopram on Markers of Bone Turnover: A Randomized Clinical Trial

Susan J. Diem, Hadine Joffe, Joseph C. Larson, Joy N. Tsai, Katherine A. Guthrie, Andrea Z. LaCroix, Kristine E. Ensrud, Ellen W. Freeman, and Benjamin Z. Leder

University of Minnesota (S.J.D., K.E.E.), Minneapolis, Minnesota 55415; Brigham and Women's Hospital and Dana Farber Cancer Institute (H.J.), Boston, Massachusetts 02115; Fred Hutchinson Cancer Research Center (J.C.L., A.Z.L.), Seattle, Washington 98109; Massachusetts General Hospital (J.N.T., B.Z.L.), Boston, Massachusetts 02114; Minneapolis Veterans Affairs Health Care System (K.E.E.), Minneapolis, Minnesota 55417; and Perelman School of Medicine (E.W.F.), University of Pennsylvania, Philadelphia, Pennsylvania 19104

Context: Recent observational studies have suggested that the use of selective serotonin reuptake inhibitors is associated with an increased fracture risk and an accelerated bone loss, although conflicting results have been reported. Furthermore, because many of these studies have been performed in depressed women, confounding by indication may influence these findings.

Objective: The objective of the study was to determine whether selective serotonin reuptake inhibitors affect bone metabolism

Design: This was a randomized controlled trial.

Setting: The study was conducted in four US clinical sites.

Participants: Healthy peri- and postmenopausal women participated in the study.

Intervention: The intervention was escitalopram (10–20 mg/d) for the treatment of vasomotor symptoms.

Main Outcome Measures: Serum carboxyterminal collagen crosslinks (CTX) and serum amino-terminal propeptide of type I collagen (P1NP) were measured.

Results: One hundred forty-one peri- or postmenopausal nondepressed women (mean age 53.7 y, SD 4.1) had baseline and 8-week follow-up samples available for analysis and were included in the study (69 escitalopram, 72 placebo). The groups were balanced across a broad range of baseline characteristics, including age, race, body mass index, smoking status, and mood symptoms. The between-group differences in the change in CTX and P1NP from baseline to week 8 were compared by a repeated-measures linear regression model adjusted for race, clinical center, and baseline measurement. Treatment with escitalopram reduced serum P1NP by 1.02 ng/mL on average [95% confidence interval (CI) −5.17, 3.12] compared with a reduction of 1.88 ng/mL (95% CI −4.82, 1.06) in the placebo group ($P = .65$). Similarly, serum CTX decreased 0.02 ng/mL on average (95% CI −0.05, 0.01) in the escitalopram group compared with 0.00 ng/mL (95% CI −0.02, 0.02) in the placebo group ($P = .24$). The results were similar when the analysis was restricted to those women whose adherence to study medication was 70% or greater.

Conclusions: Although the study was limited to 8 weeks, these results suggest that escitalopram does not significantly alter bone metabolism in the short term. **(*J Clin Endocrinol Metab* 99: E1732–E1737, 2014)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received May 9, 2014. Accepted July 2, 2014.
First Published Online July 11, 2014

Abbreviations: BMD, bone mineral density; BMI, body mass index; CTX, carboxy-terminal collagen crosslinks; GAD-7, Generalized Anxiety Disorder 7; PHQ-9, Patient Health Questionnaire 9; P1NP, procollagen type 1 amino-terminal propeptide; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Evidence from in vitro and animal studies has suggested a role for serotonin and the serotonin transporter in bone metabolism, thus raising concern that inhibition of the serotonin transporter, the primary mechanism of action of selective serotonin reuptake inhibitors (SSRIs), may have adverse effects on bone health (1, 2). Observational studies examining an association between SSRI use, bone mineral density (BMD), and rates of bone loss have yielded inconsistent results (3–5) but are limited by the potential for confounding by indication. Based on this previous work, SSRI use has been identified as a contributor to osteoporosis by some (6), with calls for increased surveillance of BMD in those taking SSRIs (1).

Given the limitations of existing work, there remains considerable uncertainty regarding the potential effect of SSRIs on bone health. We used data from a placebo-controlled randomized trial of the SSRI escitalopram for the treatment of menopausal vasomotor symptoms to determine the effect of escitalopram on bone turnover markers in nondepressed and generally healthy peri- and postmenopausal women.

Materials and Methods

Study design

The parent study was a randomized, placebo-controlled, double-blind multicenter trial of escitalopram vs. placebo for treatment of menopausal vasomotor symptoms (N = 205) (7). Participants were randomized to receive either escitalopram 10-mg/d or matching placebo for 8 weeks. Women whose hot flash frequency did not improve at least 50% or whose hot flash severity did not decrease after four treatment weeks increased their study medication to 20 mg/d (or matched placebo) without unblinding the randomization. In these analyses, we compared the 8-week change in serum levels of the bone formation marker amino-terminal propeptide of type 1 procollagen (P1NP) and the bone resorption marker serum carboxyterminal collagen crosslinks (CTX) from baseline to 8-week follow-up between the two treatment groups.

Study population

We included 141 women who provided a fasting blood sample at the beginning and end of the trial and gave consent for use of their stored biological specimens (69 in escitalopram arm, 72 in placebo arm).

Eligible women were aged 40–62 years, in good health, and in the menopause transition or postmenopausal. They had at least 28 hot flashes or night sweats per week rated as severe or bothersome on most days, as recorded on daily diaries for 3 weeks. Exclusionary criteria included use of psychotropic medications; prescription, over-the-counter, or herbal therapies for hot flashes in the past 30 days; hormone therapy, hormonal contraceptives, selective estrogen receptor modulators, or aromatase inhibitors in past 2 months; or major depressive episode in the past year. Women with evidence of current major depressive disorder on the Patient Health Questionnaire (PHQ-9) (8) were excluded. Further details regarding eligibility are described elsewhere (7).

Measurement of biochemical markers of bone turnover

Biochemical markers of bone turnover analyses were performed on banked fasting (at least 8 h) specimens from the trial repository and stored at −70°F. We selected P1NP and CTX as the biochemical markers of bone formation and resorption, respectively. All samples were collected in the morning, and all markers from individual subjects were measured at the Clinical and Translational Science Center Core Laboratory at Massachusetts General Hospital. Serum P1NP was measured by RIA (Orion Diagnostica). The detection limit of this assay is 2 ng/mL; the inter- and intraassay coefficients of variation are 6%-10% and 7%-10%, respectively. CTX was measured by a double-antibody ELISA (Roche Diagnostics); the inter- and intraassay coefficients of variation are 2%-6% and 1%-5%, respectively.

Other measurements

Serum TSH and 25-hydroxyvitamin D were measured on banked specimens. Demographic data, menopausal status, and anthropometric measures were collected at the baseline visit. Self-report questionnaires assessed health status, smoking status, alcohol use, and medication use. Depressive and anxiety symptoms were assessed using the PHQ-9 (8) and the Generalized Anxiety Disorder (GAD-7) (9), respectively. Frequency and severity of hot flashes or night sweat were recorded in daily diaries throughout the study.

Statistical analysis

Change from baseline to week 8 values in P1NP and CTX were compared between treatment groups using linear regression models of the week 8 values as a function of treatment arm, clinical site (Boston, Massachusetts; Indianapolis, Indiana; Oakland, California; and Philadelphia, Pennsylvania), race, and corresponding baseline value of the marker.

In sensitivity analyses, we excluded seven participants who reported bisphosphonate or oral glucocorticoid use in the previous 6 months as well as four participants with a TSH less than 0.1 or greater than 10 mIU/L. Secondary analyses restricted to 127 participants reporting at least 70% adherence to the study medication were also conducted (62 in escitalopram arm, 65 in the placebo arm).

To examine whether the effect of escitalopram on bone metabolism varied by race, depressive symptoms or vitamin D level (<20 μg/mL vs ≥ 20 μg/mL), we tested for an interaction between treatment assignment and these variables for prediction of change in bone turnover markers. To test whether the higher dose of escitalopram had an effect on markers of bone metabolism, we compared the change in P1NP and CTX relative to placebo among subjects whose dose of escitalopram (or placebo) was increased at 4 weeks.

Results

Characteristics of study population

The mean age of the 141 participants was 53.7 (SD 4.1) years; 57.4% were white and 41.1% were African Amer-

ican. There were no significant differences in baseline characteristics by treatment assignment (Table 1). The two groups were similar in age, body mass index (BMI), menopausal stage, and baseline 25-hydroxyvitamin D and TSH levels. Overall, 83% were postmenopausal, with a median of 4 years since the final menstrual period (interquartile range 2–9 y).

Change in P1NP and CTX

Treatment with escitalopram reduced serum P1NP by 1.02 ng/mL on average [95% confidence interval (CI) −5.2, 3.1] compared with a reduction of 1.88 ng/mL (95% CI −4.82, 1.06) in the placebo group ($P = .65$). Serum CTX decreased 0.02 ng/mL on average (95% CI −0.05, 0.01) in the escitalopram group compared with

Table 1. Demographic and Clinical Characteristics by Treatment Arm at Baseline

Baseline Characteristic	Escitalopram (n = 69)	Placebo (n = 72)	*P* Value[a]
Age at screening, y, mean (SD)	53.3 (4.2)	54.2 (4.0)	.21
Age group, y, n, %			
42–49	9 (13.0)	7 (9.7)	
50–54	35 (50.7)	35 (48.6)	
55–59	19 (27.5)	23 (31.9)	
60–62	6 (8.7)	7 (9.7)	
Race, n, %			.93
White	39 (56.5)	42 (58.3)	
African American	29 (42.0)	29 (40.3)	
Other	1 (1.4)	1 (1.4)	
Smoking, n, %			.74
Never	37 (53.6)	34 (47.2)	
Past	19 (27.5)	22 (30.6)	
Current	13 (18.8)	16 (22.2)	
Alcohol use, drinks per week, n (%)			.43
0	27 (39.1)	27 (37.5)	
1 to < 7	34 (49.3)	31 (43.1)	
7+	8 (11.6)	14 (19.4)	
BMI, m/kg^2, mean (SD)	28.85 (7.00)	30.13 (6.76)	.27
BMI category, n (%)			
<25	21 (30.4)	14 (19.4)	
25 to < 30	22 (31.9)	29 (40.3)	
≥ 30	26 (37.7)	28 (38.9)	
Menopause status, n, %			.80
Postmenopause	59 (85.8)	58 (80.6)	
Late transition	8 (11.6)	12 (16.7)	
Early transition	2 (2.9)	2 (2.8)	
Self-reported health, n, %			.44
Excellent	13 (18.8)	9 (12.5)	
Very Good	28 (40.6)	28 (38.9)	
Good	23 (33.3)	26 (36.1)	
Fair	4 (5.8)	9 (12.5)	
Poor	1 (1.4)	0 (0.0)	
PHQ-9 depression score (range 0–27), mean (SD)	3.20 (3.12)	2.97 (3.20)	.67
PHQ-9 depression level, n, %			
No depression (0–4)	49 (71.0)	55 (76.4)	
Mild depressive symptoms (5–9)	17 (24.6)	12 (16.7)	
Moderate depressive symptoms (10–13)	3 (4.3)	5 (6.9)	
GAD-7 anxiety score (range 0–19), mean (SD)	2.35 (3.44)	2.14 (3.26)	.71
GAD-7 anxiety level, n, %			
No anxiety (0–4)	56 (81.2)	59 (81.9)	
Mild anxiety (5–9)	9 (13.0)	11 (15.3)	
Moderate+ anxiety (10–19)	4 (5.8)	2 (2.8)	
CTX, ng/mL, mean (SD)	0.44 (0.17)	0.43 (0.16)	.68
P1NP, ng/mL, mean (SD)	53.31 (19.93)	58.68 (24.93)	.16
25OH D, μg/mL, mean (SD)	25.56 (15.37)	23.69 (13.24)	.44
TSH, μIU/mL, mean (SD)	1.79 (1.97)	1.54 (0.80)	.32

Abbreviation: 25OH, 25-hydroxyvitamin.

[a] *P* values are from a two-sample *t* test for continuous characteristics and χ^2 for categorical characteristics, except for race, employment status, marital status, menopause status, and self-reported health, which were from a Fisher's exact test due to low cell counts.

0.00 ng/mL (95% CI −0.02, 0.02) in the placebo group (P = .24) (Figure 1).

Results were not substantially altered when the analysis was limited to subjects with 70% or greater adherence to study medication. Results were also similar when subjects with an abnormal TSH (n = 4) and subjects reporting bisphosphonate use (n = 2) or oral glucocorticoid use (n = 5) were excluded. When the analysis was restricted to women who increased their dose of escitalopram or placebo at 4 weeks (36 escitalpram, 50 placebo), no significant group differences were found in the change of P1NP or CTX.

In an analysis of treatment effects by depressive symptoms at baseline, women with no depressive symptoms (PHQ-9 score 0–4) (n = 49) had a small mean increase in serum P1NP of 0.77 ng/mL (95% CI −4.71, 6.24) with escitalopram, whereas participants who had mild or moderate depressive symptoms (PHQ-9 score 5–13) (n = 20) had a mean decrease in PINP of 5.41 ng/mL (95% CI −10.49, −0.32) with escitalopram. Women with a PHQ-9 score of 0–4 assigned to placebo (n = 55) had a mean decrease in P1NP of 2.08 ng/mL (95% CI −5.66, 1.5), whereas participants with a PHQ-9 score of 5–13 on placebo (n = 17) had a mean decrease of −1.25 ng/mL (95% CI −6.47, 3.96) (P for interaction = .04). There was no evidence of an interaction between depressive symptoms and treatment group for serum CTX, between race and treatment group for serum CTX or P1NP, or between vitamin D level and treatment group for serum CTX or P1NP.

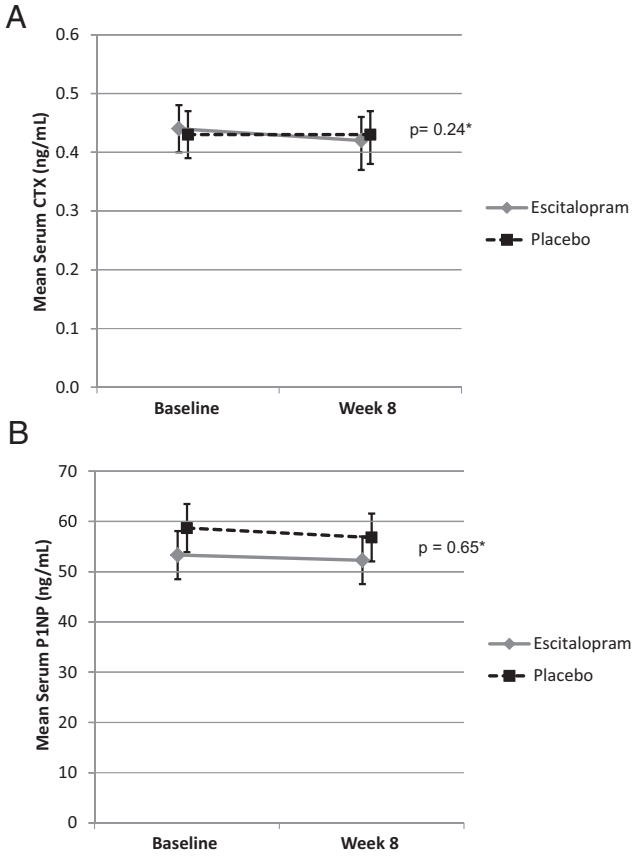

Figure 1. A and B, Change in serum CTX and serum P1NP. *, P values from coefficient comparing escitalopram vs placebo in a linear regression model of the week 8 outcome as a function of treatment arm, race, clinical center, and baseline marker value.

Discussion

This study, the first to our knowledge to measure markers of bone turnover in a randomized, placebo controlled trial of a SSRI, found no evidence for an effect of escitalopram on the bone turnover makers P1NP and serum CTX in generally healthy peri- and postmenopausal women without major depressive disorder over an 8-week period.

Concern about an adverse effect of SSRIs on bone health has been raised by observational studies suggesting an association of SSRI use with lower BMD (10), higher rates of bone loss (11), and increased risk of fractures (5, 12). In addition, functional serotonin receptors and serotonin transporters have been identified in osteoblasts, osteocytes, and osteoclasts (2, 13), lending biological plausibility to the possibility that serotonin may play a role in bone metabolism and that serotonin transporter inhibition may therefore have consequences for bone health.

However, the published work to date in humans has been exclusively observational and is subject to limitations. Confounding by indication is of particular concern because SSRIs are prescribed primarily for depression, which has itself been associated with lower BMD, increased rates of bone loss, and an increased risk of fractures (14, 15). This randomized, placebo-controlled SSRI trial in a nondepressed population eliminates this important confounder.

Others have examined markers of bone turnover in subjects using SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs), but the lack of a placebo control and the presence of major depression in all subjects significantly limit the interpretation of their work (16, 17). In an uncontrolled, open-label study, serum osteocalcin increased and serum CTX levels decreased after 3 months of escitalopram treatment in 50 premenopausal women with major depression (16). The changes in bone turnover markers were observed in subjects whose depression improved significantly but not in those whose depression only partially responded to treatment, suggesting that the change in bone turnover markers may have been related to an improvement in depression, rather than a direct effect of the medication itself. In contrast, an uncontrolled study of 76 subjects with major depression who received 12

weeks of the SNRI venlafaxine found that serum CTX increased from baseline to 12 weeks, whereas P1NP did not significantly change (17).

We found no evidence of an interaction between depressive symptoms and change in serum CTX. Although we observed a borderline statistically significant interaction between category of depressive symptoms and treatment group for P1NP, the changes in P1NP were small, and this finding may have been due to chance, given our small sample size and the multiple comparisons evaluated.

The primary limitation of the present work is the short follow-up of 8 weeks, a time frame too brief to allow for change in BMD as an outcome. However, changes in markers are generally observed within 4 weeks of exposure to bone-modifying agents. For example, in subjects treated with oral alendronate 70 mg weekly, the percentage change from baseline in serum CTX at 1 and 3 months is −62% and −65%, respectively (18). Furthermore, serum P1NP decreased by 32% after 1 month of denosumab treatment (19).

Despite the short follow-up, the absence of an effect of escitalopram on serum CTX and P1NP over 8 weeks provides reassuring evidence that this medication does not have clinically important short-term effects on bone metabolism in generally healthy women of this age. It remains uncertain whether this finding can be generalized to other SSRIs or SNRIs or to other populations, such as older postmenopausal women. Although a longer follow-up period with measurement of other bone outcomes, such as BMD and fracture incidence, would be ideal for establishing the safety of these medications for bone health, such a placebo-controlled trial would have substantial logistical hurdles. However, these results, as well as recent observational studies (3, 20) in other cohorts of women using SSRIs, provide reassurance regarding the absence of bone health effects of these medications when used in generally healthy, nondepressed midlife women.

Acknowledgments

Author contributions included the following: study design, S.J.D., B.Z.L., H.J., K.A.G., and A.Z.L.; study conduct, A.Z.L., K.E.E., E.W.F., S.J.D., and B.Z.L.; data collection, H.J., K.A.G., A.Z.L., B.Z.L., J.N.T., and E.W.F.; data analysis, J.C.L. and K.A.G.; data interpretation, S.J.D., H.J., J.C.L., J.N.T., K.A.G., K.E.E., and B.Z.L.; drafting manuscript, S.J.D.; review of manuscript for intellectual content, H.J., J.C.L., J.N.T., K.A.G., A.Z.L., K.E.E., E.W.F., and B.Z.L.; and final approval of manuscript, S.J.D., H.J., J.C.L., J.N.T., K.A.G., A.Z.L., K.E.E., E.W.F., and B.Z.L.

J.C.L. and K.A.G. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors made substantial contributions to the study and this manuscript. None were compensated for the manuscript preparation.

The sponsor funding agencies had no direct role in the design or conduct of the study; the collection, management, analyses, and interpretation of the data; or the preparation or approval of the manuscript.

The trial had a registration number of NCT00894543 (www.clinicaltrials.gov).

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Aging, National Center for Complementary and Alternative Medicine (NCCAM), Office of Research on Women's Health or the National Institutes of Health.

Address all correspondence and requests for reprints to: Susan J. Diem, MD, MPH, 1100 Washington Avenue South, Suite 201, Minneapolis, MN 55415. E-mail: sdiem@umn.edu.

This work was supported by a cooperative agreement issued by the National Institute of Aging, in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Center for Complementary and Alternative Medicine, and the Office of Research on Women's Health Grants U01 AG032656, U01AG032659, U01AG032669, U01AG032699, and U01AG032700. At the University of Indiana site, the project was supported in part with funding from the Indiana Clinical and Translational Sciences Institute, funded in part by Grant UL1 RR025761 from the National Institutes of Health, National Center for Research Resources, Clinical and Translational Sciences Award. Escitalopram and matching placebo pills were provided by Forest Research Institute.

Disclosure Summary: H.J. reports research support from Cephalon/Teva and consultant activities for Noven and Sunovion. K.E.E. serves as a consultant on a Data Monitoring Committee for Merck Sharpe & Dohme. E.W.F. reports research support from Forest Laboratories, Inc, issued to the Trustees of the University of Pennsylvania. All other authors have nothing to declare.

References

1. **Haney EM, Warden SJ, Bliziotes MM.** Effects of selective serotonin reuptake inhibitors on bone health in adults: time for recommendations about screening, prevention and management? *Bone*. 2010; 46:13–17.
2. **Warden SJ, Robling AG, Haney EM, Turner CH, Bliziotes MM.** The emerging role of serotonin (5-hydroxytryptamine) in the skeleton and its mediation of the skeletal effects of low-density lipoprotein receptor-related protein 5 (LRP5). *Bone*. 2010;46:4–12.
3. **Diem SJ, Ruppert K, Cauley JA, et al.** Rates of bone loss among women initiating antidepressant medication use in midlife. *J Clin Endocrinol Metab*. 2013;98:4355–4363.
4. **Haney EM, Warden SJ.** Skeletal effects of serotonin (5-hydroxytryptamine) transporter inhibition: evidence from clinical studies. *J Musculoskelet Neuronal Interact*. 2008;8:133–145.
5. **Schwan S, Hallberg P.** SSRIs, bone mineral density, and risk of fractures—a review. *Eur Neuropsychopharmacol*. 2009;19:683–692.
6. **National Osteoporosis Foundation.** Clinician's guide to prevention and treatment of osteoporosis. http:nof.org/hcp/clincians-guide (up-

dated April 1, 2014). Assessed July 21, 2014. http://nof.org/files/nof/public/content/file/2791/upload/919.pdf.
7. **Freeman EW, Guthrie KA, Caan B, et al.** Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA*. 2011;305:267–274.
8. **Kroenke K, Spitzer RL, Williams JB.** The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–613.
9. **Spitzer RL, Kroenke K, Williams JB, Lowe B.** A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166:1092–1097.
10. **Haney EM, Chan BK, Diem SJ, et al.** Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. *Arch Intern Med*. 2007;167:1246–1251.
11. **Diem SJ, Blackwell TL, Stone KL, et al.** Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. *Arch Intern Med*. 2007;167:1240–1245.
12. **Wu Q, Bencaz AF, Hentz JG, Crowell MD.** Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. *Osteoporos Int*. 2012;23:365–375.
13. **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;8:121–132.
14. **Diem SJ, Blackwell TL, Stone KL, et al.** Depressive symptoms and rates of bone loss at the hip in older women. *J Am Geriatr Soc*. 2007;55:824–831.
15. **Mezuk B, Eaton WW, Golden SH.** Depression and osteoporosis: epidemiology and potential mediating pathways. *Osteoporos Int*. 2008;19:1–12.
16. **Aydin H, Mutlu N, Akbas NB.** Treatment of a major depression episode suppresses markers of bone turnover in premenopausal women. *J Psychiatr Res*. 2011;45:1316–1320.
17. **Shea ML, Garfield LD, Teitelbaum S, et al.** Serotonin-norepinephrine reuptake inhibitor therapy in late-life depression is associated with increased marker of bone resorption. *Osteoporos Int*. 2013;24:1741–1749.
18. **McClung MR, Lewiecki EM, Cohen SB, et al.** Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2006;354:821–831.
19. **Bone HG, Bolognese MA, Yuen CK, et al.** Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab*. 2008;93:2149–2157.
20. **Spangler L, Scholes D, Brunner RL, et al.** Depressive symptoms, bone loss, and fractures in postmenopausal women. *J Gen Intern Med*. 2008;23:567–574.