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Increased bone turnover with venlafaxine treatment in older depressed adults

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Abstract

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Purpose—Epidemiologic data suggest older adults receiving serotonergic antidepressants may have accelerated bone loss. We examined bone turnover marker changes and patient-level variables associated with these changes in older adults receiving protocolized antidepressant treatment.

Method—In 168 older adults with major depression, we assayed serum levels of the bone resorption marker C-terminal cross-linking telopeptide of type 1 collagen (CTX), and the bone formation marker procollagen type 1 N propeptide (PINP) before and after 12 weeks of treatment with venlafaxine. We also examined whether CTX and PINP changes were associated with depression remission and duration of depression, as well as genetic polymorphisms in the serotonin transporter (5HTTLPR) and 1B receptor (HTR1B).

Results—CTX increased and PINP decreased during venlafaxine treatment, a profile consistent with accelerated bone loss. Two patient-level clinical variables correlated with bone turnover: non-remitters from depression had higher CTX levels, while those with chronic depression had reduced PINP levels. Additionally, HTR1B genotype predicted PINP change; 5HTTLPR genotype was unrelated to either biomarker.

Conclusion—Bone turnover markers change with antidepressant treatment in a pattern that suggests accelerated bone loss, although the clinical significance of these changes is unclear. These data are preliminary and argue for a larger, controlled study to confirm whether antidepressants are harmful to bone metabolism and whether certain patients might be at increased risk.

Keywords

Depression; PINP; CTX; Bone Turnover; Antidepressant

INTRODUCTION

One in six older American adults is prescribed antidepressants,¹ typically serotonin-reuptake inhibitors (SRIs) which include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).² SRIs block serotonin (5-HT) transporters, influencing 5-HT levels, centrally and peripherally.³ There are functional 5-HT receptors on bone cells,³ and some studies have shown an association between SRIs and accelerated bone loss^{4–6} among older adults. In a meta-analysis, the use of SSRIs was associated with a 70% increase in fracture risk.⁷

Bone is a dynamic tissue, undergoing remodeling throughout the lifetime.⁸ In the brain, SRIs inhibit 5-HT reuptake from the synapse causing receptor and second messenger changes.^{9,10} Peripherally, SRIs alter gut-derived 5-HT levels, leading to downstream serotonergic effects on bone cells via the 5-HT transporter and the 5-HT receptor HTR1B.¹¹ Peripheral 5-HT inhibits osteoblast proliferation by binding to HTR1B on pre-osteoblasts and inactivating CREB, a transcription factor, possibly resulting in low bone mass.^{3,11} SRIs' brain and peripheral effects might be modulated by genetic variation in 5-HT polymorphisms.^{5,9,12–14} In spite of these putative biological pathways, it remains unknown whether SRIs influence bone health or whether the epidemiological findings reflect effects

of depression itself,^{5,15,16} although a preclinical study suggests a relationship between SRIs and bone loss.¹⁷

We previously assessed bone turnover markers among 77 older adults during an antidepressant clinical trial¹⁸ and reported that C-terminal cross-linking telopeptide of type 1 collagen (CTX), a marker of osteoclast activity and bone resorption, significantly increased during treatment with the SRI venlafaxine. As well, procollagen type 1 N-propeptide (PINP), a marker of osteoblast activity and bone formation, was reduced. These changes were associated with treatment outcomes: patients whose depression remitted with the antidepressant treatment had minimal changes in their bone turnover markers, so it appeared that successful antidepressant response mitigated these bone turnover changes. We also examined genetic variation in 5-HT polymorphisms as predictors of bone loss and found reduced bone formation among high-expressing 5HTTLPR (in the 5-HT transporter) and low-expressing HTR1B carriers.¹² We concluded that bone turnover markers change during SRI treatment in a pattern suggestive of increasing bone loss, and there are clinical and genetic modulators of this effect.

In the current analysis, we combined data from the 73 participants previously analyzed with an additional 95 participants in whom we also assayed CTX and PINP before and after venlafaxine treatment. The larger sample of n=168 provides greater power to examine whether: (1) CTX increases and PINP decreases with venlafaxine; (2) these changes are more pronounced among participants who do not experience remission of depressive symptoms; and (3) these changes are modulated by 5-HT polymorphisms. We also explored other patient-level variables as predictors of biomarker changes.

METHODS

Participants

Participants were involved in the initial open-label phase of a three-site clinical trial titled “Incomplete Response to Late-Life Depression: Getting to Remission”.¹⁹ This study was approved by the sites’ Institutional Review Boards, and all participants provided written informed consent.

Participants were age 60+ and in a major depressive episode of at least four-week duration (established by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Medical Disorders-IV²⁰) with a score ≥ 15 on the Montgomery-Asberg Depression Rating Scale (MADRS)²¹ indicating at least moderate depressive symptoms. Exclusion criteria included bipolar or psychotic disorder, dementia or a score <20 on the Mini-Mental Status Examination (MMSE)²², recent alcohol or substance abuse, or unstable medical co-morbidities. Creatinine clearance levels were calculated as $[(140 - \text{age}) * \text{weight (kg)}] / 72 * \text{creatinine baseline level}$ and multiplied by 0.85 for females.

For the current analyses, we also excluded participants who had been receiving a previous SRI within two weeks of baseline specimen collection; those on bisphosphonates; those who started or stopped a medication known for its effect on bone (i.e., corticosteroids, vitamin D, estrogen, calcium) during the trial; and those whose serum was collected after 11:30 am to

minimize diurnal variation. One additional participant was excluded due to severe renal impairment.

Treatment protocol—Participants received open-label treatment with venlafaxine extended-release (XR). The initial dosage of 37.5 mg/day was titrated by 37.5 mg increments every three days to a target dosage of 150 mg/day by the end of the second week of treatment. If participants did not remit after six weeks of treatment their dosage was further titrated to a maximum dosage of 300 mg/day. Most participants received treatment for 12 weeks; a few received up to 12 additional weeks of treatment to clarify their remission status.

Participants were monitored closely throughout the trial and dosage reductions were allowed at any time to manage side effects. Participants experiencing sleep disturbance or anxiety during the trial could be prescribed lorazepam (up to 2 mg/day) or continue previously prescribed sleep medications (e.g., zolpidem, zopiclone, trazodone).

Assessments

Baseline assessments included the MMSE (range 0–28) and the MADRS (range 0–60). Physical comorbidities were quantified using the Cumulative-Illness Rating Scale for Geriatrics (CIRS-G; range 0–52).²³

Follow-up visits occurred at 1, 2, 4, 6, 8, 10, and 12 weeks and included psychoeducation for depressive symptoms, monitoring of vital signs and adverse events, and assessment of depressive symptoms with the MADRS. Remission from depressive symptoms was defined as a MADRS score ≤ 10 at the last two visits.

Sample collection and assays

Blood samples were collected between 8:30 and 11:30 am after an overnight fast at two time points: prior to venlafaxine treatment and at the last visit (typically after 12 weeks of treatment). Samples were immediately cold-centrifuged and stored at -80°C . Bone turnover markers were assayed at Core Diagnostics, Washington University School of Medicine and included the Roche Diagnostics Elecsys kit for CTX and a radioimmunoassay for P1NP (Orion Diagnostica). Venlafaxine and O-desmethylvenlafaxine (norvenlafaxine) levels at the last study visit were assayed as previously described.¹⁸

Genotyping

DNA extraction and isolation from blood followed standard procedures. The 5HTTLPR-rs25531 genotypes consist of an insertion/deletion motif designated as long (L)/short (S) element and an A/G single nucleotide polymorphism (SNP) at rs25531. These two variants are combined as Sa, Sg, La, and Lg with the La combination conferring higher transcriptional activity to the serotonin transporter. For this analysis, the genotypes were consolidated with the La/La, La/Lg, and La/S reflecting the four high-expressing activity genotypes and Lg/Lg, Lg/S, and S/S reflecting the low-expressing activity genotypes.²⁴ The serotonin receptor, HTR1B, has a SNP located in the promoter region at rs11568817; for analysis, GG and GT genotypes are marked as high-expressing and TT is marked as low-

expressing.²⁵ Five participants were missing data on both HTTLPR and HTR1B and five were missing data on HTTLPR only.

Statistical analysis

Data from the additional 95 participants were combined with the 73 participants analyzed in the previous publication.¹⁸ Standardized residual values for bone biomarker levels larger than ± 3.29 were winsorized to the next value that fell within ± 3.29 by remitter status. CTX and PINP levels were log-transformed for statistical analysis modeling change. Using output from paired t-tests, we report on the changes in bone biomarkers from baseline to end-of-treatment and changes associated with key predictor variables (remission status and gene polymorphisms). Independent t-tests and χ^2 tests were used to examine variable differences.

We next examined the relationship between key predictors and changes in bone biomarkers while holding possible confounding patient-level predictors constant using multivariable predictor models. Determination of confounding patient-level predictors first included examining separate regression models for each variables in Table 1 controlling for baseline bone turnover marker levels with end-of-treatment bone biomarker level as the outcome variable. Patient-level variables significant at $<.15$, baseline biomarker levels, and remission status were included in the r-square selection model using Proc RSQUARE, an algorithm that calculates which variable combination best explains variation in an outcome. The variables from the model with the lowest Akaike Information Criterion (AIC) were entered into a multivariable regression model. We repeated the multivariable regression models after excluding non-white participants and adding the two genetic predictors. Statistical analysis was conducted using SPSS Statistics v22 and SAS 9.3.

RESULTS

Participant characteristics

The majority of the 168 participants (Table 1) were Caucasian (91.7%) and female (60.7%) with a mean (SD) age of 68.7 (6.8). Participants were typically healthy, cognitively intact, and presented with moderate to severe depressive symptoms. Fifty-seven (33.9%) participants were taking bone protective medications.

Bone biomarker changes during treatment

Both bone turnover markers changed with venlafaxine treatment (Figure 1): CTX levels (all numbers in text are log-transformed; figures show actual numeric values) significantly increased by an average of $+0.06$ (SD 0.32; $t(167)=2.3$, $p=.025$; 55.4% had levels increase) and PINP significantly decreased by an average of -0.05 (SD 0.25; $t(165)=-2.5$, $p=.015$; 60.7% had levels decrease).

Changes in bone turnover markers by remission

Eighty (47.6%) participants remitted with treatment and 88 (52.4%) did not remit (Table 1). For CTX, the mean increase for non-remitters was $+0.09$ pg/mL (SD 0.31; $t(87)=2.68$, $p=.009$) versus $+0.02$ pg/mL (SD 0.32; $t(79)=0.49$, $p=.63$) for remitters (Figure 2A). For PINP, the mean decrease for non-remitters was -0.05 μ g/L (SD 0.25; $t(86)=-1.96$, $p=.053$) versus

−0.04 µg/L (*SD* 0.24; *t*(78)=−1.49, *p*=.14) for remitters. These results did not change in multivariable regression (Table S1) controlling for baseline biomarker levels and confounding patient-level variables: remission status remained correlated with end-of-treatment CTX levels (*p*=.008) but not end-of-treatment P1NP levels (*p*=.67).

Changes in bone biomarkers by genetic polymorphisms

In the Caucasian subsample, 44 (29.5%) participants had low-expressing HTR1B genotype and 41 (28.5%) had low-expressing HTTLPR genotype. For CTX, the mean increase for HTR1B low-expressers was +0.01 pg/mL (*SD* 0.29; *t*(43)=0.26, *p*=.79) versus +0.08 pg/mL (*SD* 0.31; *t*(104)=2.53, *p*=.013) for high-expressers. The mean increase in CTX for HTTLPR low-expressers was +0.02 pg/mL (*SD* 0.30; *t*(40)=0.45, *p*=.66) and +0.06 pg/mL (*SD* 0.31; *t*(102)=2.15, *p*=.034) for high-expressers. For P1NP, the mean decrease for HTR1B low-expressers was −0.09 µg/L (*SD* 0.24; *t*(43)=−2.47, *p*=.018) and −0.04 µg/L (*SD* 0.23; *t*(102)=−1.83, *p*=.07) for high-expressers (Figure 2B). The mean decrease in P1NP for HTTLPR low-expressers was −0.02 µg/L (*SD* 0.29; *t*(40)=−0.35, *p*=.73) and −0.07 µg/L (*SD* 0.21; *t*(100)=−3.3, *p*=.001) for high-expressers.

Controlling for baseline biomarker levels and patient-level variables in the multivariable regression (Supplementary Table 1) indicated HTR1B predicted end-of-treatment P1NP levels (*p*=.029) but not end-of-treatment CTX levels (*p*=.17). HTTLPR expression was not related to CTX or P1NP.

Changes in confounding patient-level variables

Experiencing a depressive episode duration greater than two years was associated with lower levels of P1NP at end-of-treatment. We explored this effect of depression duration (Figure 2C): among the 74 participants (44.6%) who had a current episode of depression lasting two or more years, the mean decrease was −0.09 µg/L (*SD* 0.25; *t*(73)=−3.26, *p*=.002) versus −0.01 µg/L (*SD* 0.24; *t*(91)=−0.38, *p*=.70) for participants with a current episode less than two years.

DISCUSSION

In this large sample of older depressed adults we examined how peripheral bone turnover markers changed during venlafaxine treatment. Our results indicate a novel association between duration of depression and P1NP levels and confirm our previous findings. First, CTX, a marker of bone resorption, increased, and P1NP, a marker of bone formation, decreased with antidepressant treatment. This combination of bone turnover changes suggests accelerated bone loss. Second, antidepressant response was associated with CTX levels which increased chiefly in non-remitters; in contrast, changes in P1NP were unrelated to remission status. Third, a polymorphism in the HTR1B gene predicted P1NP levels: patients with the low-expressing HTR1B genotype experienced a greater decrease in P1NP during the study. These important findings potentially identify patient subgroups (based on treatment success, genotype, and duration of depression) that may predict bone turnover with antidepressant use.

These results could help in the prevention of morbidity from osteoporosis and osteopenia. These are common conditions in older adults: prevalence is 16% and 48%, respectively,²⁶ and any adjustment in the risk for these conditions is of high public health importance. Our results point to potential factors that may enhance or mitigate this potential risk from SRIs. First, remission from depression may reduce the potential effect of SRIs on increasing bone resorption; this generates the hypothesis that, when SRIs are not inducing depression remission, other treatment options (e.g., a switch to a non-SRI antidepressant rather than augmentation) might be favorable. This is important because antidepressants are typically prescribed chronically to older depressed adults²⁷ and their use may be continued when they are insufficiently effective.²⁸ Second, HTR1B genotype influenced PINP change; this is consistent with the presence of 5-HT 1B receptors on osteoblasts, and suggests genetic testing could be used to assess patients' risk for accelerated bone loss, or this receptor could be targeted by antidote strategies to reduce bone loss. Third, longer duration of current depression episode correlated with decreased bone formation. We speculate that chronic depression is physiologically different than persons with an acute episode. Some literature posits individuals in a prolonged state of distress have adapted physiologically or acquired resilience to ongoing stressors.²⁹ Thus, among individuals chronically depressed, treatment with an antidepressant may perturb the allostatic state that a person has physiologically learned to maintain.

Our study has several limitations, and we stress that our study does not confirm that SRI use accelerates bone loss in older adults. While our findings suggest an association of bone loss and SRI treatment independent of depression, they should be considered preliminary data that argue for a larger randomized study to disentangle effects of SRIs from effects of depression itself in humans. First, this was a relatively small study. Second, the magnitude of changes in bone turnover markers (6–7%) is less than the minimum significant change in bone turnover markers for osteoporosis (12–23%) indicating that SRIs effects on bone metabolism may be insufficiently robust to be of clinical significance.³⁰ Third, we did not have a control group and are unable to exclude all possible confounds. Fourth, we measured bone turnover markers, not actual bone loss; to do so would require a longer period of medication exposure (i.e., at least one year to demonstrate changes in bone mineral density). Finally, we examined only one medication, venlafaxine; its binding affinity is predominantly serotonergic¹³ suggesting our findings are broadly applicable to SRIs in general, but research should test other SRIs. In the absence of such a confirmatory study, our data are insufficient to change the prescribing or labeling of SRIs for elders and should not be taken as a recommendation to do so. Indeed, major depression in older adults is a disabling and often lethal illness, and SRIs are a mainstay of treatment for it.

Strengths of our study include a well-characterized sample that received protocolized treatment. Depression was carefully diagnosed and its severity was assessed using standardized instruments. Also, antidepressant concentrations were used to monitor adherence during the clinical trial. In contrast, epidemiological data may be confounded by the complex relationship among depression, risk of falls, bone mineral density, common side effects (e.g., dizziness), polypharmacy, and the dosage and duration of antidepressant medications.¹⁶

CONCLUSION

Our findings implicate SRI use as a risk factor for accelerated bone loss in older depressed adults by increasing osteoclast activity and reducing osteoblast activity. Randomized studies using bone mineral density testing are needed to clarify the risk/benefit ratio of these commonly-prescribed medications and to determine whether some patient-level variables, such as treatment response, duration of depression, and genetic variability, may influence their risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Significant and deleterious changes in bone turnover markers were found during venlafaxine treatment. Raw winsorized means are presented in the figures and figure descriptions; log-transformed winsorized values are used in the statistical analyses presented in the text. (a) C-terminal cross-linking telopeptide of type 1 collagen (CTX) levels significantly changed with an average increase of +24.59 (SD 112.50; $t(167) = 2.83$, $p = .005$). (b) Procollagen type 1 N propeptide (P1NP) levels significantly changed with an average decrease of -2.44 (SD 10.56; $t(165) = -2.98$, $p = .003$)

Figure 2.

Changes in bone turnover markers by patient-level variables during treatment with venlafaxine. Raw winsorized means are presented in the figures and figure descriptions; log-transformed winsorized values are used in the statistical analyses presented in the text. (a) Non-remitters experienced a significant increase in C-terminal cross-linking telopeptide of type 1 collagen (CTX). The mean increase in CTX for non-remitters was +40.89 pg/mL (SD 120.50; $t(92) = 3.2$, $p = .002$) versus +6.66 pg/mL (SD 100.70; $t(79) = 0.59$, $p = .56$) for remitters. (b) For Procollagen type 1 N propeptide (P1NP), the mean decrease for HTR1b low-expressors was -3.54 (SD 9.83; $t(44) = -2.39$, $p = .021$) and for high expressors the mean decrease was -2.26 (SD 9.94; $t(102) = -2.31$, $p = .023$). (c) For P1NP, the mean decrease for individuals experiencing a duration of current episode > 2 years was -4.3 (SD 10.22; $t(73) = -3.64$, $p = .001$) versus -0.92 (SD 10.63; $t(91) = -0.83$, $p = .409$) for episodes ≤ 2 years

Table 1

Characteristics of study participants

	All	Non-remitters	Remitters	Test statistic
<i>Demographic variables</i>				
Age, <i>M (sd)</i>	68.7 (6.8)	68.2 (6.6)	69.2 (7.0)	$t(166) = -0.9, p = .35$
Education, <i>M (sd)</i>	14.5 (2.9)	14.2 (2.9)	14.9 (2.8)	$t(166) = -1.5, p = .15$
Gender, <i>n (%) Female</i>	102 (60.7)	48 (54.6)	54 (67.5)	$\chi^2 = 2.9 (1), p = .09$
Ethnicity, <i>n (%)</i>				
Caucasian	154 (91.7)	81 (92.1)	73 (91.3)	$\chi^2 = 0.0 (2), p = .98$
African American	12 (7.1)	6 (6.8)	6 (7.5)	
Asian	2 (1.2)	1 (1.1)	1 (1.2)	
<i>Depression-related variables</i>				
Age at first episode, <i>M (sd)</i>	38.4 (21.6)	38.4 (23.4)	38.5 (19.6)	$t(166) = -0.0, p = .98$
Baseline MADRS, <i>M (sd)</i>	27.0 (5.7)	28.4 (5.3)	25.4 (5.6)	$t(166) = 3.7, p < .01$
Duration of current episode ^a , <i>M (sd)</i>	366.5 (771.0)	480.3 (896.6)	241.3 (583.2)	$t(166) = 2.1, p = .04$
Recurrent, <i>n (%)</i>	128 (76.2)	62 (70.5)	66 (82.5)	$\chi^2 = 3.4 (1), p = .07$
<i>Health-related variables</i>				
BMI, <i>M (sd)</i>	30.5 (6.7)	30.7 (7.4)	30.3 (5.9)	$t(164) = 0.4, p = .72$
Creatinine clearance, <i>M (sd)</i>	90.6 (36.9)	95.3 (39.8)	85.1 (32.7)	$t(162) = 1.8, p = .08$
CIRS-G, <i>M (sd)</i>	9.5 (4.3)	9.4 (3.9)	9.6 (4.8)	$t(166) = -0.2, p = .85$
Diabetes, <i>n (%)</i>	29 (17.9)	14 (16.5)	15 (19.5)	$\chi^2 = 0.2 (1), p = .62$
MMSE, <i>M (sd)</i>	28.7 (1.4)	28.8 (1.3)	28.7 (1.6)	$t(145) = 0.4, p = .69$
<i>Medication-related variables</i>				
Vitamin D, <i>n (%)</i>	50 (29.8)	24 (27.3)	26 (32.5)	$\chi^2 = 0.5 (1), p = .46$
Calcium, <i>n (%)</i>	30 (17.9)	12 (13.6)	18 (22.5)	$\chi^2 = 2.2 (1), p = .13$
Estrogen ^b , <i>n (%)</i>	5 (3.0)	2 (2.3)	3 (3.8)	$p = .67$
Pre-study antidepressant, <i>n (%)</i>	61 (36.3)	39 (44.3)	22 (27.5)	$\chi^2 = 5.1 (1), p = .03$
<i>Bone turnover markers</i>				
CTX, <i>M (sd)</i>	367.8 (170.5)	383.0 (168.6)	351.1 (172.1)	$t(166) = 1.2, p = .23$
P1NP, <i>M (sd)</i>	46.2 (18.6)	48.4 (20.0)	43.9 (16.7)	$t(166) = 1.6, p = .12$
<i>Final dosage and drug level</i>				
Venlafaxine, <i>ng/mL M (sd)</i>	201.0 (208.7)	221.3 (239.5)	177.4 (164.6)	$t(162) = 1.4, p = .18$
Norvenlafaxine, <i>ng/mL M (sd)</i>	307.2 (155.4)	324.4 (148.5)	287.3 (161.7)	$t(162) = 1.5, p = .13$
Total, <i>ng/mL M (sd)</i>	508.1 (277.8)	545.7 (278.5)	464.7 (272.4)	$t(162) = 1.9, p = .06$
Dosage, <i>mg M (sd)</i>	235.3 (70.9)	268.0 (58.1)	199.2 (66.3)	$t(166) = 7.2, p < .01$
Venlafaxine duration, days <i>M (sd)</i>	91.8 (17.1)	93.0 (19.6)	90.4 (13.6)	$t(162) = 1.0, p = .33$

^aIndependent t-test conducted using log-transformed values for duration of current depression episode

^bMore than 2 cells had expected values less than 5, Fisher's exact p-value reported.