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Normal Vitamin D and Low Free Estradiol in Women on Enzyme-Inducing Antiepileptic Drugs

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Abstract

Relationships between reproductive hormones, bone turnover markers (BTMs), bone mineral density (BMD) and rates of bone loss were evaluated in premenopausal women with epilepsy on enzyme inducing antiepileptic drugs (EIAEDs; phenytoin or carbamazepine) or lamotrigine. Calcitropic and reproductive hormones, BTMs, and BMD were measured at baseline and one year. BMD did not differ between groups. Serum calcium ($p < 0.001$) and estrone ($p < 0.001$) were lower in the EIAED group. Sex hormone binding globulin (SHBG) was higher ($p < 0.001$) and percent free estradiol was lower ($p < 0.001$) in the EIAED group. We detected no relationship between BMD change and calcitropic hormones or BTMs. Women with higher SHBG and lower free estradiol sustained more bone loss at the total hip ($p = 0.04$ and $p = 0.02$) and a trend toward more bone loss at the lumbar spine ($p = 0.07$ and $p = 0.08$). These findings suggest that lower estrogen levels may contribute to bone loss in premenopausal women with epilepsy.

Keywords

Epilepsy; antiepileptic drugs; vitamin D; estradiol

Introduction

Fracture rates are at least two fold higher in persons with epilepsy than the general population^{1–3}. Although the higher fracture rates may be attributable in part to seizure-related injuries, many clinical studies suggest that abnormalities in bone mineral density (BMD) and bone and mineral metabolism contribute to the pathogenesis of increased fracture rates in epilepsy^{1, 4, 5}. These abnormalities have traditionally been attributed to adverse effects on the vitamin D-parathyroid hormone (PTH) endocrine system, thought to be associated with hepatic cytochrome (CYP) P450 enzyme inducing antiepileptic drugs (EIAEDs). However, recent studies suggest that the impact of EIAEDs on the vitamin D-PTH axis may be less than previously observed^{6, 78–11}, prompting new questions about the pathogenesis of bone loss and fractures in persons with epilepsy.

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Sex steroid hormones, and in particular estrogen, are central to peak bone mass acquisition during adolescence and maintaining bone mass during adulthood and senescence in women and men^{12, 13}. Estrogen is a key factor in the control of intestinal calcium absorption, as well as in bone modeling and remodeling^{14–16}. Estrogen is metabolized by the hepatic CYP450 system, specifically CYP3A4^{14, 17}. Interestingly, adverse effects on sex steroid hormones have also been described in premenopausal women with epilepsy treated with antiepileptic drugs (AEDs)^{18–20}. In addition, oral contraceptive failures rates are higher in women taking concomitant CYP EIAEDs²¹. Thus, it is biologically plausible that accelerated metabolism of endogenous estrogens to inactive metabolites could compromise bone health.

We hypothesized that women with epilepsy treated with EIAEDs have lower estrogen concentrations, higher bone turnover, and lower BMD than women treated with an AED that does not affect the hepatic CYP enzyme system. To test this hypothesis, we measured serum gonadal hormones on archived sera from a cohort of premenopausal women with epilepsy receiving monotherapy with one of two EIAEDs, carbamazepine (CBZ) or phenytoin (PHT), or with lamotrigine (LTG), a non-enzyme inducing AED. We then compared serum gonadal and calciotropic hormones and bone turnover markers among the treatment groups. We also related serum gonadal and calciotropic hormones to bone mineral density (BMD) measurements, bone turnover markers and, in a subset, percent change in BMD over one year of observation.

Methods

Subjects

Normally cycling premenopausal women with epilepsy (n=115) between ages 18–40 participating in a study of bone health had blood drawn at a random time of the menstrual cycle^{6, 22}. In addition, a subset (n=30) also had blood drawn during the early follicular phase as part of a study of reproductive health in women with epilepsy^{20, 23}. Subjects were enrolled at Stanford University (n = 78) and Columbia University (n = 37). All had received either an EIAED (CBZ or PHT) or LTG for at least 6 months before enrollment. Data on duration of AED treatment for studied AED and total length of AED treatment were ascertained by history and chart review. Excluded were pregnant, lactating and postmenopausal women, women receiving hormonal contraceptive agents, those with impaired motor function, diseases that affect the skeleton (primary hyperparathyroidism, Paget's disease, multiple myeloma), and those taking glucocorticoids.

Study Design and Analytical Methods

Questionnaires—As described previously^{6, 22} each subject completed validated nutritional and physical activity questionnaires. The nutrition questionnaire is a food frequency questionnaire from the National Cancer Institute²⁴ that assesses daily diet, vitamin intake, tobacco, and alcohol. The exercise questionnaire includes questions on specific exercises and exercise frequency²⁵. In addition, detailed clinical histories were taken, including age at menarche and parity. Height and weight were measured and body mass index (BMI) calculated.

Bone Mineral Density—Each subject had BMD measured by dual X-ray absorptiometry (DXA; Hologic (1000 and 4500) densitometers, Hologic, Waltham, MA). BMD measurements were repeated on the same DXA scanner in 74 subjects after one year of observation on the same AED. Forty-one subjects did not have one-year BMD measurements because they were lost to follow up (n= 15), changed AED (n= 15), became pregnant (n= 6), declined further participation (n= 3), or relocated (n= 2). Lumbar spine

BMD was expressed as Z-scores, which compare subjects to age-, race- and sex-matched normative data provided by the manufacturer. Proximal femur results were expressed as Z-scores calculated from the National Health and Nutrition Examination Survey (NHANES 2) of adult women in the United States.

Serologic and Urine Studies—Fasting morning blood was obtained for measurements of albumin, total calcium, 25 hydroxyvitamin D (25-OHD), 1,25 dihydroxyvitamin D (1,25(OH)₂D), PTH, markers of bone formation (bone specific alkaline phosphatase and osteocalcin), and reproductive hormones. Second void morning urine was collected for analysis of N-telopeptide (NTx), a marker of bone resorption. Serum and urine were stored at -70°C until batch analysis at Columbia University's Irving Center for Clinical Research Core Laboratory. Reproductive hormones from the subgroup of women with measurements during the early follicular phase of the menstrual cycle were reported previously^{20, 23}.

Serum calcium concentrations were measured by standard autoanalyzer technique (normal, 8.4–10.2 mg/dl) and were corrected for albumin. Serum 25-OHD (normal, 9–55 ng/ml) was measured after extraction by radioimmunoassay (DiaSorin, Stillwater, MN; intra-assay CV 10.5%, inter-assay CV 8.2%). Serum 1,25(OH)₂D (normal, 25–66 pg/ml) was measured by radioimmunoassay (DiaSorin, Stillwater, MN; intra-assay CV 7.7%, inter-assay CV 11.1%). PTH (normal, 10–65 pg/ml) was measured by an immunoradiometric assay (Nichols Institute Diagnostics, San Clemente, CA; intra-assay CV 3.4%, inter-assay CV 5.6%). Serum bone alkaline phosphatase (BSAP; normal range for premenopausal women, 11.6–29.6 µg/l) was measured by competitive enzyme immunoassay (Metra Biosystems, San Diego, CA; intra-assay CV 5.8%; inter-assay CV 5.2%). Osteocalcin (normal range for premenopausal women, 2.4–10.0 ng/ml) was measured using an immunoradiometric assay (Immunotopics, Inc. San Clemente, CA, intra-assay CV 3.9%, inter-assay CV 5.5%). Urine NTx (normal range for premenopausal women, 3.0–63.0 nM BCE /mM creatinine) was measured by ELISA (Wampole Laboratories, Princeton, NJ; intra-assay CV 19.0%, inter-assay CV 5.0%).

Estrone was measured by a radioimmunoassay (Diagnostic Systems Laboratories, Inc, Webster, TX; intra-assay CV 5.6%, inter-assay CV 11.1%). The normal range for non-pregnant premenopausal women is between 37.2 and 229.2 pg/ml depending on the stage of the menstrual cycle. The follicular stage range is between 32.2 and 137.7 pg/ml. Estradiol (normal range 9–281 pg/ml depending on phase of menstrual cycle; normal range for follicular phase 9–175 pg/ml) was measured using a double antibody ¹²⁵I radioimmunoassay (Siemens Medical Solutions Diagnostics, New York, NY; intra-assay CV 4.8%, inter-assay CV 4.9%). Sex hormone binding globulin (SHBG; normal range 12–305 nmol/l depending on phase of menstrual cycle; normal range for follicular phase 12–155 nmol/l) was quantified by a Coated-Tube Immunoradiometric Assay (Diagnostic Systems Laboratories, Inc, Webster TX; intra-assay CV 3.7%, inter-assay CV 11.5%). Percent free estradiol was calculated using the formula of Sodergard et al²⁶.

Statistical Analysis

Data from both the total group and the sub-group of women with reproductive hormones measured during the early follicular phase were summarized with means, standard errors and 95% confidence intervals surrounding the means for continuous measures and frequencies and percents for categorical data. Between AED group differences were analyzed using one-way ANOVA: Scheffé-adjusted pairwise comparisons were performed when the overall F-test was significant. Pearson correlation analyses were performed in the total group to estimate associations among markers of bone turnover, reproductive hormones, and BMD measurements in the AED groups. Pearson correlation analyses were performed among

calciotropic hormones, markers of turnover, reproductive hormones, and percent of BMD loss at the total hip, femoral neck of the hip and lumbar spine.

Results

Characteristics of the Study Population

Of the 115 premenopausal women, 76 were taking EIAEDs (53 on CBZ and 23 on PHT) and 39 were taking LTG. Of the 30 women with measurements during the early follicular phase of the menstrual cycle, 17 were taking EIAEDs (12 on CBZ and 5 on PHT) and 13 were treated with LTG. Twenty-one women on LTG and 53 women on EIAEDs (38 on CBZ and 15 on PHT) had BMD measurements repeated after one year of observation.

The average age was 32.1 ± 0.6 (Table I). Women receiving LTG were approximately 4 years younger than women on EIAEDs ($p = 0.002$) and had been treated with LTG for less time than those on EIAEDs ($p < 0.002$). The mean dose was therapeutic for all AEDs studied. Dietary intake of calcium and vitamin D, amount of exercise, age at menarche, percent ever pregnant, and number of pregnancies among those who had been pregnant did not differ between groups.

Bone Mineral Density

BMD did not differ significantly between women treated with EIAEDs and LTG at the lumbar spine, total hip or femoral neck (Table 2).

Calciotropic Hormones and Bone Turnover Markers

Serum calcium was lower in the combined EIAED than the LTG group ($p < 0.001$). In contrast, serum 25-OHD, $1,25(\text{OH})_2\text{D}$ and PTH did not differ among the groups (Table 2). Serum osteocalcin, a marker of bone formation, did not differ between groups. Although serum BSAP, another formation marker, and urine NTx, a resorption marker were higher in women receiving EIAEDs, suggesting higher bone turnover (Table 2), the differences were not statistically significant ($p = 0.08$ for BSAP and $p = 0.07$ for urine NTx).

Reproductive Hormones

Estrone was significantly lower in the EIAED group than the LTG group, whereas total estradiol did not differ between groups. Women on EIAEDs had significantly higher SHBG and lower calculated percent free estradiol (Table 2). Lower serum estrone and percent free estradiol and higher SHBG were observed in both PHT and CBZ treated women compared to LTG treated women.

Timed Sample

In the subset of women with serum obtained during the early follicular phase of the menstrual cycle, results were similar to those with samples obtained throughout the menstrual cycle: compared to the LTG-treated women, the group on EIAEDs showed lower estrone and percent free estradiol and higher SHBG levels. Both PHT and CBZ-treated women demonstrated a similar pattern (Table 3).

Correlations

Total estradiol was positively but weakly associated with osteocalcin among women on EIAEDs (0.28, $p = 0.01$). There were no other significant associations between reproductive hormones and BMD or bone turnover markers in either the EIAED or LTG treated groups (data not shown).

Among the 74 women with baseline and one-year BMD measurements, we detected no relationship between percent change in BMD at any site and calciotropic hormones (PTH, vitamin D metabolites) or markers of bone turnover. In contrast, women with higher SHBG and lower percent free estradiol sustained significantly more bone loss at the total hip (SHBG: $r = -0.24$, $p = 0.04$; percent free estradiol: $r = 0.26$, $p = 0.02$) and a trend toward more bone loss at the lumbar spine (SHBG: $r = -0.21$, $p = 0.07$; percent free estradiol: $r = 0.21$, $p = 0.08$) (Figure 1). The AED groups differed significantly in the relationships between SHBG, percent free estradiol and rates of bone loss at the hip or spine.

Discussion

In this study, we aimed to investigate the effect of EIAEDs on reproductive and calciotropic hormones and their relationship to bone mass and bone turnover markers in premenopausal women with epilepsy. As we reported previously, although serum calcium was significantly lower in women on EIAEDs than those on the non-inducer, LTG, we found no differences in serum 25-OHD, 1,25(OH)₂D or PTH to account for this difference. With regard to reproductive hormones, serum estrone and percent free estradiol were significantly lower and serum SHBG was significantly higher in women on EIAEDs than on LTG. Although serum osteocalcin was directly but weakly associated with total estradiol, we did not detect any consistent associations between serum calciotropic or gonadal hormones and BMD or bone turnover markers. In the subset with longitudinal BMD measurements, there was no association between rates of bone loss and calciotropic hormones or markers of bone turnover. In contrast, higher SHBG levels and lower percent free estradiol levels were associated with higher rates of bone loss. Our findings, although preliminary, suggest that in premenopausal women with epilepsy, low bioavailable estrogen is more closely linked to maintenance of bone mass than calciotropic hormones.

Much emphasis has been placed on the effect of EIAEDs on the vitamin D-PTH endocrine system^{10, 11}. It has been hypothesized that EIAEDs enhance hepatic metabolism of 25-OHD to inactive metabolites, resulting in lower serum 25-OHD and serum calcium, higher PTH and increased bone turnover and bone loss. However, recent studies suggest that vitamin D metabolites are not lower in persons treated with EIAEDs than those on non-enzyme inducing AEDs^{6, 7}. Consistent with these studies, we detected no differences in serum 25-OHD between women on EIAEDs and LTG. In contrast, estrone and percent free estradiol were significantly lower. In addition, among those who completed BMD assessments at baseline and one year later we found that higher SHBG and lower percent free estradiol were associated with more bone loss, although the latter relationship did not reach statistical significance.

Lower estrogen levels have been associated with bone loss in studies of men, postmenopausal women, and premenopausal women. Estrone was associated with lower BMD and higher markers of bone turnover in a study of premenopausal Indian women²⁷ [28]. Although relative estradiol deficiency in postmenopausal women and older men results in bone loss^{12, 13}, the relationship between estradiol and BMD is not as well studied in premenopausal women. Sowers et al.²⁸ found that baseline total estradiol was a poor predictor of incremental BMD change. Similar to the studies by Sowers et al.^{28–30}, we did not find significant correlations between estrogen and either baseline BMD or bone turnover markers. We did find lower percent free estradiol among the EIAED treated women and that lower percent free estradiol was associated with more bone loss in premenopausal women with epilepsy, regardless of whether they were receiving an EIAED or LTG. Higher SHBG was also associated with more bone loss. As SHBG reduces biologically available estradiol, this relationship may be related to lower percent free estradiol concentrations. In this regard, however, Bjornerem et al. have reported that SHBG independently and negatively predicts

BMD in postmenopausal women³⁰. In addition, positive relationships have been shown between SHBG and bone turnover markers as well as fracture risk³¹. Thus it is possible that SHBG affects bone remodeling independent of its effects on serum concentrations of free gonadal hormones.

Consistent with our findings, other studies³² have found that EIAED treatment results in lower endogenous and exogenous reproductive sex steroid hormones as well as increased SHBG. EIAEDs lower reproductive sex steroid hormones by increasing their metabolism through induction of the cytochrome P450 enzyme system^{18–20}. Clinically this is evident in the reported increased failure rate of oral contraceptive agents taken in combination with EIAEDs²¹. Another possible mechanism for low free estradiol levels is that SHBG is primarily synthesized in hepatocytes and EIAED treatment increases its production^{18–20}.

Our study has several limitations. The majority of subjects had reproductive hormones collected at various time points during the menstrual cycle, and only a subset had reproductive hormones obtained in the early follicular phase. However, the levels themselves and the differences between treatment groups were similar regardless of the timing of the venipuncture. Calcitropic hormones and bone turnover markers were not measured at the same time point as the reproductive hormones in some cases; although these indices may also change throughout the reproductive cycle, it is likely that they change to a lesser extent than reproductive hormones. Given that all subjects were normally cycling women of reproductive age, the inverse relationship we observed between rates of bone loss and percent free estradiol is of uncertain long-term significance. A control group of women without epilepsy who were not taking AEDs would have strengthened the interpretation of our findings. Many of the subjects had taken other AEDs prior to the studied AED, and we were not able to control for prior AED exposure. Women had been treated with LTG for a shorter time than those receiving EIAEDs, although all treated had been treated with the studied AED for at least six months prior to enrollment. In contrast to other studies¹¹, we did not find significant differences in baseline BMD between the studied groups. This discrepancy may be related to the patients studied. Participants in this study were healthy women treated with a single AED. As such, our findings may not be generalizable to more severely affected patients who require polypharmacy or different AEDs to control their condition.

In summary, we explored relationships among reproductive and calcitropic hormones, bone turnover markers, baseline BMD and rates of bone loss in a group of premenopausal women with epilepsy on monotherapy with LTG, a non-inducer and two different EIAEDs. While calcitropic hormones did not differ, serum estrone and percent free estradiol were markedly lower and bone turnover markers were slightly although not significantly higher in women on EIAEDs than those on LTG. Higher SHBG and lower percent free estradiol were associated with more bone loss, while no relationship was detected between serum PTH or vitamin D metabolites and change in BMD. This finding confirms prior reports of normal calcitropic hormones in patients with epilepsy. Moreover, these results suggest that chronic exposure to lower estrogen levels may contribute to the bone loss observed in women with epilepsy. Subclinical estrogen deficiency over many years could result in higher rates of bone loss in premenopausal women, and ultimately result in increased fracture risk observed in other studies of patients with epilepsy^{1–3}. These findings are novel as this is the first report to directly study the impact of reproductive hormones on bone health in premenopausal women with epilepsy treated with AEDs. Additional research is necessary to explore the effects of epilepsy and its treatment on estrogen metabolism and bone health.

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Figure 1. Relationships as assessed by Pearson correlation coefficients between percent free E2 or SHBG and percent change in BMD at the total hip and lumbar spine among women with epilepsy treated with either EIAEDs or LTG.

Table 1

Baseline Characteristics of the Subjects

	EIAED (n=76)	CBZ (n=53)	PHT (n=23)	LTG (n=39)	p-value
Age (years)	33.6 ± 0.66	33.5 ± 0.79 ^a	33.7 ± 1.2 ^b	29.3 ± 92 ^{ab}	0.002
Height (cm)	163. ± 1	162 ± 1	166 ± 2	(162 ± 1	ns
Weight (kg)	66.8 ± 2.1	65.7 ± 2.5	69.4 ± 4.0	73.8 ± 2.9	ns
Race/Ethnicity					
Asian	3 (4%)	3 (6%)	0 (0%)	0 (0%)	
African-American	5 (7%)	2 (4%)	3 (13%)	1 (3%)	
Hispanic	7 (9%)	6 (11%)	1 (4%)	2 (5%)	ns
Other	9 (12%)	5 (9%)	4 (17%)	7 (18%)	
Caucasian	52 (68%)	37 (70%)	15 (65%)	29 (65%)	
<i>Reproductive History</i>					
Menarchal Age (years)	12.5 ± 0.2	12.3 ± 0.3	13.0 ± 0.4	12.5 ± 0.3	ns
Ever Pregnant	26 (34%)	18 (34%)	8 (35%)	9 (24%)	ns
Age first pregnancy	24.8 ± 1.2	24.9 ± 1.4	24.4 ± 2.1	22.0 ± 2.0	ns
Number of pregnancies	2.0 ± 0.2	1.8 ± 0.3	2.4 ± 0.4	1.7 ± 0.4	ns
Hormones Ever	34 (45%)	24 (45%)	10 (43%)	23 (59%)	ns
<i>Lifestyle History</i>					
Ever Smoke	40 (53%)	27 (51%)	13 (57%)	15 (38%)	ns
Among Smokers	4.4 ± 6.7	5.0 ± 9.3	3.5 ± 11.5	19.3 ± 8.1	ns
Current Alcohol	59 (78%)	43 (81%)	16 (70%)	23 (59%)	ns
Among Drinkers	2.7 ± 0.3	2.5 ± 0.4	3.5 ± 0.7	1.9 ± 0.5	ns
Current Exercise	68 (89%)	47 (89%)	21 (91%)	35 (90%)	ns
Among Exercisers	5.5 ± 0.8	4.8 ± 1.0	7.3 ± 1.5	6.5 ± 1.0	ns
Calcium intake	1017 ± 95	1000 ± 113	1057 ± 178	1255 ± 142	ns
Vitamin D intake	252 ± 29	231 ± 34	304 ± 54	245 ± 42	ns
<i>AED History</i>					
Years on Current AED	8.0 ± 1.0	7.6 ± 1.2 ^a	9.1 ± 1.9 ^b	1.5 ± 1.4 ^{ab}	0.002

Data presented are means $\pm$ standard errors with (95% confidence intervals) or number and (percent of group)

AEDs sharing a superscript are statistically different from each other

bolded p-values are significant when the combined EIAED group is compared to LTG

Table II

Bone Mineral Density, Calcitropic Hormones, Bone Turnover Markers, and Reproductive Hormone Measurements from Total Sample

<i>DXA</i>	EIAED (n=76)	CBZ (n=53)	PHT (n=23)	LTG (n=39)	p-value
FN BMD (g/cm²)	0.818±0.014	0.809±0.017	0.838±0.026	0.840±0.020	ns
FN Z score	-0.2±0.1	-0.4±0.2	0.0±0.2	-0.1±0.2	ns
TH BMD (g/cm²)	0.907±0.014	0.896±0.017	0.932±0.025	0.937±0.019	ns
TH Z score	-0.3±0.1	-0.4±0.1	-0.0±0.2	-0.1±0.2	ns
LS BMD (g/cm²)	1.024±0.014	1.017±0.017	1.041±0.026	1.069±0.020	ns
LS Z score	-0.1±0.1	-0.2±0.2	0.0±0.2	0.3±0.2	ns
<i>Biochemistries</i>					
Serum Calcium *	9.6±0.1	9.6±0.1 ^a	9.6±0.1 ^b	10.0±0.1 ^{ab}	<0.001
25-OHD	24.1±0.9	24.0±1.1	24.1±1.7	25.5±1.3	ns
1,25(OH)₂D	35.6±1.5	36.5±1.8	33.6±2.8	36.6±2.1	ns
PTH	25.5±1.4	25.0±1.7	26.6±2.7	29.4±2.0	ns
Osteocalcin	8.9±0.4	9.0±0.5	8.8±0.8	8.9±0.6	ns
BSAP	23.6±0.8	23.6±0.9	23.6±1.4	20.5±1.1	0.08
Urine NTX	48.8±3.3	47.1±3.9	53.5±6.4	35.8±4.9	0.07
<i>Sex Steroids</i>					
Estrone	38.5±3.4	41.3±4.0 ^a	31.7±6.3 ^b	65.6±4.8 ^{ab}	<0.001
Estradiol	61.8±6.3	65.3±7.5	53.3±11.6	57.1±9.1	ns
SHBG	155±7	159±8 ^a	145±12 ^b	106±10 ^{ab}	<0.001
Free Estradiol (%)	0.82±0.03	0.81±0.04 ^a	0.85±0.06 ^b	1.09±0.05 ^{ab}	<0.001

Mean ± SEM

p-values for one-way ANOVA comparing LTG vs. CBZ vs. PHT

AEDs sharing a superscript are statistically different from each other

bolded p-values are significant when the combined EIAED group is compared to LTG

* Corrected for albumin

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Reproductive Hormone Measurements for the Subset (n=30) who had Reproductive Measurements Drawn in Early Follicular Phase of the Menstrual Cycle

Table III

	IND (n=17)	CBZ (n=12)	PHT (n=5)	LTG (n=13)	p-value
E1	36.8 ± 4.7	37.2 ± 5.7 ^a	35.9 ± 8.7	60.6 ± 5.4 ^a	0.02
E2	52.6 ± 10.5	55.5 ± 12.7	45.8 ± 19.7	48.1 ± 12.7	ns
SHBG	153 ± 12	163 ± 14 ^a	128 ± 21	78 ± 14 ^a	0.001
Free E2 (%)	0.82 ± 0.08	0.77 ± 0.10 ^a	0.94 ± 0.15	1.3 ± 0.10 ^a	0.004

Mean ± SEM

p-values for one-way ANOVA comparing LTG vs. CBZ vs. PHT

AEDs sharing a superscript are statistically different from each other

bolded p-values have p-values less than 0.05 when all women receiving an inducer (either PHT or CBZ) are compared to LTG