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Effects of Estrogen or Venlafaxine on Menopause Related Quality of Life in Healthy Postmenopausal Women with Hot Flashes: A Placebo-Controlled Randomized Trial

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Abstract

OBJECTIVE—To evaluate the effects of low-dose estradiol (ET) or venlafaxine on menopause-related quality of life and associated symptoms in healthy peri- and postmenopausal women with hot flashes.

METHODS—A double-blind, placebo-controlled randomized trial of low-dose oral 17-beta-estradiol 0.5-mg/day, venlafaxine XR 75-mg/day, vs. identical placebo was conducted among 339 women ages 40–62 years with ≥ 2 (mean 8.07, SD 5.29) daily VMS recruited at 3 clinical sites from November 2011 to October 2012. The primary trial outcome, reported previously, was the frequency of VMS at 8 weeks. Here, we report on secondary endpoints of total and domain scores from the Menopause-Specific Quality of Life Questionnaire (MENQOL) and measures of pain (PEG), depression (PHQ-9), anxiety (GAD-7) and perceived stress (PSS).

RESULTS—Treatment with both estradiol and venlafaxine resulted in significantly greater improvement in quality of life, as measured by total MENQOL scores compared to placebo (mean difference for ET at 8 weeks of -0.4 ; 95% confidence interval (CI) -0.7 to -0.2 ; $p < 0.001$ and for venlafaxine of -0.2 ; 95% CI -0.5 to 0.0 ; $p = 0.04$). Quality of life (QOL) domain analyses revealed that ET had beneficial treatment effects in all domains of the MENQOL except psychosocial, while venlafaxine benefits were observed only in the psychosocial domain. Neither ET nor venlafaxine improved pain, anxiety or depressive symptoms, although baseline symptom levels were low. Modest benefits were observed for perceived stress with venlafaxine.

CONCLUSIONS—Both low-dose estradiol and venlafaxine are effective pharmacologic agents for improving menopause-related quality of life in healthy women with vasomotor symptoms.

Keywords

Estrogen; Venlafaxine; Menopause; Quality of life; Pain; Stress

Introduction

Over 38 million US women ages 45–64 years old (88%) experience daytime hot flashes or night sweats during the midlife transition (1). Vasomotor symptoms (VMS) have been shown to affect multiple role functions including work, social activity, leisure activity and sexual activity (2). In addition, many women with VMS report that the symptoms affect or

are accompanied by problems with sleep, mood, pain, concentration and energy levels, resulting in significant negative impact on women's quality of life (2). Sixty percent of midlife women seek medical care or advice for these symptoms at least once (3). Clearly, there is a compelling need for effective treatments to relieve VMS in midlife women, and the evaluation of such treatments should include the impact on commonly affected quality of life domains. Since use of estradiol at low doses and both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) for VMS are increasing, evidence on the magnitude of treatment effects for low-dose estrogen and serotonergic agents vs. placebo is needed for quality of life outcomes so that women can be properly informed and counseled about their options.

The Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) clinical trials network recently completed a 3-arm double-blinded trial of low-dose oral 17-beta-estradiol (ET), the low-dose serotonergic agent venlafaxine, and placebo for 8 weeks to examine the efficacy of both ET and venlafaxine relative to placebo in reducing the number of VMS that women experience. We previously described that both ET and venlafaxine were superior to placebo for reducing the frequency of VMS compared to placebo (4). The purpose of this report is to examine the impact of both low-dose estrogen and the non-hormonal SNRI alternative venlafaxine compared to placebo on menopause-related quality of life, pain symptoms, anxiety, depressive symptoms, and perceived stress. The consistency of these interventions on overall quality of life across subgroups of women defined by race/ethnicity, menopausal stage, pre-treatment VMS frequency or severity, and other baseline characteristics was also evaluated.

Methods

A 3-arm double-blind, placebo-controlled randomized trial of low-dose oral 17-beta-estradiol 0.5-mg/day, venlafaxine XR 75-mg/day, or placebo for 8 weeks for relief of hot flash frequency was conducted among symptomatic women ages 40–62 years in the menopause transition recruited at three MsFLASH network sites (Boston, MA; Philadelphia, PA; and Seattle, WA). Details of the MsFLASH Research Network (5), study trial design, methods and primary trial results have been published previously (4). The protocol was approved by the institutional review board at each site. All women provided written informed consent.

The trial enrolled 339 women from November 2011 to October 2012. Women were eligible if they were aged 40–62 years, in general good health, in the menopause transition or postmenopausal, and reported 14 hot flashes/night sweats per week (recorded on daily diaries for three weeks) rated as bothersome or severe at least 4 times per week. Screening procedures were designed to exclude women whose PHQ9 suggested a current episode of major depression or who reported: use of psychotropic medications in the past month; use of prescription, nonprescription or herbal therapies for hot flashes in the past month; use of systemic hormone therapy, hormonal contraceptives, selective estrogen receptor modulators or aromatase inhibitors in the past two months; current severe illness, major depressive episode, drug or alcohol abuse in the past year; suicide attempt in the past three years; a lifetime diagnosis of bipolar disorder or psychosis; uncontrolled hypertension; history of

cardiovascular disease, venous thromboembolic events; endometrial disease; and breast or gynecologic cancer.

Treatment and Study Procedures

Mass mailings to age-eligible women in the three clinical site metropolitan areas were the main recruitment strategy. Potentially eligible women, identified using a screening telephone call, were mailed a baseline questionnaire and daily diaries for recording frequency, severity, and bother of hot flashes each morning and evening. Women who continued to meet eligibility criteria were scheduled for 2 clinic visits (screening and randomization) within a 2–3 week interval. At Visit 2, eligible participants were randomly assigned to estrogen (n=97), venlafaxine (n=96) or placebo treatment (n=146) for 8 weeks, using a dynamic randomization algorithm (6) which allows for treatment balance across clinical sites. Randomization was conducted in a secure web-based database, maintained at the MsFLASH Data Coordinating Center (DCC), and implemented by the use of numbered containers with identical-appearing pills. All study participants took one identical appearing pill orally each day. Participants and clinical site personnel were blinded to treatment assignment until all data were collected at the 8-week visit. Study pills were counted at week 8 to estimate adherence.

Estrogen therapy was administered as 17 β -estradiol (0.5 mg/d) for 8 weeks; after unblinding, medroxyprogesterone acetate (10 mg/d) orally for 14 days was given for endometrial protection. Those assigned to venlafaxine hydrochloride received 37.5 mg/d for 1 week then 75 mg/d for 7 weeks; after unblinding, the dosage was tapered to 37.5 mg/d for another 14 days to minimize potential SNRI withdrawal effects.

Data Collection

The trial included a telephone screen, 3 clinic-based study visits (screening, randomization, 8 weeks), and telephone assessments at weeks 1 and 4 on treatment. Participants completed questionnaires at baseline, 4 and 8 weeks, and recorded VMS and vaginal bleeding pattern diaries daily for 3 weeks before randomization and throughout the 8-week trial.

Outcomes Questionnaires

Quality of life related to menopause was evaluated by the MENQOL, a 29-item self-report measure of quality of life designed to capture information on the presence and bother of symptoms, feelings and experiences in the domains of vasomotor, physical, psychosocial and sexual functioning among midlife women in the menopause transition. For each item, women were asked to report if they had experienced that symptom or feeling in the past four weeks, and if they had, to rate, bother, on a scale of 0–6 corresponding to “not bothered at all” to “extremely bothered.” These two items were combined to create a score from 1 (not experiencing symptoms or feeling) to 8 (extremely bothered). Each domain score was the average of the item scores in that domain (higher scores indicated poorer quality of life). Validity, reliability and responsiveness to change have been shown to be adequate to excellent (7).

Pain was measured by the PEG, a 3-item scale asking participants to report on a scale of 0–10 their level of average pain over the past week (0 = “no pain”, 10 = “pain as bad as you can imagine”); how much pain has interfered with enjoyment over the past week; and how much pain has interfered with general activity (0 = “does not interfere”, 10 = “completely interferes”) (8). Depression was measured with the 9-item version of the depression module of the Patient Health Questionnaire (PHQ-9) (9). The PHQ-9 depression scale can be scored either continuously (as a depression severity score) or categorically (to indicate a probable DSM-IV depressive diagnosis) (9). Anxiety was evaluated using the 7-item Generalized Anxiety Disorder questionnaire (GAD-7), which can likewise be scored either continuously (as an anxiety severity score) or categorically (with cut-points that indicate a probable anxiety disorder) (10). Perceived stress was assessed with the Perceived Stress Scale (PSS), a widely-used, validated self-report measure of perceived stress (11).

Other Measurements

Frequency and severity of hot flashes/night sweats were recorded on daily diaries in the morning and evening throughout the study. VMS frequency was calculated as the total number of hot flashes/night sweats in a 24-hour period, and expressed as mean daily frequency from the first 2 weeks of screening. Demographic factors, smoking status, alcohol intake, menopausal status (menopause transition, post menopause, previous hysterectomy and/or oophorectomy) and health status were assessed by questionnaire at baseline. Weight and height were measured at baseline and used to calculate body mass index (BMI). Validated questionnaires at baseline were also used to evaluate possible effect modifiers in this analysis. The effect modifiers were insomnia severity (7-item Insomnia Severity Index (ISI)) (12); subjective sleep quality (Pittsburgh Sleep Quality Index (PSQI)) (13; 14); depressive symptoms (PHQ-9) (9); anxiety (GAD-7) (10); and sexual function (19-item Female Sexual Function Index (FSFI)) (15).

Statistical Analysis

A modified intent-to-treat analyses included all randomized participants who provided follow-up QOL or symptom data at week 4, week 8, or both, regardless of treatment adherence.

Of the cohort of 339 randomized participants, data on one or more domains of the MENQOL were available on 336 women (99.1%) at baseline and 331 (97.6%) at four and/or eight weeks of follow-up. Similarly for the PEG, PHQ-9, GAD-7 and PSS data were available respectively on 339 (100%) women at baseline and 331 (96.7%) at follow-up. Primary analyses consisted of treatment group contrasts from linear regression models summarizing each of the nine outcomes (the four domains of the MENQOL, total MENQOL, PEG, PHQ-9, GAD-7 and PSS) at both four and eight weeks as a function of treatment assignment, adjusting each model for race, site, and baseline value of the outcome measure. Robust standard errors were calculated using generalized estimating equations to account for correlation between repeated measures from each participant. Sensitivity analyses were conducted to determine if the results differed among women who were adherent to the medication using the same linear regression approach but limiting the data to women who took at least 80 % of their study pills. We hypothesized that the effect of

treatment on quality of life related to menopause, as measured by the MENQOL might be modified by baseline characteristics, including race, menopausal status, VMS frequency, anxiety, depressive symptoms, insomnia or poor sleep quality, pain intensity and interference, sexual function, and/or BMI. Tests of interaction between treatment assignment and each of these variables were performed within the repeated measures linear regression models estimating mean follow-up MENQOL as a function of treatment arm, visit (weeks 4 or 8), the covariate of interest, and the interaction between treatment assignment and covariate with models adjusted for race, site, and baseline MENQOL. Reported p-values were based on the Wald statistic, with 2-sided p-value <0.05 considered statistically significant. Analyses were conducted using SAS Version 9.2 (SAS Institute, Cary, NC).

Results

A total of 339 women were randomly assigned to estradiol (n=96), venlafaxine (n=97) or placebo (n=146), including 116 African-American women (34.2%). The mean age of study participants was 54.6 years, 75.2% were postmenopausal, 15.6 % were in the menopause transition, and the mean number of VMS per day at enrollment was 8.1 (SD 5.3). There were no significant differences between the randomized treatment groups in baseline characteristics (Table 1). During the 8 week treatment period, 94% of the women in each group were adherent to their study medication as defined by taking at least 80% of dispensed pills.

Mean total MENQOL scores were 3.5 (estradiol), 3.7 (venlafaxine), and 3.5 (placebo) at baseline, and scores declined (i.e., QOL improved) in both treatment groups compared to placebo at weeks 4 and 8 (Figure 1).

The mean difference from baseline to 8 week MENQOL between estradiol and placebo at eight weeks was -0.4; 95% confidence interval (CI) -0.7 to -0.2; $p < 0.001$ and between venlafaxine and placebo was -0.2; 95% CI -0.5 to -0.0; $p = 0.042$ (Table 2). Statistically significant treatment group differences favoring estradiol relative to placebo (Table 2) were also seen for the individual vasomotor, physical and sexual domains with the greatest effect seen in the vasomotor domain and no effect on the psychosocial domain. In contrast, for venlafaxine compared to placebo, the only statistically significant treatment group improvement was for the psychosocial domain.

Results were nearly identical in the sensitivity analysis among adherent women (data not shown).

Neither treatment group showed improvement compared with placebo with respect to changes in pain (PEG), depressive symptoms (PHQ-9) or anxiety (GAD-7) (Table 3). For perceived stress (PSS), there was a mean difference between venlafaxine and placebo, at 4 weeks of -1.7; 95% confidence interval (CI) -3.4, -0.1 and at eight weeks of -1.4; 95% confidence interval (CI) -3.1 to -0.2; $p = 0.02$. No significant differences in PSS were observed between estradiol and placebo groups (Table 3).

When treatment effects on total MENQOL scores were examined in the 10 specified subgroups (Table 4), there were few statistically significant interactions. Non-obese women

(BMI < 30) showed greater improvement than obese women (BMI > 30) for venlafaxine compared to placebo (p for interaction 0.03). Also for venlafaxine compared to placebo, women with higher scores on the Female Sexual Function Index (indicating more sexual activity or less sexual stress/dysfunction) appeared to improve on the MENQOL more than women with lower scores (p for interaction 0.01).

Discussion

This is the first trial to simultaneously investigate the efficacy of low-dose oral estradiol and the SNRI venlafaxine on quality of life related to menopause using the MENQOL and validated measures of pain, anxiety, depression and stress in peri- and postmenopausal women with bothersome VMS. In this double-blind, placebo controlled randomized trial of healthy midlife women with VMS and without evidence of major depression, treatment with both low-dose estradiol and venlafaxine significantly improved overall menopause-specific quality of life. For estrogen, beneficial treatment effects were seen in all domains of the MENQOL except psychosocial while for venlafaxine benefits were observed only in the psychosocial domain. Venlafaxine also modestly improved perceived stress. Neither agent improved pain, depressive or anxious symptoms in this general population of women not selected on the basis of these specific symptoms.

Of note is that venlafaxine reduced VMS frequency and severity compared to placebo in our primary trial analyses (4) but in this study we did not see an improvement in the VMS domain on the MENQOL. This suggests that the way the MENQOL asks about VMS elicits information differently than the number and severity of events and that these aspects of VMS may be more importantly tied to improving quality of life. In addition, it is interesting to note that while the improvement with venlafaxine in the psychosocial domain was the only one that reached statistical significance, all of the other domains also improved with venlafaxine while not reaching statistical significance, thus contributing to the statistically significant improvement in overall QOL. Two other trials, but with slightly different patient populations, provide insight into improvements in the MENQOL following treatment with estrogen formulations (16; 17). In a trial of 318 women with seven or more moderate-to-severe VMS daily, treatment with bazedoxifene 20 mg/day plus conjugated estrogen (0.45 or 0.625 mg/day) resulted in significant improvements in total and domain-specific MENQOL scores (17). Both lower dose and higher estrogen treatment groups showed significant improvements in vasomotor and total scores on the MENQOL questionnaire relative to placebo ($P < 0.001$). However participants treated with BZA 20 mg/CE 0.625 mg also had significant improvements in psychosocial ($P < 0.05$), physical ($P < 0.01$), and sexual function scores ($P < 0.01$) compared with placebo. In a second smaller trial, among 32 women with depressive disorders as well as menopause symptoms ethinyl estradiol 5 ug/day (a dose comparable to conjugated equine estrogen 0.625 mg/day) plus norethindrone acetate 1 mg/day, was directly compared to escitalopram, an SSRI rather than the SNRI antidepressant evaluated in the present study. Improvements on the MENQOL total and domain scores were statistically similar, but treatment with escitalopram resulted in greater improvements than estradiol on the psychosocial domain, similar to findings in the present trial (16).

In a double-blind, placebo-controlled randomized trial of the SSRI escitalopram, 10–20mg/day vs. identical placebo, among 205 women ages 40–62 years with an average of 4 daily hot flashes, treatment with escitalopram, similar to the results seen in this study, resulted in significantly greater improvement in total MENQOL scores. In that study, escitalopram also improved scores in the vasomotor, psychosocial, and physical domains of the MENQOL (18) which were not seen with the SNRI venlafaxine in our study. When estradiol was compared directly to venlafaxine (results not shown), effects favoring estradiol were observed on the vasomotor domain. These current findings are consistent with our main trial report (4) where low-dose ET reduced daily diary-recorded VMS frequency by an additional 0.6 VMS events per day compared to venlafaxine, translating into a 5% greater reduction in VMS frequency (53% vs. 48%).

Neither estradiol nor venlafaxine when compared to placebo significantly improved pain, anxiety, or depression. Lack of statistical significance could be due to the low prevalence of these symptoms in this generally healthy group of women without current major depression. While venlafaxine is an antidepressant specifically used to treat depression and anxiety, it would not be expected to improve scores on depression and anxiety scales, except in the sub-population experiencing these symptoms.

We know of only one other vasomotor treatment trial in which PEG scores were evaluated (19). Escitalopram compared to placebo treatment improved pain scores most in women with higher depression or anxiety scores (16). Unfortunately, the present trial had limited power to examine differences by these pre-existing conditions. In other trials of participants with major depressive disorder (MDD), SNRIs such as venlafaxine and duloxetine were shown to be effective for relieving physical pain. Venlafaxine, was investigated in an open-label, prospective cohort study of 186 participants with MDD (20) where patients received venlafaxine at a standard dose used to treat depression (150 mg/day or more) for 1 year. Venlafaxine (mean dose 225 mg/day) significantly improved pain symptoms compared with baseline. In another trial, duloxetine (a similar SNRI) was studied in 512 participants with MDD (21). Participants received either duloxetine 60 mg/day or placebo. Duloxetine was associated with significant improvements in back pain ($p = .020$) and shoulder pain ($p = .021$) at week 9. Similarly, two additional randomized, double-blind studies found that duloxetine 60 mg once/day significantly reduced painful symptoms compared with placebo in participants with MDD (22; 23). While duloxetine is FDA approved to treat neuropathic pain in a non-depressed population, the nature of pain in our study was not characterized and so we don't know whether patients had neuropathic pain or another type which would not be expected to be treated by Venlafaxine. Conversely, estrogen would be expected to treat menopausal-related pain (mostly joint pain) and lack of estrogen's effect on pain is likely due to a low level of reported pain symptoms at baseline.

In this relatively healthy population, venlafaxine appeared to modestly improve perceived stress. Only one other study has measured the effect of SSRIs or SNRIs on perceived stress in a population of healthy individuals. Eighty healthy first-degree relatives of participants with depression were randomly assigned to receive escitalopram 10mg (n=41) or placebo (n=39) for 4 weeks. Scores on sleep, pain, aggression, quality of life, and perceived stress assessed at entry were compared to values following 4 weeks of intervention; however no

statistically significant differences in perceived stress was found between the groups (24). Effects of both venlafaxine and ET on total QOL were greater for non-obese women (BMI <30) compared to obese women. Obese women report a greater frequency of hot flashes consistent with the theory that body fat acts an insulator and hot flashes represent heat dissipation events occurring in the context of the narrowed thermoneutral zone (25). In terms of overall quality of life related to menopause, obese women may obtain less relief from these treatments due to multiple residual effects related to their excess body mass, both physiological and psychological.

While efficacy of estradiol and venlafaxine relative to placebo appeared similar in magnitude in improving overall quality of life and slightly better for estradiol compared to venlafaxine for the vasomotor symptoms subscale, our trial was not adequately powered to determine with confidence that one treatment was non-inferior to another. Additionally, the effects of low-dose venlafaxine treatment and low-dose estradiol treatment on menopausal quality of life, pain, anxiety, depression and perceived stress beyond 8 weeks are unknown. Although the FDA requires 12 week data, an 8 week trial is very common. In addition to minimizing endometrial hyperplasia that can occur after 8wk in response to unopposed ET, Guttuso et al. (2010), in a study examining time required to show drug efficacy, concluded that 8 weeks was the most efficient duration for a hot flash trial (26). To determine long-term effects, a well-designed maintenance study is required.

In the present trial, we evaluated low-dose formulations because of recommendations to use the lowest effective ET dosage and because others have demonstrated that use of low-dose SSRI/SNRI in non-depressed patients are effective for hot flashes and associated with fewer side effects.

Lastly, we did not evaluate subgroup differences in the MENQOL subscales or other outcomes to avoid an excessive number of statistical comparisons.

Strengths of this study include utilizing a robust measure of QOL specific to menopausal women. The MENQOL was chosen for the MsFLASH trials because of the breadth of the domains covered by its 29 questions and its robust psychometric properties, brevity and sensitivity to change over time. By not restricting this trial to women with seven or more moderate to severe VMS per day (as indicated by the draft FDA guidelines for vasomotor trials) (17), we were able to include the vast majority of women experiencing VMS in the population, many of whom seek treatment to relieve these symptoms. Only 7–9% of US women report symptoms that reach the 7 or greater frequency and severity, whereas 88% report having experienced some hot flashes in midlife (1). Eliminating women with major depression was an additional strength of this study. Trials that include women with depressive disorders (16) may obscure the effects of pharmacological treatments in non-depressed women who constitute the majority of women that experience distressing hot flashes. Other strengths were the high adherence to treatment, high retention rates, high outcome data collection rate, and a large racially diverse cohort of peri- and postmenopausal women with sample size sufficient to examine the consistency of treatment effects for the total MENQOL across various subgroups of women.

Conclusions

Treatment with both low-dose oral 17-beta-estradiol 0.5-mg/day, and venlafaxine XR 75-mg/day in healthy women with vasomotor symptoms were each significantly more effective than placebo in improving overall menopause-related quality of life. ET was most effective for QOL related to vasomotor symptoms but improved physical and sexual symptoms as well. Venlafaxine was most effective at improving QOL related to psychosocial symptoms and perceived stress. These findings provide evidence that should inform clinicians and women considering pharmacologic therapy for relief of menopause symptoms associated with quality of life.

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Figure 1.

Total MENQOL and 95% confidence intervals by Treatment Arm at Baseline, Week 4, and Week 8

p-value comparing Estradiol vs. Placebo, $p < 0.001$; p-value comparing Venlafaxine vs. Placebo, $p = 0.042$;

p-values from contrasts comparing treatment vs. placebo in a repeated measures linear model of total MENQOL as a function of intervention arm and adjusted for clinical center, visit week (4 or 8), and baseline total MENQOL. for main effects of intervention and week on 50% reduction in hot flashes over 8 weeks of follow-up = $p < 0.001$ for both.

Table 1

Baseline characteristics

Baseline Characteristic	All Participants			Estradiol			Venlafaxine			Placebo	Est vs. Plc	Vnl vs. Plc
	N	%		N	%		N	%		N	%	
<i>Total Participants</i>	339			97			96			146		
Age at screening, mean (SD)	54.6 (3.8)			54.9 (4.1)			54.8 (3.7)			54.3 (3.8)		
< 50	30	8.8		9	9.3		8	8.3		13	8.9	
50 – 54	147	43.4		39	40.2		41	42.7		67	45.9	
55 – 59	123	36.3		34	35.1		36	37.5		53	36.3	
60+	39	11.5		15	15.5		11	11.5		13	8.9	
Race												
White	203	59.9		60	61.9		53	55.2		90	61.6	
African American	116	34.2		32	33.0		38	39.6		46	31.5	
Other/Unknown	20	5.9		5	5.2		5	5.2		10	6.8	
Clinical Center												
Boston BWH	43	12.7		12	12.4		12	12.5		19	13.0	
Boston MGH	57	16.8		16	16.5		16	16.7		25	17.1	
Philadelphia	121	35.7		35	36.1		35	36.5		51	34.9	
Seattle	118	34.8		34	35.1		33	34.4		51	34.9	
Education												
High school diploma/GED	55	16.2		16	16.5		15	15.6		24	16.4	
School/training after high school	111	32.7		32	33.0		33	34.4		46	31.5	
College graduate	172	50.7		49	50.5		48	50.0		75	51.4	
Marital Status												
Never married	53	15.6		13	13.4		18	18.8		22	15.1	
Divorced	65	19.2		20	20.6		20	20.8		25	17.1	
Widowed	9	2.7		5	5.2		2	2.1		2	1.4	
Married/living with partner	210	61.9		58	59.8		56	58.3		96	65.8	

Baseline Characteristic	All Participants			Estradiol			Venlafaxine			Placebo	Est vs. Plc	Vnl vs. Plc
	N	%		N	%		N	%		N	%	
<i>Total Participants</i>		339			97			96		146		
Baseline Characteristic	N	%		N	%		N	%		N	%	p-value
Smoking												0.65
Never	174	51.3		50	51.5		54	56.3		70	47.9	
Past	107	31.6		30	30.9		27	28.1		50	34.2	
Current	55	16.2		17	17.5		14	14.6		24	16.4	
Alcohol use (drinks/week)												0.26
0	116	34.2		28	28.9		36	37.5		52	35.6	
1-<7	149	44.0		43	44.3		41	42.7		65	44.5	
7+	61	18.0		21	21.6		13	13.5		27	18.5	
BMI (m/kg²), mean (SD)	28.3 (6.8)			28.5 (6.5)			29.3 (6.9)			27.6 (6.8)		0.06
<25	118	34.8		31	32.0		27	28.1		60	41.1	
25 – 29	107	31.6		35	36.1		32	33.3		40	27.4	
30	107	31.6		30	30.9		34	35.4		43	29.5	
Age at Starting Hot Flashes												0.95
<40	25	7.4		7	7.2		9	9.4		9	6.2	
40 – 49	146	43.1		40	41.2		42	43.8		64	43.8	
50+	163	48.1		48	49.5		44	45.8		71	48.6	
Screening VMS Frequency/day	8.1 (5.3)			8.5 (5.7)			8.2 (5.5)			7.7 (4.8)		0.44
5.5	112	33.0		28	28.9		28	29.2		56	38.4	
>5.5 – 8	108	31.9		30	30.9		35	36.5		43	29.5	
> 8	119	35.1		39	40.2		33	34.4		47	32.2	
Self-reported health												0.95
Excellent	72	21.2		23	23.7		15	15.6		34	23.3	
Very Good	124	36.6		35	36.1		36	37.5		53	36.3	
Good	107	31.6		29	29.9		36	37.5		42	28.8	

Baseline Characteristic	All Participants			Estradiol			Venlafaxine			Placebo			Est vs. Plc		Vnl vs. Plc	
	N	%		N	%		N	%		N	%		p-value		p-value	
Total Participants	339			97			96			146						
Fair	35	10.3		10	10.3		9	9.4		16	11.0					
Menopause Status													0.99		0.83	
Perimenopausal	53	15.6		14	14.4		17	17.7		22	15.1					
Postmenopausal	255	75.2		74	76.3		71	74.0		110	75.3					
Indeterminate	31	9.1		9	9.3		8	8.3		14	9.6					
Depression score, mean (SD)	3.4 (3.7)			3.9 (4.4)			3.0 (2.9)			3.4 (3.7)			0.38		0.32	
No depression (0–4)	246	72.6		68	70.1		70	72.9		108	74.0					
Mild depression (5–9)	64	18.9		18	18.6		23	24.0		23	15.8					
Moderate+ depression (10+)	29	8.6		11	11.3		3	3.1		15	10.3					
Anxiety score, mean (SD)	2.5 (3.6)			3.0 (4.3)			2.2 (3.0)			2.4 (3.4)			0.21		0.65	
No anxiety (0–4)	265	78.2		73	75.3		76	79.2		116	79.5					
Mild anxiety (5–9)	51	15.0		15	15.5		17	17.7		19	13.0					
Moderate+ anxiety (10+)	23	6.8		9	9.3		3	3.1		11	7.5					
PSQI, mean (SD)	7.5 (3.4)			7.6 (3.6)			7.6 (3.2)			7.3 (3.5)			0.58		0.50	
Good sleep quality (<5)	67	19.8		23	23.7		14	14.6		30	20.5					
Moderate sleep quality (5 – <8)	102	30.1		21	21.6		35	36.5		46	31.5					
Poor sleep quality(8)	151	44.5		46	47.4		40	41.7		65	44.5					
ISI, mean (SD)	11.0 (6.0)			11.0 (6.3)			11.7 (6.0)			10.4 (5.8)			0.52		0.10	
No clinically significant insomnia (7)	106	31.3		28	28.9		26	27.1		52	35.6					
Subthreshold insomnia (8–14)	133	39.2		40	41.2		39	40.6		54	37.0					
Clinical insomnia (moderate, 15–21)	78	23.0		21	21.6		25	26.0		32	21.9					
Clinical insomnia (severe, 22+)	14	4.1		5	5.2		5	5.2		4	2.7					

Table 2

Effects of Estradiol and Venlafaxine on Menopausal Quality of Life

Variable	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	Mean Difference (95% CI)	p-value ^f	Mean Difference (95% CI)	p-value ^f
MENQOL TOTAL												
Baseline	82	3.5 (3.2, 3.7)	84	3.7 (3.4, 3.9)	132	3.5 (3.3, 3.7)			-0.1 (-0.4, 0.2)	<0.001	0.1 (-0.2, 0.4)	0.042
Week 4 – baseline	70	-0.9 (-1.1, -0.7)	69	-0.9 (-1.1, -0.7)	103	-0.6 (-0.7, -0.4)			-0.3 (-0.6, 0.0)		-0.3 (-0.6, 0.0)	
Week 8 – baseline	73	-1.1 (-1.3, -0.9)	73	-0.9 (-1.1, -0.7)	115	-0.7 (-0.9, -0.5)			-0.4 (-0.7, -0.2)		-0.2 (-0.5, 0.0)	
MENQOL VASOMOTOR												
Baseline	94	5.7 (5.4, 6.0)	95	5.9 (5.5, 6.2)	142	5.6 (5.4, 5.9)			0.1 (-0.3, 0.5)	<0.001	0.2 (-0.2, 0.6)	0.211
Week 4 – baseline	76	0.7 (0.3, 1.1)	75	0.8 (0.3, 1.2)	118	1.2 (0.9, 1.5)			-0.5 (-1.0, 0.0)		-0.4 (-1.0, 0.1)	
Week 8 – baseline	77	-0.1 (-0.5, 0.4)	79	0.7 (0.3, 1.1)	125	1.0 (0.7, 1.3)			-1.0 (-1.6, -0.5)		-0.3 (-0.8, 0.2)	
MENQOL PSYCHOSOCIAL												
Baseline	92	2.8 (2.4, 3.1)	94	2.9 (2.5, 3.2)	142	2.7 (2.4, 2.9)			0.1 (-0.3, 0.5)	0.120	0.2 (-0.2, 0.6)	0.008
Week 4 – baseline	73	-1.3 (-1.6, -1.1)	76	-1.5 (-1.8, -1.3)	112	-1.2 (-1.4, -1.0)			-0.1 (-0.5, 0.2)		-0.3 (-0.7, 0.0)	
Week 8 – baseline	79	-1.4 (-1.7, -1.1)	77	-1.5 (-1.8, -1.3)	126	-1.3 (-1.5, -1.1)			-0.1 (-0.4, 0.3)		-0.2 (-0.5, 0.1)	
MENQOL PHYSICAL												
Baseline	89	3.0 (2.7, 3.3)	88	3.2 (2.9, 3.5)	138	3.0 (2.8, 3.2)			0.0 (-0.3, 0.3)	0.039	0.2 (-0.1, 0.6)	0.082
Week 4 – baseline	73	-1.3 (-1.5, -1.0)	71	-1.3 (-1.5, -1.0)	109	-1.1 (-1.3, -0.9)			-0.2 (-0.5, 0.1)		-0.2 (-0.5, 0.1)	
Week 8 – baseline	77	-1.3 (-1.6, -1.1)	76	-1.3 (-1.5, -1.1)	119	-1.2 (-1.4, -1.0)			-0.1 (-0.4, 0.2)		-0.1 (-0.4, 0.2)	
MENQOL SEXUAL												
Baseline	87	2.8 (2.3, 3.2)	93	3.0 (2.5, 3.4)	143	3.0 (2.6, 3.4)			-0.2 (-0.8, 0.4)	0.047	0.0 (-0.6, 0.6)	0.447
Week 4 – baseline	76	-1.5 (-1.8, -1.1)	78	-1.5 (-1.8, -1.1)	120	-1.2 (-1.4, -0.9)			-0.3 (-0.7, 0.1)		-0.3 (-0.7, 0.2)	
Week 8 – baseline	77	-1.7 (-2.1, -1.4)	78	-1.6 (-1.9, -1.3)	124	-1.2 (-1.5, -1.0)			-0.5 (-0.9, -0.1)		-0.3 (-0.7, 0.1)	

^f p-values from contrasts comparing treatment vs. placebo in a repeated measures linear model of outcome as a function of intervention arm and adjusted for clinical center, visit week (4 or 8), and baseline outcome

Table 3

Effects of Estradiol and Venlafaxine on Pain, Anxiety, Depression and Perceived Stress

Variable	Estradiol		Venlafaxine		Placebo		Estradiol vs Placebo		Venlafaxine vs Placebo	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	Mean Difference (95% CI)	p-value ^I	Mean Difference (95% CI)	p-value ^I
Pain (PEG)								0.477		0.298
Baseline	96	1.6 (1.1, 2.1)	94	1.5 (1.0, 1.9)	143	1.6 (1.2, 1.9)	0.0 (-0.6, 0.6)		-0.1 (-0.7, 0.5)	
Week 4 – baseline	88	-0.0 (-0.5, 0.4)	88	-0.3 (-0.8, 0.2)	129	-0.2 (-0.6, 0.1)	0.2 (-0.4, 0.8)		-0.1 (-0.7, 0.5)	
Week 8 – baseline	92	-0.1 (-0.5, 0.4)	89	-0.4 (-0.8, 0.0)	136	-0.2 (-0.6, 0.2)	0.2 (-0.4, 0.8)		-0.2 (-0.8, 0.4)	
Depression (PHQ-8)								0.294		0.546
Baseline	97	3.9 (3.0, 4.8)	96	3.0 (2.4, 3.6)	146	3.4 (2.8, 4.0)	0.5 (-0.6, 1.5)		-0.4 (1.3, 0.4)	
Week 4 – baseline	89	-1.2 (-2.3, -0.2)	89	0.2 (-0.4, 0.8)	127	-0.4 (-1.0, 0.3)	-0.9 (-2.1, 0.3)		0.5 (-0.3, 1.4)	
Week 8 – baseline	91	-0.8 (-1.6, 0.0)	90	-0.5 (-1.1, 0.1)	136	-0.3 (-0.9, 0.3)	-0.5 (-1.5, 0.5)		-0.2 (-1.1, 0.7)	
Anxiety (GAD-7)								0.946		0.152
Baseline	97	3.0 (2.2, 3.9)	96	2.2 (1.6, 2.8)	146	2.4 (1.9, 3.0)	0.6 (-0.4, 1.7)		-0.2 (-1.0, 0.6)	
Week 4 – baseline	90	-1.0 (-1.8, -0.2)	91	-0.9 (-1.3, -0.4)	132	-0.5 (-1.0, 0.0)	-0.5 (-1.5, 0.4)		-0.4 (-1.1, 0.3)	
Week 8 – baseline	93	-0.9 (-1.7, -0.1)	90	-0.7 (-1.3, -0.1)	139	-0.7 (-1.2, -0.1)	-0.2 (-1.2, 0.7)		-0.1 (-0.9, 0.7)	
Stress (PSS)								0.977		0.020
Baseline	92	12.5 (11.2, 13.8)	91	12.2 (10.8, 13.6)	140	12.2 (11.0, 13.4)	0.3 (-1.5, 2.1)		0.0 (-1.9, 1.8)	
Week 4 – baseline	82	-1.9 (-3.1, -0.7)	83	-3.1 (-4.3, -1.8)	123	-1.3 (-2.4, -0.3)	-0.5 (-2.2, 1.1)		-1.7 (-3.4, -0.1)	
Week 8 – baseline	87	-1.8 (-2.9, -0.8)	86	-3.4 (-4.9, -2.0)	129	-2.0 (-3.0, -1.1)	0.2 (-1.2, 1.6)		-1.4 (-3.1, 0.2)	

^I p-values from contrasts comparing treatment vs. placebo in a repeated measures linear model of outcome as a function of intervention arm and adjusted for clinical center, visit week (4 or 8), and baseline outcome

Table 4

Effects of estradiol, venlafaxine on Menopause-related Quality of Life by baseline characteristics

Characteristic	Estradiol			Venlafaxine			Placebo		Estradiol vs. Placebo		Venlafaxine vs. Placebo	
	N	Baseline	Diff ¹	N	Baseline	Diff ¹	N	Baseline	Diff ¹	Mean Diff. in Change ² (95% CI)	Mean Diff. in Change ² (95% CI)	p for interaction ³
Overall Model	73	3.5	-1.1	73	3.6	-0.9	115	3.5	-0.9	-0.37 (-0.56, -0.17)	-0.23 (-0.45, -0.01)	
Ethnicity												
African American	15	4.3	-1.4	23	4.0	-0.9	30	3.7	-0.9	-0.28 (-0.71, 0.14)	-0.13 (-0.61, 0.34)	0.60
White	55	3.4	-1.0	47	3.4	-0.9	77	3.4	-0.6	-0.36 (-0.59, -0.14)	-0.28 (-0.52, -0.03)	
Menopause Status (03 Definition)												
Perimenopausal	10	3.4	-1.0	14	3.6	-1.0	18	3.5	-0.6	-0.25 (-0.81, 0.31)	-0.42 (-1.00, 0.15)	0.40
Postmenopausal	57	3.4	-1.1	53	3.6	-0.9	87	3.5	-0.9	-0.39 (-0.60, -0.17)	-0.15 (-0.40, 0.09)	
Screening VMS Frequency/day												
5.5	22	3.5	-1.2	21	3.6	-0.7	44	3.6	-0.7	-0.53 (-0.88, -0.18)	0.01 (-0.41, 0.42)	0.33
>5.5 – 8	23	3.4	-1.0	26	3.3	-1.0	36	3.5	-0.9	-0.15 (-0.49, 0.18)	-0.21 (-0.57, 0.14)	
> 8	28	3.6	-1.1	26	3.8	-1.0	35	3.4	-0.5	-0.43 (-0.77, -0.09)	-0.40 (-0.77, -0.03)	
GAD-7 Anxiety												
< 5	59	3.3	-1.0	61	3.4	-0.8	90	3.3	-0.7	-0.35 (-0.55, -0.15)	-0.16 (-0.40, 0.07)	0.98
5	14	4.3	-1.4	12	4.4	-1.4	25	4.3	-0.8	-0.43 (-0.99, 0.14)	-0.50 (-1.04, 0.05)	
PHQ-9 Depression												
< 5	51	3.3	-1.1	54	3.4	-0.9	85	3.2	-0.6	-0.38 (-0.58, -0.18)	-0.19 (-0.44, 0.06)	0.97

Characteristic	Estradiol			Venlafaxine			Placebo			Estradiol vs. Placebo			Venlafaxine vs. Placebo		
	N	Baseline	Diff/I	N	Baseline	Diff/I	N	Baseline	Diff/I	Mean Diff. in Change ² (95% CI)	p for interaction ³	Mean Diff. in Change ² (95% CI)	p for interaction ³	Mean Diff. in Change ² (95% CI)	p for interaction ³
5	22	4.0	-1.2	19	4.1	-1.1	30	4.3	-1.0	-0.36 (-0.80, 0.07)		-0.33 (-0.76, 0.10)			
Pain in last week (0-10)															
0	32	3.4	-1.1	34	3.4	-1.0	51	3.3	-0.7	-0.44 (-0.74, -0.14)	0.39	-0.31 (-0.60, -0.01)			0.50
1-5	35	3.5	-1.1	31	3.7	-0.9	52	3.6	-0.6	-0.42 (-0.69, -0.15)		-0.16 (-0.52, 0.20)			
6-10	5	4.2	-0.7	6	4.0	-0.4	11	3.8	-1.0	0.22 (-0.23, 0.67)		-0.05 (-0.54, 0.64)			
PEG Construct															
0	32	3.4	-1.1	33	3.4	-1.0	47	3.3	-0.6	-0.44 (-0.74, -0.13)	0.44	-0.34 (-0.64, -0.05)			0.62
1-<4	29	3.5	-1.1	30	3.6	-0.8	49	3.5	-0.6	-0.37 (-0.67, -0.07)		-0.05 (-0.39, 0.28)			
4+	11	3.7	-1.1	8	4.3	-1.0	17	3.9	-1.0	-0.18 (-0.66, 0.29)		-0.30 (-1.04, 0.45)			
BMI (kg/m²)															
< 30	52	3.4	-1.2	50	3.5	-1.0	78	3.3	-0.6	-0.50 (-0.73, -0.27)	0.06	-0.34 (-0.60, -0.09)			0.03
30	20	3.7	-1.1	21	3.7	-0.8	34	3.9	-0.9	-0.05 (-0.41, 0.30)		0.07 (-0.32, 0.46)			
Poor Sleep (PSQI>8 or ISI>14)															
No	41	3.2	-1.1	39	2.9	-1.0	63	3.2	-0.6	-0.32 (-0.57, -0.07)	0.53	-0.16 (-0.40, 0.08)			0.39
Yes	30	4.0	-1.3	32	3.7	-1.6	49	3.9	-0.8	-0.45 (-0.77, -0.14)		-0.36 (-0.76, 0.03)			
FSFI															
< 26	41	3.8	-1.3	40	3.8	-1.0	57	3.8	-0.8	-0.54 (-0.83, -0.25)	0.94	-0.29 (-0.60, 0.01)			0.01

Characteristic	Estradiol			Venlafaxine			Placebo		Estradiol vs. Placebo	Venlafaxine vs. Placebo	
	N	Baseline	Diff ¹	N	Baseline	Diff ¹	N	Baseline	Diff ¹	Mean Diff. in Change ² (95% CI)	p for interaction ³
26	21	3.1	-0.9	16	2.9	-0.8	33	3.0	-0.5	-0.42 (-0.75, -0.09)	

¹Week 8 – baseline differences

²adjusted change in MENQOL score in the Estradiol group on average versus placebo

³interaction p-values for continuous variables are computed from the interaction term between the continuous subgroup variable of interest and treatment arm in a separate model.