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Randomized Controlled Trial of Low-Dose Estradiol and the SNRI Venlafaxine for Vasomotor Symptoms

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Abstract

Importance—Estrogen therapy is the gold standard treatment for hot flashes and night sweats, but some women are unable or unwilling to use it because of associated risks. The serotonin-norepinephrine reuptake inhibitor venlafaxine is used widely as a non-hormonal treatment. While clinical impression is that serotonin-norepinephrine reuptake inhibitors are less effective than estrogen, these medications have not been simultaneously evaluated in one clinical trial.

Objective—To determine the efficacy and tolerability of low-dose oral 17-beta-estradiol and low-dose venlafaxine XR in alleviating vasomotor symptoms.

Design and Participants—339 peri- and postmenopausal women with ≥2 bothersome vasomotor symptoms per day (mean 8.1, SD 5.3/day) were recruited from the community to MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) clinical network sites November 2011—October 2012.

Interventions—Participants were randomized to double-blinded treatment with low-dose oral 17-beta-estradiol 0.5-mg/day (n=97), low-dose venlafaxine XR 75-mg/day (n=96), or placebo (n=146) for 8 weeks.

Main Outcomes—Primary outcome was the mean daily frequency of vasomotor symptoms after 8 weeks of treatment. Secondary outcomes were vasomotor symptom severity, bother and interference. Intent-to-treat analyses compared change in vasomotor symptom frequency between each active intervention and placebo and between the two active treatments.

Results—Compared to baseline, mean vasomotor symptom frequency at week 8 decreased by 53% with estradiol, 48% with venlafaxine, and 29% with placebo. Estradiol reduced the frequency of symptoms by 2.3 (95% CI 1.3–3.4) more per day than placebo ($p<0.001$), and venlafaxine by 1.8 (95% CI 0.8–2.7) more per day than placebo ($p=0.005$). Results were consistent for VMS severity, bother and interference. Low-dose estradiol reduced symptom frequency by 0.6 more per day than venlafaxine (95% CI, 1.8 more per day to 0.6 fewer per day than venlafaxine; $p=0.09$). Treatment satisfaction was highest (69%) on estradiol ($p<0.001$ versus placebo), lowest (39%) on placebo, and intermediate (52%) for venlafaxine ($p=0.06$ versus placebo). Both interventions were well tolerated.

Conclusions—Low-dose oral estradiol and venlafaxine are both effective treatments for vasomotor symptoms in midlife women. While efficacy of low-dose estradiol may be slightly superior to that of venlafaxine, the difference is small in magnitude and of uncertain clinical relevance.

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BACKGROUND

Hot flashes and night sweats, together called vasomotor symptoms (VMS), are highly prevalent in women during midlife, affecting up to 80% of women.[1] VMS are the primary menopause-related symptom leading peri- and postmenopausal women to seek medical attention.[2] Estrogen therapy (ET) remains the gold standard treatment for VMS and was the only FDA-approved treatment for VMS until a selective serotonin reuptake inhibitor (SSRI) was recently approved.[3] However, prescriptions for ET have declined markedly since findings from the Women's Health Initiative (WHI) demonstrated associated risks in postmenopausal women.[4] Because of these risks, current recommendations are that ET be used at the lowest possible dose for the shortest possible duration,[5] shifting usage patterns to lower-dose preparations. Studies suggest that low-dose ET preparations diminish VMS, but to a lesser extent than standard doses and with a slower onset of action.[6]

Since the publication of WHI results, investigation of non-hormonal treatments for VMS has intensified. Many SSRI/SNRI have been shown to be more effective than placebo in reducing VMS,[7–9] with one SSRI recently FDA-approved to treat VMS.[3,9] The SNRI venlafaxine is one of the most widely studied serotonergic agents with accumulating evidence showing that low doses (75–150 mg/day) reduce VMS more than placebo.[10–12] SSRI/SNRI are used widely to treat VMS, with venlafaxine a first-line treatment in women unable or unwilling to take ET.[13,14]

While clinical impression is that SSRI/SNRI medications are less effective than ET,[8,15] trials simultaneously examining the efficacy of these agents have not been conducted. In addition, the majority of ET trials have used doses higher than currently recommended low-dose regimens.[16] As a result, no data on the relative efficacy of the widely used low-dose oral ET and serotonergic agents are available to guide VMS treatment decisions.

MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) is an NIH-funded research network designed to test treatments for menopause-related symptoms. We report here results of a 3-arm double-blinded trial randomizing healthy peri- and postmenopausal women with bothersome VMS to low-dose oral 17-beta-estradiol, low-dose venlafaxine, or placebo for 8 weeks. The primary objective of this trial was to determine the efficacy of both ET and venlafaxine relative to placebo in reducing the number of VMS reported. We hypothesized that both ET and venlafaxine would be superior to placebo for reducing VMS frequency and, secondarily, that both active agents would improve VMS severity, bother and interference more than would placebo.

METHODS

Trial design

This was a multi-site, randomized placebo-controlled 8-week trial of oral 17-β-estradiol 0.5-mg/day, venlafaxine XR 75-mg/day, or placebo. Those randomized to venlafaxine were titrated from 37.5-mg/day up to 75-mg/day over a one-week period. Details about the MsFLASH Research Network and study designs are published elsewhere.[17,18] The study

was approved by the each site's Institutional Review Board. All participants provided written informed consent.

Eligible women were randomly assigned to treatment in a 2:2:3 ratio (ET:venlafaxine:placebo) to increase the efficiency of the trial design for the two primary comparisons between each active treatment and placebo. Allowing for a 10% loss to follow-up, a sample size of 304 (339 enrolled) provided >90% power to detect a 0.52 standard deviation unit difference in change in VMS frequency between placebo and active groups using a 2-sided 2.5% type I error for each comparison.

Participant selection

Participants at MsFLASH sites in Boston, Philadelphia, and Seattle were recruited from November 2011—October 2012 by mass mailings to age-eligible women using purchased mailing lists and health-plan enrollment files.

Eligible participants were healthy women ages 40–62 years, in the menopause transition (amenorrhea ≥60 days in past year), or postmenopausal (≥12 months since last menstrual period or bilateral oöphorectomy), or FSH >20 mIU/mL and estradiol ≤50 pg/mL in the absence of a reliable menstrual marker (hysterectomy with ovarian preservation, progesterone- releasing intra-uterine device, endometrial ablation). Participants were required to have ≥14 VMS/week, at least some of which were considered bothersome or severe, recorded prospectively on daily diaries for 2 weeks. A third week of VMS diaries was collected to ensure that VMS ratings did not decline by more than 50% from the first 2 screening weeks.[17,18]

Exclusion criteria included hypersensitivity, contraindication to study medications; recent or current use of hormone therapy, hormonal contraceptives, selective estrogen receptor modulators, or aromatase inhibitors (past 2 months); psychotropic medications or treatments for VMS (past month); pregnancy or breastfeeding; major depressive episode, drug/alcohol abuse in past year; suicide attempt in past 3 years; diagnosis of bipolar disorder or psychosis; or history of uncontrolled hypertension, cardiovascular, thrombotic, or endometrial disease, pre-breast cancer conditions, breast or gynecologic cancer, or unstable medical illness.

Data collection

The trial included a telephone screen, 3 clinic-based study visits (screening, randomization, 8-weeks) and 2 telephone assessments (1- and 4-weeks). Participants completed questionnaires at baseline and 8 weeks, and recorded VMS and vaginal bleeding pattern diaries twice daily for 3 weeks before randomization to establish baseline VMS and then throughout the 8-week trial.[18]

Treatment

All participants took one identical appearing pill orally each day. Using a dynamic randomization algorithm,[19] participants were randomized to one of three arms: ET, venlafaxine or placebo (Figure 1), stratified on clinical site. Participants and clinical site

personnel were blinded to treatment assignment until all 8-week data were collected, after which assignment was unblinded so that specific post-treatment medications could be administered. Study pills were counted at week 8 to estimate adherence.

ET was administered as 17-beta-estradiol 0.5-mg/day for 8 weeks; after unblinding, medroxyprogesterone 10-mg/day orally for 14 days was given for endometrial protection. Those assigned to venlafaxine received 37.5-mg/day for one week then 75-mg/day for 7 weeks; after unblinding, they were tapered to 37.5-mg/day for another 14 days to minimize potential SNRI withdrawal effects.

Measurements

VMS frequency, bother, and severity were recorded daily in the morning and evening. The primary outcome was VMS frequency. Secondary outcomes were VMS bother (rated from 1–4: none, a little, moderately, a lot), VMS severity (rated from 1–3: mild, moderate, severe), and perceived VMS interference (Hot Flash Related Daily Interference Scale, HFRDIS,[20] evaluated at baseline, 4 and 8 weeks).

Adverse events (AEs) were assessed at each contact using open-ended questions and a self-administered questionnaire listing specific expected side effects for ET and venlafaxine. Newly emergent AEs were identified by comparing AE reports during treatment to each subject's baseline report.

Statistical analysis

Baseline characteristics were compared between treatment groups using t-tests or chi-square tests. Baseline VMS frequency was calculated as the mean of daily reported VMS in the first two screening weeks. The primary hypotheses for this trial were that low-dose oral ET and venlafaxine would each be superior to placebo in treating VMS frequency. Intent-to-treat analyses included all randomized participants who provided follow-up VMS diary data at week 4 and/or week 8 (n=330, 97%), regardless of treatment adherence. The primary outcome was the mean daily VMS frequency for the week prior to the week 4 and 8 study assessments. VMS severity and bother were similarly defined.

Treatment contrasts between placebo and each active group were computed as Wald-statistics from linear regression models summarizing VMS frequency, severity, bother, and HFRDIS at weeks 4 and 8 as a function of randomization assignment, clinical site, visit, and the baseline value of the outcome. Natural logarithm transformations were applied to VMS frequencies to accommodate modeling assumptions. Robust standard errors were calculated via generalized estimating equations to account for within-woman correlations between repeated measures. A post-hoc analysis of the relative efficacy of estradiol and venlafaxine for VMS frequency was conducted using the methods applied to the active vs. placebo comparisons.

Baseline menopausal symptoms and demographic characteristics hypothesized *a priori* to modify treatment response relative to placebo included: age, race, body mass index (BMI), menopausal status, smoking, VMS frequency, VMS duration, insomnia symptoms, sleep quality, depressive symptoms, anxiety symptoms, sexual function, and perceived stress.

Tests for interaction between these variables and treatment assignment were performed within the linear regression models, using continuous values of variables where possible, for each active vs. placebo comparison.

VMS clinical improvement (≥50% VMS frequency reduction), participant satisfaction, and adverse events were compared between each active treatment and placebo using chi-square or Fisher's exact test. Analyses were conducted using SAS Version 9.2 (SAS Institute, Inc.). All statistical tests were 2-sided. Primary analyses were considered statistically significant at $p<0.025$. Secondary analyses are exploratory and considered nominally statistically significant at $p<0.05$.

RESULTS

Among 339 women randomized, 96 (28.3%) received estradiol, 97 (28.6%) received venlafaxine, and 146 (43.1%) received placebo (Figure 1). There were no significant differences in baseline characteristics between groups (Table 1). 319 (94%) participants were adherent to study medication (taking ≥80% of dispensed pills), and 318 (94%) women provided completed diaries at 8 weeks of follow-up. Diary adherence was high: over 95% of analyzed weekly diaries were completed on at least 6 days at week 4, and similarly at week 8.

VMS frequency

The mean VMS frequency at baseline was 8.1 (SD 5.3)/day. Treatment with ET or venlafaxine was associated with a significant reduction in VMS frequency relative to placebo (Table 2). Mean VMS frequency at week 8 decreased to 3.9 (95% CI 2.9–4.9) VMS/day (53% reduction) in the estradiol group, to 4.4 (95% CI 3.5–5.3) VMS/day (48% reduction) in the venlafaxine group, and to 5.5 (95% CI 4.7–6.3) VMS/day (29% reduction) in the placebo group (Table 2 and Figure 2). Linear model estimates can be expressed as a 32% (95% CI 20–43%) decrease in mean VMS frequency through week 8 in the estradiol group relative to placebo, and a 20% (95% CI 7–31%) decrease in the venlafaxine group relative to placebo. Low-dose ET reduced VMS frequency by an additional 0.6 VMS/day relative to venlafaxine (95% CI ranges from 1.8 VMS/day greater reduction on ET relative to venlafaxine to 0.6 VMS/day greater reduction on venlafaxine relative to ET, $p=0.09$). This difference translates into a 15% greater decrease (95% CI ranging from a 30% greater reduction on ET relative to venlafaxine to a 2% greater reduction on venlafaxine relative to ET) based on model estimates.

There were no statistically significant interactions of treatment effects with age, race, BMI, smoking, menopause status, VMS duration, or baseline symptom levels (VMS frequency, insomnia symptoms, sleep quality, depressive symptoms, anxiety symptoms, sexual function, and perceived stress) for either venlafaxine or ET vs. placebo (all $p>0.05$, see eTables 1 and 2).

Secondary outcomes

Both ET and venlafaxine reduced VMS severity more than did placebo (Table 3). For VMS bother, the magnitude of each active intervention effect was similar, but the reduction was

statistically significant for ET relative to placebo, and not for venlafaxine. ET and venlafaxine each reduced HFRDIS scores more than did placebo. Clinical improvement at week 8 was significantly more common in both the ET and venlafaxine groups relative to placebo (56%, 51%, and 31%, $p<0.001$ and $p=0.003$, respectively). Results of analyses restricted to treatment-adherent participants were consistent with those of the intent-to-treat analyses.

Adverse events

Tolerability of treatment was high. Only 11 (3.2%) subjects stopped treatment due to AEs (4 ET, 5 venlafaxine, 2 placebo). Newly-emergent AEs were reported by 56%, 69%, and 62% of the ET, venlafaxine, and placebo groups, respectively (no significant differences from placebo; eTable 3). The most frequently reported AEs were insomnia on ET and fatigue on venlafaxine and placebo. Three participants reported suicidal ideation while on study medication (2.5% on ET; 0.7% on placebo; none on venlafaxine). Mean changes in systolic and diastolic blood pressure (SBP, DBP) were small, with SBP and DBP declining by 6.0 (SD 16.0) and 0.9 (SD 9.4) mmHg on ET, by 5.6 (SD 15.4) and 1.4 (SD 9.5) mmHg on placebo, and increasing by 0.5 (SD 14.5) and 2.1 (SD 8.7) mmHg on venlafaxine. Twelve women developed SBP >165 mmHg or DBP >95 mmHg (2.1% on ET, 10.4% on venlafaxine, 0 on placebo), all of whom had baseline SBP or DBP above the study population mean (SBP 123.4, SD 13.5 mmHg; DBP 76.2, SD 9.4 mmHg); the majority also had a baseline BMI above the population mean (28.3, SD 6.8 kg/m^2). Among women with a uterus, 6/73 (8.2%) on ET, 2/124 (1.6%) on placebo, and none on venlafaxine developed abnormal vaginal bleeding (any bleeding in postmenopausal women; 2+ cycles <21 days in perimenopausal women) on treatment, which was evaluated with a transvaginal ultrasound. Three of 6 estradiol-treated participants with abnormal bleeding had an endometrial echo complex >5 mm and underwent an endometrial biopsy, all of which revealed no evidence of hyperplasia or malignancy.

Participant satisfaction

Of 319 responding, treatment ssatisfaction was highest on ET (70%, $p<0.001$ compared to placebo), lowest on placebo (39%), and intermediate for venlafaxine (51%, $p=0.06$ compared to placebo). 23% on ET, 28% on venlafaxine, and 40% on placebo group guessed their treatment assignment correctly.

DISCUSSION

This is the first randomized controlled trial designed to simultaneously investigate the efficacy of low-dose oral estradiol and the SNRI venlafaxine in the treatment of menopause-related vasomotor symptoms. Results of this study show that during an 8-week treatment period, ET and venlafaxine were each more effective than placebo in reducing VMS frequency. We observed a 53% reduction with ET, 48% with venlafaxine, and 29% with placebo, translating into a 32% and 20% greater reduction with ET and venlafaxine relative to placebo, respectively. Consistent with the effect of each treatment on VMS frequency, ET and venlafaxine both improved the severity of VMS and the interference of VMS with daily life; the small reduction in VMS bother was significant only for ET. No demographic,

menopause, or symptom characteristics predicted differential response to either intervention. Both treatments were well tolerated, with newly emergent AEs consistent with their known side effects. These findings provide critical data for clinicians and midlife women making treatment decisions for VMS by showing that first-line hormonal and non-hormonal pharmacologic treatments for VMS are both well-tolerated and effective options for alleviating VMS.

The magnitude of reduction in VMS frequency we observed with each treatment is consistent with RCTs for low-dose estradiol,[21–23] venlafaxine,[11,12] and other serotonergic agents.[7,9] However, eligibility criteria in previous trials varied widely and doses of ET differed, precluding direct comparison. In contrast to previous ET trial eligibility criteria of 7+ moderate-to-severe VMS/day,[6,22,23] we required fewer VMS (2+/day) and not all VMS were required to be moderate or severe. The mean frequency of VMS at baseline was therefore lower than seen in previous ET trials,[6,22,23] and consistent with the majority of SSRI/SNRI trials targeting VMS.[7,11,12,24,25] Because stringent screening procedures established that participants had stable levels of VMS,[18] we were able to minimize our placebo response relative to those in other trials.[26,27]

We observed that low-dose ET reduced VMS frequency by an additional 0.6 VMS per day than did venlafaxine, with a 95% confidence interval ranging from a larger improvement with ET relative to venlafaxine to a small advantage of venlafaxine relative to ET. These data suggest that, if a difference in efficacy between the two active interventions exists, it is small and the magnitude is of uncertain clinical relevance. However, the sample size was not large enough to provide adequate power for a direct non-inferiority comparison between the two active treatments.

Results of this trial provide clinically relevant data about the magnitude of the effect of low-dose oral ET and an SNRI in improving VMS frequency, severity, bother and interference in the same population of symptomatic women, enabling standardization of the baseline symptom profile of treated participants for the first time. Our findings extend results of previous placebo-controlled trials of these individual treatments alone by demonstrating that SNRI have a meaningful therapeutic effect on VMS which is in the range of low-dose ET. Such validation supports a serotonergic mechanism of action for VMS reduction.

Our findings may be specific to the particular dose of each agent used, as well as the preparation and oral administration of ET. Previous studies have highlighted the dose-dependent efficacy of low-dose oral ET and conjugated equine estradiol (CEE).[6,21–23,28] In a 12-week trial, 17-beta-estradiol 0.5-mg reduced VMS by 65.5% (SD 34.0%) whereas 1.0-mg reduced VMS by 83.2% (SD 25.6%) and placebo reduced VMS by 47.5% (SD 37.2%).[23] Because of endometrial stimulation risks with prolonged us of unopposed ET,[23] our trial was restricted to 8 weeks of treatment. While our study is limited by the short-term duration of treatment and the relative efficacy beyond 8 weeks was not investigated, previous studies have shown limited additional improvement in VMS after 8 weeks of treatment with ET,[6,22,23] or venlafaxine.[11] In the current trial, we used low-dose ET because of recommendations to use the lowest effective ET dose.

An important strength of this trial is our racially diverse study population (one-third African-American) midlife cohort of both peri- and postmenopausal women. Our results show that, while VMS are reported more commonly by African-American women[1], there is no difference in their VMS frequency response to these treatments. Other patient-level characteristics, including baseline menopause status, VMS burden, sleep and mood symptoms, also did not identify subgroups with differential response to treatment.

Tolerability of both active treatments was high. Discontinuation due to adverse events was uncommon and did not differ significantly between treatments. While previous SSRI/SNRI studies in young adults with depression suggest treatment-emergent suicidal ideation occurs rarely, we did not observe this AE on the SNRI or in a prior SSRI trial conducted in non-depressed midlife women.[7] As expected, higher rates of abnormal vaginal bleeding warranting investigation occurred with ET, while increases in SBP and DBP to clinically significant thresholds occurred more commonly on venlafaxine. Elevated blood pressure on venlafaxine is well-described, with monitoring recommended, especially in those at greater baseline risk for hypertension.[29] The profile of women developing high blood pressure suggests that those at risk were disproportionately overweight or obese and had higher baseline SBP/DBP. Taken together, these data suggest that the active agents investigated were well tolerated but had distinct adverse effect profiles consistent with their respective known effects.

Overall, the results of this trial provide robust evidence of the efficacy of low-dose oral 17-beta estradiol and the non-hormonal SNRI venlafaxine for treatment of VMS associated with menopause. Low-dose oral estradiol and venlafaxine were both effective and well-tolerated treatments for peri- and postmenopausal women with bothersome vasomotor symptoms. Treatment decisions should weigh the risk profile of each agent for each individual woman, taking into account her risk factor status and personal preferences regarding treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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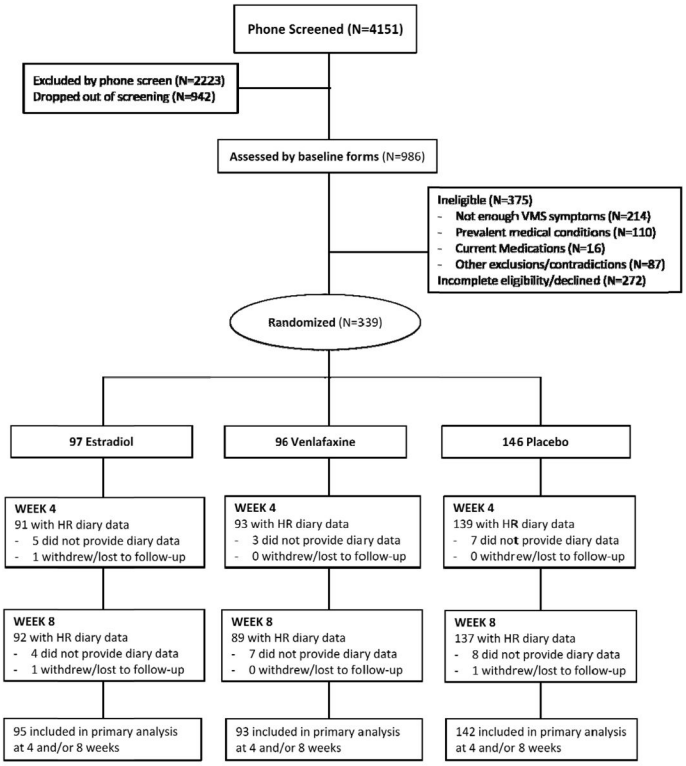

Figure 1.
CONSORT Diagram

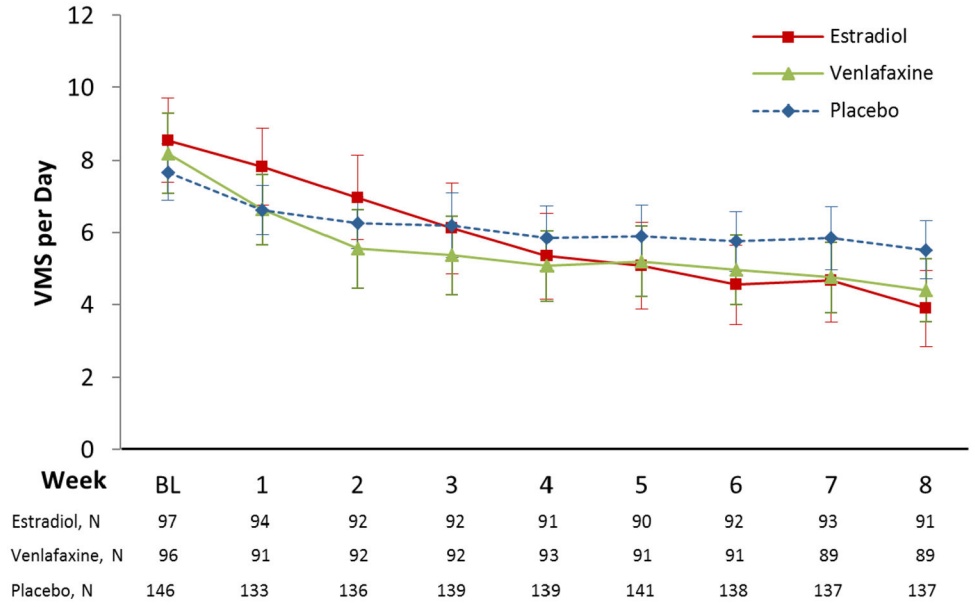

Figure 2.
Vasomotor Symptom (VMS) Frequency by Treatment Arm

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Table 1

Demographic and Clinical Characteristics by Treatment Arm at Baseline[1]

	All Participants		Estradiol		Venlafaxine		Placebo	
Total Participants	***339***		***97***		***96***		***146***	
Baseline Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age (years), mean (SD)	54.6 (3.8)		54.9 (4.1)		54.8 (3.7)		54.3 (3.8)	
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
BMI (kg/m^2), mean (SD)	28.3 (6.8)		28.5 (6.5)		29.3 (6.9)		27.6 (6.8)	
<30	225	66.4	66	68.0	59	61.5	100	68.5
≥ 30	107	31.6	30	30.9	34	35.4	43	29.5
Smoking								
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)								
<7	265	78.2	71	73.2	77	80.2	117	80.1
≥ 7	61	18.0	21	21.6	13	13.5	27	18.5
Marital status								
Never married/Divorced/Widowed	127	37.5	38	39.2	40	41.7	49	33.6
Married/living with partner	210	61.9	58	59.8	56	58.3	96	65.8
Education								
< College graduate	166	49.0	48	49.5	48	50.0	70	47.9
College graduate	172	50.7	49	50.5	48	50.0	75	51.4
Menopause status[1]								

	All Participants		Estradiol		Venlafaxine		Placebo	
Total Participants	*339*		*97*		*96*		*146*	
Baseline Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Perimenopausal	52	15.3	14	14.4	16	16.7	22	15.1
Postmenopausal	256	75.5	74	76.3	72	75.0	110	75.3
Indeterminate	31	9.1	9	9.3	8	8.3	14	9.6
Years since final menstrual period (postmenopausal only)								
0 - 5	135	52.7	32	43.2	37	51.4	66	60.0
6 - 10	72	28.1	23	31.1	20	27.8	29	26.4
> 10	42	16.4	16	21.6	13	18.1	13	11.8
VMS frequency/day	8.1 (5.3)		8.5 (5.7)		8.2 (5.5)		7.7 (4.9)	
<6	139	41.0	36	37.1	36	37.5	67	45.9
6 - <9	102	30.1	32	33.0	31	32.3	39	26.7
9 - <12	45	13.3	11	11.3	15	15.6	19	13.0
≥ 12	53	15.6	18	18.6	14	14.6	21	14.4
Age at starting VMS (years)								
<50	171	50.4	47	48.5	51	53.1	73	50.0
≥ 50	163	48.1	48	49.5	44	45.8	71	48.6
ISI, mean (SD)	11.0 (6.0)		11.0 (6.3)		11.7 (6.0)		10.4 (5.8)	
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
PSQI, mean (SD)	7.5 (3.4)		7.6 (3.6)		7.6 (3.2)		7.3 (3.5)	
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
PHQ-9 Depression, mean (SD)	3.4 (3.7)		3.9 (4.4)		3.0 (2.9)		3.4 (3.7)	

	All Participants		Estradiol		Venlafaxine		Placebo	
Total Participants	***339***		***97***		***96***		***146***	
Baseline Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
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
GAD-7 Anxiety, mean (SD)	2.5 (3.6)		3.0 (4.3)		2.2 (3.0)		2.4 (3.4)	
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

[1] No significant active vs. placebo group differences.

SD = standard deviation; BMI = body mass index; VMS = vasomotor symptoms; ISI = Insomnia Severity Index[30]; PSQI = Pittsburgh Sleep Quality Index[31]; PHQ = Patient Health Questionnaire[32]; GAD = Generalized Anxiety Disorder[33]

Table 2

Daily Vasomotor Symptom (VMS) Frequency at Weeks 4 and 8 by Treatment Arm

		Estradiol		Placebo	Difference	
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	p-value[1]
VMS Frequency[2]						<0.001
Baseline	97	8.5 (7.4, 9.7)	146	7.7 (6.9, 8.5)	0.9 (−0.5, 2.2)	
Week 4 – baseline	91	−3.1 (−4.0, −2.3)	139	−1.9 (−2.5, −1.3)	−1.2 (−2.2, −0.2)	
Week 8 – baseline	92	−4.5 (−5.4, −3.6)	137	−2.2 (−2.8, −1.6)	−2.3 (−3.4, −1.3)	

		Venlafaxine		Placebo	Difference	
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	p-value[1]
VMS Frequency[2]						0.005
Baseline	96	8.2 (7.1, 9.3)	146	7.7 (6.9, 8.5)	0.5 (−0.8, 1.8)	
Week 4 – baseline	93	−3.3 (−4.0, −2.5)	139	−1.9 (−2.5, −1.3)	−1.4 (−2.3, −0.4)	
Week 8 – baseline	89	−3.9 (−4.7, −3.1)	137	−2.2 (−2.8, −1.6)	−1.8 (−2.7, −0.8)	

CI = confidence interval; VMS = vasomotor symptoms

[1] p-values from active treatment vs. placebo contrasts in a repeated measures linear model of outcome as a function of treatment arm, clinical site, week (4 or 8), and baseline outcome

[2] VMS frequency values were log transformed for modeling

Table 3

Secondary Outcomes of Vasomotor Symptom (VMS) Severity, Bother, and Interference, at Week 8 by Treatment Group

Intervention	Estradiol	Placebo	Difference[1]		Venlafaxine	Placebo	Difference[1]	
	N	N	Mean (95% CI)	p-value[2]	N	N	Mean (95% CI)	p-value[2]
VMS Severity				0.02				0.02
Baseline	97	146	0.1 (0.0, 0.2)		96	146	0.0 (−0.1, 0.1)	
Week 8 – baseline	73	133	−0.3 (−0.4, −0.1)		86	133	−0.2 (−0.3, 0.0)	
VMS Bother				0.01				0.07
Baseline	97	146	0.1 (0.0, 0.2)		96	146	0.0 (−0.2, 0.1)	
Week 8 – baseline	73	133	−0.3 (−0.5, −0.1)		86	133	−0.2 (−0.3, 0.0)	
HFRDIS				<0.001				0.03
Baseline	90	141	4.2 (−1.7, 10.1)		92	141	4.0 (−1.8, 9.8)	
Week 8 – baseline	86	132	−9.3 (−15.3, −3.4)		84	132	−6.4 (−12.7, −0.1)	

CI = confidence interval; VMS = vasomotor symptoms; HFRDIS =Hot Flash-Related Daily Interference Scale[20]

[1] Outcome differences between active treatment and placebo

[2] P-values from active treatment vs. placebo contrasts in a repeated measures linear model of outcome as a function of treatment arm, clinical site, week (4 or 8), and baseline outcome