Original Investigation

Low-Dose Estradiol and the Serotonin-Norepinephrine Reuptake Inhibitor Venlafaxine for Vasomotor Symptoms
A Randomized Clinical Trial

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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 hydrochloride is used widely as a nonhormonal treatment. While the clinical impression is that serotonin-norepinephrine reuptake inhibitors are less effective than estrogen, these medications have not been simultaneously evaluated in one clinical trial to date.

OBJECTIVE To determine the efficacy and tolerability of low-dose oral 17β-estradiol and low-dose venlafaxine extended release in alleviating vasomotor symptoms (VMS).

DESIGN, SETTING, AND PARTICIPANTS In total, 339 perimenopausal and postmenopausal women with at least 2 bothersome VMS per day (mean, 8.1 per day) were recruited from the community to MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) clinical network sites between December 5, 2011, and October 15, 2012.

INTERVENTIONS Participants were randomized to double-blind treatment with low-dose oral 17β-estradiol (0.5 mg/d) (n = 97), low-dose venlafaxine hydrochloride extended release (75 mg/d) (n = 96), or placebo (n = 146) for 8 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was the mean daily frequency of VMS after 8 weeks of treatment. Secondary outcomes were VMS severity, bother, and interference with daily life. Intent-to-treat analyses compared the change in VMS frequency between each active intervention and placebo and between the 2 active treatments.

RESULTS Compared with baseline, the mean VMS frequency at week 8 decreased to 3.9 (95% CI, 2.9-4.9) VMS per day (52.9% reduction) in the estradiol group, to 4.4 (95% CI, 3.5-5.3) VMS per day (47.6% reduction) in the venlafaxine group, and to 5.5 (95% CI, 4.7-6.3) VMS per day (28.6% reduction) in the placebo group. Estradiol reduced the frequency of symptoms by 2.3 more per day than placebo (P < .001), and venlafaxine reduced the frequency of symptoms by 1.8 more per day than placebo (P = .005). The results were consistent for VMS severity, bother, and interference. Low-dose estradiol reduced the frequency of symptoms by 0.6 more per day than venlafaxine (P = .09). Treatment satisfaction was highest (70.3%) for estradiol (P < .001 vs placebo), lowest (38.4%) for placebo, and intermediate (51.1%) for venlafaxine (P = .06 vs placebo). Both interventions were well tolerated.

CONCLUSIONS AND RELEVANCE Low-dose oral estradiol and venlafaxine are effective treatments for VMS in women during midlife. While the efficacy of low-dose estradiol may be slightly superior to that of venlafaxine, the difference is small and of uncertain clinical relevance.

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Hot flashes and night sweats, together called vasomotor symptoms (VMS), are prevalent among women during midlife, affecting up to 80% of women.[1] Vasomotor symptoms are the primary menopause-related symptom leading perimenopausal and postmenopausal women to seek medical attention.[2] Estrogen therapy (ET) remains the gold standard treatment for VMS and was the only Food and Drug Administration-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[4] demonstrated associated risks in postmenopausal women. Because of these risks, current recommendations are that ET should be used at the lowest possible dosage for the shortest possible duration,[5] shifting use patterns to lower-dose preparations. Evidence suggests that low-dose ET preparations diminish VMS but to a lesser extent than standard dosages and with a slower onset of action.[6]

Since the publication of the Women's Health Initiative[4] results, investigation of nonhormonal treatments for VMS has intensified. Many SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been shown to be more effective than placebo in reducing VMS,[7-9] with one SSRI recently approved by the Food and Drug Administration to treat VMS.[3,9] The SNRI venlafaxine hydrochloride is one of the most widely studied serotonergic agents, with accumulating evidence showing that low dosages (75-150 mg/d) reduce VMS more than placebo.[10-12] The SSRIs and SNRIs are widely used to treat VMS, with venlafaxine being a first-line treatment in women unable or unwilling to use ET.[13,14]

While the clinical impression is that SSRI and SNRI medications are less effective than ET,[8,15] to our knowledge, trials simultaneously examining the efficacy of these agents have not been conducted. In addition, most ET trials have used dosages higher than the 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 a National Institutes of Health–funded research network designed to test treatments for menopause-related symptoms.[17] We report the results of a 3-arm double-blind trial randomizing healthy perimenopausal and postmenopausal women with bothersome VMS to low-dose oral 17β-estradiol, low-dose venlafaxine, or placebo for 8 weeks. The primary objective of this trial was to determine the efficacy and tolerability of ET and venlafaxine relative to placebo in reducing the number of VMS reported. We hypothesized that ET and venlafaxine would be superior to placebo in reducing VMS frequency and, secondarily, that both active agents would improve VMS severity, bother, and interference with daily life more than placebo.

Methods

Trial Design

The study was approved by each site's institutional review board. All participants provided written informed consent. This was a multisite, randomized, placebo-controlled 8-week trial of oral 17β-estradiol (0.5 mg/d), low-dose venlafaxine hydrochloride extended release (75 mg/d), and placebo. Those randomized to venlafaxine hydrochloride were titrated from 37.5 up to 75 mg/d during a 1-week period. Details about the MsFLASH research network and study designs are published elsewhere.[17,18]

Eligible women were randomly assigned to treatment in a 2:2:3 ratio (ratio of ET to venlafaxine to placebo) to increase the efficiency of the trial design for the 2 primary comparisons between each active treatment and placebo. Allowing for a 10% follow-up loss, a sample size of 304 (339 enrolled) provided greater than 90% power to detect a 0.52-SD unit difference in the 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 clinical network sites in Boston, Massachusetts, Philadelphia, Pennsylvania, and Seattle, Washington, were recruited between December 5, 2011, and October 15, 2012. Mass mailings to age-eligible women were performed using purchased mailing lists and health plan enrollment files.

Eligible participants were healthy women aged 40 to 62 years in the menopause transition (amenorrhea ≥60 days in the past year), were postmenopausal (≥12 months since the last menstrual period or bilateral oophorectomy), or had a follicle-stimulating hormone level exceeding 20 mIU/mL and an estradiol level not exceeding 50 pg/mL in the absence of a reliable menstrual marker (hysterectomy with ovarian preservation, progesterone-releasing intrauterine device, or endometrial ablation) (to convert follicle-stimulating hormone level to international units per liter, multiply by 1.0; to convert estradiol level to picomoles per liter, multiply by 3.671). Participants were required to have at least 14 VMS per week, at least some of which were considered bothersome or severe, recorded prospectively in 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 were applied. These included pregnancy or breastfeeding; suicide attempt in the past 3 years; diagnosis of bipolar disorder or psychosis; hypersensitivity or contraindication to study medications; psychotropic medications or treatments for VMS (past month); major depressive episode or drug or alcohol abuse in the past year; recent or current use (past 2 months) of hormone therapy, hormonal contraceptives, selective estrogen receptor modulators, or aromatase inhibitors; and history of uncontrolled hypertensive, cardiovascular, thrombotic, or endometrial disease, prebreast 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, and at 8 weeks), and 2 telephone assessments (at 1 and 4 weeks). Participants com-

Figure 1. Consolidated Standards of Reporting Trials Diagram
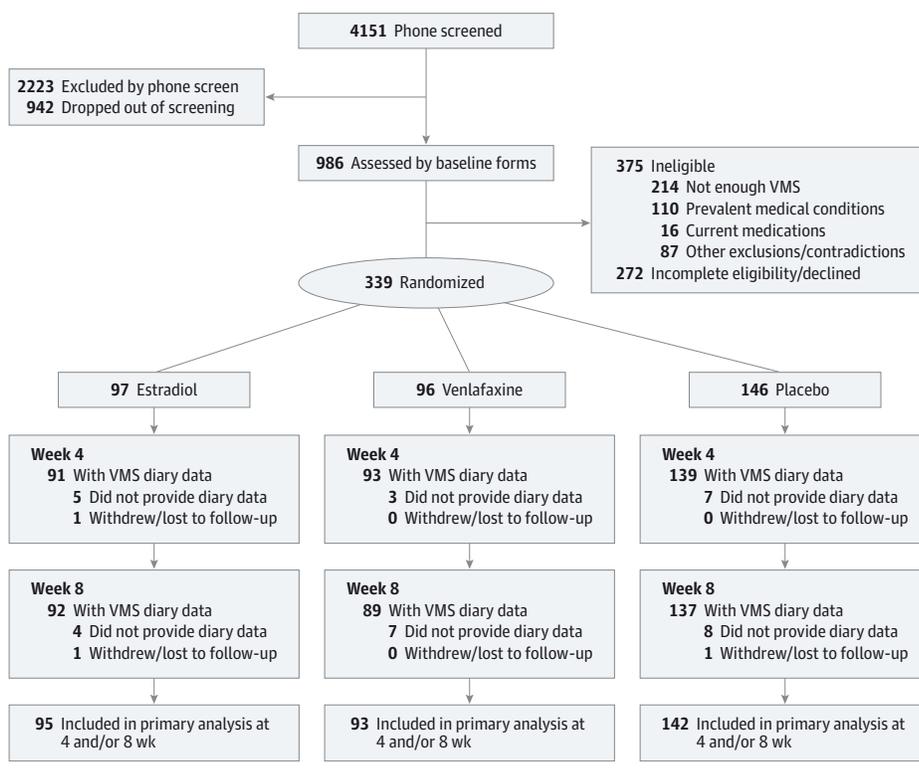
VMS indicates vasomotor symptoms.

pleted questionnaires at baseline and at 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 1 identical-appearing pill orally each day. Using a dynamic randomization algorithm,[19] participants were randomized to 1 of 3 arms (ET, venlafaxine, or placebo) (Figure 1), stratified by 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 posttreatment medications could be administered. Study pills were counted at week 8 to estimate adherence.

Estrogen therapy was administered as 17β-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.

Measurements

Vasomotor symptom frequency, bother, and severity were recorded daily in the morning and evening. The primary outcome was VMS frequency. Secondary outcomes were VMS severity (rated as 1 [mild], 2 [moderate], or 3 [severe]), VMS bother (rated as 1 [none], 2 [a little], 3 [moderate], or 4 [a lot]), and

perceived VMS interference (Hot Flash Related Daily Interference Scale[20] scores evaluated at baseline, 4 weeks, and 8 weeks).

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

Statistical Analysis

Baseline characteristics were compared between treatment groups using t test or χ^2 test. Baseline VMS frequency was calculated as the mean of daily reported VMS in the first 2 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, week 8, or both (provided by 330 participants [97.3%]), regardless of treatment adherence. The primary outcome was the mean daily VMS frequency for the week before the week 4 and week 8 study assessments. Vasomotor symptom 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 the Hot Flash Related Daily Interference Scale scores at week 4 and week 8 as a function of randomization assignment, clini-

Table 1. Demographic and Clinical Characteristics by Treatment Group at Baseline[a]

Baseline Characteristic	All Participants (N = 339)	Estradiol (n = 97)	Venlafaxine (n = 96)	Placebo (n = 146)
Age, mean (SD), y	54.6 (3.8)	54.9 (4.1)	54.8 (3.7)	54.3 (3.8)
Race/ethnicity, No. (%)				
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 or unknown	**20** (5.9)	5 (5.2)	5 (5.2)	10 (6.8)
BMI				
Mean (SD)	28.3 (6.8)	28.5 (6.5)	29.3 (6.9)	27.6 (6.8)
<30, No. (%)	**225** (66.4)	66 (68.0)	59 (61.5)	100 (68.5)
≥30, No. (%)	**107** (31.6)	30 (30.9)	34 (35.4)	43 (29.5)
Smoking, No. (%)				
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 drinks per week, No. (%)				
<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, No. (%)				
Never married, divorced, or widowed	**127** (37.5)	38 (39.2)	40 (41.7)	49 (33.6)
Married or living with partner	**210** (61.9)	58 (59.8)	56 (58.3)	96 (65.8)
Education, No. (%)				
<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)
Menopausal status, No. (%)				
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)

(continued)

cal site, visit, and 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/ethnicity, body mass index, 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.

Vasomotor symptom clinical improvement (≥50% VMS frequency reduction), participant satisfaction, and AEs were compared between each active treatment and placebo using χ² test or Fisher exact test. Analyses were conducted using statistical software (SAS version 9.2; SAS Institute, Inc). All statistical tests were 2-sided. Primary analyses were considered sta-

tistically significant at *P* < .025. Secondary analyses were exploratory and considered nominally statistically significant at *P* < .05.

Results

Among 339 women randomized, 97 (28.6%) received estradiol, 96 (28.3%) received venlafaxine, and 146 (43.1%) received placebo (Figure 1). No significant differences in baseline characteristics were observed between groups (**Table 1**). In total, 319 participants (94.1%) were adherent to study medication (taking ≥80% of dispensed pills), and 318 participants (93.8%) provided completed diaries at follow-up week 8. Diary adherence was high: more than 95% of analyzed weekly diaries were completed on at least 6 days at week 4 and similarly at week 8.

VMS Frequency
The mean (SD) VMS frequency at baseline was 8.1 (5.3) per day. Treatment with ET or venlafaxine was associated with a significant reduction in VMS frequency relative to placebo (**Table 2**). Compared with baseline, the mean VMS frequency at week 8 decreased to 3.9 (95% CI, 2.9-4.9) VMS per day (52.9%

Table 1. Demographic and Clinical Characteristics by Treatment Group at Baseline[a] (continued)

Baseline Characteristic	All Participants (N = 339)	Estradiol (n = 97)	Venlafaxine (n = 96)	Placebo (n = 146)
Time since final menstrual period among postmenopausal women only, No. (%)[b]	(n = 256)	(n = 74)	(n = 72)	(n = 110)
0-5 y	142 (55.5)	35 (47.3)	39 (54.2)	68 (61.8)
6-10 y	72 (28.1)	23 (31.1)	20 (27.8)	29 (26.4)
>10 y	42 (16.4)	16 (21.6)	13 (18.1)	13 (11.8)
VMS frequency per day, No. (%)	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 to <9	102 (30.1)	32 (33.0)	31 (32.3)	39 (26.7)
9 to <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 first VMS, No. (%)				
<50 y	171 (50.4)	47 (48.5)	51 (53.1)	73 (50.0)
≥50 y	163 (48.1)	48 (49.5)	44 (45.8)	71 (48.6)
Insomnia symptoms (ISI score)				
Mean (SD)	11.0 (6.0)	11.0 (6.3)	11.7 (6.0)	10.4 (5.8)
No clinically significant insomnia score ≤7, No. (%)	106 (31.3)	28 (28.9)	26 (27.1)	52 (35.6)
Subthreshold insomnia score 8-14, No. (%)	133 (39.2)	40 (41.2)	39 (40.6)	54 (37.0)
Moderate clinical insomnia score 15-21, No. (%)	78 (23.0)	21 (21.6)	25 (26.0)	32 (21.9)
Severe clinical insomnia score ≥22, No. (%)	14 (4.1)	5 (5.2)	5 (5.2)	4 (2.7)
Sleep quality (PSQI score)				
Mean (SD)	7.5 (3.4)	7.6 (3.6)	7.6 (3.2)	7.3 (3.5)
Good quality (<5), No. (%)	67 (19.8)	23 (23.7)	14 (14.6)	30 (20.5)
Moderate quality (5 to <8), No. (%)	102 (30.1)	21 (21.6)	35 (36.5)	46 (31.5)
Poor quality (≥8), No. (%)	151 (44.5)	46 (47.4)	40 (41.7)	65 (44.5)
Depressive symptoms (PHQ-9 score)				
Mean (SD)	3.4 (3.7)	3.9 (4.4)	3.0 (2.9)	3.4 (3.7)
No symptoms (0-4), No. (%)	246 (72.6)	68 (70.1)	70 (72.9)	108 (74.0)
Mild symptoms (5-9), No. (%)	64 (18.9)	18 (18.6)	23 (24.0)	23 (15.8)
Moderate symptoms (≥10), No. (%)	29 (8.6)	11 (11.3)	3 (3.1)	15 (10.3)
Anxiety symptoms (GAD-7 score)				
Mean (SD)	2.5 (3.6)	3.0 (4.3)	2.2 (3.0)	2.4 (3.4)
No symptoms (0-4), No. (%)	265 (78.2)	73 (75.3)	76 (79.2)	116 (79.5)
Mild symptoms (5-9), No. (%)	51 (15.0)	15 (15.5)	17 (17.7)	19 (13.0)
Moderate symptoms (≥10), No. (%)	23 (6.8)	9 (9.3)	3 (3.1)	11 (7.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GAD-7, Generalized Anxiety Disorder 7-Item Scale[21]; ISI, Insomnia Severity Index[22]; PHQ-9, Patient Health Questionnaire[23]; PSQI, Pittsburgh Sleep Quality Index[24]; VMS, vasomotor symptom.

[a] No significant active vs placebo group differences.

[b] Includes naturally postmenopausal women with at least 12 months of amenorrhea and those who underwent bilateral oophorectomy, regardless of the time since surgery.

reduction) in the estradiol group, to 4.4 (95% CI, 3.5-5.3) VMS per day (47.6% reduction) in the venlafaxine group, and to 5.5 (95% CI, 4.7-6.3) VMS per day (28.6% reduction) in the placebo group (Table 2 and **Figure 2**). Linear model estimates can be expressed as a 32.4% (95% CI, 20.1%-42.8%) decrease in the mean VMS frequency through week 8 in the estradiol group relative to placebo and as a 19.6% (95% CI, 6.9%-30.7%) decrease in the venlafaxine group relative to placebo. Low-dose ET reduced VMS frequency by an additional 0.6 VMS per day relative to venlafaxine (the 95% CI ranges from 1.8 VMS per day greater reduction with ET relative to venlafaxine to 0.6 VMS per day greater reduction with venlafaxine relative to ET) (P = .09). This difference translates into a 15.2% greater decrease (the 95% CI ranges from a 29.8% greater reduction with ET relative to venlafaxine to a 2.4% greater reduction with venlafaxine relative to ET) based on model estimates.

No statistically significant interactions of treatment effects were observed with age, race/ethnicity, body mass index, smoking, menopausal status, VMS duration, or baseline symptom level frequency (insomnia symptoms,[22] sleep quality,[24] depressive symptoms,[23] anxiety symptoms,[21] sexual function,[25] and perceived stress[26]) for venlafaxine or ET vs placebo (P > .05 for all). These results are listed in greater detail in eTable 1 and eTable 2 in the Supplement.

Secondary Outcomes

Both ET and venlafaxine reduced VMS severity more than 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. Estrogen therapy and venlafaxine each reduced the Hot Flash Related Daily Interference Scale scores more than pla-

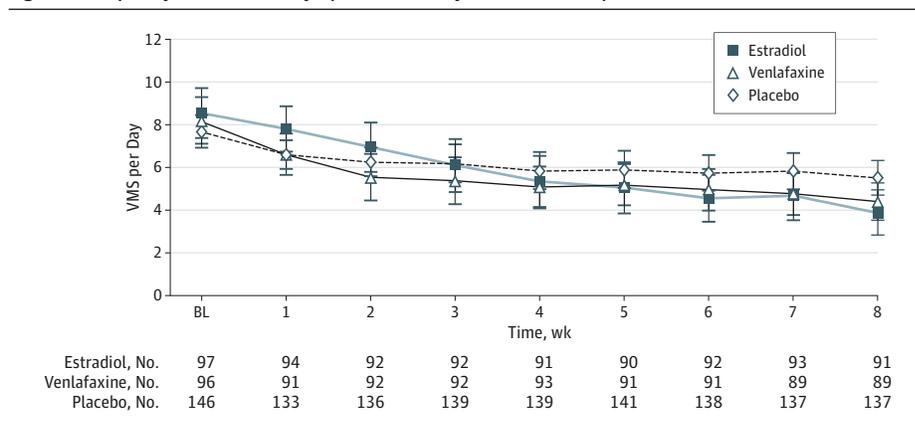Table 2. Daily Vasomotor Symptom (VMS) Frequency at Week 4 and Week 8 by Treatment Group

VMS Frequency[a]	No.	Mean (95% CI)	No.	Mean (95% CI)	Mean (95% CI)	P Value[b]
		Estradiol		Placebo	Difference	
Baseline	97	8.5 (7.4 to 9.7)	146	7.7 (6.9 to 8.5)	0.9 (−0.5 to 2.2)	
Week 4 minus baseline	91	−3.1 (−4.0 to −2.3)	139	−1.9 (−2.5 to −1.3)	−1.2 (−2.2 to −0.2)	<.001
Week 8 minus baseline	92	−4.5 (−5.4 to −3.6)	137	−2.2 (−2.8 to −1.6)	−2.3 (−3.4 to −1.3)	
		Venlafaxine		Placebo	Difference	
Baseline	96	8.2 (7.1 to 9.3)	146	7.7 (6.9 to 8.5)	0.5 (−0.8 to 1.8)	
Week 4 minus baseline	93	−3.3 (−4.0 to −2.5)	139	−1.9 (−2.5 to −1.3)	−1.4 (−2.3 to −0.4)	.005
Week 8 minus baseline	89	−3.9 (−4.7 to −3.1)	137	−2.2 (−2.8 to −1.6)	−1.8 (−2.7 to −0.8)	

[a] Vasomotor symptom frequency values were natural logarithm transformed for modeling.

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

Figure 2. Frequency of Vasomotor Symptoms (VMS) by Treatment Group

	BL	1	2	3	4	5	6	7	8
Estradiol, No.	97	94	92	92	91	90	92	93	91
Venlafaxine, No.	96	91	92	92	93	91	91	89	89
Placebo, No.	146	133	136	139	139	141	138	137	137

BL indicates baseline.

cebo. Clinical improvement at week 8 was significantly more common in the ET and venlafaxine groups relative to placebo (56.5%, 50.6%, and 30.7%, respectively) (*P* < .001 and *P* = .003, respectively). The 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 participants (3.2%) stopped treatment because of AEs (4 with ET, 5 with venlafaxine, and 2 with placebo). Newly emergent AEs were reported by 56.4%, 69.2%, and 62.0% in the ET, venlafaxine, and placebo groups, respectively (no significant differences from placebo) (eTable 3 in the Supplement). The most frequently reported AEs were insomnia with ET and fatigue with venlafaxine and placebo. Three participants reported suicidal ideation when taking study medication (2.5% with ET, 0.7% with placebo, and none with venlafaxine). The mean changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were small, with the mean (SD) SBP and DBP, respectively, declining by 6.0 (16.0) and 0.9 (9.4) mm Hg with ET and by 5.6 (15.4) and 1.4 (9.5) mm Hg with placebo and increasing by 0.5 (14.5) and 2.1 (8.7) mm Hg with venlafaxine. Twelve women developed an SBP exceeding 165 mm Hg or a DBP exceeding 95 mm Hg (2.1% with ET,

10.4% with venlafaxine, and none with placebo), all of whom had baseline SBP or DBP above the mean (SD) of the study population (123.4 [13.5] mm Hg for SBP and 76.2 [9.4] mm Hg for DBP); most also had a mean (SD) baseline body mass index (calculated as weight in kilograms divided by height in meters squared) above the mean (SD) of the study population (28.3 [6.8]). Among women with a uterus, 6 of 73 (8.2%) receiving ET, 2 of 124 (1.6%) receiving placebo, and none receiving venlafaxine developed abnormal vaginal bleeding (any bleeding in postmenopausal women or ≥2 cycles during <21 days in perimenopausal women) when receiving treatment, which was evaluated with transvaginal ultrasonography. Three of 6 estradiol-treated participants with abnormal bleeding had an endometrial echo complex exceeding 5 mm and underwent an endometrial biopsy, all of which revealed no evidence of hyperplasia or malignancy.

Participant Satisfaction

Of 319 responding, treatment satisfaction was highest at 70.3% for ET (*P* < .001 compared with placebo), lowest at 38.4% for placebo, and intermediate at 51.1% for venlafaxine (*P* = .06 compared with placebo). In total, 22.8% receiving ET, 27.8% receiving venlafaxine, and 40.3% receiving placebo guessed their treatment assignment correctly.

Table 3. Secondary Outcomes of Vasomotor Symptom (VMS) Severity, Bother, and Interference at Week 8 by Treatment Group

Intervention	Estradiol, No.	Placebo, No.	Difference, Mean (95% CI)[a]	P Value[b]	Venla-faxine, No.	Placebo, No.	Difference, Mean (95% CI)[a]	P Value[b]
VMS severity								
Baseline	97	146	0.1 (0.0 to 0.2)	.02	96	146	0.0 (−0.1 to 0.1)	.02
Week 8 minus baseline	73	133	−0.3 (−0.4 to −0.1)		86	133	−0.2 (−0.3 to 0.0)	
VMS bother								
Baseline	97	146	0.1 (0.0 to 0.2)	.01	96	146	0.0 (−0.2 to 0.1)	.07
Week 8 minus baseline	73	133	−0.3 (−0.5 to −0.1)		86	133	−0.2 (−0.3 to 0.0)	
HFRDIS								
Baseline	90	141	4.2 (−1.7 to 10.1)	<.001	92	141	4.0 (−1.8 to 9.8)	.03
Week 8 minus baseline	86	132	−9.3 (−15.3 to −3.4)		84	132	−6.4 (−12.7 to −0.1)	

Abbreviation: HFRDIS, Hot Flash Related Daily Interference Scale.[20]

[a] Outcome difference between active treatment and placebo.

[b] P value from active treatment vs placebo contrasts in a repeated-measures

linear model of outcome as a function of treatment group, clinical site, week (4 or 8), and baseline outcome.

Discussion

This is the first randomized clinical trial to date designed to simultaneously investigate the efficacy of low-dose oral estradiol and the SNRI venlafaxine in the treatment of menopause-related VMS. The 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 52.9% reduction with ET, a 47.6% reduction with venlafaxine, and a 28.6% reduction with placebo, translating into a 32.4% and 19.6% greater reduction with ET and venlafaxine relative to placebo, respectively. Consistent with the effect of each treatment on VMS frequency, ET and venlafaxine 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, menopausal, or symptom characteristics predicted differential response to either intervention. Both treatments were well tolerated, with newly emergent AEs consistent with their known adverse effects. These findings provide critical data for physicians and women making treatment decisions for VMS by showing that first-line hormonal and nonhormonal pharmacologic treatments for VMS are well tolerated and effective options for alleviating VMS.

The magnitude of reduction in VMS frequency that we observed with each treatment is consistent with the results of randomized clinical trials for low-dose estradiol,[27-29] venlafaxine,[11,12] and other serotonergic agents.[7,9] However, eligibility criteria in previous trials varied widely, and dosages of ET differed, precluding direct comparison. In contrast to previous ET trial eligibility criteria of at least 7 moderate to severe VMS per day,[6,28,29] we required fewer VMS (≥2 per day), and not all VMS were required to be moderate or severe. Therefore, the mean frequency of VMS at baseline was lower than that seen in previous ET trials[6,28,29] and was consistent with most SSRI and SNRI trials targeting VMS.[7,11,12,30,31] Because stringent screening procedures established that participants had stable levels of VMS,[18] we were able to minimize our placebo response relative to that in other trials.[32,33]

We observed that low-dose ET reduced VMS frequency by an additional 0.6 VMS per day compared with venlafaxine, with the 95% CI ranging from a larger improvement with ET relative to venlafaxine to a smaller advantage with venlafaxine relative to ET. If a difference in the efficacy between the 2 active interventions exists, these data suggest that it is small and that the magnitude is of uncertain clinical relevance. However, the sample size was not large enough to provide adequate power for a direct noninferiority comparison between the 2 active treatments.

The 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 baseline symptom profiles of treated participants for the first time to date. Our findings extend the results of previous placebo-controlled trials[11,34] of these individual treatments alone by demonstrating that SNRIs have a meaningful therapeutic effect on VMS, which is in the range of that with low-dose ET. Such validation supports a serotonergic mechanism of action for VMS reduction.

Our findings may be specific to the particular dosage of each agent used, as well as the preparation and oral administration of ET. Previous studies[6,27-29,35] have highlighted the dose-dependent efficacy of low-dose oral ET and conjugated equine estradiol. In a 12-week trial of mean (SD) symptom reduction, 17β-estradiol (0.5 mg/d) reduced VMS by 65.5% (34.0%), 17β-estradiol at a higher dosage (1.0 mg/d) reduced VMS by 83.2% (25.6%), and placebo reduced VMS by 47.5% (37.2%).[29] Because of endometrial stimulation risks with prolonged use of unopposed ET,[29] our trial was restricted to 8 weeks of treatment. While our study was limited because the short-term duration of treatment and the relative efficacy beyond 8 weeks were not investigated, previous studies have shown limited additional improvement in VMS after 8 weeks of treatment with ET[6,28,29] or venlafaxine.[11] In the present trial, we evaluated low-dose ET because of recommendations to use the lowest effective ET dosage.[5]

An important strength of this trial is our racially/ethnically diverse (one-third African American) midlife cohort of perimenopausal and postmenopausal women. Although VMS are reported more commonly by African American women,[1] no difference was observed herein in their VMS frequency response to these treatments. Other patient-level characteristics, including baseline menopausal status, VMS frequency, sleep quality, and mood symptoms, also did not identify subgroups with differential response to treatment.

Tolerability of both active treatments was high. Discontinuation because of AEs was uncommon and did not differ significantly between treatments. While previous SSRI and SNRI investigations in young adults with depression suggest that treatment-emergent suicidal ideation occurs rarely,[36] we did not observe this AE for the SNRI or in a prior SSRI trial conducted in nondepressed women during midlife.[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 with venlafaxine. Elevated blood pressure associated with the use of venlafaxine is well described,

with monitoring recommended, especially in those at greater baseline risk for hypertension.[37] The profile of women developing high blood pressure suggests that those at risk were disproportionately overweight or obese and had higher baseline SBP and 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.

Conclusions

Overall, the results of this trial provide robust evidence of the efficacy of low-dose oral 17β-estradiol and the nonhormonal SNRI venlafaxine for the treatment of VMS associated with menopause. Low-dose oral estradiol and venlafaxine were effective and well-tolerated treatments for perimenopausal and postmenopausal women with bothersome VMS. 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.

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