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Effects of estrogen and 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: This study aims to evaluate the effects of low-dose estradiol (E_2) or venlafaxine on menopause-related quality of life and associated symptoms in healthy perimenopausal and postmenopausal women with hot flashes.

Methods: A double-blind, placebo-controlled, randomized trial of low-dose oral 17β-E_2 0.5 mg/day and venlafaxine XR 75 mg/day, versus identical placebo, was conducted among 339 women (aged 40-62 y) experiencing two or more vasomotor symptoms (VMS) per day (mean [SD], 8.07 [5.29]) who were recruited at three clinical sites from November 2011 to October 2012. The primary trial outcome, as reported previously, was 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 from measures of pain (Pain, Enjoyment in life, and General activity scale), depression (Patient Health Questionnaire-9), anxiety (Generalized Anxiety Disorder Questionnaire-7), and perceived stress (Perceived Stress Scale).

Results: Treatment with both E_2 and venlafaxine resulted in significantly greater improvement in quality of life, as measured by total MENQOL scores, compared with placebo (E_2: mean difference at 8 wk, −0.4; 95% CI, −0.7 to −0.2; $P < 0.001$; venlafaxine: mean difference at 8 wk, −0.2; 95% CI, −0.5 to 0.0; $P = 0.04$). Quality-of-life domain analyses revealed that E_2 had beneficial treatment effects on all domains of the MENQOL except for the psychosocial domain, whereas venlafaxine benefits were observed only in the psychosocial domain. Neither E_2 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 E_2 and venlafaxine are effective pharmacologic agents for improving menopause-related quality of life in healthy women with VMS.

Key Words: Estrogen – Venlafaxine – Menopause – Quality of life – Pain – Stress.

More than 38 million US women aged 45 to 64 years (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

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that the symptoms affect, or are accompanied by, problems with sleep, mood, pain, concentration, and energy levels, resulting in a 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 evaluation of such treatments should include the impact on commonly affected quality-of-life domains. Because use of estradiol (E_2; at low doses), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for VMS is increasing, we need evidence on the magnitude of the treatment effects of low-dose estrogen and serotonergic agents versus placebo on 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) network recently completed a three-arm double-blind trial of low-dose oral 17β-E_2, low-dose venlafaxine (serotonergic agent), and placebo for 8 weeks to examine the efficacy of both E_2 and venlafaxine, relative to placebo, in reducing the number of VMS that women experience. We have previously described that both E_2 and venlafaxine were superior to placebo in reducing the frequency of VMS.[4] The purpose of this report is to examine the impact of both low-dose estrogen and the nonhormonal SNRI alternative venlafaxine, compared with placebo, on menopause-related quality of life, pain, anxiety, depressive symptoms, and perceived stress. The consistency of these interventions on overall quality of life across subgroups of women defined by race/ethnicity, menopause stage, pretreatment VMS frequency or severity, and other baseline characteristics was also evaluated.

METHODS

An 8-week three-arm, double-blind, placebo-controlled, randomized trial of low-dose oral 17β-E_2 0.5 mg/day, venlafaxine XR 75 mg/day, or placebo was conducted for relief of hot flash frequency among symptomatic women (aged 40-62 y) in the menopausal transition who were 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 a written informed consent form.

The trial enrolled 339 women from November 2011 to October 2012. Women were eligible for the study if they were aged 40 to 62 years, were in generally good health, were in the menopausal transition or postmenopausal, and reported 14 or more hot flashes/night sweats per week (recorded on daily diaries for 3 wk) rated as bothersome or severe at least four times per week. Screening procedures were designed to exclude women whose Patient Health Questionnaire-9 (PHQ-9) 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 2 months; current severe illness, major depressive episode, drug abuse, or alcohol abuse in the past year; suicide attempt in the past 3 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

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

Estrogen therapy was administered as 17β-E_2 (0.5 mg/d) for 8 weeks; after unblinding, medroxyprogesterone acetate (10 mg/d) was given orally for 14 days for endometrial protection. Those assigned to venlafaxine hydrochloride received 37.5 mg/day for 1 week and then 75 mg/day for 7 weeks; after unblinding, the dose was tapered to 37.5 mg/day for another 14 days to minimize potential SNRI withdrawal effects.

Data collection

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

Outcomes questionnaires

Menopause-related quality of life was evaluated by the Menopause-Specific Quality of Life Questionnaire (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 vasomotor, physical, psychosocial, and sexual functioning domains among midlife women in the menopausal transition. For each item, women were asked to report if they had experienced that symptom or feeling in the past

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4 weeks and, if they had, to rate bother on a scale of 0 (*not bothered at all*) to 6 (*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 mean of 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 Pain, Enjoyment in life, and General activity (PEG) scale, a three-item scale asking participants to report their level of average pain during the past week on a scale of 0 (*no pain*) to 10 (*pain as bad as you can imagine*); how much pain has interfered with enjoyment during 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 nine-item version of the depression module of the 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 seven-item Generalized Anxiety Disorder Questionnaire-7 (GAD-7), which can likewise be scored either continuously (as an anxiety severity score) or categorically (with cutpoints indicating 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, menopause status (menopausal transition, postmenopause, and 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 (seven-item Insomnia Severity Index),[12] subjective sleep quality (Pittsburgh Sleep Quality Index),[13,14] depressive symptoms (PHQ-9),[9] anxiety (GAD-7),[10] and sexual function (19-item Female Sexual Function Index).[15]

Statistical analysis

A modified intent-to-treat analysis included all randomized participants who provided follow-up quality of life or symptom data on week 4, week 8, or both, regardless of treatment adherence.

Among the cohort of 339 randomized participants, data on one or more MENQOL domains were available for 336 women (99.1%) at baseline and for 331 women (97.6%) at 4 weeks and/or 8 weeks of follow-up. Similarly for the PEG scale, PHQ-9, GAD-7, and PSS, data were available, respectively, for 339 women (100%) at baseline and for 331 women (96.7%) on 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 scale, PHQ-9, GAD-7, and PSS) at both 4 and 8 weeks as a function of treatment assignment, with each model adjusted 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 whether 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 menopause-related quality of life, as measured by the MENQOL, might be modified by baseline characteristics, including race, menopause 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 (week 4 or week 8), covariate of interest, and interaction between treatment assignment and covariate, with models adjusted for race, site, and baseline MENQOL. Reported P values were based on Wald statistics, with two-sided $P < 0.05$ considered statistically significant. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 339 women, including 116 African-American women (34.2%), were randomly assigned to E_2 (n = 96), venlafaxine (n = 97), or placebo. The mean age of study participants was 54.6 years, 75.2% were postmenopausal, 15.6% were in the menopausal transition, and the mean (SD) number of VMS per day at enrollment was 8.1 (5.3). There were no significant differences in baseline characteristics between the randomized treatment groups (Table 1). During the 8-week treatment period, 94% of the women in each group were adherent to their study medication (adherence defined as taking at least 80% of dispensed pills).

The mean total MENQOL scores were 3.5 (E_2), 3.7 (venlafaxine), and 3.5 (placebo) at baseline; scores declined (i.e., quality of life improved) in both treatment groups compared with placebo on weeks 4 and 8 (Fig.).

For MENQOL, the mean difference from baseline to 8 weeks was −0.4 (95% CI, −0.7 to −0.2; $P < 0.001$) between E_2 and placebo and −0.2 (95% CI, −0.5 to −0.0; $P = 0.042$) between venlafaxine and placebo (Table 2). Statistically significant treatment group differences favoring E_2 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 with no effect seen in the psychosocial domain. In contrast, for venlafaxine compared with placebo, the only statistically significant treatment group improvement was that in the psychosocial domain.

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TABLE 1. *Baseline characteristics*

Baseline characteristics	All participants (N = 339)	Estradiol (n = 97)	Venlafaxine (n = 96)	Placebo (n = 146)	*P*	
					Estradiol vs placebo	Venlafaxine vs placebo
Age at screening, mean (SD), y	54.6 (3.8)	54.9 (4.1)	54.8 (3.7)	54.3 (3.8)		
Age category, n (%)					0.23	0.28
<50 y	30 (8.8)	9 (9.3)	8 (8.3)	13 (8.9)		
50-54 y	147 (43.4)	39 (40.2)	41 (42.7)	67 (45.9)		
55-59 y	123 (36.3)	34 (35.1)	36 (37.5)	53 (36.3)		
≥60 y	39 (11.5)	15 (15.5)	11 (11.5)	13 (8.9)		
Race, n (%)					0.86	0.42
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, n (%)					1.00	1.00
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, n (%)					0.87	0.84
High school diploma/GED or lower	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, n (%)					0.43	0.69
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)		
Smoking, n (%)					0.26	0.16
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, n (%)					0.26	0.16
0 drink weekly	116 (34.2)	28 (28.9)	36 (37.5)	52 (35.6)		
1-6 drinks weekly	149 (44.0)	43 (44.3)	41 (42.7)	65 (44.5)		
≥7 drinks weekly	61 (18.0)	21 (21.6)	13 (13.5)	27 (18.5)		
BMI, mean (SD), kg/m^2	28.3 (6.8)	28.5 (6.5)	29.3 (6.9)	27.6 (6.8)		
BMI category, n (%)					0.30	0.06
<25 kg/m^2	118 (34.8)	31 (32.0)	27 (28.1)	60 (41.1)		
25-29 kg/m^2	107 (31.6)	35 (36.1)	32 (33.3)	40 (27.4)		
≥30 kg/m^2	107 (31.6)	30 (30.9)	34 (35.4)	43 (29.5)		
Age at start of hot flashes, n (%)					0.95	0.81
<40 y	25 (7.4)	7 (7.2)	9 (9.4)	9 (6.2)		
40-49 y	146 (43.1)	40 (41.2)	42 (43.8)	64 (43.8)		
≥50 y	163 (48.1)	48 (49.5)	44 (45.8)	71 (48.6)		
Screening VMS frequency, mean (SD), VMS/d	8.1 (5.3)	8.5 (5.7)	8.2 (5.5)	7.7 (4.8)		
Screening VMS frequency category, n (%)					0.21	0.44
≤5.5 VMS/d	112 (33.0)	28 (28.9)	28 (29.2)	56 (38.4)		
5.6-8 VMS/d	108 (31.9)	30 (30.9)	35 (36.5)	43 (29.5)		
>8 VMS/d	119 (35.1)	39 (40.2)	33 (34.4)	47 (32.2)		
Self-reported health, n (%)						
Excellent	72 (21.2)	23 (23.7)	15 (15.6)	34 (23.3)	0.95	0.42
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)		
Fair	35 (10.3)	10 (10.3)	9 (9.4)	16 (11.0)		
Menopause status, n (%)						
Perimenopausal	53 (15.6)	14 (14.4)	17 (17.7)	22 (15.1)	0.99	0.83
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)		
Depression score category, n (%)					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 to severe 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)		
Anxiety score category, n (%)					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 to severe anxiety (≥10)	23 (6.8)	9 (9.3)	3 (3.1)	11 (7.5)		

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TABLE 1. *(Continued)*

Baseline characteristics	All participants (N = 339)	Estradiol (n = 97)	Venlafaxine (n = 96)	Placebo (n = 146)	*P*	
					Estradiol vs placebo	Venlafaxine vs placebo
PSQI score, mean (SD)	7.5 (3.4)	7.6 (3.6)	7.6 (3.2)	7.3 (3.5)		
PSQI score category, n (%)					0.58	0.50
Good sleep quality (<5)	67 (19.8)	23 (23.7)	14 (14.6)	30 (20.5)		
Moderate sleep quality (5-7)	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 score, mean (SD)	11.0 (6.0)	11.0 (6.3)	11.7 (6.0)	10.4 (5.8)		
ISI score category, n (%)					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)		
Moderate clinical insomnia (15-21)	78 (23.0)	21 (21.6)	25 (26.0)	32 (21.9)		
Severe clinical insomnia (≥22)	14 (4.1)	5 (5.2)	5 (5.2)	4 (2.7)		

BWH, Brigham and Women's Hospital; MGH, Massachusetts General Hospital; BMI, body mass index; VMS, vasomotor symptoms; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index.

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

Neither treatment group, compared with placebo, showed improvement in pain (PEG scale), depressive symptoms (PHQ-9), or anxiety (GAD-7; Table 3). For perceived stress (PSS), we found a mean difference of −1.7 (95% CI, −3.4 to −0.1) between venlafaxine and placebo at 4 weeks and a mean difference of −1.4 (95% CI, −3.1 to −0.2) between venlafaxine and placebo at 8 weeks (P = 0.02). No significant differences in PSS were observed between E_2 and placebo (Table 3).

When treatment effects on total MENQOL scores were examined in the 10 specified subgroups (Table 4), few statistically significant interactions were observed. Nonobese women (BMI <30 kg/m^2) showed greater improvement than obese women (BMI ≥30 kg/m^2) for venlafaxine compared with placebo (P for interaction = 0.03). For venlafaxine compared with placebo, women with higher Female Sexual Function Index scores (indicating more sexual activity or less sexual stress/dysfunction) seemed to improve on the MENQOL more than women with lower scores (P for interaction = 0.01).

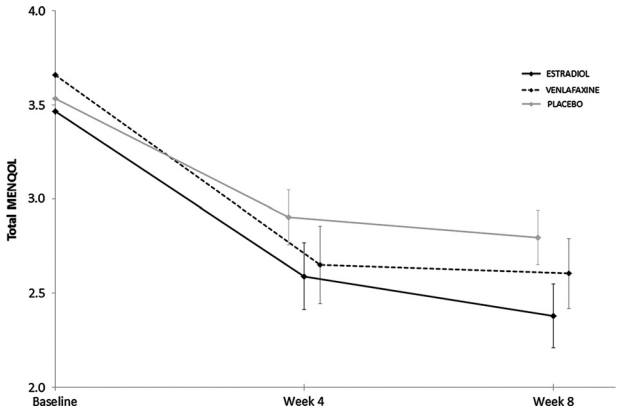

FIG. Total Menopause-Specific Quality of Life Questionnaire (MENQOL) score and 95% CI, by treatment arm, at baseline, on week 4, and on week 8. Estradiol versus placebo, $P < 0.001$; venlafaxine versus placebo, $P = 0.042$. P values are derived from contrasts comparing treatment versus placebo in a repeated-measures linear model of total MENQOL score as a function of intervention arm and adjusted for clinical center, visit week (week 4 or week 8), and baseline total MENQOL score. For main effects of intervention and week on 50% reduction in hot flashes across 8 weeks of follow-up, $P < 0.001$ for both.

DISCUSSION

This is the first trial to simultaneously investigate the efficacy of low-dose oral E_2 and the SNRI venlafaxine for improving menopause-related quality of life using the MENQOL and validated measures of pain, anxiety, depression, and stress in perimenopausal 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 E_2 and venlafaxine significantly improved overall menopause-specific quality of life. For estrogen, beneficial treatment effects were seen on all domains of the MENQOL except for the psychosocial domain, whereas for venlafaxine, benefits were observed only in the psychosocial domain. Venlafaxine also modestly improved perceived stress. Neither agent improved pain, depressive, or anxiety symptoms in this general population of women who were not selected based on these specific symptoms.

Venlafaxine reduced VMS frequency and severity, compared with placebo, in our primary trial analyses[4]; however, in this study, we did not see an improvement in the MENQOL VMS domain. This suggests that the manner by which the MENQOL asks about VMS elicits information different from the number and severity of events and that these aspects of VMS may be more importantly tied to improving quality of life. In addition, although the improvement in the psychosocial domain with venlafaxine was the only one to reach statistical significance, all of the other domains also improved with venlafaxine, though not reaching statistical significance, thus contributing to the statistically significant improvement in overall quality of life. Two other trials, but with slightly different participant populations, provide insight into improvements in the MENQOL after treatment with estrogen formulations.[16,17] In a trial of 318 women with seven or more

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TABLE 2. *Effects of estradiol and venlafaxine on menopausal quality of life*

Variables	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^a	Mean difference (95% CI)	P^a
MENQOL total								<0.001		0.042
Baseline	82	3.5 (3.2 to 3.7)	84	3.7 (3.4 to 3.9)	132	3.5 (3.3 to 3.7)	−0.1 (−0.4 to 0.2)		0.1 (−0.2 to 0.4)	
Week 4 − baseline	70	−0.9 (−1.1 to −0.7)	69	−0.9 (−1.1 to −0.7)	103	−0.6 (−0.7 to −0.4)	−0.3 (−0.6 to 0.0)		−0.3 (−0.6 to 0.0)	
Week 8 − baseline	73	−1.1 (−1.3 to −0.9)	73	−0.9 (−1.1 to −0.7)	115	−0.7 (−0.9 to −0.5)	−0.4 (−0.7 to −0.2)		−0.2 (−0.5 to 0.0)	
MENQOL vasomotor								<0.001		0.211
Baseline	94	5.7 (5.4 to 6.0)	95	5.9 (5.5 to 6.2)	142	5.6 (5.4 to 5.9)	0.1 (−0.3 to 0.5)		0.2 (−0.2 to 0.6)	
Week 4 − baseline	86	−1.4 (1.9 to −1.0)	86	−1.3 (−1.7 to −0.9)	125	−0.8 (−1.1 to −0.6)	−0.6 (−1.1 to −0.1)		−0.5 (−0.9 to 0.0)	
Week 8 − baseline	86	−2.3 (−2.8 to −1.8)	89	−1.4 (−1.8 to −1.0)	132	−1.1 (−1.4 to −0.8)	−1.2 (−1.8 to −0.6)		−0.3 (−0.8 to 0.2)	
MENQOL psychosocial								0.120		0.008
Baseline	92	2.8 (2.4 to 3.1)	94	2.9 (2.5 to 3.2)	142	2.7 (2.4 to 2.9)	0.1 (−0.3 to 0.5)		0.2 (−0.2 to 0.6)	
Week 4 − baseline	82	−0.6 (−0.8 to −0.3)	86	−0.8 (−1.0 to −0.5)	121	−0.3 (−0.5 to −0.2)	−0.2 (−0.5 to 0.0)		−0.4 (−0.7 to −0.1)	
Week 8 − baseline	87	−0.6 (−0.8 to −0.3)	86	−0.8 (−1.1 to −0.5)	134	−0.4 (−0.6 to −0.3)	−0.1 (−0.4 to 0.1)		−0.4 (−0.7 to 0.0)	
MENQOL physical								0.039		0.082
Baseline	89	3.0 (2.7 to 3.3)	88	3.2 (2.9 to 3.5)	138	3.0 (2.8 to 3.2)	0.0 (−0.3 to 0.3)		0.2 (−0.1 to 0.6)	
Week 4 − baseline	77	−0.7 (−1.0 to −0.5)	74	−0.8 (−1.0 to −0.6)	112	−0.5 (−0.6 to −0.3)	−0.3 (−0.6 to 0.0)		−0.3 (−0.6 to −0.1)	
Week 8 − baseline	83	−0.8 (−1.0 to −0.6)	80	−0.8 (−1.0 to −0.6)	124	−0.6 (−0.8 to −0.5)	−0.2 (−0.4 to 0.1)		−0.2 (−0.4 to 0.1)	
MENQOL sexual								0.047		0.047
Baseline	87	2.8 (2.3 to 3.2)	93	3.0 (2.5 to 3.4)	143	3.0 (2.6 to 3.4)	−0.2 (−0.8 to 0.4)		0.0 (−0.6 to 0.6)	
Week 4 − baseline	78	−0.7 (−1.0 to −0.3)	87	−0.6 (−0.9 to −0.3)	129	−0.5 (−0.8 to −0.2)	−0.2 (−0.6 to 0.3)		−0.1 (−0.5 to 0.3)	
Week 8 − baseline	81	−1.0 (−1.3 to −0.6)	87	−0.7 (−1.0 to −0.4)	132	−0.6 (−0.9 to −0.4)	−0.4 (−0.8 to 0.1)		−0.1 (−0.5 to 0.3)	

MENQOL, Menopause-Specific Quality of Life Questionnaire.
[a]*P* values from contrasts comparing treatment versus placebo in a repeated-measures linear model of outcome as a function of intervention arm and adjusted for clinical center, visit week (week 4 or week 8), and baseline outcome.

moderate to severe VMS per day, treatment with bazedoxifene 20 mg/day plus conjugated estrogens (0.45 or 0.625 mg/d) 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 relative to placebo ($P < 0.001$). However, participants treated with bazedoxifene 20 mg/conjugated estrogens 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 and menopause symptoms, ethinyl E_2 5 μg/day (a dose comparable with conjugated equine estrogens 0.625 mg/d) plus norethindrone acetate 1 mg/day was directly compared with escitalopram (an SSRI) rather than with the SNRI antidepressant evaluated in the present study. Improvements in the MENQOL total and domain scores were statistically similar; however, treatment with escitalopram, compared with E_2, resulted in greater improvements in the psychosocial domain, similar to findings in the present trial.[16]

In a double-blind, placebo-controlled, randomized trial of the SSRI escitalopram 10 to 20 mg/day versus identical placebo among 205 women aged 40 to 62 years with an average of four or more hot flashes per day, 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 E_2 was compared directly with venlafaxine (results not shown), effects favoring E_2 were observed in the vasomotor domain. These current findings are consistent with our main trial report,[4] which showed that low-dose E_2 reduced daily diary-recorded VMS frequency by an additional 0.6 VMS per day compared with venlafaxine, translating into a 5% greater reduction in VMS frequency (53% vs 48%).

Neither E_2 nor venlafaxine, compared with placebo, significantly improved pain, anxiety, or depression. Lack of statistical significance could be attributable to the low prevalence of these symptoms in this generally healthy group of women without current major depression. Although 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 subpopulation experiencing these symptoms.

We know of only one other vasomotor treatment trial in which PEG scale scores were evaluated.[19] Escitalopram treatment compared with placebo treatment improved pain scores most among women with higher depression or anxiety scores.[16] Unfortunately, the present trial had limited power to examine differences by these preexisting 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

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TABLE 3. *Effects of estradiol and venlafaxine on pain, anxiety, depression, and perceived stress*

	Estradiol		Venlafaxine		Placebo	Estradiol vs placebo		Venlafaxine vs placebo	
Variables	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	Mean difference (95% CI)	P^a	Mean difference (95% CI)	P^a
Pain (PEG scale)								0.477		0.298
Baseline	96	1.6 (1.1 to 2.1)	94	1.5 (1.0 to 1.9)	143	1.6 (1.2 to 1.9)	0.0 (−0.6 to 0.6)		−0.1 (−0.7 to 0.5)	
Week 4 − baseline	88	−0.0 (−0.5 to 0.4)	88	−0.3 (−0.8 to 0.2)	129	−0.2 (−0.6 to 0.1)	0.2 (−0.4 to 0.8)		−0.1 (−0.7 to 0.5)	
Week 8 − baseline	92	−0.1 (−0.5 to 0.4)	89	−0.4 (−0.8 to 0.0)	136	−0.2 (−0.6 to 0.2)	0.2 (−0.4 to 0.8)		−0.2 (−0.8 to 0.4)	
Depression (PHQ-8)								0.294		0.546
Baseline	97	3.9 (3.0 to 4.8)	96	3.0 (2.4 to 3.6)	146	3.4 (2.8 to 4.0)	0.5 (−0.6 to 1.5)		−0.4 (1.3 to 0.4)	
Week 4 − baseline	89	−1.2 (−2.3 to −0. 2)	89	0.2 (−0.4 to 0.8)	127	−0.4 (−1.0 to 0.3)	−0.9 (−2.1 to 0.3)		0.5 (−0.3 to 1.4)	
Week 8 − baseline	91	−0.8 (−1.6 to 0.0)	90	−0.5 (−1.1 to 0.1)	136	−0.3 (−0.9 to 0.3)	−0.5 (−1.5 to 0.5)		−0.2 (−1.1 to 0.7)	
Anxiety (GAD-7)								0.946		0.152
Baseline	97	3.0 (2.2 to 3.9)	96	2.2 (1.6 to 2.8)	146	2.4 (1.9 to 3.0)	0.6 (−0.4 to 1.7)		−0.2 (−1.0 to 0.6)	
Week 4 − baseline	90	−1.0 (−1.8 to −0.2)	91	−0.9 (−1.3 to −0.4)	132	−0.5 (−1.0 to 0.0)	−0.5 (−1.5 to 0.4)		−0.4 (−1.1 to 0.3)	
Week 8 − baseline	93	−0.9 (−1.7 to −0.1)	90	−0.7 (−1.3 to −0.1)	139	−0.7 (−1.2 to −0.1)	−0.2 (−1.2 to 0.7)		−0.1 (−0.9 to 0.7)	
Stress (PSS)								0.977		0.020
Baseline	92	12.5 (11.2 to 13.8)	91	12.2 (10.8 to 13.6)	140	12.2 (11.0 to 13.4)	0.3 (−1.5 to 2.1)		0.0 (−1.9 to 1.8)	
Week 4 − baseline	82	−1.9 (−3.1 to −0.7)	83	−3.1 (−4.3 to −1.8)	123	−1.3 (−2.4 to −0.3)	−0.5 (−2.2 to 1.1)		−1.7 (−3.4 to −0.1)	
Week 8 − baseline	87	−1.8 (−2.9 to −0.8)	86	−3.4 (−4.9 to −2.0)	129	−2.0 (−3.0 to −1.1)	0.2 (−1.2 to 1.6)		−1.4 (−3.1 to 0.2)	

PEG, Pain, Enjoyment in life, and General activity; PHQ-8, Patient Health Questionnaire-8; GAD-7, Generalized Anxiety Disorder Questionnaire-7; PSS, Perceived Stress Scale.
[a]*P* values from contrasts comparing treatment versus placebo in a repeated-measures linear model of outcome as a function of intervention arm and adjusted for clinical center, visit week (week 4 or week 8), and baseline outcome.

186 participants with MDD,[20] where participants received venlafaxine at a standard dose used to treat depression (≥150 mg/d) for 1 year. Venlafaxine (mean dose, 225 mg/d) 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 ($P = 0.020$) and shoulder pain ($P = 0.021$) on week 9. Similarly, two additional randomized double-blind studies found that duloxetine 60 mg once daily significantly reduced painful symptoms, compared with placebo, in participants with MDD.[22,23] Although duloxetine is Food and Drug Administration (FDA)–approved to treat neuropathic pain in a nondepressed population, the nature of pain in our study was not characterized; thus, we do not know whether participants had neuropathic pain or another type that would not be expected to be treated by venlafaxine. Conversely, estrogen would be expected to treat menopause-related pain (mostly joint pain), and the effect of lack of estrogen on pain is probably attributable to the low level of reported pain symptoms at baseline.

In this relatively healthy population, venlafaxine seemed to modestly improve perceived stress. Only one other study has measured the effects 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 10 mg (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 with Scores after 4 weeks of intervention; however, no statistically significant differences in perceived stress were found between the groups.[24] Effects of both venlafaxine and E_2 on total quality of life were greater for nonobese women (BMI <30 kg/m^2) than for obese women. Obese women reported a greater frequency of hot flashes, consistent with the theory that body fat acts an insulator and that hot flashes represent heat dissipation events occurring in the context of a narrowed thermoneutral zone.[25] For overall menopause-related quality of life, obese women may obtain less relief (both physiological and psychological) from these treatments because of the multiple residual effects of their excess body mass.

Although the efficacy of E_2 and venlafaxine (relative to placebo) in improving overall quality of life seemed to be similar in magnitude (efficacy slightly better for E_2 than for venlafaxine in the VMS subscale), our trial was not adequately powered to determine with confidence that one treatment was not inferior to the other. In addition, the effects of low-dose venlafaxine treatment and low-dose E_2 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 8 weeks in response to unopposed E_2, Guttuso and Evans,[26] in a study examining time required to show drug efficacy, concluded that 8 weeks was the most efficient

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TABLE 4. *Effects of estradiol and venlafaxine on menopause-related quality of life, by baseline characteristics*

	Estradiol			Venlafaxine			Placebo			Estradiol vs placebo		Venlafaxine vs placebo	
Characteristics	n	Baseline	Difference[a]	n	Baseline	Difference[a]	n	Baseline	Difference[a]	Mean difference in change (95% CI)[b]	*P* for interaction[c]	Mean difference in change (95% CI)[b]	*P* for interaction[c]
Overall model	73	3.5	−1.1	73	3.6	−0.9	115	3.5	−0.9	−0.37 (−0.56 to −0.17)		−0.23 (−0.45 to −0.01)	
Ethnicity											0.74		0.60
African American	15	4.3	−1.4	23	4.0	−0.9	30	3.7	−0.9	−0.28 (−0.71 to 0.14)		−0.13 (−0.61 to 0.34)	
White	55	3.4	−1.0	47	3.4	−0.9	77	3.4	−0.6	−0.36 (−0.59 to −0.14)		−0.28 (−0.52 to −0.03)	
Menopause status (03 definition)											0.65		0.40
Perimenopausal	10	3.4	−1.0	14	3.6	−1.0	18	3.5	−0.6	−0.25 (−0.81 to 0.31)		−0.42 (−1.00 to 0.15)	
Postmenopausal	57	3.4	−1.1	53	3.6	−0.9	87	3.5	−0.9	−0.39 (−0.60 to −0.17)		−0.15 (−0.40 to 0.09)	
Screening VMS frequency											0.35		0.33
≤5.5 VMS/d	22	3.5	−1.2	21	3.6	−0.7	44	3.6	−0.7	−0.53 (−0.88 to −0.18)		0.01 (−0.41 to 0.42)	
5.6-8 VMS/d	23	3.4	−1.0	26	3.3	−1.0	36	3.5	−0.9	−0.15 (−0.49 to 0.18)		−0.21 (−0.57 to 0.14)	
>8 VMS/d	28	3.6	−1.1	26	3.8	−1.0	35	3.4	−0.5	−0.43 (−0.77 to −0.09)		−0.40 (−0.77 to −0.03)	
GAD-7 anxiety											0.56		0.98
<5	59	3.3	−1.0	61	3.4	−0.8	90	3.3	−0.7	−0.35 (−0.55 to −0.15)		−0.16 (−0.40 to 0.07)	
≥5	14	4.3	−1.4	12	4.4	−1.4	25	4.3	−0.8	−0.43 (−0.99 to 0.14)		−0.50 (−1.04 to 0.05)	
PHQ-9 depression											0.76		0.97
<5	51	3.3	−1.1	54	3.4	−0.9	85	3.2	−0.6	−0.38 (−0.58 to −0.18)		−0.19 (−0.44 to 0.06)	
≥5	22	4.0	−1.2	19	4.1	−1.1	30	4.3	−1.0	−0.36 (−0.80 to 0.07)		−0.33 (−0.76 to 0.10)	
Pain during the last week (0-10)											0.39		0.50
0	32	3.4	−1.1	34	3.4	−1.0	51	3.3	−0.7	−0.44 (−0.74 to −0.14)		−0.31 (−0.60 to −0.01)	
1-5	35	3.5	−1.1	31	3.7	−0.9	52	3.6	−0.6	−0.42 (−0.69 to −0.15)		−0.16 (−0.52 to 0.20)	
6-10	5	4.2	−0.7	6	4.0	−0.4	11	3.8	−1.0	0.22 (−0.23 to 0.67)		−0.05 (−0.54 to 0.64)	
PEG scale construct											0.44		0.62
0	32	3.4	−1.1	33	3.4	−1.0	47	3.3	−0.6	−0.44 (−0.74 to −0.13)		−0.34 (−0.64 to −0.05)	
1-3	29	3.5	−1.1	30	3.6	−0.8	49	3.5	−0.6	−0.37 (−0.67 to −0.07)		−0.05 (−0.39 to 0.28)	
≥4	11	3.7	−1.1	8	4.3	−1.0	17	3.9	−1.0	−0.18 (−0.66 to 0.29)		−0.30 (−1.04 to 0.45)	
BMI											0.06		0.03
<30 kg/m^2	52	3.4	−1.2	50	3.5	−1.0	78	3.3	−0.6	−0.50 (−0.73 to −0.27)		−0.34 (−0.60 to −0.09)	
≥30 kg/m^2	20	3.7	−1.1	21	3.7	−0.8	34	3.9	−0.9	−0.05 (−0.41 to 0.30)		0.07 (−0.32 to 0.46)	
Poor sleep (PSQI score >8 or ISI score >14)											0.53		0.39
No	41	3.2	−1.1	39	2.9	−1.0	63	3.2	−0.6	−0.32 (−0.57 to −0.07)		−0.16 (−0.40 to 0.08)	
Yes	30	4.0	−1.3	32	3.7	−1.6	49	3.9	−0.8	−0.45 (−0.77 to −0.14)		−0.36 (−0.76 to 0.03)	
FSFI score											0.94		0.01
<26	41	3.8	−1.3	40	3.8	−1.0	57	3.8	−0.8	−0.54 (−0.83 to −0.25)		−0.29 (−0.60 to 0.01)	
≥26	21	3.1	−0.9	16	2.9	−0.8	33	3.0	−0.5	−0.26 (−0.54 to 0.02)		−0.42 (−0.75 to −0.09)	

VMS, vasomotor symptoms; GAD-7, Generalized Anxiety Disorder Questionnaire-7; PHQ-9, Patient Health Questionnaire-9; PEG, Pain, Enjoyment in life, and General activity; BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; FSFI, Female Sexual Function Index.

[a]Week 8 − baseline differences.

[b]Mean adjusted change in Menopause-Specific Quality of Life Questionnaire score for the estradiol group versus the placebo group.

[c]Interaction *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.

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duration for a hot flash trial. A well-designed maintenance study is required to determine long-term effects.

In the present trial, we evaluated low-dose formulations because of recommendations to use the lowest effective E_2 dose and because others have demonstrated that use of low-dose SSRI/SNRI in nondepressed women is effective for relieving hot flashes and is associated with fewer adverse 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 the use of a robust measure of quality of life specific for perimenopausal women. The MENQOL was chosen for the MsFLASH trials because of the breadth of domains covered by its 29 questions and its robust psychometric properties, brevity, and sensitivity to change across 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 most women in the population who were experiencing VMS, many of whom seek treatment to relieve these symptoms. Only 7% to 9% of US women report symptoms with frequency and severity of 7 or greater, 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 pharmacologic treatments on nondepressed women, who constitute most of the women experiencing distressing hot flashes. Other strengths included high adherence to treatment, high retention rates, high outcome data collection rate, and use of a large racially diverse cohort of perimenopausal and postmenopausal women in a sample size sufficient to examine the consistency of treatment effects on total MENQOL score across various subgroups of women.

CONCLUSIONS

Treatment with low-dose oral 17β-E_2 0.5 mg/day and venlafaxine XR 75 mg/day among healthy women with VMS is each significantly more effective than treatment with placebo in improving overall menopause-related quality of life. E_2 is most effective in improving quality of life related to VMS but also improves physical and sexual symptoms. Venlafaxine is most effective in improving quality of life related to psychosocial symptoms and perceived stress. These findings provide information to clinicians and women considering pharmacologic therapy for relief of menopause symptoms associated with quality of life.

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