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Effects of escitalopram on menopause-specific quality of life and pain in healthy menopausal women with hot flashes: A randomized controlled trial

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ABSTRACT

Objective: To evaluate the effects of escitalopram 10–20 mg/day on menopause-related quality of life and pain in healthy menopausal women with hot flashes.
Study design: A double-blind, placebo-controlled randomized trial of escitalopram 10–20 mg/day vs. identical placebo was conducted among 205 women ages 40–62 years with an average of ≥4 daily hot flashes recruited at 4 clinical sites from July 2009 to June 2010.
Main outcome measures: The primary trial outcomes, reported previously, were the frequency and severity of vasomotor symptoms at 8 weeks. Here, we report on the pre-specified secondary endpoints of total and domain scores from the Menopause-Specific Quality of Life Questionnaire (MENQOL) and the pain intensity and interference scale (PEG).
Results: Outcome data were collected on 97% of randomized women and 87% of women took at least 70% of their study medication. Treatment with escitalopram resulted in significantly greater improvement in total MENQOL scores (mean difference at 8 weeks of −0.41; 95% confidence interval (CI) −0.71 to −0.11; $p < 0.001$), as well as Vasomotor, Psychosocial, and Physical domain scores with the largest difference seen in the Vasomotor domain (mean difference −0.75; 95% CI −1.28 to −0.22; $p = 0.02$). There was no significant treatment group difference for the Sexual Function domain. Escitalopram treatment resulted in statistically significant improvements in PEG scores compared to placebo (mean treatment group difference at 8 weeks of −0.33; 95% CI −0.81 to 0.15; $p = 0.045$).
Conclusions: Treatment with escitalopram 10–20 mg/day in healthy women with vasomotor symptoms significantly improved menopause-related quality of life and pain.

1. Introduction

Over 38 million US women ages 45–64 years old (88%) experience daytime hot flashes or night sweats during the midlife transition [1]. Vasomotor symptoms (VMS) have been shown to affect multiple role functions including work, social activity, leisure activity and sexual activity [2]. In addition, many women with VMS report that the symptoms affect or are accompanied by problems with sleep, mood, pain, concentration and energy levels [2]. Sixty percent of midlife women seek medical care or advice for these symptoms at least once [3]. Clearly, there is a compelling need for effective treatments to relieve VMS in midlife women, and the

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evaluation of such treatments should include the impact on multiple quality of life domains.

Effective treatment choices for VMS are limited with low dose estrogen formulations being the only FDA-approved and most frequently recommended pharmacologic therapy. Since many women cannot or prefer not to use hormone treatments, comprehensive evaluations of alternative pharmacologic and behavioral therapies are needed. In 2008, the Menopausal Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) clinical trials network, supported by a cooperative agreement from the National Institute on Aging, initiated a series of randomized controlled trials. The first trial compared escitalopram to placebo in 205 women without major depression who reported an average of at least four VMS daily and revealed statistically significant decreases in the number, severity, and bother of VMS in the active vs. placebo groups [4]. Subsequent reports showed that escitalopram also improved sleep quality and decreased insomnia symptoms [5], decreased daytime and nighttime hot flashes, reduced hot flash interference with daily life [6], and did not significantly affect sexual function [7]. The purpose of this report is to evaluate treatment effects on menopause-related quality of life as well as pain symptoms and to evaluate the consistency of intervention effects across subgroups of women defined by race/ethnicity, menopausal stage, pre-treatment VMS frequency or severity, and other baseline characteristics.

2. Methods

2.1. Study setting

A double-blind, placebo-controlled randomized trial of escitalopram for relief of VMS frequency and severity at 8 weeks was conducted among symptomatic women ages 40–62 recruited at four MsFLASH network sites (Boston, MA; Indianapolis, IN; Oakland, CA; Philadelphia, PA). Details of the trial design, methods and primary trial results have been published previously [4]. The Menopause-Specific Quality of Life Questionnaire (MENQOL), a validated self-reported questionnaire with four domains developed by Hilditch et al. [8], and the three-item pain intensity and interference scale (PEG) [9] were a priori specified secondary outcomes. The protocol was approved by the institutional review board at each site. All women provided written informed consent.

2.2. Participants

The trial enrolled 205 women from July 2009 to June 2010 with the goal of recruiting 50% African American women. Women were eligible if they were aged 40–62 years, in general good health, in the menopause transition or postmenopausal, and reported $\geq$28 hot flashes/night sweats per week (recorded on daily diaries for three weeks) rated as bothersome or severe on $\geq$4 days per week. Screening procedures were designed to exclude women who reported use of psychotropic medications in the past month, use of prescription, nonprescription or herbal therapies for hot flashes in the past month; use of systemic hormone therapy, hormonal contraceptives, selective estrogen receptor modulators or aromatase inhibitors in the past two months; current severe illness, major depressive episode, drug or alcohol abuse in the past year; suicide attempt in the past three years; a lifetime diagnosis of bipolar disorder or psychosis; uncontrolled hypertension; or history of cardiovascular disease, endometrial or ovarian cancer.

2.3. Treatment and study procedures

Mass mailings to age-eligible study participants in the four clinical site metropolitan areas were the main recruitment strategy. Potentially eligible study participants, identified using a screening telephone call, were mailed a baseline questionnaire and daily diaries for recording frequency, severity, and bother of hot flashes each morning and evening. Women who continued to meet eligibility criteria were scheduled for 2 clinic visits (screening and randomization) within a 2–3 week interval. Eligible women were randomized to treatment groups of escitalopram 10 mg/day or identical-appearing placebo using a dynamic algorithm in a 1:1 ratio to ensure comparability among treatment groups with respect to race and clinical center. Participants, investigators, and clinical center staff were blinded to treatment assignment. After randomization, a telephone contact was made at week 1 (to assess protocol adherence and adverse events) and clinic visits were conducted at 4 and 8 weeks including completion of outcome questionnaires. The dose of blinded study medication was increased to two pills per day at four weeks for women reporting less than a 50% decrease in hot flash frequency or no decrease in hot flash severity, unless precluded by unacceptable side effects.

2.4. MENQOL and PEG questionnaires

The MENQOL is a 29-item assessment of quality of life designed to capture self-reported information on the presence and bother of symptoms, feelings and experiences in the domains of vasomotor, physical, psychosocial and sexual functioning among midlife women in the menopause transition. For each item, women were asked to report if they had experienced that symptom or feeling in the past four weeks, and if they had, to rate bother on a scale of 0–6 corresponding to "not bothered at all" to "extremely bothered". These two items were combined to create a score from 1 (not experiencing symptoms or feeling) to 8 (extremely bothered). Each domain score was the average of the item scores in that domain (higher scores indicated poorer quality of life). Validity, reliability and responsiveness to change have been shown to be adequate to excellent [8]. A factor analysis published by an independent group of investigators using a representative sample of 2703 US postmenopausal women aged 40–65 years found internal consistency coefficients (Cronbach's alpha) for the four domains of: 0.87 for vasomotor; 0.85 for psychosocial; 0.88 for physical; and, 0.77 for sexual [10]. An overall total MENQOL score summarizing the average of the domain-specific scores has also been evaluated [11].

The PEG is a three-item scale asking participants to report on a scale of 0–10 their level of average pain over the past week (0 = "no pain", 10 = "pain as bad as you can imagine"), how much pain has interfered with enjoyment over the past week, and how much pain has interfered with general activity (0 = "does not interfere", 10 = "completely interferes") [9]. Responses to the questions were averaged to get a final PEG score. The PEG scale has shown internal consistency ranging from 0.73 to 0.89 in two separate samples of outpatients. Construct validity and responsiveness to change have been documented [9]. Responsiveness to change in pain in a randomized trial of adults with musculoskeletal pain has been found to be equal or superior to several longer pain scales [12].

2.5. Other measurements

Frequency and severity of hot flashes/night sweats were recorded on daily diaries in the morning and evening throughout the study. Hot flash frequency was calculated as the total number of hot flashes/night sweats in a 24-hour period. Demographic factors, smoking status, alcohol intake, menopausal status (menopause transition, postmenopause, previous hysterectomy and/or oophorectomy) and health status were assessed by questionnaire at baseline. Validated questionnaires at baseline were also used to evaluate several secondary outcomes which were assessed as possible effect modifiers in this analysis. The secondary

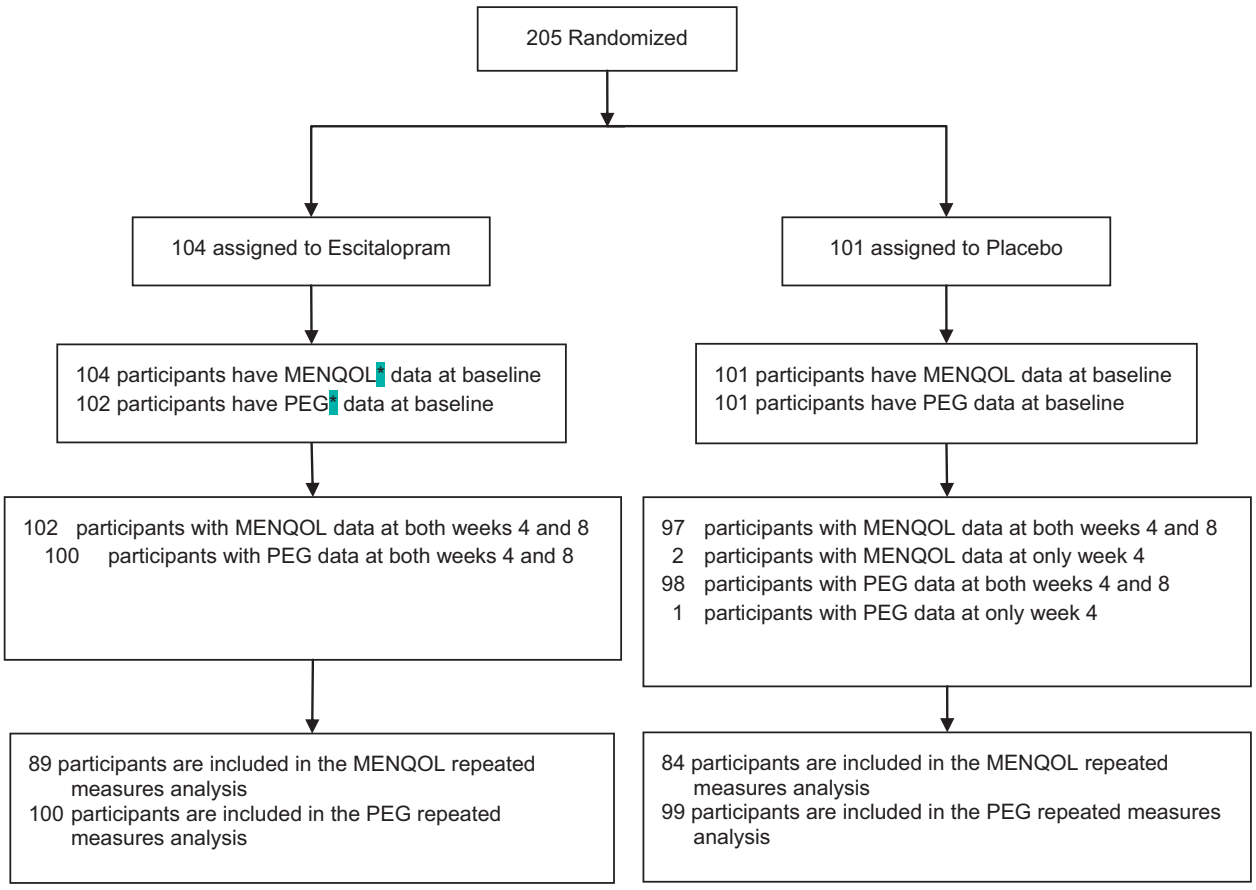


Fig. 1. Participant flow diagram.

outcomes included insomnia severity (7-item Insomnia Severity Index (ISI)) [13]; and subjective sleep quality (Pittsburgh Sleep Quality Index (PSQI)) [14,15], depressive symptoms (9-item scale from the Patient Health Questionnaire (PHQ-9)) [16], anxiety (7-item Generalized Anxiety Disorder scale (GAD-7)) [17], and sexual function (19-item Female Sexual Function Index (FSFI)) [18]. Weight and height were measured at baseline and used to calculate body mass index (BMI).

2.6. Statistical analysis

The statistical approach, based on the intention-to-treat principle, included the data collected from all randomized participants in all of the main analyses irrespective of adherence to study medication. Of the cohort of 205 randomized participants, data on one or more domains of the MENQOL were available on 205 women (100%) at baseline and 199 (97%) at eight weeks of follow-up (Fig. 1). For the PEG, data were available on 203 (99%) women at baseline and 198 (97%) at follow-up.

Primary analyses consisted of treatment group contrasts from linear regression models summarizing each of the six outcomes (the four domains of the MENQOL, the total MENQOL score, and the PEG) at both four and eight weeks as a function of treatment assignment, adjusting each model for race, site, visit (week 4 or 8), and baseline value of the outcome measure. Robust standard errors were calculated using generalized estimating equations to account for correlation between repeated measures from each participant. Sensitivity analyses were conducted to determine if the results differed among women who were adherent to the medication using the same linear regression approach but limiting the data to women who took at least 70% of their study pills.

We hypothesized that the effect of treatment on quality of life and pain measures might be modified by the following characteristics measured at baseline: race, menopausal status, VMS frequency, anxiety (GAD-7), depressive symptoms (PHQ-9), insomnia (IS) or poor sleep quality (PSQI), pain intensity and interference ((PEG) for the MENQOL outcome only), total MENQOL score (for the PEG outcome only), sexual function (FSFI), and BMI. These subgroup analyses were limited to examining total MENQOL and PEG scores. 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 (PEG) as a function of treatment arm, visit (weeks 4 or 8), the covariate of interest, and the interaction between treatment assignment and covariate; models were adjusted for race, site and baseline MENQOL (PEG). Nominal p-values were calculated for the 20 potential interactions examined. Thus, on average, about 1 p-value would be expected to be statistically significant by chance alone at the 0.05 level.

The planned sample size of the trial (90 women per treatment group) was determined by the primary trial endpoints (VMS frequency and severity) [4]. Reported p-values are based on the Wald

statistic. Analyses were conducted using SAS Version 9.2 (SAS Institute, Cary, NC) with 2-sided p-value <0.05 considered statistically significant.

3. Results

A total of 205 women were randomly assigned to the escitalopram (n = 104) or placebo (n = 101) groups, including 95 African-American women (46.3%) (Fig. 1). The mean age of study participants was 54 years, 81.5% were postmenopausal, 18.5% were in the menopause transition, and the mean number of VMS per day at enrollment was 9.78 (SD 5.60). One-fourth of women had PHQ-9 depression scores indicating mild (19.0%) or moderate (5.9%) depressive symptoms and 21.0% had GAD-7 anxiety scores indicating mild (16.6%) or moderate (4.4%) levels of anxiety. There were no significant differences between the randomized treatment groups in baseline characteristics (Table 1). Eighty-seven percent of women (n = 179) took at least 70% of their assigned study medication.

4. MENQOL

Total MENQOL scores were 3.80 (S.D. 1.26) at baseline, and scores declined (i.e., improved) in both treatment groups at weeks 4 and 8 (Fig. 2a). Treatment with escitalopram resulted in significantly greater improvement in MENQOL scores in linear regression models adjusted for race, visit, clinical center and baseline MENQOL score (mean difference at eight weeks of −0.41; 95% confidence interval (CI) −0.71 to −0.11; p < 0.001). Statistically significant treatment group differences favoring the escitalopram group were also seen for the Vasomotor, Psychosocial, and Physical domains (Table 2) with the largest difference seen in the Vasomotor domain (mean difference −0.75; 95% CI −1.28 to −0.22; p = 0.02). There was no significant difference by treatment group for the Sexual Function domain, although the difference in domain scores also favored the escitalopram group (mean difference −0.31; 95% CI −0.82 to 0.21; p = 0.15).

Results were nearly identical in the sensitivity analysis among adherent women (data not shown). When treatment effects on total MENQOL scores were examined in the 9 specified subgroups, there were no statistically significant interaction terms (p-values ranged from 0.12 to 0.99). Mean differences appeared consistent across strata of all 9 baseline characteristic, as illustrated by the PHQ-9 depression and GAD-7 anxiety subgroup results (Fig. 3).

5. PEG

The mean PEG score at baseline was 1.60 (S.D. 2.3). Scores also declined in both treatment groups at weeks 4 and 8. Statistically significant mean differences, again favoring the escitalopram group, were observed (mean difference at 4 weeks −0.53; 95% CI −1.03 to −0.02; at 8 weeks −0.33; 95% CI −0.81 to 0.15; p = 0.05; Fig. 2b). Results were nearly identical in adherent women (mean difference −0.35; p = 0.06). In the eight subgroups examined, interaction p-values were statistically significant in two subgroups providing some evidence that escitalopram treatment effects were stronger among women with higher GAD-7 anxiety (interaction p = 0.05) and PHQ-9 depression (interaction p = 0.05) scores compared to women with lower scores at baseline (Fig. 3).

6. Discussion

In this double-blind, placebo controlled randomized trial of healthy midlife women with VMS and no major depression, treatment with escitalopram significantly improved menopause-specific quality of life and reduced pain intensity and interference. Consistent, statistically significant, beneficial treatment effects were seen for the Total MENQOL and the Vasomotor, Psychosocial, and Physical domains. The effect of escitalopram treatment on pain intensity and interference appeared stronger among women with higher vs. lower levels of depression and anxiety at baseline.

Many vasomotor symptom trials have not evaluated treatment effects on menopause-related quality of life. For those that have, the available measures of quality of life are numerous and of variable quality [19]. The MENQOL was chosen for the MsFLASH trials because of the breadth of the domains covered by its 29 questions, its salutary psychometric properties, its brevity and its sensitivity to change over time. In addition, this measure has been used in previous trials that evaluate hot flash interventions ranging from hormone therapies [20], to dietary supplements [21], to Chinese herbal treatments [22], which facilitates cross-study comparisons. While comparisons between clinical trials must be considered with caution, two trials that evaluated escitalopram [23] or its isomer,

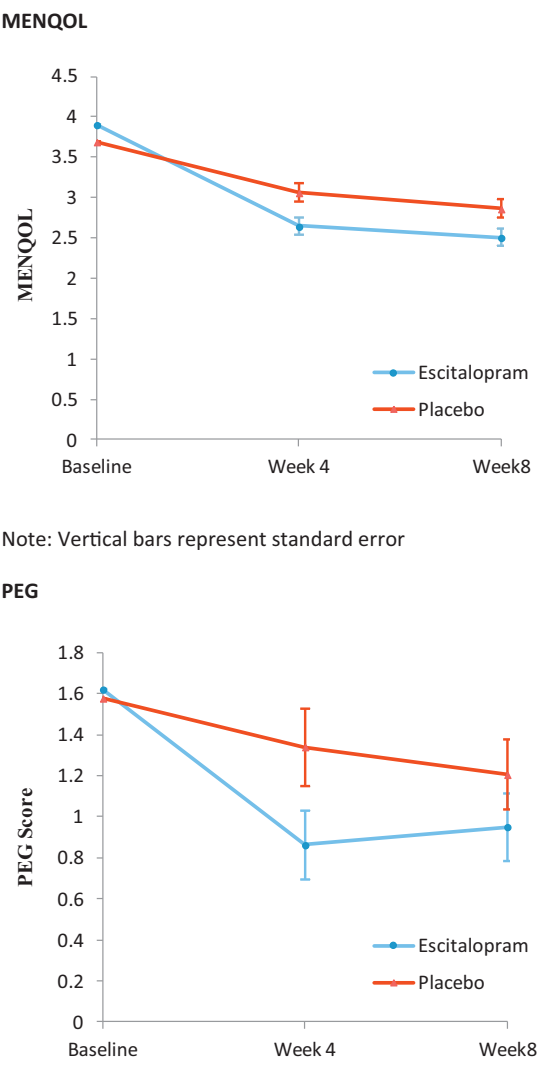


Fig. 2. Mean MENQOL* and PEG* scores from baseline to week 8 by treatment assignment.

Table 1
Demographic and clinical characteristics by treatment group at baseline.

Baseline characteristic[a]	Escitalopram (*N* = 104)		Placebo (*N* = 101)	
	N	%	*N*	%
Age at screening, mean (SD)	53.45 (4.20)		54.36 (3.86)	
42–49	16	15.4	8	7.9
50–54	48	46.2	47	46.5
55–59	30	28.8	36	35.6
60–62	10	9.6	10	9.9
Race				
White	53	51.0	49	48.5
African American	47	45.2	48	47.5
Other	4	3.8	4	4.0
Clinic site				
Boston	24	23.1	19	18.8
Indianapolis	17	16.3	18	17.8
Oakland	31	29.8	26	25.7
Philadelphia	32	30.8	38	37.6
Education				
≤High school diploma or GED	15	14.4	23	22.8
School/training after high school	46	44.2	41	40.6
College graduate	43	41.3	37	36.6
Smoking				
Never	53	51.0	46	45.5
Past	30	28.8	29	28.7
Current	21	20.2	26	25.7
Alcohol use (drinks/week)				
0	41	39.4	41	40.6
1–<7	51	49.0	41	40.6
7+	12	11.5	17	16.8
BMI (m/kg^2), mean (SD)	28.58 (6.59)		29.70 (6.42)	
<25	32	30.8	22	21.8
25–<30	34	32.7	38	37.6
≥30	38	36.5	40	39.6
Menopause status				
Post-menopause	84	80.8	83	82.2
Late transition	17	16.3	15	14.9
Early transition	3	2.9	3	3.0
Self-reported health				
Excellent	18	17.3	13	12.9
Very good	41	39.4	40	39.6
Good	36	34.6	37	36.6
Fair	7	6.7	11	10.9
Poor	1	1.0	0	0.0
PEG construct, mean (SD)	1.62 (2.21)		1.58 (2.40)	
None (0)	46	44.2	46	45.5
Low (>0–<4)	37	35.6	38	37.6
High (4–10)	19	18.3	17	16.8
PHQ-9 depression score, mean (SD)	3.24 (3.06)		2.94 (3.24)	
No depression (0–4)	76	73.1	77	76.2
Mild depression (5–9)	24	23.1	15	14.9
Moderate + depression (10–13)	4	3.8	8	7.9
GAD-7 anxiety score, mean (SD)	2.50 (3.34)		2.19 (3.33)	
No anxiety (0–4)	80	76.9	82	81.2
Mild anxiety (5–9)	19	18.3	15	14.9
Moderate + anxiety (10–19)	5	4.8	4	4.0
Hot flashes/night sweats, mean (SD)	9.88 (6.24)		9.66 (4.88)	
≤7	40	38.5	29	28.7
>7–10	31	29.8	37	36.6
>10	33	31.7	35	34.7
FSFI score, mean (SD)	16.06 (11.21)		16.44 (12.56)	
Sexual dysfunction (<26.55)	81	77.9	70	69.3
Sexual dysfunction (≥26.55)	20	19.2	29	28.7
Poor sleep (PSQI > 8 or ISI > 14)				
No	51	49.0	52	51.5
Yes	51	49.0	44	43.6
MENQOL vasomotor, mean (SD)	6.05 (1.56)		5.78 (1.74)	
≤5	29	27.9	36	35.6
>5–7	46	44.2	41	40.6
>7	25	24.0	22	21.8
MENQOL psychosocial, mean (SD)	2.97 (1.62)		2.74 (1.47)	
≤2	32	30.8	37	36.6
>2–3	24	23.1	27	26.7
>3	41	39.4	30	29.7
MENQOL physical, mean (SD)	3.20 (1.32)		3.23 (1.31)	
≤2.5	33	31.7	29	28.7
>2.5–3.5	31	29.8	30	29.7
>3.5	33	31.7	33	32.7

Table 1 (*Continued*)

Baseline characteristic[a]	Escitalopram (*N* = 104)		Placebo (*N* = 101)	
	N	%	*N*	%
MENQOL sexual function, mean (SD)	3.48 (2.55)		3.09 (2.36)	
≤1	33	31.7	42	41.6
>1–5	32	30.8	31	30.7
>5	31	29.8	22	21.8
MENQOL total, mean (SD)	3.91 (1.30)		3.69 (1.22)	
≤3.1	28	26.9	31	30.7
>3.1–4.4	30	28.8	32	31.7
>4.4	34	32.7	24	23.8

MENQOL, Menopause-Specific Quality of Life Questionnaire; PEG, Pain Intensity and Interference Scale; GAD-7, Generalized Anxiety Disorder Scale; PHQ-9, Patient Health Questionnaire.

[a] There are no significant differences between the two study groups as tested by *t*-test or Chi-square.

citalopram [24], in small samples of symptomatic women (16 and 25 women per group, respectively), reported improvements in the total and domain-specific MENQOL scores as a result of SSRI treatment.

Two other trials provide insight into improvements in the MENQOL following treatment with estrogen formulations [20,23]. In a trial of 318 women with seven or more moderate-to-severe VMS daily, treatment with bazedoxifene 20 mg/day plus conjugated estrogen (0.45 or 0.625 mg/day) resulted in significant improvements in total and domain-specific MENQOL scores [20]. Escitalopram in the present trial appeared less effective than low dose estrogen therapy for the Vasomotor and Sexual function domains, slightly more effective for the Psychosocial domain and similar for Physical symptoms. In a second trial, escitalopram was directly compared to ethinyl estradiol 5 μg/day (a dose comparable to conjugated equine estrogen 0.625 mg/day) plus norethindrone acetate 1 mg/day among 32 women with depressive disorders and menopause symptoms (16 per group). Improvements on the MENQOL total and domain scores were statistically similar but escitalopram appeared to have greater improvements than estradiol on the Psychosocial domain, and smaller improvement in Sexual function [23]. In the present trial, the largest effect of escitalopram was observed for the Vasomotor domain and there was no significant difference in Sexual function compare to placebo.

It should be noted that the study populations differ among these trials, most importantly in the frequency of hot flashes at baseline. The restriction of trials to women with seven or more moderate to severe VMS per day (as indicated by the FDA guidelines) [20] eliminates the vast majority of women experiencing VMS in the population, many of whom seek treatment to relieve these symptoms. Only 7–9% of US women report symptoms that reach this frequency and severity, whereas 88% report having experienced hot flashes in midlife [1]. Trials that include women with depressive disorders [23] may obscure the effects of pharmacological treatments in non-depressed women who constitute the majority of women that experience distressing hot flashes. Nonetheless, the results of these trials are consistent in supporting a benefit of escitalopram on menopause-related quality of life in general, and for the vasomotor, psychosocial and physical domains, in particular.

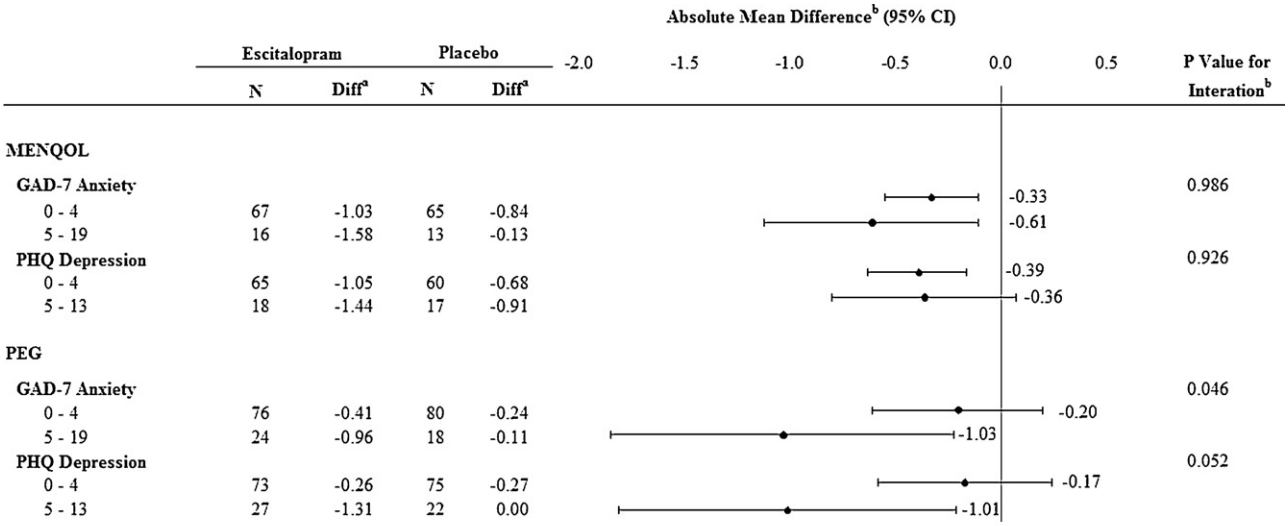
We know of no other vasomotor treatment trials in which pain scores have been evaluated. However, recent cohort studies have reported a high prevalence of aches, joint pain and stiffness and

Table 2
MENQOL constructs and PEG score at weeks 4 and 8, by treatment arm.

MENQOL construct	Escitalopram		Placebo		Difference	
	N	Mean (95% CI)	*N*	Mean (95% CI)	Mean (95% CI)	*P* value[a]
Total MENQOL						<0.001
Baseline	92	3.91 (3.64, 4.17)	87	3.69 (3.43, 3.95)	0.21 (−0.16, 0.58)	
Week 4 – baseline	85	−1.01 (−1.20, −0.81)	80	−0.48 (−0.68, −0.28)	−0.53 (−0.80, −0.25)	
Week 8 – baseline	83	−1.13 (−1.34, −0.92)	78	−0.72 (−0.95, −0.50)	−0.41 (−0.71, −0.11)	
Vasomotor						0.015
Baseline	100	6.05 (5.74, 6.36)	99	5.78 (5.43, 6.13)	0.27 (−0.20, 0.73)	
Week 4 – baseline	97	−1.54 (−1.89, −1.19)	96	−0.99 (−1.33, −0.65)	−0.55 (−1.03, −0.07)	
Week 8 – baseline	97	−1.78 (−2.14, −1.43)	95	−1.04 (−1.44, −0.63)	−0.75 (−1.28, −0.22)	
Psychosocial						<0.001
Baseline	97	2.98 (2.65, 3.30)	94	2.74 (2.44, 3.04)	0.23 (−0.21, 0.68)	
Week 4 – baseline	95	−0.82 (−1.04, −0.61)	88	−0.31 (−0.52, −0.10)	−0.52 (−0.82, −0.21)	
Week 8 – baseline	93	−0.97 (−1.21, −0.72)	91	−0.61 (−0.82, −0.39)	−0.36 (−0.68, −0.04)	
Physical						0.002
Baseline	97	3.20 (2.93, 3.47)	92	3.23 (2.96, 3.50)	−0.03 (−0.41, 0.34)	
Week 4 – baseline	92	−0.93 (−1.16, −0.69)	88	−0.46 (−0.66, −0.27)	−0.46 (−0.77, −0.16)	
Week 8 – baseline	91	−0.91 (−1.16, −0.65)	86	−0.71 (−0.93, −0.49)	−0.19 (−0.53, 0.14)	
Sexual function						0.151
Baseline	96	3.48 (2.96, 4.00)	95	3.09 (2.61, 3.57)	0.39 (−0.31, 1.09)	
Week 4 – baseline	92	−0.91 (−1.24, −0.57)	92	−0.47 (−0.80, −0.15)	−0.43 (−0.90, 0.03)	
Week 8 – baseline	94	−1.02 (−1.39, −0.65)	89	−0.72 (−1.07, −0.36)	−0.31 (−0.82, 0.21)	
PEG score						0.045
Baseline	102	1.62 (1.19, 2.05)	101	1.58 (1.10, 2.05)	0.04 (−0.60, 0.68)	
Week 4 – baseline	100	−0.63 (−0.99, −0.27)	99	−0.10 (−0.46, 0.25)	−0.53 (−1.03, −0.02)	
Week 8 – baseline	100	−0.54 (−0.90, −0.19)	98	−0.22 (−0.54, 0.11)	−0.33 (−0.81, 0.15)	

MENQOL, Menopause-Specific Quality of Life Questionnaire; PEG, Pain Intensity and Interference Scale; GAD-7, Generalized Anxiety Disorder Scale; PHQ-9, Patient Health Questionnaire.

[a] *p*-Values from coefficient comparing escitalopram vs. placebo in a repeated measures linear model of the outcome as a function of intervention arm and adjusted for race, visit (weeks 4 or 8), clinical center, and baseline outcome.



[a]Unadjusted week 8 - baseline differences in total MENQOL (PEG) score

[b]Estimates, confidence intervals, and interaction p-values from repeated measures linear model of the MENQOL as a function of intervention arm covariate of interest, and their interaction. Models are adjusted for race, visit (week 4 or 8), clinical center, and baseline total MENQOL (PEG analysis). Interaction p-values from a separate model with a continuous variable interaction with treatment arm.

*MENQOL = Menopause-Specific Quality of Life Questionnaire; PEG = Pain Intensity and Interference Scale; GAD-7 = Generalized Anxiety Disorder Scale; PHQ-9 = Patient Health Questionnaire.

Fig. 3. Mean change in MENQOL and PEG scores from baseline to week 8 by treatment assignment according to levels of anxiety and depression.

robust associations of these symptoms with menopausal stages [25–27]. Although, PEG scores were low in this generally healthy sample, and the treatment group difference was small, statistically significant interaction tests suggested that escitalopram treatment might improve pain scores more in women with higher depression or anxiety scores. These findings are consistent with the evidence that both depression and anxiety dimensions are significantly correlated with hot flashes [28,29] and with other evidence that women who were most troubled by hot flashes, depression, and anxiety experienced significantly greater back pain [30]. It may also reflect a reduction in pain distress associated with escitalopram. However, it is also possible that the observed results were caused by chance inasmuch as 20 subgroups were examined. The prevalence of pain symptoms and the responsiveness of these symptoms to treatment warrant their evaluation in future vasomotor symptom trials.

Strengths of this trial were the use of reliable and valid measures of menopause-related quality of life and pain, inclusion of women with moderate levels of VMS as well as those of less severity to reflect the experience of women in the population, inclusion of many African American women, and high adherence to treatment and retention rates. While the large sample size was sufficient to examine the consistency of treatment effects across various subgroups of women, the trial was not designed to definitively test for treatment efficacy within subgroups. The trial was limited to 8-weeks of follow-up and did not include women with major depression or other mental illness requiring treatment.

Treatment with escitalopram 10–20 mg/day in healthy women with vasomotor symptoms significantly improved menopause-related quality of life and pain. These findings provide evidence that should inform women considering pharmacologic therapy for relief of menopause symptoms.

Contributors

Dr. LaCroix had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conceptualisation and design were done by LaCroix, Freeman, Cohen, Joffe, Carpenter, and Newton. Data were acquired by Freeman, Sternfeld, Joffe, and Carpenter. Analysis and interpretation of data were done by LaCroix, Freeman, Cohen, Joffe, Carpenter, Larson, Ensrud, and Reed. LaCroix, Freeman, and Carpenter drafted the manuscript. Critical revision of the manuscript for important intellectual content was done by LaCroix, Freeman, Sternfeld, Joffe, Carpenter, Ensrud, Reed, and Newton. Statistical analysis was performed by Larson, and LaCroix. Funds were obtained by LaCroix, Freeman, Cohen, Reed, Newton, Carpenter, and Sternfeld. Administrative, technical, or material support was given by LaCroix, Freeman, Sternfeld, Cohen, and Carpenter. Study supervision was done by LaCroix, Freeman, and Ensrud.

Competing interest

Dr. LaCroix reported serving on scientific advisory boards for Pfizer, Sanofi-Adventis and Amgen. Dr. Freeman reported research support from Forest Laboratories, Inc., Wyeth, Pfizer, and Xanodyne Pharmaceuticals; honoraria for consulting and presentations from Wyeth, Forest Laboratories, Inc., Pherin Pharmaceuticals, and Bayer Health Care. Dr. Cohen reported research support from National Alliance for Research on Schizophrenia and Depression, Astra-Zeneca Pharmaceuticals, Sepracor, Inc., Bayer HealthCare, Bristol-Myers, Stanley Foundation, Ortho-McNeill Jansen, Pfizer, Inc.; Advisory/consulting: Eli Lilly, GlaxoSmithKline, JDS/Noven Pharmaceuticals, Wyeth-Ayerst Pharmaceuticals; Honoraria: Eli Lilly, Forest Laboratories, Inc., GlaxosmithKline, Pfizer, Inc., and

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NIH staff critically reviewed the study protocol and drafts of the manuscript prior to journal submission. Forest Institute had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or in the preparation of the manuscript.

Ethical approval

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

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