

Efficacy of Escitalopram for Hot Flashes in Healthy Menopausal Women

A Randomized Controlled Trial

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HORMONAL AGENTS HAVE BEEN the predominant therapy for menopausal hot flashes, but their use decreased substantially following the shifts in risk-benefit ratios that were identified in the Women's Health Initiative Estrogen plus Progestin randomized controlled trial.^{1,2} However, no other treatments have US Food and Drug Administration approval for menopausal hot flashes, and the efficacy of alternative pharmacologic and nonpharmacologic agents is inconclusive.³⁻⁵

Selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs and SNRIs) have been investigated for hot flash treatment with mixed results⁶⁻¹¹; a pooled analysis of 7 SSRI and SNRI studies showed that decreases in hot flash scores ranged from 3% to 41% compared with placebo.⁶ Differences among the serotonergic antidepressants,¹¹ study popu-

Context Concerns regarding the risks associated with estrogen and progesterone to manage menopausal symptoms have resulted in its declining use and increased interest in nonhormonal treatments with demonstrated efficacy for hot flashes.

Objective To determine the efficacy and tolerability of 10 to 20 mg/d escitalopram, a selective serotonin reuptake inhibitor, in alleviating the frequency, severity, and bother of menopausal hot flashes.

Design, Setting, and Patients A multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel group trial that enrolled 205 women (95 African American; 102 white; 8 other) between July 2009 and June 2010.

Intervention Women received 10 to 20 mg/d of escitalopram or a matching placebo for 8 weeks.

Main Outcome Measures Primary outcomes were the frequency and severity of hot flashes assessed by prospective daily diaries at weeks 4 and 8. Secondary outcomes were hot flash bother, recorded on daily diaries, and clinical improvement (defined as hot flash frequency $\geq 50\%$ decrease from baseline).

Results Mean (SD) daily hot flash frequency was 9.78 (5.60) at baseline. In a modified intent-to-treat analysis that included all randomized participants who provided hot flash diary data, the mean difference in hot flash frequency reduction was 1.41 (95% CI, 0.13-2.69) fewer hot flashes per day at week 8 among women taking escitalopram ($P < .001$), with mean reductions of 4.60 (95% CI, 3.74-5.47) and 3.20 (95% CI, 2.24-4.15) hot flashes per day in the escitalopram and placebo groups, respectively. Fifty-five percent of women in the escitalopram group vs 36% in the placebo group reported a decrease of at least 50% in hot flash frequency ($P = .009$) at the 8-week follow-up. Reductions in hot flash severity scores were significantly greater in the escitalopram group (-0.52 ; 95% CI, -0.64 to -0.40 vs -0.30 ; 95% CI, -0.42 to -0.17 for placebo; $P < .001$). Race did not significantly modify the treatment effect ($P = .62$). Overall discontinuation due to adverse events was 4% (7 in the active group, 2 in the placebo group). Three weeks after treatment ended, women in the escitalopram group reported a mean 1.59 (95% CI, 0.55-2.63; $P = .02$) more hot flashes per day than women in the placebo group.

Conclusion Among healthy women, the use of escitalopram (10-20 mg/d) compared with placebo resulted in fewer and less severe menopausal hot flashes at 8 weeks of follow-up.

Trial Registration clinicaltrials.gov Identifier: NCT00894543

JAMA. 2011;305(3):267-274

www.jama.com

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lations that include women with other medical or psychiatric problems, and differences in measurement of hot flashes and menopausal status contribute to the inconsistent study results. The SSRI escitalopram reduced hot flashes with minimal toxicities in 2 pilot investigations, but conclusions were limited by the small samples and unblinded treatment.^{12,13} No studies have examined racial differences in treatment response, although African American women are more likely to report bothersome hot flashes.¹⁴

We evaluated the efficacy of escitalopram vs placebo to reduce the frequency, severity, and bother of hot flashes in African American and white women and examined whether race, menopausal status, depressed mood, and anxiety are important modifiers of any observed effect.

METHODS

Study Design

The study was a multisite, randomized, placebo-controlled, double-blind clinical trial with enrollment stratified by self-reported race (African American, white, or other). Eligible women were randomized in equal proportions to receive either escitalopram 10 mg/d or a matching placebo pill for 8 weeks. If women did not report a reduction in hot flash frequency of at least 50% or a decrease in hot flash severity after 4 treatment weeks, their study medication dose was increased to 20 mg/d (or matched placebo) without unblinding the randomization.

The study was approved by the institutional review board at each participating site and participants provided written informed consent.

Patient Selection

The trial was conducted at 4 MsFlash network sites (eAppendix 1 available at <http://www.jama.com>). Participants were recruited from July 2009 to June 2010, primarily by mass mailings to age-eligible women using purchased mailing lists and health-plan enrollment files. Eligible women were aged 40 through 62 years in the menopause transition (amenorrhea ≥ 60 days in the past year), or postmenopausal (≥ 12 months since last

menstrual period or bilateral oophorectomy), or had a hysterectomy with 1 or both ovaries remaining and follicle-stimulating hormone levels higher than 20 mIU/mL and estradiol of 50 pg/mL or less; and were in general good health as determined by medical history, a brief physical examination, and standard blood tests.

Hot flash enrollment criteria were as follows: at least 28 hot flashes or night sweats per week recorded on daily diaries for 3 weeks; hot flashes or night sweats rated as bothersome or severe on 4 or more days per week; the frequency in week 3 did not decrease by more than 50% from the mean weekly levels in weeks 1 and 2. Exclusion criteria included use of psychotropic medications, prescription, over-the-counter, or herbal therapies for hot flashes in the past 30 days; hormone therapy, hormonal contraceptives, selective estrogen receptor modulators (SERMs), or aromatase inhibitors in the past 2 months; current severe medical illness, major depressive episode, drug or alcohol abuse in the past year, suicide attempt in the past 3 years, lifetime diagnosis of bipolar disorder, or psychosis; or uncontrolled hypertension, history of endometrial or ovarian cancer, myocardial infarction, angina or cerebrovascular events, or other preexisting medical conditions (FIGURE 1).

Data Collection

After a brief telephone screening, eligible volunteers were mailed a baseline questionnaire to assess self-reported health and demographics and daily diaries to record frequency, severity, and bother of hot flashes each morning and evening. After review of these, women who continued to meet eligibility criteria were scheduled for 2 clinic visits within a 2- to 3-week interval. Participants continued to rate hot flashes daily for a total of 3 screening weeks.

At the first visit, written consent was obtained, symptoms and health were reviewed, a urine pregnancy test and blood samples were obtained for safety laboratory tests, and daily diaries were dispensed to rate hot flashes for the following week. At the second clinic visit,

participants completed baseline self-report questionnaires, hot flash diaries were reviewed, and a brief physical examination with a urine pregnancy test was conducted. Eligible women were randomly assigned to receive escitalopram or placebo for 8 weeks, using a dynamic randomization algorithm,¹⁵ to ensure comparability between treatment groups with respect to race and clinical site. Randomization was conducted in a secure Web-based database, maintained at the Fred Hutchinson Cancer Research Center's MsFlash Data Coordinating Center, Seattle, Washington, and implemented by the use of a computerized inventory system for dispensing identical-appearing pills in bottles with unique identifiers. Participants and study site personnel were blinded to treatment assignments. The study remained blinded until all data were collected (through week 11) and entered in the computer database.

A telephone contact was made a week after randomization to assess protocol adherence and adverse events. Clinic visits were conducted 4 weeks and 8 weeks after randomization. Another telephone contact occurred at week 11 (≈ 3 weeks after stopping study medication) to evaluate return of symptoms, adverse events, and withdrawal symptoms. Participants were paid after each of 3 clinic visits and the final follow-up contact, for a possible total of \$180.

Treatment

For the first 4 weeks, participants took 1 pill daily (escitalopram 10 mg or placebo). At 4 weeks, if hot flash frequency was not reduced by at least 50% or there was no decrease in severity, the dose was increased to 2 pills per day unless precluded by unacceptable adverse events. At 8 weeks, participants taking 1 pill per day stopped treatment; participants taking 2 pills per day tapered the dose over a week.

Measurements

Frequency and severity of hot flashes or night sweats were recorded in daily

diaries in the morning and evening throughout the study. The primary outcomes were 7-day means of hot flash frequency and severity at weeks 4 and 8. Hot flash frequency was calculated as the total number of hot flashes or night sweats in a 24-hour period. Hot flash severity was rated from 1 to 3 (mild, moderate, severe).

Secondary outcomes were hot flash bother (rated in the daily diaries from 1-4 signifying none, a little, moderately, a lot), and a categorical variable to indicate clinical improvement (defined as a decrease of $\geq 50\%$ in the frequency of hot flashes or night sweats at 8 weeks from baseline). A decrease of at least 75% in hot flash frequency was also evaluated.

Possible correlates of treatment response were assessed using self-report questionnaires completed at baseline and at weeks 4 and 8 of treatment. These included menopausal status (transition, postmenopause), self-reported health on a 5-point scale, depressed mood as assessed by Patient Health Questionnaire domains of depression (PHQ-9),¹⁶ anxiety as assessed by Generalized Anxiety Disorder (GAD-7)¹⁷ and the Hopkins Symptom Checklist (HSCL) anxiety factor,¹⁸ smoking status, alcohol use, body mass index, and demographic variables.

Adverse events were assessed at each visit using a self-administered questionnaire listing 12 common SSRI adverse events. Newly emergent adverse events were identified by comparing adverse event reports during treatment to each woman's baseline report. At week 11, symptoms that emerged after cessation of study drug were assessed using a standard 17-item list of possible SSRI withdrawal symptoms.¹⁹

Statistical Analysis

The necessary sample size was based on data from the Herbal Alternatives for Menopause²⁰ (HALT) study that compared reduction of menopausal hot flashes among multiple botanical treatments, estradiol, and placebo. In this study, among participants with a baseline mean of 4 hot flashes per day, the

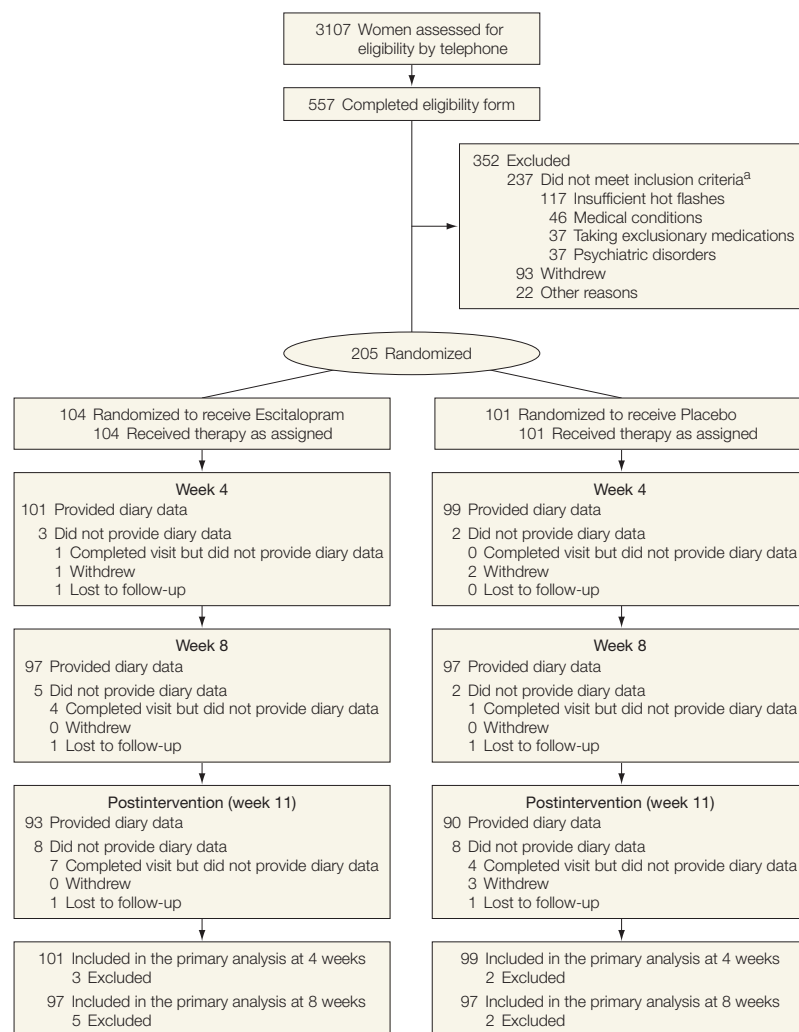
placebo response rate was 28%, with a mean (SD) decrease of 2.14 (3.55) per day.²⁰ We then estimated a 52% reduction in hot flashes as a clinically relevant change. Under these assumptions, 90 women in each treatment group provide 90% power to detect a difference between drug and placebo with a 2-sided α of .025 to account for 2 primary outcomes of hot flash frequency and severity. This design also provides 90% power to detect an effect size of 0.52 SD units between groups in the mean change of severity scores, for which effect size is defined as the difference in means divided by the com-

mon SD, and 80% power to detect a difference of 3 hot flashes per day with escitalopram by race.

The modified intent-to-treat analysis included all randomized participants who provided diary data, which were analyzed regardless of adherence to treatment assignment. Of 205 women randomized to treatment, 98% provided diary data for the primary analysis. The numbers of women at each assessment are shown in Figure 1.

Baseline hot flash frequency was calculated as the mean of the daily totals reported in the first 2 screening weeks. Hot flash frequency at weeks 4 and 8

Figure 1. Participant Flow Diagram.



^aSome women had more than 1 reason for exclusion.

Table 1. Demographic and Clinical Characteristics by Groups at Baseline

Baseline Characteristic ^a	No. (%) of Women ^b	
	Escitalopram (n = 104)	Placebo (n = 101)
Age at screening, mean (SD), y	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 or training after high school	46 (44.2)	41 (40.6)
College graduate	43 (41.3)	37 (36.6)
Employment status		
Retired or no employment	23 (22.1)	28 (27.7)
Homemaker	9 (8.7)	6 (5.9)
Full-time	48 (46.2)	46 (45.5)
Part-time	19 (18.3)	16 (15.8)
Other	5 (4.8)	5 (5.0)
Marital status		
Never married	18 (17.3)	13 (12.9)
Divorced	18 (17.3)	26 (25.7)
Widowed	4 (3.8)	6 (5.9)
Married or living with partner	64 (61.5)	56 (55.4)
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/wk)		
0	41 (39.4)	41 (40.6)
1-<7	51 (49.0)	41 (40.6)
≥7	12 (11.5)	17 (16.8)
BMI, 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 ^c		
Postmenopause	84 (80.8)	83 (82.2)
Late transition	17 (16.3)	15 (14.9)
Early transition	3 (2.9)	3 (3.0)
Hysterectomy		
Hysterectomy	13 (13)	13 (13)
Hysterectomy + oophorectomy	11 (10)	8 (8)
Oophorectomy only	3 (3)	1 (1)
None	77 (74)	78 (78)

(continued)

were calculated as the mean of the daily frequencies for the week prior to each visit. Hot flash severity and bother scores were calculated by selecting the highest severity or bother rating for hot flashes or night sweats for each woman in each 24-hour day. The score was set to missing on any day that data were missing or hot flashes equaled 0. The mean of daily ratings for the first 2 screening weeks (baseline severity or bother) and for the week preceding the 4 and 8 week clinic visits were included in analysis.

Treatment group contrasts were computed as Wald statistics from linear regression models summarizing the frequency, severity, or bother of hot flashes at weeks 4 and 8 as a function of randomization assignment and were adjusted for race, clinical site, and the baseline value of the outcome measure. Natural logarithm transformations were applied to hot flash frequencies to accommodate modeling assumptions. Robust standard errors were calculated via generalized estimating equations to account for correlation between repeated measures from each participant. To test for week-specific treatment-group differences, the model was expanded to include an interaction term between intervention and study time.

Four variables were hypothesized a priori to modify treatment response: race (African American vs white), menopausal status (postmenopausal vs menopause transition), depressed mood (PHQ-9, continuous score), and anxiety (GAD-7, continuous score). Tests for interaction between these variables and treatment assignment were performed within the linear regression model.

Baseline characteristics were compared between treatment groups using *t* tests or χ^2 tests. Adverse events were compared between the 2 treatment groups using the Fisher exact test. Analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) with a 2-sided *P* value ≤ .025, which was considered statistically significant for primary analyses and a 2-sided *P* ≤ .05 for secondary analyses.

RESULTS

Two hundred five women were randomly assigned to receive escitalopram or placebo (Figure 1). There were no statistically significant differences in baseline characteristics between treatment groups (TABLE 1).

Hot Flash Frequency

The mean (SD) frequency of hot flashes at baseline was 9.78 (5.60) per day. Escitalopram was associated with a significant reduction in the frequency of hot flashes relative to placebo, adjusted for race, site, and baseline hot flash frequency (*P* < .001 overall treatment effect, TABLE 2). In the escitalopram group, mean hot flash frequency at week 8 decreased to 5.26 (95% confidence interval [CI], 4.08-6.43) hot flashes per day (47% decrease or a mean of 4.60 fewer hot flashes per day than baseline). In the placebo group, hot flash frequency decreased to 6.43 (95% CI, 5.12-7.73) hot flashes per day (33% decrease or a mean of 3.20 fewer hot flashes per day; Table 2).

Hot flash frequency was also significantly lower at week 4 in the escitalopram group than in the placebo group. In the escitalopram group, mean hot flash frequency at week 4 decreased to 5.65 (95% CI, 4.55-6.75) hot flashes per day (44% decrease or a mean of 4.37 fewer hot flashes per day than baseline). In the placebo group, hot flash frequency decreased to 7.19 (95% CI, 5.80-8.58) hot flashes per day (26% decrease or a mean of 2.49 fewer hot flashes per day; overall *P* = .001; Table 2). Reductions in hot flash frequency were observed for escitalopram vs placebo groups at each treatment week (FIGURE 2).

Race did not significantly modify the treatment effect (*P* = .62), although the reduction in daily hot flash frequency associated with escitalopram was smaller in African American women (-0.48; 95% CI, -2.95 to 2.00) than in white women (-2.18; 95% CI, -3.50 to -0.87) and other or unknown race/ethnicity (-2.30; 95% CI, -7.76 to 3.15). There were also no significant interactions between treatment and menopausal status (*P* = .57), PHQ-9 de-

pression ($P=.38$), or GAD-7 anxiety ($P=.14$) scores (eFigure 1 and eFigure 2 available at <http://www.jama.com>).

Clinical improvement at week 8 (decrease of $\geq 50\%$ from baseline in hot flash frequency) was significantly greater in the escitalopram group than in the placebo group (55% vs 36%, respectively, $P=.009$). A decrease of at least 75% from baseline in hot flash frequency was experienced by 19% of women in the escitalopram group and 9% in the placebo group ($P=.06$).

Hot Flash Severity

The baseline mean (SD) hot flash severity score was 2.17 (0.45), indicating moderate to severe on a 3-point scale. Escitalopram significantly reduced hot flash severity compared with placebo, adjusted for race, site, and baseline severity ($P<.001$ for overall treatment effect; Table 2). At week 8, mean severity scores were reduced to mild to moderate: 1.63 (95% CI, 1.51-1.76) in the escitalopram group (a decrease of 24% or a mean decrease of 0.52 from baseline) and 1.89 (95% CI, 1.77-2.02) in the placebo group (a decrease of 14% or a mean decrease of 0.30; Table 2). The decreases in severity scores paralleled the decreases in hot flash frequency (Figure 2).

Hot Flash Bother

Reports of bother and severity were highly correlated ($r=0.94$), indicating

that participants rated these domains similarly. The mean (SD) baseline rating for hot flash bother was 3.14 (0.51) on a 4-point scale. Escitalopram significantly reduced hot flash bother compared with placebo, adjusted for race, site, and baseline bother ($P=.001$ for overall treatment effect; Table 2). At week 8, mean bother scores in the escitalopram group were 2.48 (95% CI, 2.32-2.64), a decrease of 20% or a mean decrease of 0.63 from baseline and 2.76 (95% CI, 2.61-2.91), a decrease of 18% or a mean decrease of 0.39 in the placebo group (Table 2).

Return of Hot Flashes

By week 11, approximately 3 weeks after cessation of therapy, the frequency of hot flashes reported by women in the escitalopram group increased from week 8 to week 11 by a mean of 1.83 (95% CI, 1.05-2.62) hot flashes per day to 7.18 (95% CI, 5.88-8.48) hot flashes per day. In the placebo group, hot flashes increased by a mean of 0.24 (95% CI, -0.45-0.93) hot flashes per day to 6.65 (95% CI, 5.54-7.76) hot flashes per day. The increase from week 8 to week 11 was significantly higher in the escitalopram group than in the placebo group (mean difference, 1.59; 95% CI, 0.55 to 2.63; $P=.02$). Ratings of severity and bother also worsened between weeks 8 and 11 in the escitalopram group but were unchanged in the placebo group (Figure 2).

Dose Escalation and Adherence

Seventy-one of 101 women (70%) in the placebo group vs 53 of 104 (51%) in the

Table 1. Demographic and Clinical Characteristics by Groups at Baseline (continued)

Baseline Characteristic ^a	No. (% of Women) ^b	
	Escitalopram (n = 104)	Placebo (n = 101)
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)
PHQ-9 Depression score, mean (SD) ^d	3.24 (3.06)	2.94 (3.24)
No depression (0-4)	76 (73.1)	77 (76.2)
Mild symptoms (5-9)	24 (23.1)	15 (14.9)
Moderate + symptoms (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)

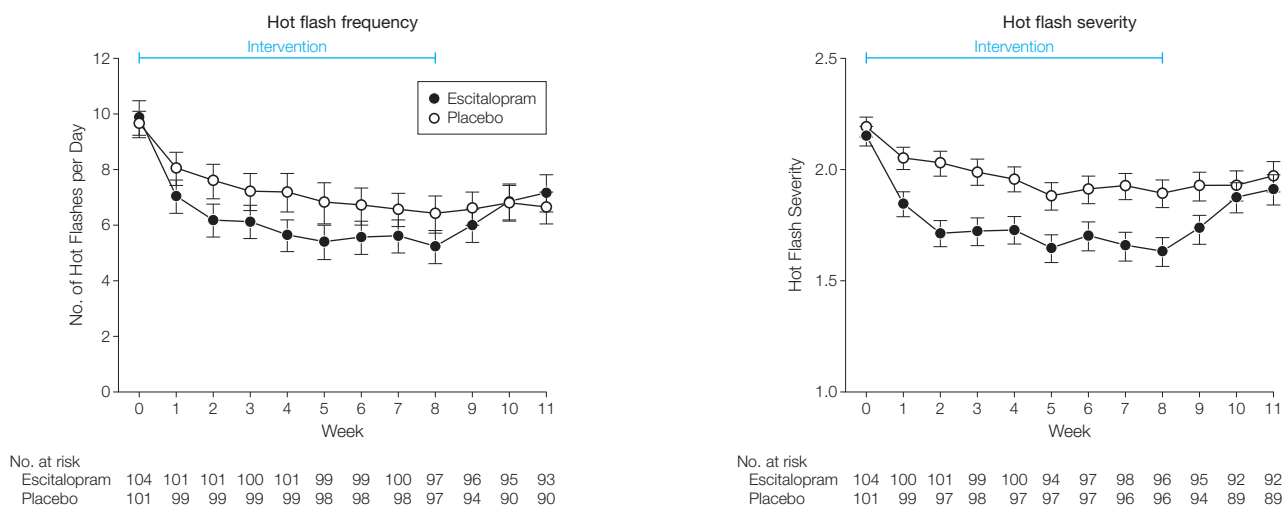
Abbreviations: BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; GAD, generalized anxiety disorder; GED, general equivalency diploma; PHQ, Patient Health Questionnaire
^a $P>.05$ for all comparisons by treatment group as tested by t test or χ^2 .
^bPercentages may not sum to 100 due to rounding.
^cLate transition menopause is defined as 90 days to 12 months of amenorrhea; early transition, 60 days to less than 90 days of amenorrhea.
^dThe PHQ-9 score range is 0-27. Cut points of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe levels of depressive symptoms, respectively. The highest score in this study was 13.

Table 2. Hot Flash Frequency, Severity, and Bother at Weeks 4 and 8 by Treatment

	Escitalopram		Placebo		Difference Mean (95% CI)	P Value ^a
	No. (%)	Mean (95% CI)	No. (%)	Mean (95% CI)		
Primary outcomes						
Hot flashes/d						
Baseline	104 (100)	9.88 (8.67 to 11.10)	101 (100)	9.66 (8.70 to 10.63)	0.22 (-1.32 to 1.76)	<.001
Week 4	101 (97)	-4.37 (-5.24 to -3.50)	99 (98)	-2.49 (-3.31 to -1.66)	-1.89 (-3.07 to -0.70)	
Week 8	97 (93)	-4.60 (-5.47 to -3.74)	97 (96)	-3.20 (-4.15 to -2.24)	-1.41 (-2.69 to -0.13)	
Severity (1-3)						
Baseline	104 (100)	2.16 (2.07 to 2.24)	101 (100)	2.19 (2.10 to 2.28)	-0.04 (-0.16 to 0.08)	<.001
Week 4	100 (96)	-0.43 (-0.54 to -0.33)	97 (96)	-0.23 (-0.34 to -0.13)	-0.20 (-0.35 to -0.05)	
Week 8	96 (92)	-0.52 (-0.64 to -0.40)	96 (95)	-0.30 (-0.42 to -0.17)	-0.22 (-0.40 to -0.05)	
Secondary outcome						
Bother (1-4)						
Baseline	104 (100)	3.12 (3.03 to 3.22)	101 (100)	3.16 (3.06 to 3.26)	-0.04 (-0.18 to 0.10)	.001
Week 4	100 (96)	-0.59 (-0.73 to -0.45)	97 (96)	-0.29 (-0.41 to -0.16)	-0.30 (-0.49 to -0.12)	
Week 8	96 (92)	-0.63 (-0.78 to -0.49)	96 (95)	-0.39 (-0.55 to -0.24)	-0.24 (-0.45 to -0.03)	

^a P values from comparison of Escitalopram vs placebo in a linear model of the outcome as a function of intervention group and adjusted for race, clinical center, baseline outcome, and visit (week 4 or 8).

Figure 2. Hot Flash Frequency and Severity Over Time



Data points represent mean standard error at each week; error bars, 95% confidence intervals. Hot flash severity was rated from 1 to 3 (mild, moderate, severe).

Table 3. Participants Reporting Newly Emergent Adverse Events During Intervention by Treatment

Symptom ^a	Escitalopram		Placebo	
	No. of Events	No. (%) of Women With No Baseline Symptoms	No. of Events	No. (%) of Women With No Baseline Symptoms
Fatigue, tiredness	14	58 (24.1)	14	69 (20.3)
Difficulty sleeping/insomnia	9	51 (17.7)	10	42 (23.8)
Drowsiness	14	81 (17.3)	13	82 (15.9)
Increased sweating	7	52 (13.5)	9	53 (17.0)
Dry mouth	11	92 (12.0)	12	84 (14.3)
Stomach or intestinal problems	10	84 (11.9)	18	86 (20.9)
Nausea or vomiting	11	98 (11.2)	5	93 (5.4)
Decreased sexual desire/ability	7	65 (10.8)	8	68 (11.8)
Headache	8	79 (10.1)	11	76 (14.5)
Vivid dreams	8	89 (9.0)	9	82 (11.0)
Appetite changes	6	85 (7.1)	4	86 (4.7)
Other symptoms	4	94 (4.3)	10	96 (10.4)
Dizziness/lightheadedness	3	94 (3.2)	7	90 (7.8)
Any new symptom	54	102 (52.9)	62	99 (62.6)

^aDifferences between treatment groups were not significant (Fisher exact test).

escitalopram group increased their study dose at week 4 due to lack of improvement ($P=.007$). The mean dose of escitalopram at week 8 was 15.4 mg/d.

Over the entire treatment period, 179 participants (87%) were adherent to their study dose as defined by taking at least 70% of dispensed pills. When only adherent participants were included in the regression models, treatment benefit increased very slightly: hot flash frequency decreased 49% in the escitalopram group and 34% in the placebo group.

Fifty-eight percent in the escitalopram group vs 38% in the placebo group reported hot flash frequency improved by at least 50% ($P=.01$). The results for hot flash severity and bother in the adherent group also remained consistent with the results of the primary modified intent-to-treat models (eTable 1 available at <http://www.jama.com>). We also analyzed hot flash frequency, severity, and bother at weeks 4 and 8 with the missing values filled in by multiple imputation.

The results were nearly identical to those shown in Table 2 and are presented in eTable 2.

Adverse Events

Newly emergent adverse events were reported by 53% in the escitalopram group and 63% in the placebo group ($P=.20$, TABLE 3). There were no serious adverse events due to study treatment that required medical intervention or study withdrawal. Tolerability of treatment was high: only 9 women stopped treatment due to adverse events (7, escitalopram; 2, placebo; $P=.17$).

At week 11, approximately 3 weeks after stopping the study medication, newly emergent symptoms compared with week 8 were reported in response to questioning¹⁹ by 52% of women in the escitalopram group and 45% in the placebo group ($P=.39$). Newly emergent (withdrawal) symptoms reported by more than 10% in the escitalopram group were dizziness or lightheadedness (14%), vivid dreams (13%), nausea (11%), and excessive sweating (11%). No symptom required medical intervention or resumption of the medication.

Participant Satisfaction

Satisfaction with treatment was greater in the escitalopram group than in the placebo group.

placebo group (70% vs 43%, $P < .001$). Only 16% of women in the escitalopram group vs 46% in the placebo group indicated that their assigned treatment had no benefit ($P < .001$). At week 8, the escitalopram group was significantly more likely than the placebo group to guess correctly their treatment assignment (59% vs 40%, respectively, $P = .007$). Women in the escitalopram group were significantly more likely to want to continue their assigned medication (64% vs 42%, $P = .005$).

COMMENT

Escitalopram at doses of 10 or 20 mg/d significantly reduced hot flash frequency relative to placebo, extending results of other SSRI and SNRI trials that reported efficacy for hot flashes.^{7,8,11-13,21} In the escitalopram group, 55% reported that hot flash frequency decreased by at least 50% from baseline vs 36% in the placebo group; significant decreases in severity and bother paralleled the decreases in hot flash frequency. Following cessation of treatment, hot flash frequency significantly increased in the escitalopram group but not in the placebo group, providing further indication of the escitalopram effect on hot flashes.

In as much as the approved indications for escitalopram are generalized anxiety and major depressive disorders, it is noteworthy that women who were not clinically anxious or depressed responded to escitalopram. Furthermore, response was rapid, with significantly greater improvement among women taking escitalopram than placebo after 1 week of treatment. Although the precise mechanism is unknown, these findings suggest that the mechanism underlying the effect on hot flashes may differ from the action of SSRIs and SNRIs in psychiatric conditions and support postulates of the role of serotonin receptors in the pathogenesis of hot flashes.²²

Although the decreases in hot flash frequency and severity appear modest, the study participants perceived these improvements as meaningful, as indicated

by their reported satisfaction with treatment and desire to continue the treatment. In a recent study to identify meaningful differences in vasomotor symptoms, women perceived 1.64 fewer moderate to severe hot flashes per day as meaningful after 12 weeks of SNRI treatment.²³ This compares with our finding of 1.40 fewer hot flashes per day for escitalopram than for placebo (4.60 fewer hot flashes per day in the escitalopram group and 3.20 fewer hot flashes per day in the placebo group) after 8 weeks of therapy. The findings suggest that both escitalopram and placebo-related decreases in hot flash frequency were meaningful to the participants and that any additional decreases from placebo can be considered an added benefit. Although comparisons with other studies must be viewed with caution, the present reduction in hot flash frequency relative to placebo was only modestly less than that reported in a meta-analysis of estrogen therapy, for which reductions ranged from 2.40 to 3.20 fewer hot flashes per day for estrogen than for placebo, depending on the estrogen formulation and dose.²⁴

The placebo effect is expected in hot flash treatment and was moderate in this study compared with other published trials. In a pooled analysis of 10 double-blind, placebo-controlled studies of hot flash treatment, the placebo responder rate (the percent of patients with reduction in hot flash frequency of $\geq 50\%$ from baseline) ranged from a low rate of 27% to a high rate of 52%.⁶ Across the 10 studies, the mean placebo responder rate was 37%, nearly identical to the 36% rate observed in this study. Other recent studies of hot flash treatment reported high placebo responder rates of 51% and 60%,^{7,8} although we underscore the importance of differences in study designs and measurement of hot flashes that contribute to the range of placebo response. Why some patients respond well to placebo treatment while others do not is not understood. The experience of treatment, whether it is active or placebo, contributes to symptom reduction. The supportive care that is provided in a clinical trial and expect-

tations of the patient (and the clinician) that treatment will be beneficial have strong effects. Maintaining a daily diary may reduce symptoms, possibly through the education and feeling more in control of distressing symptoms that daily recording provides. The results in this trial suggest the importance of non-drug factors in clinical care and the potential for nonmedical approaches as other possible therapies for reduction of hot flashes.

An important consideration for all menopausal therapies is medication tolerance and adverse events. Although a majority of women reported common adverse effects of escitalopram after initiating treatment, there were no serious adverse events and only 7 women stopped escitalopram because of them. Forty-four percent improved at the starting dose (10 mg/d). Another 11% who were unimproved after 4 weeks improved with a single-dose increase to 20 mg/d. Although response to the initial dose might have improved over time, a dose increase is a reasonable option, based on the evidence that it was well-tolerated and was associated with improvement in a small subset of women.

To our knowledge, this is the first clinical trial to examine whether there are racial differences in response to SSRI treatment for hot flashes. Studies indicate that African American are more likely than white women to report hot flashes,^{14,25-27} but race did not significantly affect the response to escitalopram in the present study.

Several limitations of our study should be noted. Although this was a community-based sample, the volunteer participants may be a select group who were motivated to seek treatment and thus, our results may not be generalizable to all women. An 8-week treatment duration is brief, but data indicate that this interval is sufficient to determine long-term efficacy of a nonhormonal compound.^{28,29} We examined several potential modulating factors of treatment response, but other factors associated with treatment response likely exist.

Strengths of this study include similar numbers of African American and

white women, the inclusion of perimenopausal and postmenopausal women, flexible dosing, high adherence to therapy, the prospective assessment of hot flashes, and a very low dropout rate (98% provided primary outcome data) that was comparable across treatment groups. The 3-week postintervention follow-up demonstrated that hot flashes increased after cessation of escitalopram but not after cessation of placebo, providing further evidence of escitalopram's effects. Our findings suggest that among healthy women, 10 to 20 mg/d of escitalopram provides a nonhormonal, off-label option that is effective and well-tolerated in the management of menopausal hot flashes. Further studies are needed to directly compare the relative efficacy of SSRIs and SNRIs with hormone therapy in the treatment of menopause-related hot flashes.

Author Contributions: Dr Guthrie 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 concept and design: Freeman, Guthrie, Cohen, Joffe, Carpenter, Anderson, Newton, Sherman, LaCroix.

Acquisition of data: Freeman, Caan, Sternfeld, Joffe, Carpenter.

Analysis and interpretation of data: Freeman, Guthrie, Caan, Cohen, Joffe, Carpenter, Anderson, Larson, Ensrud, Reed, Sammel, LaCroix.

Drafting of the manuscript: Freeman, Guthrie, Cohen, Joffe, Carpenter.

Critical revision of the manuscript for important intellectual content: Freeman, Guthrie, Caan, Sternfeld, Cohen, Joffe, Carpenter, Anderson, Larson, Ensrud, Reed, Newton, Sherman, Sammel, LaCroix.

Statistical analysis: Guthrie, Larson, Sammel.

Obtained funding: Freeman, Caan, Cohen, Anderson, Reed, Newton, LaCroix.

Administrative, technical, or material support: Freeman, Sternfeld, Cohen, Carpenter, Anderson, Sherman, LaCroix.

Study supervision: Freeman, Anderson, Ensrud, LaCroix.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. 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 Janssen; Pfizer, Inc. Advisory/Consulting: Eli Lilly; GlaxoSmithKline; JDS/Noven Pharmaceuticals; Wyeth-Ayerst Pharmaceuticals; Honoraria, Eli Lilly, Forest Laboratories, Inc; GlaxoSmithKline; Pfizer, Inc, and Wyeth-Ayerst Pharmaceuticals. Dr Joffe reported research support from Astra-Zeneca Pharmaceuticals, Bayer HealthCare, Eli Lilly,

Forest Laboratories, Inc, GlaxoSmithKline, Sanofi-Events (product support only), Sepracor, Inc, and Wyeth-Ayerst Pharmaceuticals; speaking honoraria, Eli Lilly, GlaxoSmithKline; Advisory/Consulting, Abbott Laboratories, Eli Lilly, Forest Laboratories, Inc, JDS-Noven Pharmaceuticals, Sanofi-Events, Sepracor Inc, and Wyeth-Ayerst Pharmaceuticals. No other authors reported having a financial conflict of interest.

Funding/Support: The study was supported by a cooperative agreement issued by the National Institute of Aging (NIA), in collaboration with the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD), the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Research and Women's Health (ORWH), and grants U01 AG032656, U01AG032659, U01AG032669, U01AG032682, U01AG032699, U01AG032700 from the NIA. At the Indiana University site, the project was funded in part with support from the Indiana Clinical and Translational Sciences Institute, funded in part by grant UL1 RR025761 from the National Institutes of Health, National Center for Research Resources, Clinical and Translational Sciences Award. Escitalopram and matching placebo pills were provided by Forest Research Institute.

Online-Only Material: The eAppendix, eTables 1 and 2, and eFigures 1 and 2 are available at <http://www.jama.com>.

Role of the Sponsor: 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.

REFERENCES

- Haas JS, Kaplan CP, Gerstenberger EP, Kerlikowske K. Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. *Ann Intern Med.* 2004;140(3):184-188.
- Heiss G, Wallace R, Anderson GL, et al; WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA.* 2008;299(9):1036-1045.
- National Institutes of Health. National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. *Ann Intern Med.* 2005;142(12 pt 1):1003-1013.
- Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson HD. Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review. *Arch Intern Med.* 2006;166(14):1453-1465.
- Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA.* 2006;295(17):2057-2071.
- Loprinzi CL, Sloan J, Stearns V, et al. Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. *J Clin Oncol.* 2009;27(17):2831-2837.
- Archer DF, Seidman L, Constantine GD, Pickar JH, Olivier S. A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause. *Am J Obstet Gynecol.* 2009;200(2):172.e1-172.e10.
- Suvanto-Luukkonen E, Koivuonen R, Sundström H, et al. Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study. *Menopause.* 2005;12(1):18-26.
- Kalay AE, Demir B, Haberal A, Kalay M, Kandemir O. Efficacy of citalopram on climacteric symptoms. *Menopause.* 2007;14(2):223-229.
- Grady D, Cohen B, Tice J, Kristof M, Olyae A, Sawaya GF. Ineffectiveness of sertraline for treatment of menopausal hot flashes: a randomized controlled trial. *Obstet Gynecol.* 2007;109(4):823-830.
- Barton DL, LaVasseur BI, Sloan JA, et al. Phase III, placebo-controlled trial of three doses of citalopram for the treatment of hot flashes: NCCCT trial N05C9. *J Clin Oncol.* 2010;28(20):3278-3283.
- Defronzo Dobkin R, Menza M, Allen LA, et al. Escitalopram reduces hot flashes in nondepressed menopausal women: a pilot study. *Ann Clin Psychiatry.* 2009;21(2):70-76.
- Soares CN, Arsenio H, Joffe H, et al. Escitalopram versus ethinyl estradiol and norethindrone acetate for symptomatic peri- and postmenopausal women: impact on depression, vasomotor symptoms, sleep, and quality of life. *Menopause.* 2006;13(5):780-786.
- Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Public Health.* 2006;96(7):1226-1235.
- Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics.* 1975;31(1):103-115.
- Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606-613.
- Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* 2006;166(10):1092-1097.
- Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci.* 1974;19(1):1-15.
- Michelson D, Fava M, Amsterdam J, et al. Interruption of selective serotonin reuptake inhibitor treatment: double-blind, placebo-controlled trial. *Br J Psychiatry.* 2000;176:363-368.
- Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. *Ann Intern Med.* 2006;145(12):869-879.
- Stearns V, Slack R, Greep N, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol.* 2005;23(28):6919-6930.
- Berendsen HH. The role of serotonin in hot flashes. *Maturitas.* 2000;36(3):155-164.
- Wyrwich KW, Spratt DL, Gass M, Yu H, Bobula JD. Identifying meaningful differences in vasomotor symptoms among menopausal women. *Menopause.* 2008;15(4 pt 1):698-705.
- Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. *JAMA.* 2004;291(13):1610-1620.
- Appling S, Paez K, Allen J. Ethnicity and vasomotor symptoms in postmenopausal women. *J Womens Health (Larchmt).* 2007;16(8):1130-1138.
- Whiteman MK, Staropoli CA, Langenberg PW, McCarter RJ, Kjerulff KH, Flaws JA. Smoking, body mass, and hot flashes in midlife women. *Obstet Gynecol.* 2003;101(2):264-272.
- Simpkins JW, Brown K, Bae S, Ratka A. Role of ethnicity in the expression of features of hot flashes. *Maturitas.* 2009;63(4):341-346.
- Guttuso T, Evans M. Minimum trial duration to reasonably assess long-term efficacy of nonhormonal hot flash therapies. *J Womens Health (Larchmt).* 2010;19(4):699-702.
- Loprinzi CL, Diekmann B, Novotny PJ, Stearns V, Sloan JA. Newer antidepressants and gabapentin for hot flashes: a discussion of trial duration. *Menopause.* 2009;16(5):883-887.