Menopause: The Journal of The North American Menopause Society
Vol. 19, No. 8, pp. 848-855
DOI: 10.1097/gme.0b013e3182476099

Effect of escitalopram on insomnia symptoms and subjective sleep quality in healthy perimenopausal and postmenopausal women with hot flashes: a randomized controlled trial

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Abstract

Objective: The aim of this study was to determine the effect of escitalopram on insomnia symptoms and subjective sleep quality in healthy perimenopausal and postmenopausal women with hot flashes.

Methods: A randomized, blinded, multicenter, placebo-controlled parallel-group 8-week trial with 205 women (95 African American, 102 white, 8 other) was conducted between July 2009 and June 2010. The participants received escitalopram (10-20 mg/d) or placebo. Insomnia symptoms (Insomnia Severity Index [ISI]) and subjective sleep quality (Pittsburgh Sleep Quality Index [PSQI]) at weeks 4 and 8 were the prespecified secondary outcomes. A total of 199 women (97%) provided ISI data, and 194 (95%) women provided PSQI data at follow-up.

Results: At baseline, mean hot flash frequency was 9.78 per day (SD, 5.60), mean ISI was 11.4 (SD, 6.3), and mean PSQI was 8.0 (SD, 3.7). Treatment with escitalopram reduced ISI at week 8 (mean difference, −2.00; 95% CI, −3.43 to −0.57; $P < 0.001$ overall treatment effect), with mean differences of −4.73 (95% CI, −5.72 to −3.75) in the escitalopram group and −2.73 (95% CI, −3.78 to −1.69) in the placebo group. The reduction in PSQI was greater in the escitalopram than in the placebo group at week 8 (mean difference, −1.31; 95% CI, −2.14 to −0.49; $P < 0.001$ overall treatment effect). Clinical improvement in insomnia symptoms and subjective sleep quality (≥50% decreases in ISI and PSQI from baseline) was observed more frequently in the escitalopram group than in the placebo group (ISI, 50.0% vs 35.4%, $P = 0.04$; PSQI, 29.6% vs 19.2%, $P = 0.09$).

Conclusions: Among healthy perimenopausal and postmenopausal women with hot flashes, escitalopram at 10 to 20 mg/day compared with placebo reduced insomnia symptoms and improved subjective sleep quality at 8 weeks of follow-up.

Key Words: Randomized trial – Escitalopram – Sleep – Hot flashes – Menopause.

Self-reported sleep complaints are common in perimenopausal and postmenopausal women[1-3] and have been identified as a key symptom of the menopausal transition.[4] Menopause-related sleep disturbance has often been attributed, at least partly, to nocturnal hot flashes. Previous cross-sectional studies have reported a graded association between

Received October 14, 2011; revised and accepted December 19, 2011.

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K.A.G. 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. All authors made substantial contributions to the study and this manuscript. None of the authors were compensated for manuscript preparation.

Funding/support: This study was supported by a cooperative agreement issued by the National Institute on Aging (NIA), in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Center for Complementary and Alternative Medicine, and the Office of Research on Women's Health (U01 AG032656, U01AG032659, U01AG032669, U01AG032699, U01AG032700). At the University of Indiana site, the project was funded, in part, with support from the Indiana Clinical and Translational Sciences Institute, 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.

Financial disclosure/conflicts of interest: Dr. Joffe reports research support from Cephalon and advisory/consultant activities for Sunovion, Noven.

Trial registration: NCT00894543 at www.clinicaltrials.gov.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.menopause.org).

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hot flashes and insomnia symptoms,[5,6] although the exact role that hot flashes play in sleep complaints of perimenopausal and postmenopausal women remains controversial.[7,8]

Hormone therapy (estrogen with or without progestin) remains the predominant and only Food and Drug Administration–approved treatment of menopausal hot flashes, but its use markedly decreased after the release of the findings from the Women's Health Initiative Estrogen Plus Progestin Trial, which identified the delicate balance of risks and benefits of combined hormone therapy.[9,10] Increasingly prescribed to women in midlife,[11] selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs and SNRIs) have shown modest efficacy in reducing hot flash frequency and severity in previous randomized controlled trials,[12,13] but the use of SSRIs/SNRIs for treatment of hot flashes is limited by concerns about commonly reported adverse effects, including insomnia and somnolence.[4,14] However, it is also plausible that SSRIs/SNRIs may improve sleep in parallel with reducing hot flash frequency and severity.

We systematically collected validated, self-reported sleep measures in a randomized double-blind placebo-controlled trial designed primarily to evaluate the effect of the SSRI escitalopram on the frequency and severity of menopausal hot flashes. As previously reported,[15] treatment with escitalopram compared with placebo resulted in fewer and less severe hot flashes at 8 weeks. We now report the effect of escitalopram versus placebo on insomnia symptoms and subjective sleep quality (a priori specified secondary outcomes) and examine whether any observed effect varied across any risk subgroup at baseline.

METHODS

Overview

The study was a double-blind placebo-controlled randomized trial conducted at four Menopause Strategies Finding Lasting Answers for Symptoms and Health (MsFLASH) network sites (see Appendix, Supplemental Digital Content 1, which lists the funding sources, sites, and investigators of the MsFLASH research network; http://links.lww.com/MENO/A19), with enrolment stratified by race (African American and white as self-reported). The study design, methods, and main trial results have been reported elsewhere.[15] The primary objective of the trial was to determine the efficacy of escitalopram on self-reported hot flash frequency and severity (7-d averages for both measures) at 4 and 8 weeks. Self-reported sleep measures (insomnia symptoms as assessed using the Insomnia Severity Index [ISI] and subjective sleep quality as assessed using the Pittsburgh Sleep Quality Index [PSQI]) at 4 and 8 weeks were a priori specified secondary outcomes. The protocol was approved by the appropriate institutional review board at each site. All women provided written informed consent.

Participants

Between July 2009 and June 2010, the study enrolled 205 women. The eligible women were aged 40 to 62 years and were in generally good health; were in the menopausal transition (amenorrhea ≥60 d in the past year), postmenopausal (≥12 mo since last menstrual period or bilateral oophorectomy), or had undergone hysterectomy with one or more ovaries remaining and had a follicle-stimulating hormone level higher than 20 mIU/mL and an estradiol level 50 pg/mL or lower; and reported 28 or more hot flashes or night sweats per week (recorded on daily diaries for 3 wk) rated as bothersome or severe on 4 or more days per week. Exclusion criteria, described in detail elsewhere,[15] included the following: use of psychotropic medications in the past month; use of prescription, nonprescription, or herbal therapies for hot flashes in the past month; use of hormone therapy, hormonal contraceptives, selective estrogen receptor modulators, or aromatase inhibitors in the past 2 months; current severe illness; major depressive episode and drug or alcohol abuse in the past year; suicide attempt in the past 3 years; and lifetime diagnosis of bipolar disorder or psychosis. Women with uncontrolled hypertension; history of myocardial infarction, angina, or cerebrovascular events; or history of endometrial or ovarian cancer were also excluded from participation.

Treatment and study procedures

After a telephone screen, women who were potentially eligible and interested in participation 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 two clinic visits (screening and randomization) within a 2- to 3-week interval. At the randomization visit, eligible women were randomized using a dynamic algorithm[15] in a 1:1 ratio to treatment groups of escitalopram 10 mg/day or identical-appearing placebo for 8 weeks. Participants, investigators, and clinical center staff were blinded to treatment assignment. After randomization, a telephone contact was made at 1 week (to assess protocol adherence and adverse events), and clinic visits were conducted at 4 and 8 weeks. The dose of study medication was increased to 20 mg/day in a blinded manner at 4 weeks for women reporting a less than 50% decrease in hot flash frequency or no decrease in hot flash severity, unless precluded by unacceptable adverse effects.

Assessment of insomnia symptoms

Participants completed the ISI,[16-18] a valid and reliable self-administered instrument that measures perception of current (past 2 wk) insomnia symptoms, at baseline and at 4 and 8 weeks of treatment. The index consists of seven items assessing difficulty in falling asleep, difficulty in staying asleep, problems with early awakening, satisfaction with the current sleep pattern, interference of sleep problem with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress caused by the sleep problem. Each item is rated on a scale from 0 to 4 (total score, 0-28), with higher scores suggesting more severe insomnia symptoms. The absence of insomnia is indicated by scores 0 to 7; subthreshold or mild insomnia, by scores 8 to 14; clinical

insomnia of moderate severity, by scores 15 to 21; and severe clinical insomnia, by scores 22 to 28. Trials of pharmacologic and behavioral interventions in patients with insomnia have suggested that the ISI is sensitive in measuring treatment response.[19,20]

Assessment of subjective sleep quality

Participants also completed the PSQI at baseline and at 4 and 8 weeks of treatment. A validated measure of subjective sleep quality and sleep disturbances over a 1-month time period, the PSQI assesses subjective sleep quality, latency, duration, and efficiency; sleep disturbances; use of sleeping medication; and daytime dysfunction.[21,22] Global PSQI scores range from 0 to 21, with higher scores indicating poorer sleep quality. Cutoffs of 5 and 8 have been reported to indicate poor sleep quality[21,23]; the higher cutpoint was used in this trial because of previous studies suggesting that self-reported sleep disturbance is common among perimenopausal and postmenopausal women.[1-3] The PSQI has been shown to be sensitive in measuring response to cognitive behavioral therapy in randomized trials conducted in persons with insomnia.[24]

Other measurements

The frequency and severity of hot flashes/night sweats were recorded in 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, menopause status (the menopausal transition, postmenopause), and health status were assessed by questionnaire at baseline. Validated questionnaires at baseline also evaluated depressive symptoms (nine-item scale from the Patient Health Questionnaire),[25] anxiety (seven-item Generalized Anxiety Disorder scale),[26] and pain intensity and interference (three-item PEG scale).[27] Height and body weight were measured at baseline and were used to calculate standard body mass index (BMI).

Statistical analysis

All analyses included all randomized participants with follow-up sleep measurements, which were collected irrespective of adherence to study medication. Of the participants, 199 completed the ISI and 194 (95%) completed the PSQI at follow-up (Fig. 1).

Primary analyses consisted of treatment group contrasts from repeated-measures linear regression models summarizing ISI and PSQI at both 4 and 8 weeks as a function of treatment assignment and baseline value of the sleep outcome measure. The model was adjusted for race, visit, and clinical center. Robust standard errors were calculated using generalized estimating equations to account for correlation between repeated measures from each participant. We hypothesized that the effect of treatment on sleep outcome measures might be modified by the following characteristics measured at baseline: race, menopause status, nocturnal hot flash frequency, depressive symptoms (nine-item scale from the Patient Health Questionnaire), anxiety (seven-item Generalized Anxiety Disorder scale), pain intensity and interference (PEG), and body mass index (BMI). Tests of interaction between treatment assignment and each of these variables were performed within the linear regression models, estimating mean week 8 ISI (PSQI) as a function of treatment arm, the covariate of interest, and the interaction between treatment assignment and covariate; models were adjusted for race, site, and baseline ISI (PSQI). Nominal P values are presented for the 14 potential interactions examined. Therefore, on average, about one P value would be expected to be statistically significant by chance alone at the 0.05 level.

Secondary analyses examined the proportion of women in each treatment group with clinical improvement in sleep measures, defined as a 50% decrease from baseline to 8 weeks in the ISI (PSQI); comparisons between treatment groups were performed using unadjusted χ^2 tests. To determine the effect

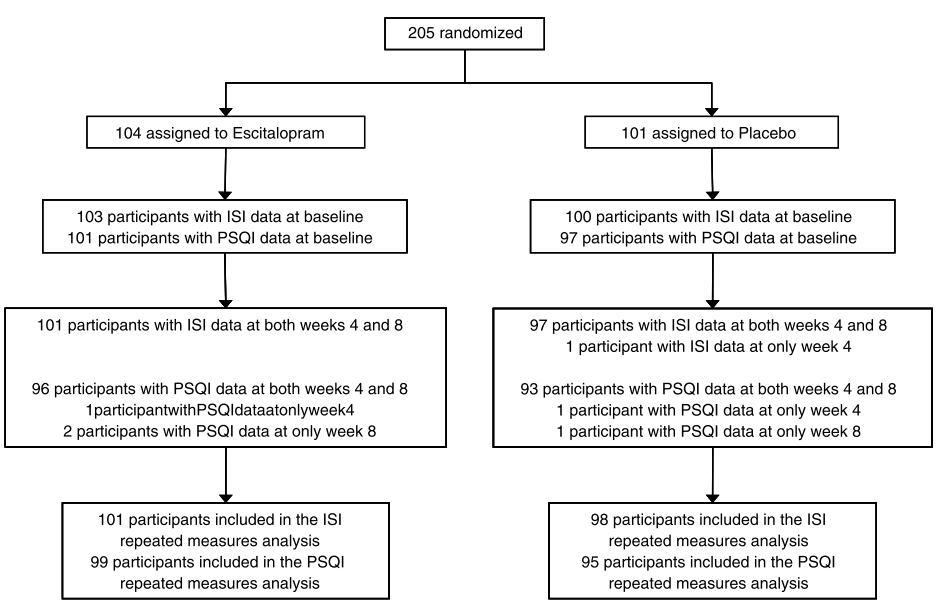


FIG. 1. Participant flow diagram for data collection of sleep outcome measures. ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index.

of treatment among women with moderate to severe clinical insomnia, we repeated the primary ISI analysis, limiting the cohort to the 67 women with an ISI greater than 14 at baseline. To examine the effect of treatment among women with poor sleep quality, we repeated the primary PSQI analysis, limiting the cohort to the 81 women with a PSQI greater than 8 at baseline.

The planned sample size of the trial (90 women per treatment group) was determined by the primary trial endpoints (hot flash frequency and severity).[15] Reported *P* values are based on the Wald statistic. Analyses were conducted using SAS Version 9.2 (SAS Institute, Cary, NC) with two-sided *P* values less than 0.05 considered statistically significant.

Role of the funding source

National Institutes of Health staff critically reviewed the study protocol and drafts of the manuscript before journal submission. Forest Research Institute, a subsidiary of Forest Laboratories, Inc. (New York, NY), provided escitalopram and matching placebo but had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation of the manuscript.

RESULTS

A total of 205 women were randomly assigned to receive escitalopram (n = 104) or placebo (n = 101; Fig. 1). The mean age of the participants was 53.9 (SD, 4.0) years, and mean daily hot flash frequency was 9.78 (SD, 5.60). There were no significant differences in baseline characteristics between the treatment groups (Table 1).

TABLE 1. *Baseline characteristics by treatment assignment*

Baseline characteristics[a]	Escitalopram group (n = 104)	Placebo group (n = 101)
Age at screening, mean (SD), y	53.45 (4.20)	54.36 (3.86)
Age group, n (%)		
42-49 y	16 (15.4)	8 (7.9)
50-54 y	48 (46.2)	47 (46.5)
55-59 y	30 (28.8)	36 (35.6)
60-62 y	10 (9.6)	10 (9.9)
Race, n (%)		
White	53 (51.0)	49 (48.5)
African American	47 (45.2)	48 (47.5)
Other	4 (3.8)	4 (4.0)
Clinic site, n (%)		
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, n (%)		
≤High school diploma or GED	15 (14.4)	23 (22.8)
School/training after high school	46 (44.25)	41 (40.6)
College graduate	43 (41.3)	37 (36.6)
Marital status, n (%)		
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, n (%)		
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, n (%)		
0	41 (39.4)	41 (40.6)
1-6	51 (49.0)	41 (40.6)
≥7	12 (11.5)	17 (16.8)
BMI, kg/m^2, mean (SD)	28.58 (6.59)	29.70 (6.42)
Menopause status, n (%)		
Postmenopause	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, n (%)		
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 score (range, 0-10), mean (SD)	1.62 (2.21)	1.58 (2.40)
PHQ-9 Depression score (range, 0-13), mean (SD)	3.24 (3.06)	2.94 (3.24)
GAD-7 Anxiety score (range, 0-19), mean (SD)	2.50 (3.34)	2.19 (3.33)
Hot flashes per 24 h, mean (SD)	9.88 (3.34)	9.66 (4.88)
Nocturnal hot flashes, mean (SD)	3.83 (2.82)	4.08 (2.32)

GAD-7, seven-item Generalized Anxiety Disorder scale; PHQ, Patient Health Questionnaire; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; BMI, body mass index.
[a] $P > 0.05$ for all comparisons by treatment groups as tested by *t* test or χ^2 test.

Insomnia symptoms

At baseline, the mean ISI was 11.4 (SD, 6.3). A total of 77 (37.6%) women were classified with mild (subthreshold) insomnia (ISI, 8-14); 55 (26.8%), with moderate clinical insomnia (ISI, 15-21); and 12 (5.9%), with severe clinical insomnia (ISI, 22-28). Treatment with escitalopram reduced the ISI compared with placebo, adjusted for race, site, and baseline ISI ($P < 0.001$ overall treatment effect; Table 2, Fig. 2A). The overall effect of escitalopram on insomnia symptoms was consistent with its effect on insomnia symptoms at the individual timepoints of weeks 8 and 4. The average ISI at week 8 in the escitalopram group decreased to 6.75 (95% CI, 5.54-7.95), a 41% decrease or an average of 4.73 points compared with baseline, whereas the average ISI at week 8 decreased, in the placebo group, to 8.41 (95% CI, 7.16-9.66), a 24% decrease or an average of 2.73 points compared with baseline. Findings were similar at week 4 (a 43% decrease in ISI relative to baseline in the escitalopram group vs a 21% decrease relative to baseline in the placebo group). Clinical improvement at week 8 (≥50% decrease from baseline in ISI) was greater in the escitalopram group than in the placebo group (50.0% in escitalopram group and 35.4% in placebo group, $P = 0.04$).

The effectiveness of escitalopram in reducing ISI was similar across strata of baseline participant characteristics (Fig. 3A). There was no evidence of an interaction between treatment assignment and race, menopause status, nocturnal hot flash frequency, depressive symptoms, anxiety symptoms, pain intensity and interference, or BMI (for interaction terms, $P \geq 0.17$).

The effect of escitalopram treatment on insomnia symptoms among the 67 women with moderate to severe clinical insomnia (ISI, >14) at baseline was similar to its effect in the overall study population. Among these women, the average ISI in the escitalopram group decreased from 18.56 to 11.77 at week 8, a 37% decrease or an average reduction of 6.86 points

TABLE 2. *Mean ISI and PSQI by treatment assignment*

	Escitalopram		Placebo		Difference	
Outcome	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	P^a
ISI						<0.001
Baseline	103	11.57 (10.32-12.83)	100	11.15 (9.93-12.37)	0.42 (−1.32 to 2.16)	
Week 4 − baseline	101	−4.98 (−5.97 to −3.99)	98	−2.34 (−3.26 to −1.42)	−2.64 (−3.99 to −1.30)	
Week 8 − baseline	101	−4.73 (−5.72 to −3.75)	97	−2.73 (−3.78 to −1.69)	−2.00 (−3.43 to −0.57)	
PSQI						<0.001
Baseline	101	8.23 (7.52-8.93)	97	7.78 (6.99-8.57)	0.44 (−0.60 to 1.49)	
Week 4 − baseline	97	−2.63 (−3.17 to −2.08)	95	−1.21 (−1.80 to −0.62)	−1.42 (−2.22 to −0.62)	
Week 8 − baseline	98	−2.64 (−3.19 to −2.10)	94	−1.33 (−1.96 to −0.70)	−1.31 (−2.14 to −0.49)	

ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; BMI, body mass index.
[a]*P* values from comparison of escitalopram versus placebo in repeated-measures linear models of each outcome as a function of intervention arm and adjusted for race, visit (week 4 or 8), site, and baseline value of outcome.

compared with baseline, whereas the average ISI decreased in the placebo group from 18.48 to 13.65 at 8 weeks, a 26% decrease or an average of 4.84 points compared with baseline ($P = 0.02$ overall treatment effect).

Subjective sleep quality

At baseline, the mean PSQI was 8.0 (SD, 3.7). A total of 81 women (39.5%) were classified with poor subjective sleep quality (PSQI, >8). Treatment with escitalopram reduced the PSQI compared with placebo, adjusted for race, site, and baseline PSQI ($P < 0.001$ overall treatment effect; Table 2, Fig. 2B). The overall effect of escitalopram on subjective sleep quality was consistent with its effect on sleep quality at the individual timepoints of weeks 8 and 4. The average PSQI at week 8 in the escitalopram group decreased to 5.56 (95% CI, 4.92-6.21), a 32% decrease or an average of 2.64 points compared with baseline, whereas the average PSQI at week 8 decreased in the placebo group to 6.40 (95% CI, 5.64-7.16), a 17% decrease or an average of 1.33 points compared with baseline. Findings were similar at 4 weeks (a 32% decrease in PSQI relative to baseline in the escitalopram group vs a 16% decrease relative to baseline in the placebo group). Clinical improvement at week 8 (≥50% decrease from baseline in PSQI) occurred more often in the escitalopram group than in the placebo group (29.6% in escitalopram group and 19.2% in placebo group), but the difference did not reach statistical significance ($P = 0.09$).

The effectiveness of escitalopram in reducing PSQI was similar across strata of baseline participant characteristics (Fig. 3B). There was no evidence of an interaction between treatment assignment and race, menopause status, nocturnal hot flash frequency, depressive symptoms, symptoms of anxiety, pain intensity and interference, or BMI (for interaction terms, $P \geq 0.11$).

The effect of escitalopram treatment on subjective sleep quality among the 81 women with poor sleep quality (PSQI, >8) at baseline was similar to its effect in the overall study population. Among these women, the average PSQI in the escitalopram group decreased from 11.60 to 7.68 at 8 weeks, a 34% decrease or an average of 3.89 points compared with baseline, whereas the average PSQI decreased in the placebo group from 11.94 to 9.21 at 8 weeks, a 24% decrease or an average of 2.88 points compared with baseline ($P = 0.06$ overall treatment effect).

Adherence

During the 8-week treatment period, 87% (179 of 205) of the women were adherent to their study dose, as defined by taking at least 70% of dispensed pills. At 8 weeks, the average absolute difference between escitalopram and placebo groups among adherent women was 2.36 points in ISI ($P < 0.001$ overall treatment effect) and 1.16 points in PSQI ($P < 0.001$ overall treatment effect).

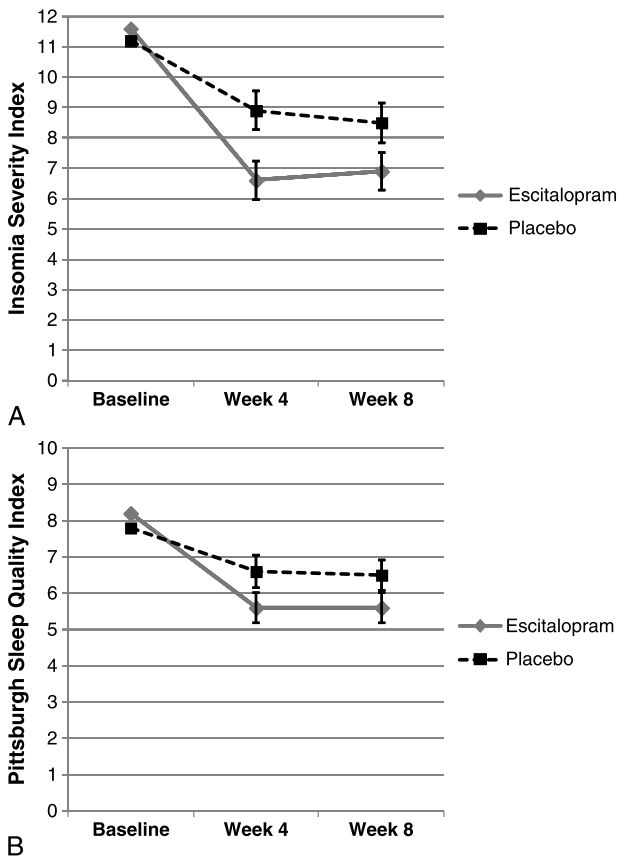
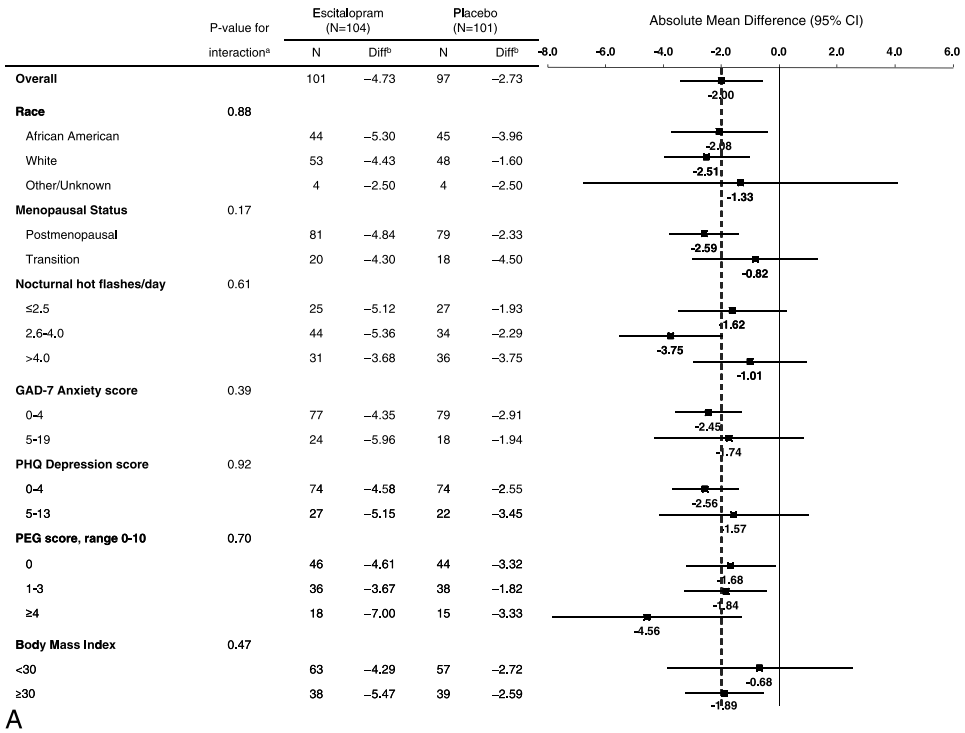


FIG. 2. A: Mean Insomnia Severity Index from baseline to week 8 by treatment assignment. **B:** Mean Pittsburgh Sleep Quality Index from baseline to week 8 by treatment assignment. Vertical bars represent SE.



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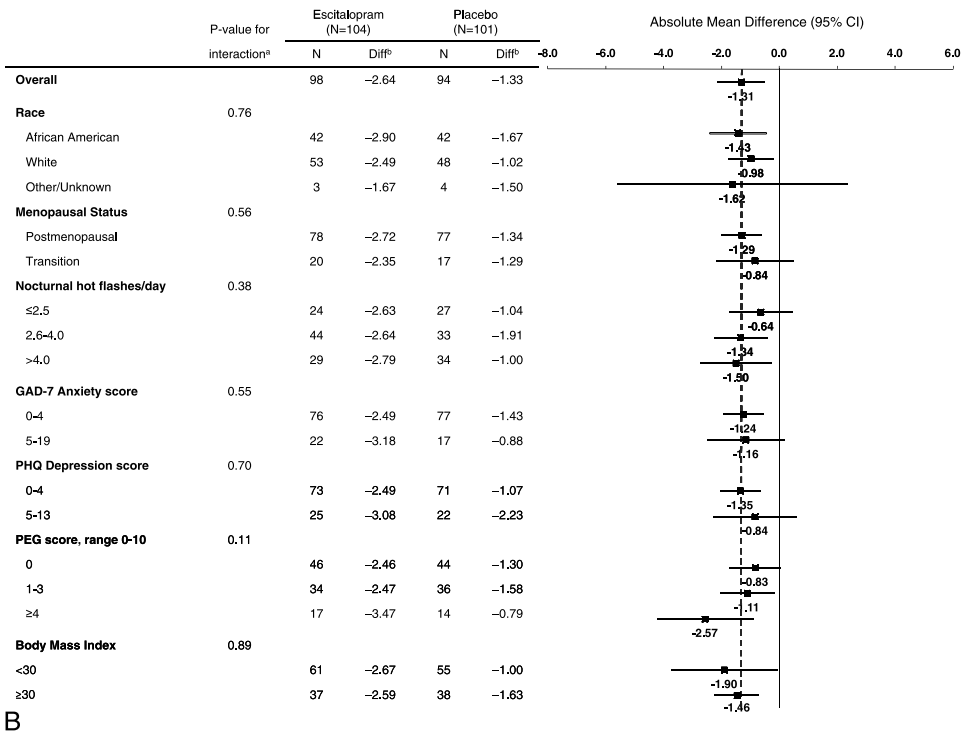

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FIG. 3. A: Mean change in ISI from baseline to week 8 by treatment assignment overall and within risk subgroups. The dotted vertical line indicates the overall absolute mean difference between treatment groups. [a]Adjusted absolute mean differences and interaction *P* values are computed from a linear model estimating mean week 8 ISI as a function of treatment arm, the subgroup of interest, and the interaction between treatment assignment and subgroup. In addition, all models are adjusted for race, site, and baseline ISI, with the exception of the model examining the effect of treatment within race subgroups, which is adjusted for site and baseline ISI. [b]Mean week 8 ISI − baseline ISI difference. **B:** Mean change in PSQI from baseline to week 8 by treatment assignment overall and within risk subgroups. The dotted vertical line indicates the overall absolute mean difference between treatment groups. [a]Adjusted absolute mean differences and interaction *P* values are computed from a linear model estimating mean week 8 PSQI as a function of treatment arm, the subgroup of interest, and the interaction between treatment assignment and subgroup. In addition, all models are adjusted for race, site, and baseline PSQI, with the exception of race subgroup, where the model is adjusted for site and baseline PSQI. [b]Mean week 8 PSQI − baseline PSQI difference. GAD, seven-item Generalized Anxiety Disorder scale; PHQ, Patient Health Questionnaire; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index.

Sleep adverse events

Newly emergent adverse events were reported by 53% of women in the escitalopram group and 63% of women in the placebo group ($P = 0.20$). There were no differences between the escitalopram and placebo groups in newly emergent complaints of fatigue/tiredness (24.1% vs 20.3%, $P = 0.15$), difficulty sleeping/insomnia (17.7% vs 23.8%, $P = 0.61$), or drowsiness (17.3% vs 15.9%, $P = 0.84$).

DISCUSSION

In healthy women with menopausal hot flashes, treatment with escitalopram at doses of 10 or 20 mg/day relative to placebo reduced insomnia symptoms and improved subjective sleep quality. These results do not support the concern[4] that insomnia is an anticipated adverse effect of escitalopram treatment in this population and should provide reassurance to clinicians and women considering use of escitalopram therapy for relief of hot flash symptoms.

It is notable that insomnia and poor subjective sleep quality were common in this cohort despite excluding women with a diagnosis of major depression or anxiety disorder from participation and enrolling women who, on average, reported minimal depressive or anxiety symptoms. More than one third of the women at baseline had an ISI greater than 14, which is suggestive of a clinical diagnosis of moderate to severe insomnia, and nearly 40% had poor subjective sleep quality (defined using a conservative cutpoint of 8 on the PSQI). These findings are consistent with those reported in a similar randomized trial study population[5] and are in agreement with population-based studies in women not selected based on hot flashes, which have reported a strong association between the presence of hot flashes or greater hot flash frequency and self-reported sleep complaints.[1,6,28]

Contrary to conventional wisdom that sleep difficulties may emerge with the initiation of SSRI treatment, we found that treatment with escitalopram compared with placebo reduced ISI by 2.0 points and PSQI by 1.3 points at week 8, demonstrating a modest benefit of escitalopram in decreasing insomnia symptoms and improving subjective sleep quality. One half of the women in the escitalopram group versus 35% in the placebo group reported that insomnia symptoms decreased by at least 50% from baseline; clinical improvement in self-reported sleep quality was similar to the reduction in insomnia symptoms, although the comparison did not reach statistical significance. The effects of escitalopram versus placebo on insomnia symptoms and subjective sleep quality were consistent across risk subgroups. Few previous placebo-controlled randomized trials of SSRIs for treatment of menopausal hot flashes have systematically collected sleep outcome data, with one trial of citalopram reporting benefit,[29] a dose-ranging trial of paroxetine reporting mixed results,[30] and another dose-ranging trial of paroxetine reporting no effect.[31]

Systematic reviews of the evidence from efficacy studies evaluating SSRIs[32] including escitalopram[33] for the treatment of major depression and anxiety disorders have noted that insomnia is a commonly reported adverse event. The applicability of findings from trials of participants selected based on major depression or anxiety disorder to this population of healthy women with hot flashes without clinical psychiatric diagnoses is uncertain. We found no differences in the frequency of newly emergent adverse events of insomnia, fatigue, or drowsiness between the escitalopram and placebo groups. In contrast, previous trials of paroxetine,[31] citalopram,[34] venlafaxine (a SNRI),[35] and desvenlafaxine (a SNRI)[36] in women with hot flashes reported that these adverse events were more common among women assigned to active treatment versus placebo, albeit not always at the level of significance. Differences in effects of specific SSRIs on self-reported sleep in women with hot flashes may be caused by several reasons, including differences in pharmacologic properties of specific drugs, study populations, choice of sleep outcome measures, and reporting of adverse events.

This trial has limitations as well as strengths. The study population comprised healthy women selected based on hot flash frequency. Therefore, the results may not be generalizable to other groups such as unselected midlife women or women selected based on psychiatric conditions. The effects of escitalopram treatment on self-reported sleep measures beyond 8 weeks are unknown. We evaluated several potential modifiers of treatment response, but analyses were limited by suboptimal power; hence, multiple comparisons were performed. In-home overnight polysomnography was not performed; the results of a trial with objectively measured sleep outcomes might differ from the findings of this study of self-reported sleep measures. The strengths of this trial include the use of valid and reliable instruments to measure insomnia symptoms and subjective sleep quality, the representation of African American women, high adherence to treatment, and nearly complete collection of sleep outcome measures.

CONCLUSIONS

Treatment with escitalopram 10 to 20 mg/day in healthy perimenopausal and postmenopausal women with hot flashes reduced insomnia symptoms and improved subjective sleep quality. These results should provide reassurance to clinicians and women considering escitalopram treatment of hot flash symptoms who have concerns about insomnia as a potential adverse effect. Future trials should evaluate the efficacy of SSRIs/SNRIs in improving insomnia symptoms in perimenopausal and postmenopausal women selected based on hot flashes and sleep disturbance and directly compare the efficacy of these agents with hormone therapy in the treatment of these commonly co-occurring menopausal complaints.

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