Original Investigation

Telephone-Based Cognitive Behavioral Therapy for Insomnia in Perimenopausal and Postmenopausal Women With Vasomotor Symptoms
A MsFLASH Randomized Clinical Trial

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IMPORTANCE Effective, practical, nonpharmacologic therapies are needed to treat menopause-related insomnia symptoms in primary and women's specialty care settings.

OBJECTIVE To evaluate the efficacy of telephone-based cognitive behavioral therapy for insomnia (CBT-I) vs menopause education control (MEC).

DESIGN, SETTING, AND PARTICIPANTS A single-site, randomized clinical trial was conducted from September 1, 2013, to August 31, 2015, in western Washington State among 106 perimenopausal or postmenopausal women aged 40 to 65 years with moderate insomnia symptoms (Insomnia Severity Index [ISI] score, ≥12) and 2 or more daily hot flashes. Blinded assessments were conducted at baseline, 8, and 24 weeks postrandomization. An intent-to-treat analysis was conducted.

INTERVENTIONS Six CBT-I or MEC telephone sessions in 8 weeks. Participants submitted weekly electronic sleep diaries and received group-specific written educational materials. The CBT-I sessions included sleep restriction, stimulus control, sleep hygiene education, cognitive restructuring, and behavioral homework; MEC sessions provided information about menopause and women's health.

MAIN OUTCOMES AND MEASURES Primary outcome was scores on the ISI (score range, 0-28; scores ≥15 indicate moderate to severe insomnia). Secondary outcome was scores on the Pittsburgh Sleep Quality Index (score range, 0-21; higher scores indicate worse sleep quality). Additional outcomes included sleep and hot flash diary variables and hot flash interference.

RESULTS At 8 weeks, ISI scores had decreased 9.9 points among 53 women receiving CBT-I (mean [SD] age, 55.0 [3.5] years) and 4.7 points among 53 women receiving MEC (age, 54.7 [4.7] years), a mean between-group difference of 5.2 points (95% CI, −6.1 to −3.3; $P < .001$). Pittsburgh Sleep Quality Index scores decreased 4.0 points in women receiving CBT-I and 1.4 points in women receiving MEC, a mean between-group difference of 2.7 points (95% CI, −3.9 to −1.5; $P < .001$). Significant group differences were sustained at 24 weeks. At 8 and 24 weeks, 33 of 47 women (70%) and 37 of 44 (84%) in the CBT-I group, respectively, had ISI scores in the no-insomnia range compared with 10 of 41 (24%) and 16 of 37 (43%) in the MEC group, respectively. The CBT-I group also had greater improvements in diary-reported sleep latency, wake time, and sleep efficiency. There were no between-group differences in frequency of daily hot flashes, but hot flash interference was significantly decreased at 8 weeks for the CBT-I group (−15.7; 95% CI, −20.4 to −11.0) compared with the MEC group (−7.1; 95% CI, −14.6 to 0.4) ($P = .03$), differences that were maintained at 24 weeks for the CBT-I group (−22.8; 95% CI, −28.6 to −16.9) and MEC group (−11.6; 95% CI, −19.4 to −3.8) ($P = .003$).

CONCLUSIONS AND RELEVANCE Telephone-based CBT-I improved sleep in perimenopausal and postmenopausal women with insomnia and hot flashes. Results support further development and testing of centralized CBT-I programs for treating menopausal insomnia.

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Sleep disturbances are a common and often bothersome menopausal symptom[1,2] that increase throughout the menopausal transition and early postmenopause.[3,4] Insomnia is associated with increased depression, impaired daytime function, reduced libido, and increased use of health care, creating a substantial burden for women and society.[5-10] Women with combined vasomotor and insomnia symptoms have more emergency department visits and lower physical and mental quality of life than women without sleep disturbances.[11] Insomnia is also associated with increased risk for obesity, diabetes, stroke, and coronary artery disease,[12,13] conditions that increase long-term disease and economic burdens in menopausal women.[14]

Evidence-based behavioral treatments for insomnia symptoms in perimenopausal and postmenopausal women are lacking. In routine practice, insomnia is most often treated with medications.[15-17] However, because of adverse effects,[18] not all women desire or benefit from medications to treat insomnia.[19] Cognitive behavioral therapy for insomnia (CBT-I) is a well-established, evidence-based approach.[20-25] However, in-person CBT-I is rarely available in the settings in which most women receive care. Practical considerations such as cost, transportation, time required for most in-person therapies, and scheduling challenges further affect the accessibility of in-person CBT-I.

We present results from a single-site, randomized clinical trial of a telephone CBT-I intervention vs telephone-based menopause education control (MEC). We hypothesized that CBT-I would be more efficacious than MEC for improving sleep 8 and 24 weeks after randomization.

Key Points

Question What is the efficacy of brief telephone-based cognitive behavioral therapy compared with menopause education control for insomnia symptoms in perimenopausal and postmenopausal women?

Findings In this randomized clinical trial of 106 women, Insomnia Severity Index scores decreased 9.9 points in women receiving cognitive behavioral therapy and 4.7 points in women receiving menopause education control, a significant difference. Significant group differences were sustained at 24 weeks.

Meaning Results support further development and testing of centralized cognitive behavioral therapy programs for treatment of menopausal insomnia in women.

Methods

Participants

The study was conducted from September 1, 2013, to August 31, 2015, within the Menopause Strategies Finding Lasting Answers for Symptoms and Health (MsFLASH) research network.[26] Women in western Washington State were mailed recruitment postcards from November 4, 2013, to June 1, 2014, that included a telephone screening contact number. Respondents aged 40 to 65 years reporting significant insomnia symptoms and 2 or more hot flashes daily during the previous 2 weeks were mailed a consent form and questionnaires, including 2-week sleep and hot flash diaries. Menopausal status was defined as being postmenopausal, having had no menstrual periods within the past 12 months, having had a bilateral oophorectomy, or being age 55 years or older with hysterectomy or endometrial ablation. Perimenopausal was defined as having had at least 1 menses in the past 12 months or being younger than age 55 years with hysterectomy or endometrial ablation without bilateral oophorectomy.

Eligible women scored 12 or higher on the Insomnia Severity Index (ISI)[27] at both telephone screening and on mailed questionnaires. Women were excluded if they had a primary sleep disorder diagnosis, consumed more than 3 alcoholic drinks daily, had a current major illness interfering with sleep, had a job involving shift work (>3 times per week), or routinely (>3 times per week) used prescription sleeping medications. Women reporting use of over-the-counter sleep aids, melatonin, or herbal sleep remedies were not excluded. Screening, eligibility, and participation are shown in **Figure 1**. The study was approved by the institutional review boards of Fred Hutchinson Cancer Research Center and University of Washington, both in Seattle.

Randomization

Eligible women were block-randomized to receive CBT-I or MEC. Participants were told that the study compared 2 educational treatments for sleep problems in women with hot flashes, but treatments differed in their approach. Participants were not informed how their group differed from the other.

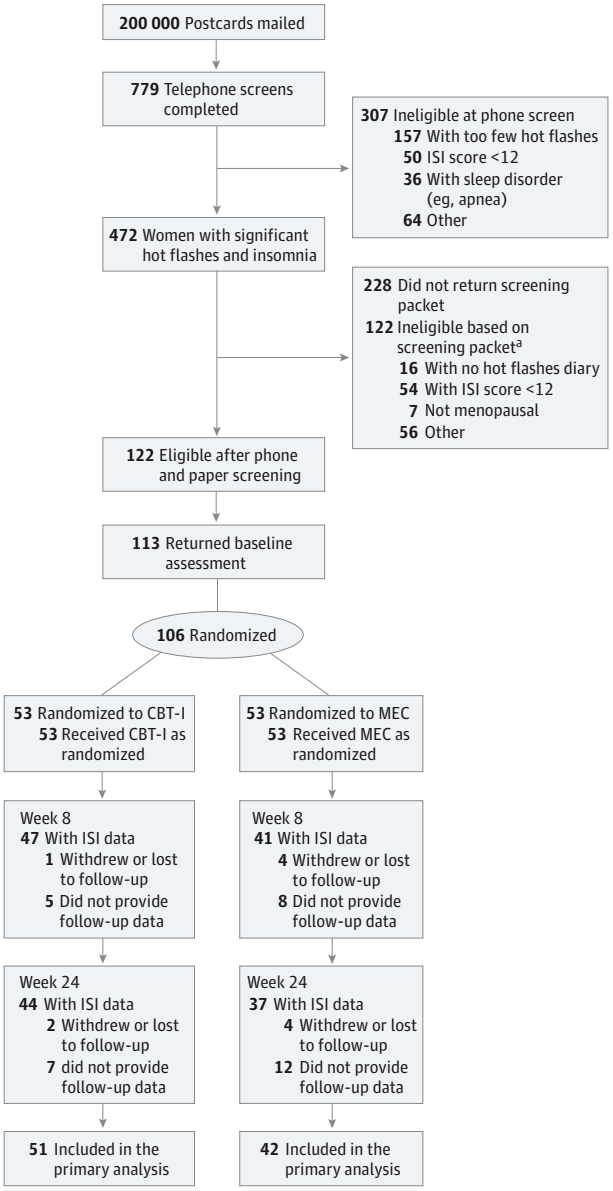
Interventions

The CBT-I and MEC interventions both consisted of six 20- to 30-minute telephone sessions conducted over 8 weeks (weeks 1-4, 6, and 8). Participants were invited to have their first session in person at a research office, but women were also permitted to have the first session by telephone. Treatment materials, including the "Menopause: Time for a Change" booklet,[28] and additional group-specific reading materials were distributed at the first session or mailed before the first telephone session. In the first session, women were taught how to complete an online daily sleep diary, which was submitted to study interventionists (called *coaches*) the day before each telephone session.

CBT-I Protocol

The CBT-I protocol provided information about age-related sleep changes, sleep hygiene, sleep restriction, and stimulus control procedures (**Table 1**).[27] Participants were instructed to keep a compressed schedule of bed and rising times. Initial sleep restriction windows were set to match the average sleep time reported in baseline screening logs but no less than 5.5 hours in bed. The sleep window was extended by 15 minutes per week when the electronic sleep diary indicated an average 85% sleep efficiency (time asleep divided by time in bed) or greater during the previous week. Stimulus control instructions strengthened the association between bed and sleep by reducing time spent in bed on nonsleep activities. Sleep hygiene education included information about improving bedtime routines and identifying behavioral and environmental factors that negatively affected sleep. Cognitive techniques were taught to reduce physiological arousal at bedtime and to change unrealistic beliefs about sleep loss.[29]

Figure 1. Participant Recruitment and Retention of Telephone-Based Cognitive Behavioral Therapy for Insomnia (CBT-I) vs Menopause Education (MEC)



ISI indicates Insomnia Severity Index.

[a] Participants could be ineligible for multiple reasons.

Table 1. Six-Session Content of CBT-I and MEC Telephone Sessions

Session	CBT-I	MEC
1	Sleep changes during menopause Rationale for behavioral approach Sleep scheduling and bed restriction	Introduction to menopause: what to expect Sleep hygiene strategies
2	Review of behavioral sleep plan Stimulus control instructions	Hot flashes: self-management techniques
3	Review of behavioral sleep plan Sleep stages and cycles across the age span	Pharmacologic supplements and natural remedies
4	Review of behavioral sleep plan Changing beliefs and attitudes about sleep	Benefits of exercise in menopause
5	Review of behavioral sleep plan Constructive worry Sleep hygiene recommendations	Postmenopausal health concerns and nutrition
6	Review of behavioral sleep plan Maintenance and relapse prevention plan	Sexuality, urinary, and vaginal tract health
Treatment components	Education Sleep monitoring Sleep scheduling and goal setting Behavioral homework and problem solving	Education Sleep monitoring Support

Abbreviations: CBT-I, cognitive behavioral therapy for insomnia; MEC, menopause education control.

MEC Protocol

The MEC protocol included educational content and readings relevant to women's health and quality of life. Sessions were designed to reduce uncertainty about changes occurring during menopause and to help women identify strategies for symptom self-management. Sessions explicitly excluded active interventions hypothesized to mediate the effect of CBT-I treatment on sleep.[30] Individual sessions were conducted in an informative, supportive format in which the coaches remained neutral but did not make recommendations. Weekly sleep logs were submitted. There was no practice or instruction in CBT-I principles (eg, no recommendations to restrict time in bed).

Study Coaches, Training, and Treatment Fidelity

Telephone sessions were led by 2 female coaches with a master's degree (1 social worker, 1 psychologist) without prior experience in menopause education or CBT-I. Coaches received 1-day training for each intervention, led by experts in CBT-I (C.M.M.) and menopause education (N.F.W.).

Both coaches delivered both interventions; all telephone sessions were recorded. Training included review by the primary investigator (S.M.M.) of all 6 recordings for 2 pilot cases (1 CBT-I, 1 MEC) for each coach. Thereafter, 2 sessions for each participant (1 randomly selected, 1 chosen by either the coach or primary investigator) were reviewed to maintain treatment fidelity and ensure there was no contamination between treatment conditions. Coaches completed weekly content checklists to ensure adherence to key session components. Feedback on reviewed audio recordings was discussed in weekly team meetings.

Measures

Blinded assessments were conducted at baseline and 8 and 24 weeks after the intervention. They included primary and secondary sleep outcomes as well as additional sleep and hot flash outcomes described below. Treatment satisfaction was measured at 8 weeks. Assessment packets and diaries were mailed to women with a prepaid return envelope. Women who failed to return packets within 4 weeks of the scheduled collection date were contacted by telephone to gather data on primary and secondary sleep outcomes. Research staff involved in data collection and analysis had no knowledge of treatment group assignment.

Baseline Characteristics

Variables included age, race, educational level, marital status, menopausal stage, depression symptoms,[31] use of sleep medications, and duration of sleep disturbances.

Primary and Secondary Sleep Outcomes

The primary outcome was score on the ISI,[27,32] a 7-item questionnaire assessing global insomnia severity. Items are rated 0 to 4 (total score range, 0-28); a score of 15 or higher is considered moderate to severe insomnia in clinical popu-lations.[27] A score higher than 10 is considered optimal for detecting cases of insomnia in community samples,[32] and a 6-point within-group reduction is a clinically meaningful change.[33]

Scores on the 19-item Pittsburgh Sleep Quality Index (PSQI)[34] was a secondary sleep outcome. Total scores range from 0 to 21; higher scores indicate worse sleep quality. A decrease to a PSQI score less than 5 or 3-point reduction in score is considered clinically meaningful.[35,36] Both the ISI and PSQI have been used in previous MsFLASH network trials.[16,37]

Additional Outcomes

Daily sleep diaries included bed and rise time, sleep latency (time to fall asleep), and number and duration of nighttime awakenings.[38] In a separate diary, participants recorded the frequency, severity, and bother of nighttime and daytime hot flashes. Sleep and hot flash diary results were calculated from 2 weeks of baseline data and 1 week of data at 8 and 24 weeks. The Hot Flash Related Daily Interference Scale[39] includes 10 areas of daily functioning that may be affected by hot flashes. Items are rated on a 10-point scale; higher scores indicate worse interference.

Treatment Satisfaction

At 8 weeks, participants rated the credibility, acceptability, and perceived effectiveness of their intervention by answering the following questions[27]: Did this treatment and its rationale make sense to you? How acceptable did you consider this treatment? How suitable was this treatment for improving your quality of life despite having menopausal symptoms? How effective did you expect this treatment to be? How well were you able to adhere to this treatment program? How would you rate the quality of your working relationship with your menopause counselor? All items were rated on a 7-point scale; higher scores indicate greater satisfaction.

Statistical Analysis

The intent-to-treat analysis included all participants who provided follow-up data, regardless of adherence to treatment assignment. Baseline characteristics were compared between arms using *t* tests or χ^2 tests. Treatment contrasts for the ISI, PSQI, sleep diary, and hot flashes outcomes were computed as Wald statistics from repeated-measures linear regression models of each outcome by intervention arm, time, and baseline value of the outcome. Repeated-measures logistic regression models were performed to compare incidence of good sleep quality (PSQI score <5) by arm. Participants who contributed baseline and either 8-week or 24-week data were included in these analyses. Robust SEs were calculated via generalized estimating equations to account for correlations between repeated measures from each participant. Treatment effect sizes (difference in mean outcome between groups, divided by the pooled SD) were computed for the ISI and PSQI scores. Treatment satisfaction ratings were compared by arm using *t* tests.

Two sensitivity analyses of the ISI and PSQI were conducted. First, outcomes data submitted more than 4 weeks past due were excluded from analysis. Second, missing outcomes data for both groups were imputed based on the observed MEC data, using multiple imputation under the assumption that data for participants in the CBT-I group who discontinued follow-up early would mirror data from participants from the MEC group who discontinued.[40] All analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

A sample size of 45 participants per group was chosen to provide 90% power to detect a 4-point difference in change in ISI scores between the randomized groups, assuming an SD of 5.6 based on observed scores in an earlier MsFLASH study[16] and a *t* test with 2-sided significance set at $P < .05$. We planned to enroll 50 women per group to compensate for up to 10% loss to follow-up.

Results

A total of 106 participants (mean [SD] age, 54.8 [4.2] years) were randomly assigned to the 2 intervention arms. The 2 arms did not differ significantly by age, race, educational level, marital status, menopausal stage, use of sleep medications, duration of sleep disturbances (**Table 2**), or any baseline sleep or hot flash outcome measure.

Adherence, Treatment Discontinuation, and Completeness of Outcomes Ascertainment

Participants in both the CBT-I and MEC groups attended an average of 5.7 sessions (range, 1-6). Sessions averaged 22.8 minutes (range, 16.4-32.6). There were no significant differences in the number of telephone sessions or session length by intervention arm or coach.

There were no between-group differences in the number of withdrawals or reasons for treatment discontinuation (Figure 1). Follow-up ISI data were collected on 88 participants (83.0%) at 8 weeks and 81 (76.4%) at 24 weeks; 10 women (3 CBT-I, 7 MEC) completed telephone ISI and PSQI forms at week 8, and 7 women (3 CBT-I, 4 MEC) completed telephone forms at week 24.

Sleep Outcomes

At baseline, 31 women (58%) in the CBT-I group and 33 (62%) in the MEC group had ISI scores in the range of moderate (score, 15-21) to severe (score, 22-28) insomnia (**Figure 2**). From baseline to 8 weeks, ISI scores decreased 9.9 points in women receiving CBT-I and 4.7 points in women receiving MEC, a mean between-group difference of 5.2 points (95% CI, -6.1 to -3.3; $P < .001$). Significant differences between the groups were sustained at 24 weeks (**Table 3**).

At baseline, 92.5% of women (49 in each arm) had PSQI scores of 5 or higher, indicating poor sleep quality. On posttreatment follow-up, PSQI scores decreased 4.0 points in women receiving

Table 2. Baseline Characteristics by Intervention Group

Baseline Characteristic[a]	Value[b] CBT-I (n = 53)	MEC (n = 53)
Age, mean (SD), y	55.0 (3.5)	54.7 (4.7)
Race		
White	49 (92.5)	48 (90.6)
African American	0	1 (1.9)
Other or unknown	4 (7.5)	4 (7.5)
Educational level		
≤High school diploma or GED	3 (5.7)	2 (3.8)
School after high school	9 (17.0)	10 (18.9)
College graduate	41 (77.4)	41 (77.4)
Married or marriage-like relationship	44 (83.0)	39 (73.6)
Alcohol use, drinks/wk		
0	19 (35.8)	21 (39.6)
1-7	27 (50.9)	27 (50.9)
>7	7 (13.2)	5 (9.4)
Smoking		
Never	40 (75.5)	42 (79.2)
Past	13 (24.5)	10 (18.9)
Current	0	1 (1.9)
Menopause status		
Postmenopausal	34 (64.2)	34 (64.2)
Perimenopausal	16 (30.2)	15 (28.3)
Indeterminate	3 (5.7)	4 (7.5)
Hot flashes per day, mean (SD), No.	7.3 (4.5)	7.8 (4.1)
Patient Health Questionnaire depression scale score, mean (SD)	7.4 (3.4)	8.1 (4.8)
Increase in sleep problems at menopause		
Yes	52 (98.1)	52 (98.1)
No	1 (1.9)	0
Answer missing	0	1 (1.9)
Sleep problem start time		
Within the past 6 mo	2 (3.8)	4 (7.5)
About 6-12 mo ago	7 (13.2)	6 (11.3)
1-5 y ago	28 (52.8)	20 (37.7)
>5 y ago	15 (28.3)	22 (41.5)
Answer missing	1 (1.9)	1 (1.9)

Abbreviations: CBT-I, cognitive behavior therapy for insomnia; GED, General Educational Development certificate; MEC, menopause education control.

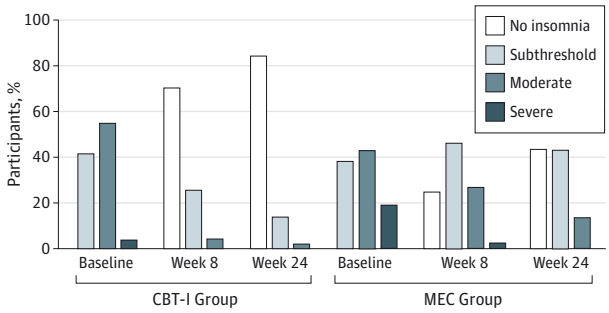
[a] No significant differences by intervention arm for any variable.

[b] Data are presented as number (percentage) of patients unless otherwise indicated.

CBT-I and 1.4 points in women receiving MEC, a mean between-group difference of 2.7 points (95% CI, -3.9 to -1.5; $P < .001$), approaching a 3-point clinically significant difference.[35] Significant differences between the groups were sustained at 24 weeks (Table 3). Women in the CBT-I group were significantly more likely than those in the MEC group to have good sleep quality (PSQI score, ≤5) at week 8 (odds ratio, 5.6; 95% CI, 2.3-14.8; $P < .001$) and week 24 (odds ratio, 3.7; 95% CI, 1.4-9.5; $P = .006$).

Women in the CBT-I group also had significantly greater 8- and 24-week improvements in diary-reported sleep latency, wake time, and sleep efficiency compared with those in the MEC group, although relative differences between treatment groups were attenuated at 24 weeks.

Figure 2. Percentage of Insomnia Severity Index Total Scores Categorized by Insomnia Category at Baseline and 8- and 24-Week Follow-up



Insomnia Severity Index categories represent the following score ranges: no insomnia, 0 to 7; subthreshold insomnia, 8 to 14; moderate insomnia, 15 to 21; and severe insomnia, 22 to 28. CBT-I indicates cognitive behavioral therapy for insomnia; MEC, menopause education control.

Standardized mean differences (ie, effect sizes) for ISI and PSQI scores at 8 weeks were 1.04 and 0.84 SDs, respectively, indicating large treatment effects for CBT-I. At 8 weeks, 33 of 47 women (70%) in the CBT-I group had total scores in a range indicating no clinically significant insomnia (score, 0-7) compared with only 10 of 41 women (24%) randomized to receive MEC; at 24 weeks, 37 of 44 women (84%) in the CBT-I group vs 16 of 37 (43%) in the MEC group were in the no insomnia range (Figure 2).

Study results for ISI and PSQI scores were not significantly different from the primary analyses when protocol violators were excluded, and were also robust to sensitivity analyses for missing data (eTable 1 and eTable 2 in the Supplement).

Hot Flash Outcomes

There were no significant differences between treatment group ratings of hot flash frequency (daily or nighttime), severity, or bother at either 8 or 24 weeks. The Hot Flash Related Daily Interference Scale score was significantly decreased at 8 weeks for those in the CBT-I group (-15.7; 95% CI, -20.4 to -11.0) compared with those in the MEC group (-7.1, 95% CI, -14.6 to 0.4) ($P = .03$). Significant between-group differences were maintained at 24 weeks (CBT-I group, -22.8; 95% CI, -28.6 to -16.9; MEC group, -11.6; 95% CI, -19.4 to -3.8; $P = .003$). When the Hot Flash Related Daily Interference Scale was analyzed excluding the single sleep item, results were comparable between groups.

Patient-Reported Satisfaction Outcomes

Average ratings of perceived suitability, acceptability, effectiveness, and trainer quality for both intervention arms at the posttreatment assessment were high (mean range, 4.2-6.7 on a 1-7 scale). There were no differences between CBT-I and MEC in acceptability, treatment adherence, or relationship quality with the menopause coach. Ratings for CBT-I were significantly higher than for MEC regarding whether the treatment made sense ($P = .005$), whether it was suitable for improving quality of life despite having menopausal symptoms ($P = .009$), and perceived treatment effectiveness ($P < .001$).

Table 3. Sleep Outcome Results by Treatment Condition

Outcome	CBT-I No.	CBT-I Mean (95% CI)	MEC No.	MEC Mean (95% CI)	Difference Mean (95% CI)	P Value[a]
Insomnia Severity Index score						
Baseline	53	15.6 (14.8 to 16.4)	53	16.8 (15.8 to 17.9)	−1.2 (−2.6 to 0.1)	
Week 8 − baseline	47	−9.9 (−11.2 to −8.7)	41	−4.7 (−6.1 to −3.3)	−5.2 (−6.1 to −3.3)	<.001
Week 24 − baseline	44	−10.7 (−11.9 to −9.4)	37	−6.7 (−8.4 to −5.0)	−4.0 (−6.0 to −1.9)	<.001
Pittsburgh Sleep Quality Index score						
Baseline	51	8.9 (8.2 to 9.6)	53	9.4 (8.6 to 10.3)	0.5 (−1.6 to 0.6)	
Week 8 − baseline	47	−4.0 (−5.0 to −3.1)	41	−1.4 (−2.1 to −0.7)	−2.7 (−3.9 to −1.5)	<.001
Week 24 − baseline	44	−4.3 (−5.1 to −3.5)	38	−2.7 (−3.5 to −1.9)	−1.6 (−2.7 to −0.5)	<.001
Diary sleep latency, min[b]						
Baseline	51	54.4 (43.8 to 65.0)	52	51.1 (42.0 to 60.2)	3.3 (−10.5 to 17.1)	
Week 8 − baseline	43	−31.5 (−39.2 to −23.8)	33	−12.2 (−22.8 to −1.7)	−19.3 (−31.8 to −6.8)	<.001
Week 24 − baseline	39	−25.3 (−32.8 to −17.8)	29	−13.4 (−25.1 to −1.8)	−11.9 (−24.9 to 1.2)	.007
Diary wake time after sleep onset, min[b]						
Baseline	51	71.7 (60.7 to 82.7)	52	83.0 (69.2 to 96.8)	−11.3 (−28.8 to 6.2)	
Week 8 − baseline	43	−37.4 (−48.3 to −26.6)	33	−17.0 (−33.5 to −0.5)	−20.4 (−39.1 to −1.7)	<.001
Week 24 − baseline	39	−32.8 (−43.9 to −21.7)	29	−26.0 (−40.3 to −11.8)	−6.7 (−24.2 to 10.7)	.02
Diary total sleep time, h[b]						
Baseline	51	6.6 (6.3 to 6.8)	52	6.4 (6.1 to 6.7)	0.1 (−0.3 to 0.5)	
Week 8 − baseline	43	0.4 (−0.1 to 0.9)	33	0.2 (−0.1 to 0.5)	0.2 (−0.3 to 0.8)	.14
Week 24 − baseline	39	0.7 (0.4 to 0.9)	29	0.5 (0.1 to 0.9)	0.1 (−0.3 to 0.6)	.17
Diary sleep efficiency[b]						
Baseline	51	75.8 (73.1 to 78.6)	52	74.6 (71.5 to 77.7)	1.3 (−2.8 to 5.3)	
Week 8 − baseline	43	12.1 (9.4 to 14.8)	33	5.1 (1.3 to 8.9)	7.0 (2.6 to 11.5)	<.001
Week 24 − baseline	39	10.7 (8.3 to 13.0)	29	7.5 (3.5 to 11.6)	3.1 (−1.5 to 7.8)	.007

Abbreviations: CBT-I, cognitive behavior therapy for insomnia; MEC, menopause education control; SL, sleep latency; TIB, time in bed; TST, total sleep time; WASO, wake time after sleep onset.

[a] *P* values from contrasts of CBT-I vs MEC in a repeated-measures linear model of outcome as a function of intervention arm, week (8, 24), and baseline outcome value.

[b] Daily sleep diary variables were computed as follows: TIB = difference between final bed and final rise time the following morning; SL = estimated time to fall asleep at night after turning out the light; WASO = estimated total time awake each night; TST = TIB − (SL + WASO); sleep efficiency = TST/TIB.

Discussion

Behavioral interventions for women with moderate menopause-associated insomnia and vasomotor symptoms are lacking. In this randomized clinical trial, brief telephone-based CBT-I resulted in significant 8- and 24-week improvements in self-reported insomnia symptoms, overall sleep quality, sleep latency, wake time after sleep onset, and sleep efficiency compared with MEC. Although CBT-I has been found to be efficacious for improving sleep in populations with other comorbid conditions,[41] this is one of the first studies, to our knowledge, to show that CBT-I helps healthy women with hot flashes sleep better. A recent small trial found that 6 sessions of CBT-I significantly improved sleep outcomes compared with placebo in middle-aged breast cancer survivors with chronic insomnia.[42] A few other small studies reported on psychologist-led groups and self-help cognitive behavioral strategies for improving hot flashes and night sweats but did not target sleep.[43,44]

Our study found no between-group differences in self-reported hot flash frequency, severity, or bother but found that CBT-I reduced self-reported hot flash interference at 8 and 24 weeks relative to MEC. This finding may indicate that for women receiving CBT-I, the cognitive strategies taught to reduce daytime dysfunction associated with sleep loss generalized to how they responded to vasomotor symptoms. Alternatively, improved sleep could have improved tolerance of hot flashes.

A strength of the study was the telephone-based MEC, which controlled for nonspecific treatment effects, including therapist attention and treatment duration but explicitly excluded active interventions hypothesized to mediate the effect of treatment on sleep.[30] Menopause education control had high ratings of acceptability and adherence as well as low dropout treatment rates equivalent to the CBT-I group, suggesting that it was a well-received attention control intervention.

Our study does not provide a comparison with placebo or active medication treatments for insomnia. Cognitive behavioral therapy and pharmacotherapy are considered effective for treating chronic insomnia,[15,45] with medications offering an advantage owing to immediate treatment effects, but CBT-I produces superior long-term outcomes.[46,47] There have been no head-to-head trials comparing CBT-I vs medication for perimenopausal and early postmenopausal women with insomnia symptoms. Reductions in ISI score with CBT-I in our trial approached those observed in previous studies examining the effect of eszopiclone on insomnia symptoms in menopausal women[48] and were larger

than have been reported in placebo-controlled trials of the effects of escitalopram, venlafaxine, or low-dose estradiol on sleep in this population.[16,49] Future direct comparison of outcomes and cost-effectiveness with pharmacotherapies for insomnia and hot flashes are warranted.

Our findings support the potential for training nonsleep specialists to deliver telephone-based CBT-I to women with insomnia and vasomotor symptoms in a variety of primary and women's health care settings. Telephone-based CBT-I allows upscaling to reach large populations of menopausal women seeking treatment for sleep problems. Centralized telephone CBT-I should be tested as a dissemination model, similar to effective telephone-based counseling programs for smoking cessation.

This study does have some limitations. The program was delivered in the Seattle, Washington, area, and women responding to recruitment mailings were predominantly college educated and white, limiting generalizablity to other populations. Participants did not undergo formal evaluation for primary sleep disorders; therefore, we were unable to examine whether the effect of CBT-I was consistent across women with and without these conditions. In studies of this type, it is not possible to mask interventionists to treatment assignment. However, all outcomes were collected by research staff blinded to treatment assignment. As expected, lower post-treatment ratings of treatment effectiveness with MEC indicated some nonequivalence between treatment groups in perceived effect on insomnia symptoms.

Sleep and vasomotor outcomes were based on self-report, the most salient and relevant efficacy indicators for clinical practice and women themselves. However, future studies incorporating polysomnography as a screening and outcome measure would have value. Changes in ISI and PSQI scores among women receiving CBT-I were significant and clinically robust after treatment, although the differences relative to MEC were somewhat attenuated at 24 weeks. Trials of the efficacy of CBT-I used in conjunction with other treatments to manage hot flashes are warranted to identify the optimal strategy for achieving long-term improvement in sleep-related symptoms among menopausal women.

Conclusions

Telephone-based CBT-I effectively improved sleep in perimenopausal and postmenopausal women with insomnia and vasomotor symptoms, both immediately after treatment and at 24 weeks of follow-up. These results support further development and testing of centralized CBT-I programs for treatment of menopausal insomnia in women.

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REFERENCES

1. Shaver JL, Woods NF. Sleep and menopause: a narrative review. *Menopause*. 2015;22(8):899-915.

2. Woods NF, Hohensee C, Carpenter JS, et al. Symptom clusters among MsFLASH clinical trial participants. *Menopause*. 2016;23(2):158-165.

3. Kravitz HM, Joffe H. Sleep during the perimenopause: a SWAN story. *Obstet Gynecol Clin North Am*. 2011;38(3):567-586.

4. Xu Q, Lang CP. Examining the relationship between subjective sleep disturbance and

menopause: a systematic review and meta-analysis. *Menopause*. 2014;21(12):1301-1318.

5. Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. *Health Qual Life Outcomes*. 2005;3(3):47.

6. Reed SD, Newton KM, LaCroix AZ, Grothaus LC, Ehrlich K. Night sweats, sleep disturbance, and depression associated with diminished libido in late menopausal transition and early postmenopause: baseline data from the Herbal Alternatives for Menopause Trial (HALT). *Am J Obstet Gynecol*. 2007;196(6):593.e1-593.e7.

7. Daley M, Morin CM, LeBlanc M, Grégoire JP, Savard J. The economic burden of insomnia: direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers. *Sleep*. 2009;32(1):55-64.

8. Woods NF, Mitchell ES. Sleep symptoms during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. *Sleep*. 2010;33(4):539-549.

9. Hartz A, Ross JJ, Noyes R, Williams P. Somatic symptoms and psychological characteristics associated with insomnia in postmenopausal women. *Sleep Med*. 2013;14(1):71-78.

10. Woods NF, Mitchell ES. Symptom interference with work and relationships during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. *Menopause*. 2011;18(6):654-661.

11. Bolge SC, Balkrishnan R, Kannan H, Seal B, Drake CL. Burden associated with chronic sleep maintenance insomnia characterized by nighttime awakenings among women with menopausal symptoms. *Menopause*. 2010;17(1):80-86.

12. Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. *J Sleep Res*. 2012;21(4):427-433.

13. Sands-Lincoln M, Loucks EB, Lu B, et al. Sleep duration, insomnia, and coronary heart disease among postmenopausal women in the Women's Health Initiative. *J Womens Health (Larchmt)*. 2013;22(6):477-486.

14. Ryan JG. Cost and policy implications from the increasing prevalence of obesity and diabetes mellitus. *Gend Med*. 2009;6(suppl 1):86-108.

15. National Institutes of Health. NIH State-of-the-Science Conference statement on manifestations and management of chronic insomnia in adults. *NIH Consens State Sci Statements*. 2005;22(2):1-30.

16. Ensrud KE, Joffe H, Guthrie KA, et al. Effect of escitalopram on insomnia symptoms and subjective sleep quality in healthy perimenopausal and postmenopausal women with hot flashes: a randomized controlled trial. *Menopause*. 2012;19(8):848-855.

17. Joffe H, Massler A, Sharkey KM. Evaluation and management of sleep disturbance during the menopause transition. *Semin Reprod Med*. 2010;28(5):404-421.

18. Brower KJ, McCammon RJ, Wojnar M, Ilgen MA, Wojnar J, Valenstein M. Prescription sleeping pills, insomnia, and suicidality in the National Comorbidity Survey Replication. *J Clin Psychiatry*. 2011;72(4):515-521.

19. Davidson JR. Insomnia treatment options for women. *Obstet Gynecol Clin North Am*. 2009;36(4):831-846, x-xi.

20. Ellis JG, Gehrman P, Espie CA, Riemann D, Perlis ML. Acute insomnia: current conceptualizations and future directions. *Sleep Med Rev*. 2012;16(1):5-14.

21. Morin CM, Benca R. Chronic insomnia. *Lancet*. 2012;379(9821):1129-1141.

22. Okajima I, Komada Y, Inoue Y. A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. *Sleep Biol Rhythms*. 2011;9(1):24-34. doi:10.1111/j.1479-8425.2010.00481.x

23. Riemann D, Spiegelhalder K, Espie C, et al. Chronic insomnia: clinical and research challenges—an agenda. *Pharmacopsychiatry*. 2011;44(1):1-14.

24. Smith MT, Huang MI, Manber R. Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. *Clin Psychol Rev*. 2005;25(5):559-592.

25. Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163(3):191-204.

26. Newton KM, Carpenter JS, Guthrie KA, et al. Methods for the design of vasomotor symptom trials: the menopausal strategies: finding lasting answers to symptoms and health network. *Menopause*. 2014;21(1):45-58.

27. Morin CM. *Insomnia: Psychological Assessment and Management*. New York, NY: Guilford Press; 1993.

28. National Institute on Aging. *Menopause: Time for a Change*. Gaithersburg, MD: National Institutes of Health, Department of Health and Human Services; 2008.

29. Morin CM, Beulieu-Bonneau S. *Cognitive-Behavioral Therapy for Insomnia in Peri- and Post-menopausal Women*. Quebec, QC: Universite Laval; 2013:32.

30. Balderson BH, McCurry SM, Vitiello MV, et al. Information without implementation: a practical example for developing a best practice education control group [published online October 20, 2015]. *Behav Sleep Med*.

31. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord*. 2009;114(1-3):163-173.

32. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. 2011;34(5):601-608.

33. Yang M, Morin CM, Schaefer K, Wallenstein GV. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. *Curr Med Res Opin*. 2009;25(10):2487-2494.

34. Buysse DJ, Reynolds CF III, Monk TH, Hoch CC, Yeager AL, Kupfer DJ. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep*. 1991;14(4):331-338.

35. Buysse DJ, Germain A, Moul DE, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med*. 2011;171(10):887-895.

36. Surman CB, Roth T. Impact of stimulant pharmacotherapy on sleep quality: post hoc analyses of 2 large, double-blind, randomized, placebo-controlled trials. *J Clin Psychiatry*. 2011;72(7):903-908.

37. Ensrud KE, Stone KL, Blackwell TL, et al. Frequency and severity of hot flashes and sleep disturbance in postmenopausal women with hot flashes. *Menopause*. 2009;16(2):286-292.

38. Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep*. 2012;35(2):287-302.

39. Carpenter JS. The Hot Flash Related Daily Interference Scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. *J Pain Symptom Manage*. 2001;22(6):979-989.

40. Mallinckrodt CH, Lin Q, Molenberghs M. A structured framework for assessing sensitivity to missing data assumptions in longitudinal clinical trials. *Pharm Stat*. 2013;12(1):1-6.

41. Wu JQ, Appleman ER, Salazar RD, Ong JC. Cognitive behavioral therapy for insomnia comorbid with psychiatric and medical conditions: a meta-analysis. *JAMA Intern Med*. 2015;175(9):1461-1472.

42. Matthews EE, Berger AM, Schmiege SJ, et al. Cognitive behavioral therapy for insomnia outcomes in women after primary breast cancer treatment: a randomized, controlled trial. *Oncol Nurs Forum*. 2014;41(3):241-253.

43. Ayers B, Smith M, Hellier J, Mann E, Hunter MS. Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial. *Menopause*. 2012;19(7):749-759.

44. Norton S, Chilcot J, Hunter MS. Cognitive-behavior therapy for menopausal symptoms (hot flushes and night sweats): moderators and mediators of treatment effects. *Menopause*. 2014;21(6):574-578.

45. Morin CM. Combined therapeutics for insomnia: should our first approach be behavioral or pharmacological? *Sleep Med*. 2006;7(S1)(suppl 1):S15-S19.

46. Morin CM, Vallières A, Guay B, et al. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. *JAMA*. 2009;301(19):2005-2015.

47. Morin CM, Beaulieu-Bonneau S, Ivers H, et al. Speed and trajectory of changes of insomnia symptoms during acute treatment with cognitive-behavioral therapy, singly and combined with medication. *Sleep Med*. 2014;15(6):701-707.

48. Soares CN, Joffe H, Rubens R, Caron J, Roth T, Cohen L. Eszopiclone in patients with insomnia during perimenopause and early postmenopause: a randomized controlled trial. *Obstet Gynecol*. 2006;108(6):1402-1410.

49. Ensrud KE, Guthrie KA, Hohensee C, et al. Effects of estradiol and venlafaxine on insomnia symptoms and sleep quality in women with hot flashes. *Sleep*. 2015;38(1):97-108.