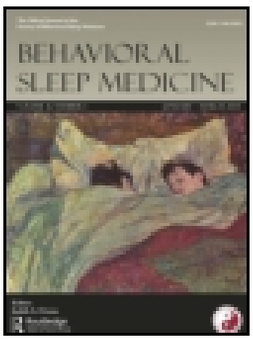

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Effects of forehead cooling and supportive care on menopause-related sleep difficulties, hot flashes and menopausal symptoms: a pilot study.

Fiona C. Baker[a], Massimiliano de Zambotti[a], Laurel Chiappetta[b], and Eric A. Nofzinger[c,d]

[a]Center for Health Sciences, SRI International, Menlo Park, California, USA; [b]DataDIVA, LLC, Pittsburgh, Pennsylvania, USA; [c]Ebb Therapeutics, Pittsburgh, Pennsylvania, USA; [d]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

ABSTRACT

Objective/Background: This pilot study explored the efficacy of a novel forehead cooling device for perceived sleep difficulties and hot flashes in menopausal-age women.

Participants: 20 women (55.1 ± 4.2 years; 19 post-menopausal) with insomnia symptoms and self-reported two or more hot flashes per day.

Methods: Participants completed daily assessments of sleep and hot flashes (via diaries) across 1 baseline week and 4 weeks of open-label, in-home, nightly treatment with a forehead cooling device (15–18°C) along with sleep hygiene instructions. They also completed ratings of insomnia and menopausal symptoms using standardized questionnaires.

Results: Women reported reductions in sleep onset latency (SOL), wakefulness after sleep onset (WASO), and nocturnal hot flash severity during the first week of treatment (SOL: 25.7 ± 18.4 min; WASO: 36.3 ± 27.3 min; hot flash severity: 3.0 ± 2.8) compared with baseline (SOL: 38 ± 26.3 min; WASO: 52.2 ± 35.6 min; hot flash severity: 6.8 ± 3.7), with further improvements after 2–4 weeks of use ($p < .001$). There were also clinically meaningful reductions in insomnia severity and hot flash-related daily interference and lower psychological and physical symptom scores on the Greene climacteric scale after treatment (all p's<0.001).

Conclusions: This exploratory, naturalistic, pilot study shows that nightly use of a forehead cooling device produces improvements in self-reported sleep and reductions in insomnia, hot flash, and other menopausal, symptoms. Controlled studies are warranted to determine the role of this therapy in the management of sleep difficulties and menopausal symptoms in women. Further mechanistic studies are needed to understand the physiological impact of forehead cooling on sleep and menopausal symptoms.

Introduction

A substantial number of women experience sleep difficulties in the approach to menopause and beyond, with 26% experiencing severe symptoms that impact daytime functioning, qualifying them for a diagnosis of insomnia (Baker et al., 2018; Ohayon, 2006). A major contributor to sleep complaints in the context of the menopausal transition is vasomotor symptoms such as hot flashes and night sweats. Hot flashes are experienced by over 70% of women (Gold et al., 2006) lasting, on average of 7–10 years into post-menopause (Avis et al., 2015; Freeman et al., 2011). For many women, hot flashes are associated with impairments in quality of life, and mood, in addition to sleep impairments (Avis et al., 2009; Bromberger et al., 2007). Research relying on objective measurement

CONTACT Eric A. Nofzinger eric.a.nofzinger@gmail.com Ebb Therapeutics, Pittsburgh, PA 15222

of nocturnal hot flashes has confirmed the link between them and poor sleep, showing that the majority of hot flashes are linked with polysomnographic-defined awakenings, with hot flash-associated wake time contributing to overall wakefulness after sleep onset (De Zambotti et al., 2014). The underlying mechanisms of hot flashes are not fully understood but appear to involve alterations in central noradrenergic activity (Freedman, 2014). Studies of nocturnal hot flash events in menopausal women further implicate the autonomic nervous system, showing that they are associated with acute vagal withdrawal (De Zambotti et al., 2013) and increased cardiac sympathetic activation (Baker et al., 2019). Emerging studies suggest that the impact of severe insomnia symptoms (Hsu & Lin, 2005; Woods & Mitchell, 2010) as well as persistent hot flashes (Thurston et al., 2008, 2011) could extend beyond immediate health-care usage and quality of life issues to long-term mental and physical health, including cardiovascular health if left untreated in midlife women. Appropriate treatment, therefore, has immediate benefit as well as advantages for maintaining optimal health in the postmenopausal years.

Hormone therapy is an effective treatment for menopausal symptoms and has a modest effect in improving sleep quality in association with relieving hot flashes (Cintron et al., 2017). However, in the wake of findings of potential risk associated with its use (Rossouw et al., 2002), many women have discontinued hormone therapy (Tsai et al., 2011). Other agents that have been found to be helpful in treating insomnia symptoms in midlife women in large, randomized, placebo-controlled clinical trials include low-dose selective serotonin/serotonin norepinephrine reuptake inhibitors (Ensrud et al., 2015, 2012; Pinkerton et al., 2015), and gabapentin (Yurcheshen et al., 2009). Inferior efficacy, lack of large definitive studies, and potential side effects limit the use of many of these agents (Barton & Loprinzi, 2004; Loprinzi et al., 2008, 2005). Cognitive-behavioral treatment of insomnia (CBTI) is considered the primary intervention for patients with chronic insomnia (Schutte-Rodin et al., 2008) and has shown good efficacy in improving insomnia with sustained effects in randomized clinical trials of peri- and postmenopausal women with insomnia symptoms (Drake et al., 2019; McCurry et al., 2016). In a follow-up analysis of pooled data from peri- and postmenopausal women with moderate-severe insomnia and bothersome hot flashes, Guthrie and colleagues (Guthrie et al., 2018) reported that CBTI led to the greatest reduction in insomnia severity scores from baseline relative to control compared with all other treatments that included escitalopram, exercise, and oral 17-beta-estradiol. Behavioral treatments for insomnia, therefore, are effective at treating menopausal insomnia; however, the lack of trained clinicians, the duration and cost of sessions limit their widespread use (Buysse et al., 2011).

New sleep solutions have become available, built on advances in sleep neuroscience and in brain therapeutics that are clinically and economically feasible. It is widely accepted that insomnia is a disorder of hyperarousal (Bonnet & Arand, 2010; "National Institutes of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults-15,2005", 2005). Increased metabolic activity in the frontal cortex during sleep may contribute to hyperarousal in insomnia patients, thereby preventing the reduction in brain metabolism that occurs in normal sleepers (Nofzinger et al., 2004, 2002). Sleep disturbances have been shown to correlate with frontal metabolism during sleep and alterations in frontal metabolism have been demonstrated following successful treatment (Altena et al., 2008; Nofzinger et al., 2006, 2000). A novel device delivering frontal cerebral thermal therapy (forehead cooling) has been developed to target hyperactivity of the frontal cortex during sleep. Findings have shown that the device reduces frontal cerebral metabolism during sleep in insomnia patients (Nofzinger et al., 2009). A double-blinded, randomized controlled trial demonstrated the efficacy and safety of the device in relation to a credible device control (sham vestibular stimulation) in insomnia patients (Roth et al., 2018). A pilot study showed that 4 weeks nightly use of the device produces improvements in insomnia, anxiety, and depressive symptoms in veterans with chronic insomnia disorder and co-morbid medical and psychiatric conditions (Mysliwiec et al., 2020). However, the efficacy of this type of therapy specifically in women with menopausal insomnia symptoms and hot flashes has not been examined.

The current study was designed as an exploratory naturalistic pilot study to determine the effects of 4 weeks of in-home, nighttime use of a forehead cooling device, combined with sleep hygiene

instructions and supportive care, in improving insomnia symptoms and severity of nocturnal hot flashes in symptomatic midlife women.

Methods

Participants

Midlife women reporting difficulty sleeping and hot flashes were recruited through online community advertising (see Figure 1: Flow Diagram). During an initial online screen, they were evaluated on medical history, including sleep disorders, medication/substance use history, and menstrual cycle history and menopausal symptoms. They also completed the Insomnia Severity Index (ISI), a validated 7-item measure (items are rated on a Likert scale, 0 = no problem; 4 = very severe problem) assessing nature, severity, and impact of insomnia over the past 2 weeks (Bastien et al., 2001), shown to be sensitive to detect changes related to treatment (Yang et al., 2009). A score of 15 or higher on the scale (range: 0–28) indicates clinical insomnia. A 6-point reduction is recommended to represent a clinically meaningful improvement after treatment in individuals with insomnia disorder (Yang et al., 2009).

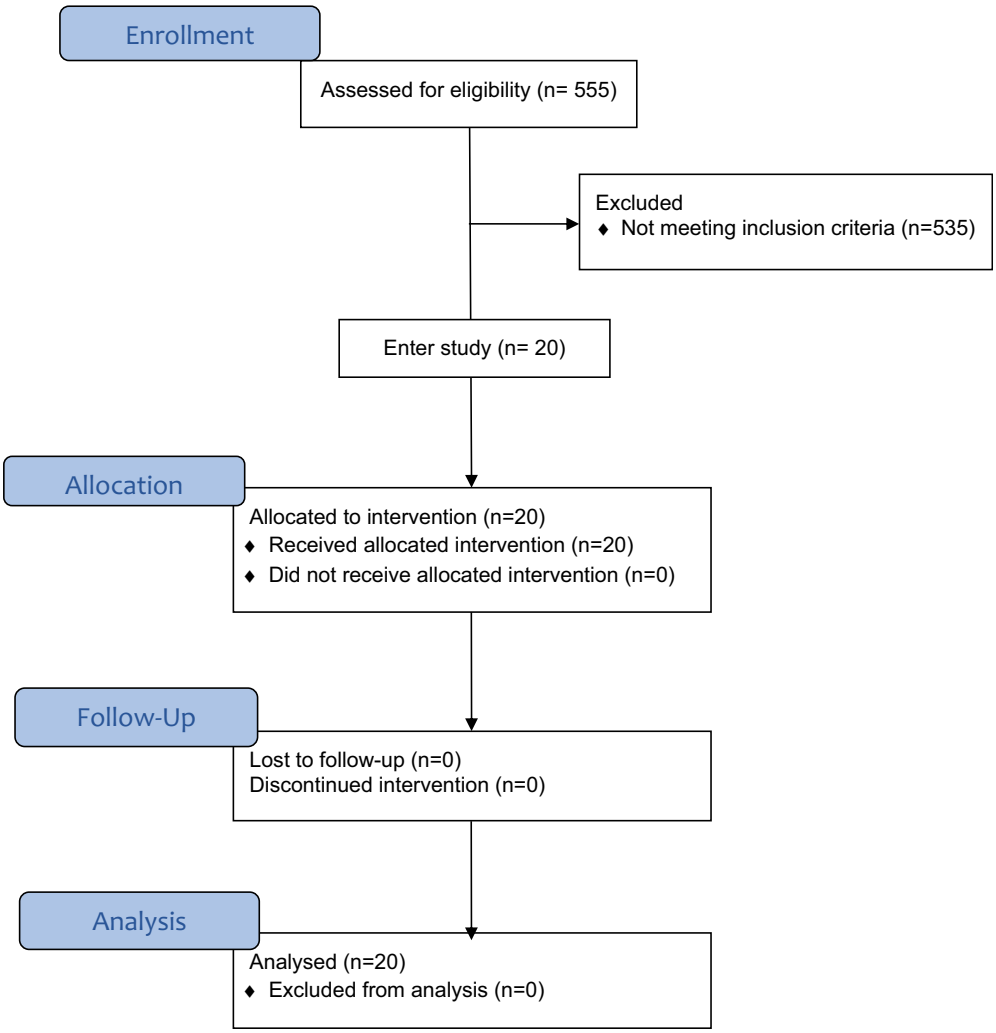

Figure 1. Flow diagram.

Inclusion criteria included women 40–65 years of age, postmenopausal (defined as no menstrual periods within the past 12 months), or peri-menopausal (defined as at least one menses in the last 12 months) with clinically meaningful insomnia symptoms (defined as an ISI score ≥15). They were required to report ≥2 hot flashes per day in the past 2 weeks that were rated as bothersome or severe 4 or more times per week with at least 1 hot flash during the day and at least 1 hot flash during the night.

Self-reported exclusion criteria included: oophorectomy/hysterectomy; recent or current hormone replacement therapy; unstable neuropsychiatric disorders (e.g., mood, anxiety, psychotic, and substance use disorders) that may independently affect sleep, brain function or cognition; unstable medical conditions including severe cardiac, liver, kidney, endocrine (e.g., diabetes), hematologic (e.g., porphyria or any bleeding abnormalities) conditions, other impairing or unstable medical conditions or impending surgery, central nervous system disorders (e.g., head injury, seizure disorder, multiple sclerosis, tumor), active peptic ulcer disease, inflammatory bowel disease, and arthritis (if the arthritis impacts sleep); Raynaud's Disease or severe cold sensitivity; irregular sleep schedules including shift workers; previous diagnosis of sleep disorders such as sleep apnea, periodic limb movement disorder, restless legs syndrome, or narcolepsy; consumption of more than one alcoholic drink per day, or more than 7 drinks per week prior to study entry; and unwillingness to wear a headband to sleep.

Procedures

The study design, risk/benefit, and informed consent procedures were approved by Campos Research. All participants provided informed consent and were financially compensated. Twenty women (age range: 45–61 years) who met study criteria were enrolled. All participants were studied concurrently over a one-month period. On enrollment, they completed an online battery of questionnaires before a baseline week assessment followed by 4-weeks of treatment with a forehead cooling device and sleep hygiene instructions and supportive care. Across baseline and treatment periods, participants completed evening and morning diaries about their sleep, hot flashes, and mood. They repeated the online battery of questionnaires post-treatment. All 20 participants completed all components of the study.

Assessments

Participants completed the following validated questionnaires before baseline and again at the end of treatment: the *Insomnia Severity Index* (Bastien et al., 2001; Morin et al., 2011), the *Patient Health Questionnaire-9 (PHQ-9)*, a 9-item scale assessing depression symptoms over the past 2 weeks (Kroenke et al., 2001), the *GAD-7 for Anxiety Disorder*, a 7-item measure assessing generalized anxiety symptoms over the past 2 weeks (Spitzer et al., 2006); the *Hot Flash Related Daily Interference Scale (HFRDIS)* (Carpenter, 2001) that includes 10 areas of daily functioning that may be affected by hot flashes, including sleep. Items are rated on a 10-point scale with higher scores indicating worse interference; and the *Greene Climacteric Scale*, (Greene, 1976) a 21-item questionnaire that measures the presence and severity of menopausal symptoms on a 4-point Likert scale (0 = "not at all" to 3 = "extremely"), yielding scores for three main symptom domains: psychological, somatic, and vasomotor and a single item about the loss of interest in sex (libido).

Across a 5 week period (1-week baseline and 4-weeks of treatment), participants completed online sleep diaries as adapted from Monk et al. (1994) including questions about hot flash frequency and intensity (Carpenter, 2005) each morning after sleeping, as used elsewhere (Baker et al., 2015). Briefly, they recorded their estimates of time getting into and out of bed, sleep and rise time, sleep latency (time to fall asleep), number of nighttime awakenings, duration of nighttime awakenings, time of awakening, subjective sleep quality, subjective mood, and alertness on awakening. Sleep quality (0 = very bad and 10 = very good), mood (0 = very tense and 10 = very calm), and alertness (0 = very sleepy and 10 = very alert) were assessed on 0– 10 visual analog scales. Participants also rated frequency (number) and intensity (mild, moderate, strong, very strong) of any hot flashes they

recalled having during the night. A hot flash severity index was calculated as hot flash frequency * intensity (Colau et al., 2012). In an evening portion of the diary, completed at bedtime, they also rated frequency and severity of any hot flashes experienced during the day and reported the number of caffeinated and alcoholic drinks consumed that day as well as number of naps.

Treatment

After a 1-week baseline assessment with no intervention, the 4-week treatment period began. Treatment consisted of forehead cooling applied across the night using the Ebb device (Ebb Therapeutics, Pittsburgh, PA, see Figure 2). The device included a bedside unit that utilized solid-state thermoelectric cooling and a pump to transport thermal fluid to a urethane forehead bladder (Ebb Therapeutics, Pittsburgh, PA). The forehead bladder was held in place by a lycra-based headband and circulated the fluid over the subject's forehead over the area of the frontal cortex at a precisely regulated temperature across the night. The temperature of the fluid could be adjusted for comfort between five settings (temperatures ranging from 15°C to 18°C, equivalent to 59–64°F). The headband holds the forehead bladder in place regardless of sleeper position. Participants received weekly 30-minute telephone support calls by individuals trained in general wellness care to provide general guidance and troubleshooting on the use of the device as well as generalized sleep hygiene instructions. Participants were instructed to wear the device beginning 20–30 minutes prior to lights out and throughout the night over the course of the study. During the weekly calls, the actual hours of use of the device were personalized according to individual needs and preferences. Participants were also encouraged to use the device during the day for 30 minutes at the onset of any daytime hot flashes. Beginning on week 2 of treatment, subjects were asked to record their estimates of how many hours they used the device at night and whether they used the device during the day on their daily diaries.

Data analysis

For daily diary measures, ratings were averaged across the baseline week and according to the week of treatment (1, 2, 3, 4) and analyses were performed on weekly averages. Weekly averages were compared using a repeated-measures analysis of variance. If the data did not meet the sphericity assumption, F-statistics with the Greenhouse-Geisser correction, which is robust to the violation, are reported. If the data did not meet the normal assumption with equal variances required of the RMANOVA, a Friedman's test was used as a non-parametric test for repeated samples. Cohen's effects sizes are reported for the RMANOVA analyses. Although there is no effect size available for

Figure 2. Ebb insomnia therapy.

a Friedman's test, the Kendal's W provides an approximation of effect size for these analyses. Interpretation of Kendal's W uses the Cohen's interpretation guidelines of 0.1 (small), 0.3 (moderate), and above 0.5 (strong) effect size groups. Following significant overall effects of time, pairwise comparisons were made between weekly averages. Paired t-tests were used to compare pre- versus post-treatment questionnaire assessments of symptoms. Non-parametric Spearman Rank correlations were used to determine associations among measures at baseline and across treatment. Analyses were performed using IBM® SPSS® Statistics Version 26. Effects were considered significant at $p < .05$.

Results

Characteristics of the sample at enrollment are shown in Table 1. The sample was predominantly comprised of non-Hispanic White (95%), college-educated (90%) women who were post-menopausal, except one. One participant reported taking antidepressants (escitalopram and bupropion), three were taking thyroid supplements and two were taking melatonin; these individuals were stable with respect to their treatment and no medication changes were made across the study. One participant was a current smoker. None of them reported ever having a serious mental illness. The group had clinically severe insomnia symptoms, as reflected by a mean ISI score of 20.0 ± 5.7, with nine women scoring 22 or above, reflecting severe insomnia (Bastien et al., 2001). Most (90%) reported a combination of sleep difficulties including difficulties falling asleep, staying asleep, waking up too early, and not feeling rested on awakening. One (5%) reported only trouble falling asleep and awakening early and one (5%) reported only trouble falling asleep, awakening early, and feeling poorly rested. Women reported between 2 and 14 hot flashes daily and reported that hot flashes interfered with daily activities based on their scores on the HFRDIS (Table 1), including interference with sleep (8.70 ± 1.5, on a 10-point scale).

The sleep complaints of the group were also reflected in their daily sleep diary ratings during the baseline week, with an average latency to fall asleep of 38.04 ± 26.32 minutes and an average amount of wakefulness after sleep onset of 52.22 ± 35.60 minutes. These values are in the clinically meaningful range of >30 minutes (Lichstein et al., 2003). Women reported, on average, less than 0.5 alcoholic drink and ~1 caffeinated drink per day across the 5-week assessment period. None of the women reported taking daily naps, with 8 of 20 reporting not taking any daytime naps across the assessment period.

Adherence/compliance with treatment

For the 3 weeks when the use of the device was recorded, the participants reported good compliance, using the device every night for about 5 hours, with use remaining stable across the study. Participants reported using the device infrequently during daytime hot flashes, on average, 2 days per week.

Treatment effects

Effects of treatment on daily diary reported sleep disturbances and nocturnal hot flashes over the 4 weeks of treatment are shown in Table 2. All measures of sleep disturbances and hot flashes showed improvements with treatment (all $p < .001$), with moderate-strong effect sizes. Following significant overall effects of time, pairwise comparisons showed improvements over baseline for all measures

Table 1. Characteristics of the 20 participants enrolled in the study.

Measure	Mean ± SD
Age (years)	55.1 ± 4.2
Body mass index (kg/m^2)	27.2 ± 4.9
Insomnia severity index(Bastien et al., 2001)	20.0 ± 5.7
Hot flash related daily interference scale(Carpenter, 2001)	71.1 ± 24.5
Number of reported waking hot flashes	4.2 ± 2.6
Number of reported nocturnal hot flashes	3.2 ± 1.9

Table 2. Daily diary reported sleep disturbances and hot flashes (mean ± SD) and statistical comparisons in 20 women across a baseline week and 4 subsequent treatment weeks with a forehead cooling device in conjunction with sleep hygiene instructions and supportive care.

Measure	Baseline	Week 1	Week 2	Week 3	Week 4	Stat, p, effect size
Sleep Latency (minutes)	38.0 ± 26.3[a]	25.7 ± 18.4[b]	21.1 ± 18.1 [c]	21.7 ± 21.2 [c]	20.8 ± 20.4[c]	χ^2 = 24.2, <0.001, 0.30
Number of awakenings	3.6 ± 0.7[a]	3.1 ± 0.8[b]	2.7 ± 0.7[c,d]	2.8 ± 0.8[c]	2.6 ± 0.9[d]	χ^2 = 33.9, <0.001, 0.42
Wake after sleep onset (minutes)	52.2 ± 35.6[a]	36.3 ± 27.3[b]	27.0 ± 19.5[c]	29.5 ± 22.5[c]	25.5 ± 22.9[c]	χ^2 = 31.5, <0.001, 0.39
Sleep Quality (0 = very poor, 10 = very good)	4.0 ± 1.6[a]	5.2 ± 1.3[b]	6.0 ± 1.7[c]	6.3 ± 1.5[c]	6.4 ± 2.1 [c]	χ^2 = 43.1, <0.001, 0.54
Number of nocturnal hot flashes	2.4 ± 0.9[a]	1.9 ± 0.7[b]	1.6 ± 0.9 [c]	1.6 ± 0.8 [c]	1.4 ± 0.9[d]	F = 13.9, <0.001, 0.42
Severity of nocturnal hot flashes (number*intensity)	6.8 ± 3.7[a]	5.2 ± 2.8[b]	4.0 ± 2.9[c]	3.6 ± 2.6[c,d]	3.0 ± 2.8[d]	F = 40.8, <0.01, 0.51
Morning Alertness (0 = very sleepy, 10 = very alert)	4.1 ± 1.7[a]	5.4 ± 1.5[b]	5.8 ± 2.1[b]	5.8 ± 1.7[b]	6.1 ± 2.1[b]	F = 12.7, <0.001, 0.40

Numbers with the same superscript letters are not different from each other based on post hoc pairwise comparisons.

within the first week of treatment followed by continued improvements at some point over weeks 2 through 4. Participants fell asleep faster (average 39% reduction), and had fewer awakenings (average 48% reduction), less wakefulness after sleep onset (average 28% reduction), and a better overall sleep quality during treatment (Figure 3). They also reported fewer nocturnal hot flashes that were less severe during treatment relative to the baseline week. Women's ratings of daytime hot flashes also showed improvements across the 4 weeks of treatment, with reported hot flash frequency (F = 19.9, $p < .001$, effect size: 0.51) and severity (χ^2 = 42.3, $p < .001$, effect size 0.53) declining from baseline (frequency: 2.6 ± 1.2; severity: 7.7 ± 4.9), to treatment week 1 (frequency: 1.9 ± 1.0; severity: 5.1 ± 4.2), week 2 (frequency: 1.6 ± 1.2; severity: 4.1 ± 3.8), week 3 (frequency: 1.5 ± 1.1; severity: 3.8 ± 3.4), and week 4 (frequency: 1.3 ± 1.0; severity: 2.9 ± 3.0).

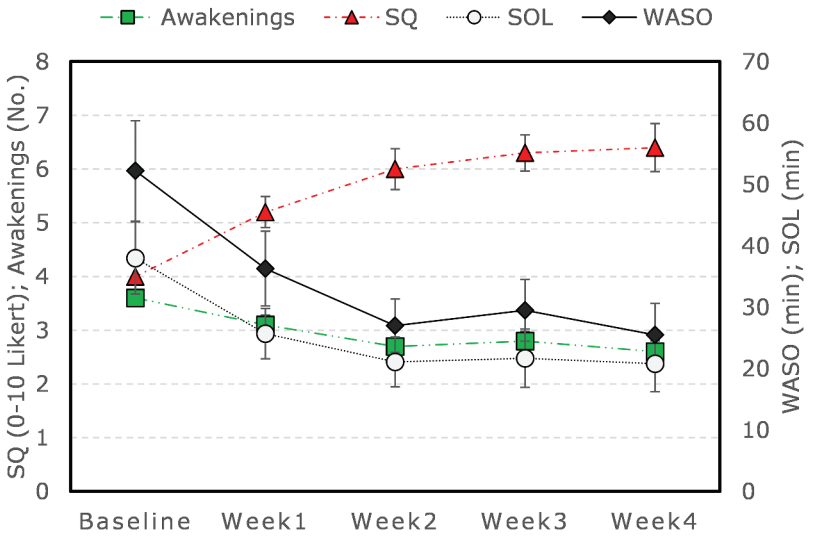

Figure 3. Changes in daily diary ratings of sleep onset latency (SOL), wakefulness after sleep onset (WASO), number of awakenings, and sleep quality (SQ) from a 1-week baseline across 4 weeks of active treatment with a forehead cooling device in conjunction with sleep hygiene instructions and supportive care in 20 mostly post-menopausal women.

Table 3. Ratings in 20 women of insomnia symptoms, hot flash interference, mood, and menopausal symptoms before and after 4 weeks of treatment with a forehead cooling device in conjunction with sleep hygiene instructions and supportive care.

Measure	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	Stat, p
Insomnia severity index (ISI)	20 ± 5.7	9.3 ± 5.8	t = 8.6, $p < .001$
Hot Flash Related Daily Interference Scale (HFRDIS)	71.1 ± 24.5	31.6 ± 23.6	t = 5.7, $p < .001$
HFRDIS (sleep interference item)	8.7 ± 1.5	4.3 ± 2.4	t = 7.3, $p < .001$
GAD-7 (anxiety)	8.4 ± 5.1	2.7 ± 2.8	t = 6.3, $p < .001$
Patient Health Questionnaire (depression)	10.7 ± 6.2	3.7 ± 3.6	t = 4.1, $p < .001$
Greene climacteric scale (total)	26.1 ± 12.6	9.0 ± 7.8	t = 7.4, $p < .001$
Greene climacteric scale (psychological)	15.3 ± 5	5 ± 5.6	t = 7.5, $p < .001$
Greene climacteric scale (physical)	4.4 ± 3.5	1.3 ± 1.3	t = 4.6, $p < .001$
Greene climacteric scale (vasomotor)	4.8 ± 1.7	2.4 ± 1.5	t = 5.1, $p < .001$

Table 3 shows average scores on the questionnaires assessing insomnia, mood, and menopausal symptoms before and after treatment. The overall severity of insomnia symptoms improved from pre- to post-treatment as evidenced by a reduction in ISI scores from pre-treatment (20.0 ± 5.7) to post-treatment (9.3 ± 5.8). Seventeen of 20 participants showed a reduction of 6 points or greater on the ISI, reflecting a clinically meaningful reduction in insomnia (Yang et al., 2009); nine participants scored 7 or below on the ISI (no insomnia) and 8 others had sub-threshold symptoms, post-treatment. There was also a significant reduction in hot flash daily interference, anxiety and depression symptoms, and improvements in all domains of the Greene Climacteric Scale (Table 3). Effects remained significant after removing sleep items from the questionnaires before analysis.

Relationships between sleep disturbances and menopausal symptoms across treatment

At baseline, insomnia severity was related to severity of menopausal symptoms and daily interference of hot flashes (baseline ISI x baseline GCS $\rho = 0.688$, $p = .001$; baseline ISI x baseline HFRDIS $\rho = 0.721$, $p < .001$). Baseline ISI scores were unrelated to change in ISI scores post-treatment ($p = .8$), indicating that the treatment effect did not depend on baseline insomnia severity. Change in Greene climacteric total scores pre- to post-treatment correlated with the change in ISI scores ($\rho = 0.64$, $p = .002$) as well as with the change in daily interference of hot flashes ($\rho = 0.64$, $p = .003$), the change in anxiety ($\rho = 0.62$, $p = .004$) and the change in depression ($\rho = 0.70$, $p = .001$).

Discussion

Here, we present preliminary data from a small, uncontrolled study showing the potential efficacy of 4 weeks of nighttime use of a forehead cooling device combined with sleep hygiene instructions and supportive care in improving sleep and menopausal symptoms in symptomatic midlife, mostly post-menopausal women relative to a baseline (no treatment) condition. Improvements were evident after just 1 week and were maintained across the 4 weeks of treatment. Remarkably, there were improvements not only in insomnia and nighttime hot flash symptoms but also in daytime hot flash symptoms and interference, depressed mood and anxiety, and overall menopausal symptoms. Improvements in sleep, mood, and anxiety were clinically important with the majority of women shifting from moderate-severe symptoms to no/mild symptoms after treatment. The improvements in insomnia symptoms replicated similar effects seen in veterans with chronic insomnia disorder and co-morbid medical and psychiatric disorders who used the forehead cooling device during sleep (Mysliwiec et al., 2020). Further large-scale randomized controlled trials are required to determine efficacy. Future studies are also needed to determine the mechanisms underlying the apparent efficacy of this device in this population of insomnia sufferers.

Interpretation of the findings is limited by the lack of a control group or sham condition. Comparisons however with results from other similar controlled trials in peri- and post-menopausal women suggest that the effects on sleep difficulties may be comparable to results seen

with CBTI, which is recommended as the first-line treatment of insomnia in published guidelines (Schutte-Rodin et al., 2008). In a comparison of the effects of 6 weeks face-to-face CBTI vs 2 weeks sleep restriction therapy delivered face-to-face vs 6 weeks sleep hygiene education delivered via e-mail on ISI and subjective sleep diary measures in post-menopausal women, Drake et al. (2019) found that, from baseline to posttreatment, ISI decreased 7.70 points in the CBTI arm ($p < .001$), 6.56 points in the sleep restriction group ($p < .001$), and 1.12 in the sleep hygiene group ($p = .01$). The average reduction in ISI of 10.7 points in the current study is comparable to the improvement in insomnia symptoms seen in both active treatment groups in the Drake et al. study. Similarly, results from the Menopausal Strategies: Finding Lasting Answers to Symptoms and Health (MsFLASH) Network (McCurry et al., 2016) showed a reduction in ISI scores of 9.9 points with CBTI sessions over a period of 8 weeks compared to 4.7 points with menopause education control in peri- or postmenopausal women with insomnia and daily hot flashes. Effects of CBTI in the MsFLASH studies were greater than the more modest effects of exercise or venlafaxine, and the small effects of escitalopram, yoga, and estradiol (Guthrie et al., 2018). Control placebo groups showed an average reduction in ISI scores after 4 weeks of 3.9 or 5.0 points (Guthrie et al., 2018), which is smaller than the average reduction we found, and suggests the effect of forehead cooling is meaningful. Our finding of a reduction in insomnia symptoms with treatment is complemented by our finding of changes in diary reported measures of difficulties falling asleep and staying asleep. After 4 weeks of treatment, women reported, on average, sleep onset latencies and wakefulness after sleep onset of less than 30 minutes each, which are outside of the clinically meaningful range (Lichstein et al., 2003). The reduction in sleep onset latency (on average, 17 min) and wakefulness after sleep onset (on average, 27 min) from baseline to 4 weeks post-treatment is more comparable to active CBTI treatment effects than to control or minimally effective therapy effects in previous studies (Drake et al., 2019; McCurry et al., 2016). As part of the therapy with the forehead cooling device, women also received a weekly 30-minute telephone call that provided guidance on how the device could be personalized for their own use as well as general assistance with personal sleep hygiene. These personal interactions may have added to the efficacy of the treatment, although the magnitude of effects is greater than what other trials have shown for these more nonspecific aspects of care (Schutte-Rodin et al., 2008). Indeed, according to AASM guidelines for the treatment of insomnia, "Although all patients with chronic insomnia should adhere to rules of good sleep hygiene, there is insufficient evidence to indicate that sleep hygiene alone is effective in the treatment of chronic insomnia. It should be used in combination with other therapies." (Schutte-Rodin et al., 2008)

We found reductions in reported hot flash frequency and severity (both during the night and day) which was not found in a clinical trial of CBTI, although hot flash-related interference was reduced, mostly due to a reduction in sleep-related interference from hot flashes (McCurry et al., 2016). We also found a reduction in perceived daily hot flash interference post-treatment, an effect that remained after removing the sleep item, indicating that treatment reduced interference from hot flashes into a wide range of daily activities. There is a substantial placebo effect on hot flash reporting, with patients who receive a placebo showing an average reduction of 1.5 hot flashes per day (24% reduction) and a 26% reduction in daily hot flash severity ratings from baseline to the end of 4 weeks of treatment (Sloan et al., 2001). We found, on average, 42% and 56% reduction in nocturnal hot flash frequency and severity, respectively, after 4 weeks of treatment, suggesting that the effect is greater than what would be expected by placebo/control condition. Our finding that women reported fewer and less severe hot flashes during the daytime across the treatment period, with large effect sizes (on average, 50% reduction in hot flash frequency and 62% reduction in hot flash severity), is unexpected. Women reported only occasionally using forehead cooling during the day, so our results cannot entirely reflect a direct hot flash reduction effect of daytime device use.

We found that not only did daily use of the forehead cooling device improve nightly sleep and insomnia and hot flash symptoms but also positively impacted more generalized menopausal symptoms, including depressed mood and anxiety. This finding is comparable to the reductions in anxiety

and depression seen in a prior study of veterans with insomnia and co-morbid medical and psychiatric disorders who also used the forehead daily cooling device nightly for a 4-week period (Mysliwiec et al., 2020). There are strong associations between poor sleep/insomnia and symptoms of depression and anxiety in general populations as well as in midlife women (reviewed in Baker et al., 2018). It is also argued that hot flashes and hot flash-related sleep disruption may impact daytime mood (Campbell & Whitehead, 1977; Thurston, 2008), although there is some differentiation between hot flash-sleep and depression–sleep relationships (Zervas et al., 2009). It is feasible, therefore, that successful treatment of insomnia would lead to improvements in depression and anxiety symptoms. Alternatively, nighttime forehead cooling therapy may have an independent effect on daytime mood and anxiety symptoms. Further studies that are placebo/sham controlled in larger samples are required to determine what are the mediating effects of any improvements in mood and anxiety with forehead cooling therapy in menopausal women.

The mechanisms by which forehead cooling may improve sleep and nighttime hot flashes are not entirely clear although prior research suggests some possibilities. A functional neuroimaging study showed that frontal cerebral thermal therapy (forehead cooling) reduced frontal cerebral metabolism during sleep in primary insomnia patients (Nofzinger et al., 2009) and a randomized controlled clinical trial showed sleep improvements in primary insomnia patients (Roth et al., 2018). While it is reasonable to assume these mechanisms in primary insomnia patients are also present in sleep disturbances in menopause, further studies in menopause are required. The reduction in nocturnal hot flash number/severity may be secondary to improvements in sleep, with women less likely to awaken or be bothered by nocturnal hot flashes. Direct cooling of the forehead could also reduce the incidence of hot flashes by stimulating receptors on trigeminal afferent fibers in the forehead (Dutschmann & Herbert, 1996), leading to an increase in cardiac vagal activity (diving reflex) (Panneton et al., 2010), counteracting the central sympathetic activation thought to be involved in the initiation of a nighttime hot flash (Freedman, 2014). Finally, the forehead is a highly thermosensitive area to warm and cold stimulation (Inoue et al., 2016) and providing cooling to the forehead may reduce sweating and give a sensation of relief during a hot flash. Further work is required to determine whether forehead cooling reduces the perception of fewer and less severe nocturnal hot flashes as well as objectively measured frequency of nocturnal hot flashes.

Potential mechanisms underlying the improvements in daytime hot flashes, depressive, anxiety, and other menopausal symptoms are unclear. Notably, there were associations between improvements in more global menopausal symptoms and all improvements in insomnia symptoms, mood, anxiety, and daytime distress of hot flashes. This raises the possibility that there is an underlying physiological disturbance associated with menopause that overlaps with the physiological systems underlying sleep/wake regulation, mood regulation, and anxiety regulation. Other studies showing that more specific sleep interventions improve sleep, but not necessarily other more global menopausal symptoms (McCurry et al., 2016) raise the possibility that forehead cooling may be impacting additional physiological systems beyond simply those of sleep/wake regulation. Future work is needed to clarify if forehead cooling may modulate some neurobiological changes underlying a broader complex of menopausal symptoms than just sleep alone.

The sample studied included female participants with severe insomnia and hot flash symptoms, and was predominantly Caucasian. Prior studies have described efficacy of the device in Primary Insomnia and in Veterans with Insomnia and comorbid medical and psychiatric conditions (Mysliwiec et al., 2020; Roth et al., 2018). Generalizability to other groups is not known.

This preliminary study was designed to explore the potential beneficial effect of forehead cooling therapy. It included rigorous methodology to screen women with clinically meaningful insomnia and daily hot flashes, and 4 weeks of daily diary assessments of sleep and hot flashes in addition to global questionnaires given before and after treatment. Women were compliant with the treatment, using it nightly across the treatment period, for around 5 hours per night. While results need to be interpreted cautiously given the lack of a placebo/sham condition, they suggest that forehead cooling is associated with improvements in sleep quality and hot flash severity, with improvements maintained over time,

as well as being associated with reductions in the severity of insomnia and other menopausal symptoms. A safe, novel, non-pharmaceutical therapy for sleep disturbances for menopausal women that could be made more widely available than approaches utilizing more time-intensive behavioral therapy could have an important public health impact. A randomized clinical trial with forehead cooling is warranted to confirm these preliminary results.

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Disclosure statement

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ORCID

Fiona C. Baker http://orcid.org/0000-0001-9602-6165
Eric A. Nofzinger http://orcid.org/0000-0001-8219-8142

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