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Adverse Effects of Induced Hot Flashes on Objectively Recorded and Subjectively Reported Sleep: Results of a Gonadotropin-Releasing Hormone Agonist Experimental Protocol

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Abstract

Objectives—The impact of hot flashes on sleep is of great clinical interest, but results are inconsistent, especially when both hot flashes and sleep are measured objectively. Using objective and subjective measurements, we examined the impact of hot flashes on sleep by inducing hot flashes with a gonadotropin-releasing hormone agonist (GnRHa).

Methods—The GnRHa leuprolide was administered to 20 healthy premenopausal volunteers without hot flashes or sleep disturbances. Induced hot flashes were assessed objectively (skin-conductance monitor) and subjectively (daily diary) during one-month follow-up. Changes from baseline in objective (actigraphy) and subjective sleep quality (Pittsburgh Sleep Quality Index [PSQI]) were compared between women who did and did not develop objective hot flashes, and, in parallel analyses, subjective hot flashes.

Results—New-onset hot flashes were recorded in 14 (70%) and reported by 14 (70%) women (80% concordance). Estradiol was universally suppressed. Objective sleep efficiency worsened in women with objective hot flashes and improved in women without objective hot flashes (median decrease 2.6%, increase 4.2%, p=0.005). Subjective sleep quality worsened more in those with than without subjective hot flashes (median increase PSQI 2.5 vs. 1.0, p=0.03). Objective hot flashes were not associated with subjective sleep quality, nor were subjective symptoms linked to objective sleep measures.

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Conclusions—This experimental model of induced hot flashes demonstrates a causal relationship between hot flashes and poor sleep quality. Objective hot flashes result in worse objective sleep efficiency, while subjective hot flashes worsen perceived sleep quality.

Keywords

hot flashes; vasomotor symptoms; sleep; quality-of-life; depressive symptoms; actigraphy

Introduction

Perimenopausal and early postmenopausal women report experiencing worse sleep quality more commonly than do premenopausal women of a similar age.[1, 2] Although it might be expected that poor sleep quality is a direct result of hot flashes, data addressing this issue are inconsistent (Table 1). When both hot flashes and sleep are reported subjectively, hot flashes are consistently linked to poor sleep quality.[1–8] In contrast, reports of the relationship between recorded hot flashes and reported sleep quality are much less consistent,[8–10] as are studies examining the association of reported and objectively recorded (i.e., skin-conductance monitor) hot flashes with recorded sleep (polysomnography or actigraphy). Findings across studies of recorded sleep show increased wakefulness and reduced sleep efficiency in some,[7, 8, 11–14] but not all,[6, 10, 15, 16] reports.

Unlike laboratory settings,[17] there is discrepancy between reported and recorded measures of hot flashes in ambulatory settings,[9, 18–20] which occurs because psychological factors influence subjective reporting[19] and recall of nocturnal events varies.[18] While both under- and over-reporting of daytime hot flashes relative to objective assessments is seen,[18, 19] nighttime hot flashes are consistently underreported relative to objective measures.[9, 18] Perception of sleep quality and recorded sleep are also poorly correlated.[21–23] Thus, while it might be expected that hot flash and sleep associations may differ depending on the way in which these core menopause-related symptoms are measured, only one study[8] has examined these associations using both objective and subjective measures of hot flashes and sleep. Results of this study[8] show that both reported and recorded hot flash measures were associated with both reported and recorded sleep measures. While this study is important because it is the only one to measure both hot flashes and sleep concurrently using subjective and objective methods, its cross-sectional design does not allow for causal inference.

Hot flashes are linked with reduced quality-of-life in midlife women,[24] either directly because hot flashes cause daytime discomfort, or indirectly, through their effects on sleep[1, 2, 4–6] and mood,[25–28] each of which independently contributes to poor quality-of-life.[24,29] Understanding the specific causal contribution of hot flashes to the development of poor sleep quality requires precise information on the temporal association between symptoms. The observational and primarily cross-sectional design of previous studies prevents causal inference about the specific impact of hot flashes on sleep quality, thereby limiting our ability to devise clinical strategies to treat these commonly co-occurring symptoms and improve quality-of-life.

We used a gonadotropin-releasing hormone agonist (GnRHa) which induces hypoestrogenism and mimics the hormonal changes of the menopause transition to isolate the specific effect of new-onset hot flashes on sleep quality. Hot flashes are induced rapidly on GnRHa in approximately two-thirds of women,[30–34] providing a natural control group of women who undergo the same hormone changes but who do not develop hot flashes. We compared within-woman changes in each sleep parameter from before to one month after initiation of GnRHa between those who did and did not develop new-onset hot flashes, as

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recorded objectively and reported subjectively. We secondarily examined the effect of hot flashes on quality-of-life using the same approach.

Materials and Methods

Twenty premenopausal healthy volunteers received one open-label intramuscular injection of the depot GnRHa leuprolide 3.75-mg/day and were then followed for one month to determine whether they developed hot flashes, at which time post-treatment assessments were completed. Pre- and post-treatment measures included sleep quality and quality-of-life questionnaires, a 24-hour period of objective recording of hot flashes, two nights of actigraphic recording of sleep, and continuous reporting of hot flashes on a daily diary throughout the study period. Serum estradiol was measured weekly on GnRHa to confirm that ovarian function was suppressed and that differences in symptom response were not explained by differences in estradiol levels.

Study participants

Healthy premenopausal women 18–45 years-old with monthly menstrual cycles and no hot flashes, sleep disorders, depression, or other psychiatric illnesses were enrolled in the study. The absence of hot flashes at baseline was established both subjectively using a 7-day hot flash diary and objectively using a sternal skin-conductance monitor for 24 hours (Biolog ambulatory recorder, UFI, Morro Bay, CA). Participants were carefully screened to select healthy women with regular menstrual cycles and evidence of ovulation (mid-luteal serum progesterone >3 ng/dL). Women with major depression and significant depressive symptoms were excluded using a standardized psychiatric diagnosis instrument (Patient Health Questionnaire, PHQ-9).[35] Eligible women were also required to have a score ≤16 on the clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS),[36,37] a threshold suggesting the absence of clinically relevant depressive symptoms,[38] and no previous psychotic symptoms, suicide attempt, or diagnosis of bipolar disorder, psychosis, anorexia nervosa, or alcohol/substance-use disorders.

Other exclusion criteria were pregnancy, lactation, abnormal prolactin, thyroid function, liver function, or renal function, primary sleep disorders (sleep apnea, periodic limb movement syndrome, narcolepsy), and use of centrally active medications (e.g., antidepressants, benzodiazepines, corticosteroids) or medications known to suppress hot flashes (e.g., birth control preparations, serotonergic agents, gabapentin).

Study Procedures

Participants received one open-label intramuscular injection of the depot GnRHa leuprolide 3.75-mg/day during the mid-luteal phase of their menstrual cycle to rapidly induce hypoestrogenism[39–41] and maintain ovarian suppression for a one-month period.[32, 33, 42] Serum estradiol, estrone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were obtained immediately prior to and after 1, 2, and 4 weeks on GnRHa therapy.

Following GnRHa administration, participants were monitored closely for a one-month period to determine the onset of hot flashes using daily diaries and a 24-hour period of skin-conductance monitoring completed at the end of the study. The Biolog monitor is used widely and has good reliability and validity.[43] Consistent with standard procedures, recorded hot flashes were defined as an increase in sternal skin conductance of ≥2μmho during a 30-second period using a 20-second lock-out period.[44]

Sleep patterns were recorded for 2 consecutive nights in each participant's home environment with the Actiwatch-Score (Mini Mitter Co., Inc, Bend, OR). Actigraphy data were used to measure sleep efficiency (percent of time spent asleep between bedtime and

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wake-up time), time spent awake after sleep-onset (WASO), and sleep-onset latency (minutes) before and after one month on GnRHa. An awake state was defined for each 30-second epoch when the total activity count was greater than a sensitivity threshold of 80. Subjective sleep quality was documented using the widely used Pittsburgh Sleep Quality Index (PSQI; range 0–21, higher score indicates poorer quality sleep).[45]

Quality-of-life was assessed with the Menopause-Specific Quality-of-Life Questionnaire (MENQOL), which measures 4 quality-of-life domains (vasomotor, psychosocial, physical, and sexual) over the past month that are averaged to generate the overall MENQOL score.[46] Daytime sleepiness and depressive symptoms, two domains of well-being commonly affected by hot flashes and sleep quality, were also measured using the Epworth Sleepiness Scale (ESS; range 0–24, higher score indicates more sleepiness),[47] the self-reported Beck Depression Inventory (BDI; range 0–63, higher score indicates more depressive symptoms),[48] and the clinician-rated MADRS (range 0–60, higher score indicates more depressive symptoms).[36, 37]

For safety monitoring purposes, participants were contacted by phone 2 and 3 months after receiving GnRHa to confirm that menses had resumed, that hot flashes had not subsequently developed, and, where previously present, that hot flashes had resolved. All participants provided written informed consent for study procedures, which were approved by the Partners HealthCare Institutional Review Boards.

Hormone Assays

Estradiol and estrone were measured using liquid chromatography, tandem mass spectrometry (Mayo Clinic, Rochester, NY),[49, 50] in order to achieve accuracy and precision in the low range seen on endocrine therapy. The interassay coefficient of variation (CV) ranges for estradiol and estrone in the low range studied was 8.6% and 8.7%, respectively.[49] The lower level of detectability for estradiol was 10 pg/ml.

Serum LH and FSH levels were measured in the Massachusetts General Hospital Reproductive Endocrine Laboratory (RELab) using a two-site monoclonal non-isotopic system according to the manufacturer's directions (Axsym, Abbott Laboratories, Abbott Park, IL, USA), as previously described.[51, 52] LH and FSH are expressed in IU per liter as equivalents of the Second International Pituitary Standard (80/552 and 92/510). The interassay coefficients of variation (CVs) for LH are 5.3, 5.5, and 7.4% for quality control sera containing 5.6, 26.2, and 69.0 IU/liter, respectively, and the interassay CVs for FSH are 5.2, 4.6 and 5.5% for quality control sera containing 7.4, 15.6 and 42.0 IU/liter, respectively.

Data Analysis

Analyses were conducted first using an objective hot flash classification and separately using subjective hot flash measurements. Baseline characteristics and serum levels of reproductive hormone at each time point were compared between women with and without hot flashes using Fisher's exact tests for categorical variables and the non-parametric Wilcoxon rank-sum testing for continuous variables. For the purpose of analysis, serum estradiol levels below the level of detectability were set at 5 pg/ml (the midpoint between 0 and the lower level of detectability).

Analyses comparing changes in recorded and reported sleep parameters were conducted using the non-parametric Wilcoxon rank-sum test. For each recorded sleep measure (sleep efficiency, WASO, sleep-onset latency), pre-and post-treatment values were calculated using the average from the two actigraphic studies conducted at each time point. The association of hot flash frequency with each sleep and quality of life outcome was estimated using Spearman correlations. Because of differences in serum estradiol at week 2 between

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hot flash groups, ordinal regression models using quartile ranking for the sleep endpoints were used to adjust for the baseline sleep measure and change in estradiol. The same approaches were used to analyze the effect of hot flashes on quality-of-life measures. Analyses were conducted using STATA software (College Station, Texas) and SAS version 9.2 (Cary, NC). Statistical significance was established using a two-sided alpha of 0.05.

Results

Study Participants

After one month on GnRHa therapy, new-onset hot flashes were reported by 14 (70%) participants, beginning after a mean of 8.4 ± 2.0 days on leuprolide. Hot flashes were recorded objectively in 14 (70%) participants. Among women with hot flashes, the median number of hot flashes reported per day over the one-month period was 2.5 (IQR 1.3–5.1), and the median number of hot flashes recorded during the 24-hour monitoring period was 5.5 (IQR 2.0–9.1). There was 80% concordance between the number of women reporting hot flashes and the number of women whose hot flashes were recorded, with hot flashes recorded in 12 (85.7%) of those who reported hot flashes and in 2 (33.3%) of those who did not report hot flashes. Among those with hot flashes, the median number of hot flashes reported at night was 1.0 (IQR 0.6–1.9) and the median number recorded during the night was 2.2 (IQR 0.8–3.4).

For all participants together, the mean age was 30.6 ± 8.9 years, mean BMI was 27.1 ± 4.6 kg/m^2, and half were African-American or Hispanic. There were no statistically significant differences between hot flash groups in baseline clinical characteristics, regardless of whether hot flashes were recorded (data not shown) or reported (Table 2), except for a trend association between age and reported hot flashes (p=0.07). However, analyses were not adjusted for age because age did not correlate with any sleep or quality-of-life endpoints.[53]

Baseline measures of reported sleep quality, recorded sleep patterns, quality-of-life, daytime sleepiness, and depressive symptoms did not differ between groups, regardless of whether hot flashes were reported (Table 2) or recorded (data not shown). In general, participants reported good sleep quality (median PSQI score = 3) and had good sleep efficiency (median 86.8%), minimal sleep-onset latency (median 14.0 minutes), and spent little time awake after sleep-onset (median WASO 25.3 minutes) on actigraphic assessment. Overall, participants had good quality-of-life, minimal daytime sleepiness, and low levels of depressive symptoms.

Effects of GnRHa on Reproductive Hormones

LH and FSH levels were rapidly suppressed on GnRHa (Figure 1c, 1d), consistent with the limited gonadotropin flare expected with mid-luteal GnRHa administration.[39–41] Serum levels of reproductive hormones (estradiol, estrone, LH, FSH) did not differ between hot flash groups, regardless of whether subjective (Figure 1a–d) or objective hot flash categorizations (data not shown) were used. The only exception was the estradiol level at week 2 (median 5.0 vs. 8.5 pg/ml, p=0.03, for those reporting vs. not reporting hot flashes; Figure 1a). Within one month on GnRHa (Figure 1a), all women had serum estradiol levels <15 pg/ml (median 6.5, interquartile range [IQR] 6–11.5, pg/mL *vs.* median 11, IQR 8–12, pg/mL, for those with versus without hot flashes, p=0.26).

Effects of Recorded Hot Flashes on Recorded Sleep Patterns, Reported Sleep Quality, and Quality-of-Life

Using recorded hot flashes (Figure 2 and Table 3), women who developed hot flashes had worsening of recorded sleep efficiency, as indicated by a median reduction in sleep

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efficiency of 2.6 % (IQR 0.9% to 10.2% lower), whereas women who did not develop recorded hot flashes had a median increase/improvement in sleep efficiency of 4.2% (IQR 0.8% to 7.5% higher). Therefore, the difference between medians in the change in sleep efficiency was 6.8% between groups (p=0.005). The within-woman change in sleep efficiency between hot flash groups remained statistically significant after adjusting for changes in estradiol levels on GnRHa (p=0.01).

There were no statistically significant differences between hot flash groups in the change in sleep-onset latency or WASO from baseline to one month on GnRHa. However, women with recorded hot flashes spent more time awake after sleep-onset (median 29.0 *vs.* 15.5 minutes, p=0.02) and had longer sleep-onset latency (median 24.5 *vs.* 10.3 minutes, p=0.05) at the end of the study. The number of recorded hot flashes correlated significantly with the magnitude of the reduction in sleep efficiency (r_S=0.76, p=0.0001, Table 3).

Within-woman change in PSQI scores did not differ between recorded hot flash groups. There were no statistically significant effects of recorded hot flashes on quality-of-life (MENQOL), sleepiness (ESS), or mood (MADRS, BDI) except for the MENQOL vasomotor domain (p=0.02).

Analyses of changes in recorded sleep efficiency scores were similar when the subgroup of women that had both subjective and objective hot flashes (n=12) was compared with the group (n=4) that had neither (p=0.01).

Effects of Reported Hot Flashes on Recorded Sleep Patterns, Reported Sleep Quality, and Quality-of-Life

There were no effects of reported hot flashes on recorded sleep patterns when hot flash groups were defined subjectively, although an increasing number of reported hot flashes correlated with a greater reduction in sleep efficiency (r_S=0.47, p=0.04, Table 3). PSQI scores increased more in women who reported hot flashes than in those who did not (median increase of 2.5, IQR 1.0 to 4.0, *vs.* median increase of 1.0, IQR 0 to 1.0, p=0.03, Figure 3 and Table 3). Adjusting for changes in serum estradiol did not alter the effect of reported hot flashes on within-woman change in PSQI scores (p=0.02). The number of hot flashes reported correlated with the extent of worsening in sleep quality, as measured by an increase in PSQI (r_S=0.53, p=0.02). PSQI scores increased by ≥3 points in 50% *vs.* 0% of women with *vs.* without hot flashes (p=0.04), suggesting a meaningful change in perceived sleep quality among the majority of women who reported developing hot flashes.[54]

Quality-of-life was reduced in women who reported hot flashes but not in those who did not (Figure 4 and Table 3), as evidenced by an increase in overall MENQOL scores in only those with hot flashes (median increase 1.1, IQR 0.5–1.8 vs. 0, IQR 0.1–0.1, p<0.001). The MENQOL domains showing a significant change from baseline to one month on GnRHa between reported hot flash groups were the psychological subscore (p=0.04) and the vasomotor subscore (p<0.001), and there was a statistical trend toward a greater reduction in quality-of-life in those who reported hot flashes for the physical (p=0.06) and the sexual (p=0.09) subscores. The number of hot flashes reported correlated with the amount of worsening in quality-of-life (increase in overall MENQOL score r_S=0.82, p<0.001).

Reduction in quality-of-life correlated with worsening in perceived sleep quality on the PSQI (r_S=0.57, p=0.01) but not with changes in recorded sleep efficiency. However, the association between hot flashes and quality-of-life remained strong after adjusting for PSQI scores (p=0.02). Worsening of quality-of-life on the MENQOL also correlated with an increase in depressive symptoms on the MADRS (r_S=0.72, p<0.001) and BDI (r_S=0.72, p<0.001), but not in sleepiness on the ESS (r_S=0.10, p=0.73). While within-woman changes

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in levels of depressive symptoms and sleepiness did not differ between subjective hot flash groups, women who reported developing hot flashes had higher levels of depressive symptoms after one month on GnRHa than those who did not on the BDI (median 2.0 *vs.* median 0, p=0.04) and on the MADRS (median 3.5 *vs.* median 1.0, p=0.07, statistical trend). As evidence of a meaningful change in depressive symptoms, BDI scores increased by ≥4 points in 28.6% and MADRS scores increased by ≥5 points in 35.7% of women who developed hot flashes (regardless of whether they were reported or recorded) and in 0% of those who did not develop hot flashes, but these differences did not reach statistical significance.

Analyses of changes in PSQI and of quality-of-life were similar when the subgroup of 12 women with both reported and recorded hot flashes was compared with the 4 women with neither (change in PSQI, p=0.07, and change in overall MENQOL, p=0.005).

Adverse Event Monitoring

The study intervention was well tolerated. Aside from the expected side effects of hot flashes, reduced sleep quality, and depressive symptoms, the most common side effects occurring in more than 5% of participants were fatigue (n=3), headache (n=2), upper respiratory tract infection (n=2), acne (n=1), bloating (n=1), irritability (n=1), malodorous urine (n=1), increased libido (n=1), and edema (n=1). No participant withdrew because of side effects. Within 3 months after GnRHa administration, hot flashes resolved and all women resumed their menstrual cycles. No one developed hot flashes after the first month on GnRHa.

Onset of clinically significant depressive symptoms was rare. Only one participant (5%) who developed hot flashes had a MADRS score on GnRHa that exceeded 15, suggesting clinically significant depression. Her depressive symptoms manifested one month after receiving the GnRH agonist (MADRS score = 28) and resolved spontaneously within 2 months.

Discussion

This study provides important evidence of a causal relationship between hot flashes and reduced sleep quality from a controlled experimental paradigm. Our results indicate that women with recorded hot flashes are more likely to have deterioration of recorded sleep, but they do not report a reduction in sleep quality or quality-of-life. In contrast, those who report hot flashes are more likely to report a reduction in sleep quality, but they do not have detectable changes in recorded sleep patterns, except when reported hot flashes are more frequent. Reported hot flashes and worsening of perceived sleep quality were associated with reduction in quality-of-life, although a similar relationship was not seen with recorded hot flashes and quality-of-life. Because changes in estradiol and gonadotropins were similar for those developing and not developing hot flashes, between-group differences in sleep parameters do not appear to be attributable to a divergent hormone response to the GnRHa. By inducing hot flashes in women without sleep disturbances at baseline and measuring hot flashes and sleep using both objective and subjective methodologies, findings from this small but rigorously controlled study provide evidence that hot flashes impair sleep.

It is not surprising that recorded hot flashes result in deterioration of recorded sleep efficiency but do not affect reported sleep quality because not all recorded nocturnal hot flashes are perceived or recalled in the morning.[55] We hypothesize that nocturnal hot flashes may not be recalled if they result in only a brief arousal or lightening of sleep stage, as a more sustained awakening may be required for a hot flash to be remembered.[53] If sleep is only minimally disturbed from repeated brief arousals or episodes of sleep stage lightening,

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recorded sleep efficiency might be reduced but reported sleep quality may not be impaired. Conversely, reported hot flashes may result in deterioration of perceived sleep quality but not influence recorded sleep efficiency because only those hot flashes associated with awakenings of sufficient length to generate memory are recalled in the morning.[53] It is notable that the number of reported hot flashes correlated with a greater reduction in sleep efficiency (Table 3). Therefore, it is only when reported hot flashes are more frequent that recorded sleep is affected.

Given the relatively small number of hot flashes that we and others[11–14] have recorded at night, it is unlikely that brief awakenings resulting from recorded hot flashes alone explain the observed reduction in sleep efficiency. We hypothesize that transient increases in core body temperature which precede objective hot flashes[56–58] may also fragment sleep because increases in core temperature are known to induce awakenings.[59] In women with hot flashes, the 1°C core temperature increase that commonly precedes a flash can last for as long as 20 minutes.[57, 58] Such transient yet prolonged temperature increases may fragment sleep enough to reduce sleep efficiency. PSG studies are needed to confirm this hypothesis.

By inducing hot flashes, the experimental design of our study advances our understanding of the impact of new-onset hot flashes on sleep, although PSG or more actigraphy nights would provide a stronger method of recording sleep than our current approach. The optimal measurement of hot flashes is a matter of intense debate.[18, 20, 60] It is increasingly clear that reported and recorded hot flashes are not identical and that, while subjective assessment is most important as a therapeutic target, objective measures play an important role for laboratory and sleep-related mechanistic studies.[18, 20] The approach to measuring reported or recorded hot flashes differ in that, while diaries can be completed over a protracted period of time, objective hot flashes are typically recorded for only 1−7 days, which makes assumptions about the stability of this symptom recording over time. These different time frames, together with discrepancies observed between reported and recorded hot flashes due to psychological factors and recall of nocturnal events,[9, 18–20] may contribute to differential effects of reported and recorded hot flashes on reported and recorded sleep quality. Our study is one of few[8] that combine measurement approaches for both hot flashes and sleep, but provides the advantage of understanding causal relationships because of the experimental design.

Our data provides further support for studies showing that recorded hot flashes are linked to recorded reductions in sleep efficiency.[8, 12, 13] Our work is also consistent with numerous studies showing that reported hot flashes are linked to a reduction in reported sleep quality.[1, 2, 4–8] Studies examining the link between recorded hot flashes and reported sleep are mixed, with our data supporting the absence of an association,[9] although differences in study design limit direct comparison. Our findings are consistent with some,[6, 15] but not all,[7, 8] studies showing the absence of an association between reported hot flashes and recorded sleep. Experimental studies of induced hot flashes using PSG to measure sleep would more definitively determine the effects of hot flashes on recorded sleep.

The baseline level of sleep efficiency we recorded and the magnitude of sleep efficiency reduction after hot flash developed are similar to that seen in other studies.[12, 13, 15] While a median reduction in sleep efficiency of 3% in those developing hot flashes is modest, it is notable that pharmacologic interventions for insomnia have been approved by the Food and Drug Association for equally small changes,[61] suggesting that relatively small changes in sleep time can have a meaningful impact on perceived sleep quality in insomniacs. Similar to changes in recorded sleep, the magnitude of change in perceived sleep quality we observed among those reporting hot flashes (PSQI score increased by ≥3 in 50%) is considered a meaningful change in perceived sleep quality.[54] Moreover, our study

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population was not highly symptomatic, with a median of 2.5 reported and 5.5 recorded hot flashes on average each day. Because we found that those with more frequent hot flashes had larger deteriorations in sleep efficiency and perceived sleep quality, it is expected that midlife women with more frequent symptoms would also have more marked disruption of their sleep.

Our data provide further support that quality-of-life is reduced in women reporting hot flashes.[24] While reduced perceived sleep quality correlated with impaired quality-of-life, sleep disruption alone does not appear to explain the negative impact of hot flashes on quality-of-life. These findings suggest that mechanisms such as episodic heat intolerance and sweating may be responsible for impaired quality-of-life in women with hot flashes.

This study uses an experimental model of hot flashes to isolate the effects of new-onset hot flashes on sleep and quality-of-life. By selecting young premenopausal women for this controlled investigation, we are by definition not studying a naturalistic population of midlife perimenopausal and postmenopausal women with hot flashes. Using the younger population has the advantage of eliminating the confound of age-related sleep changes from our study, but we may have underestimated the effect of hot flashes on sleep as this group of young women with good sleep at baseline may be more resilient to mild sleep perturbation. One important limitation of this and other studies[7, 8] is that actigraphy is an indirect objective sleep measure which can underestimate wakefulness during sleep periods.[62] Studies using PSG as the gold standard for objective sleep are needed to more definitively establish the impact of hot flashes on recorded sleep.

Consistent with other experimental studies,[63] this study was small because of cost considerations and the intensity of study procedures. While analyses of these types of studies must consider chance associations and multiple comparisons, the within-woman subtraction of pre-treatment from post-treatment symptom levels reduces variability and makes for a more precise estimate of each sleep and quality-of-life measure. The consistency of associations—recorded hot flashes versus recorded sleep outcomes, and reported hot flashes versus reported sleep and quality of life outcomes—reduces the likelihood that the observed associations were found by chance. This prospective design using a model of induced hot flashes also has the important advantage of enabling causal inference about the consequences of hot flashes on well-being.

Conclusion

In summary, our experimental model of induced hot flashes uses a novel approach to show that new-onset objective hot flashes result in a rapid reduction in recorded sleep efficiency, while new-onset subjective hot flashes impair perceived sleep quality. The close temporal association of hot flashes with changes in sleep demonstrated with this GnRHa model serves as an important experimental paradigm for studying hot flash-related changes in sleep in midlife women. The observed reduction in recorded sleep efficiency validates the symptomatic concerns of perimenopausal and postmenopausal women with hot flashes and poor sleep quality. Identification of hot flashes as a cause of poor sleep quality suggests that hot flashes can be targeted to secondarily improve sleep quality and quality-of-life in women with multiple menopausal symptoms.

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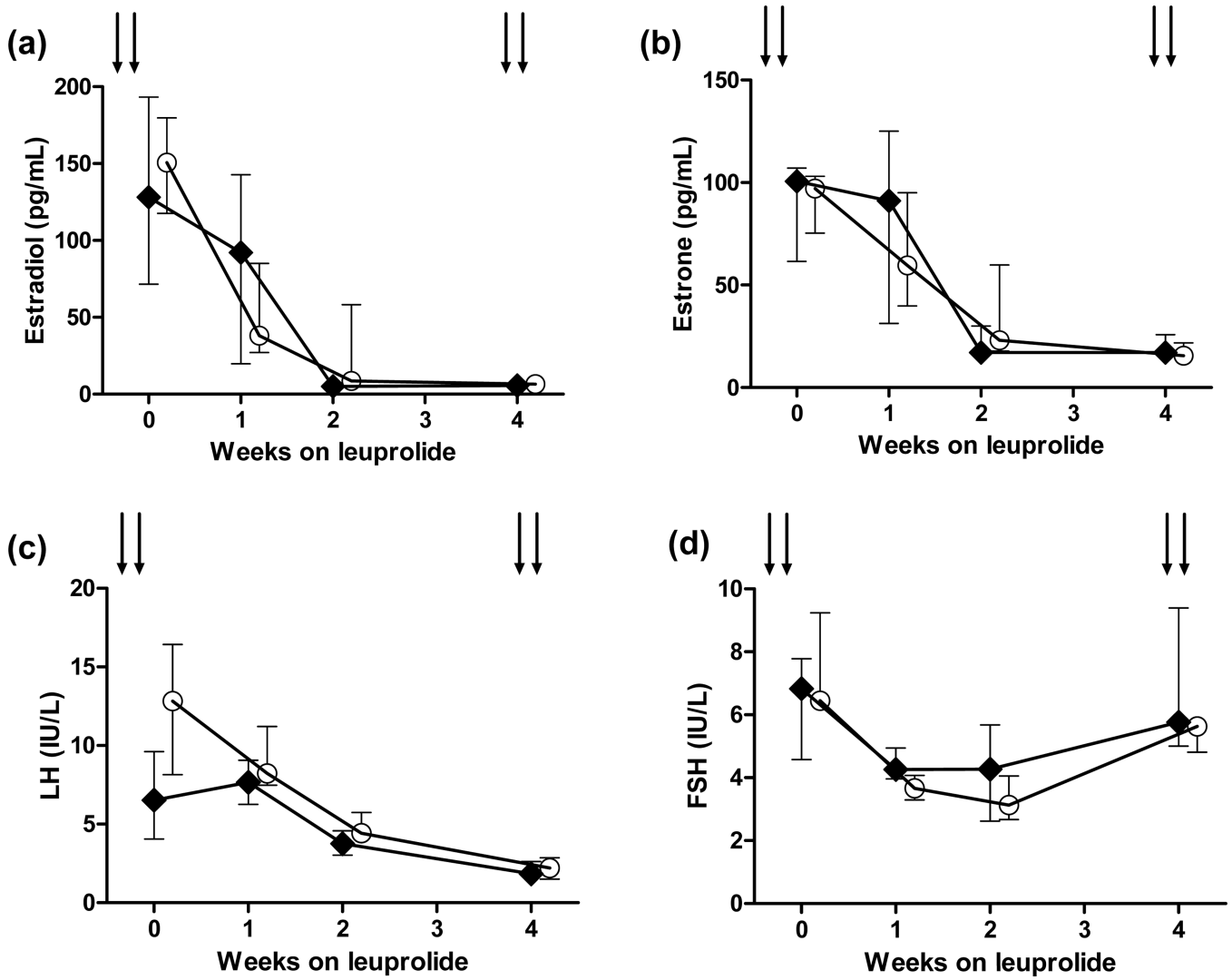

Figure 1.

Changes in serum estradiol, estrone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) for women who reported developing hot flashes versus those who did not secondary to treatment with the gonadotropin-releasing hormone agonist leuprolide. Data are shown as medians and interquartile ranges.

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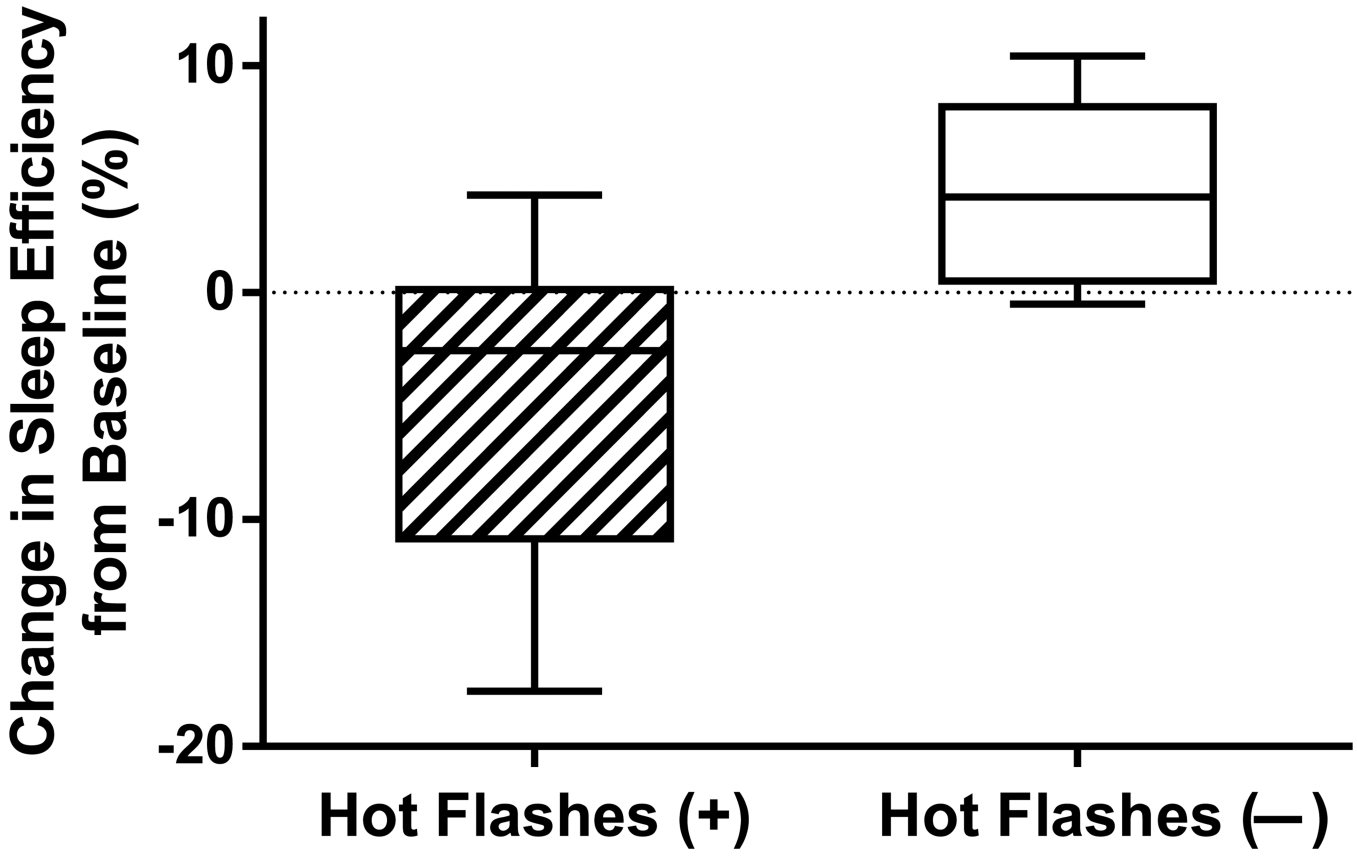

Figure 2.
Change in actigraphy-measured sleep efficiency from before ("pre") to 4 weeks on treatment ("post") with the gonadotropin-releasing hormone agonist leuprolide in women who did and did not develop objectively recorded hot flashes (p=0.005). Reduction in sleep efficiency indicates worsening.

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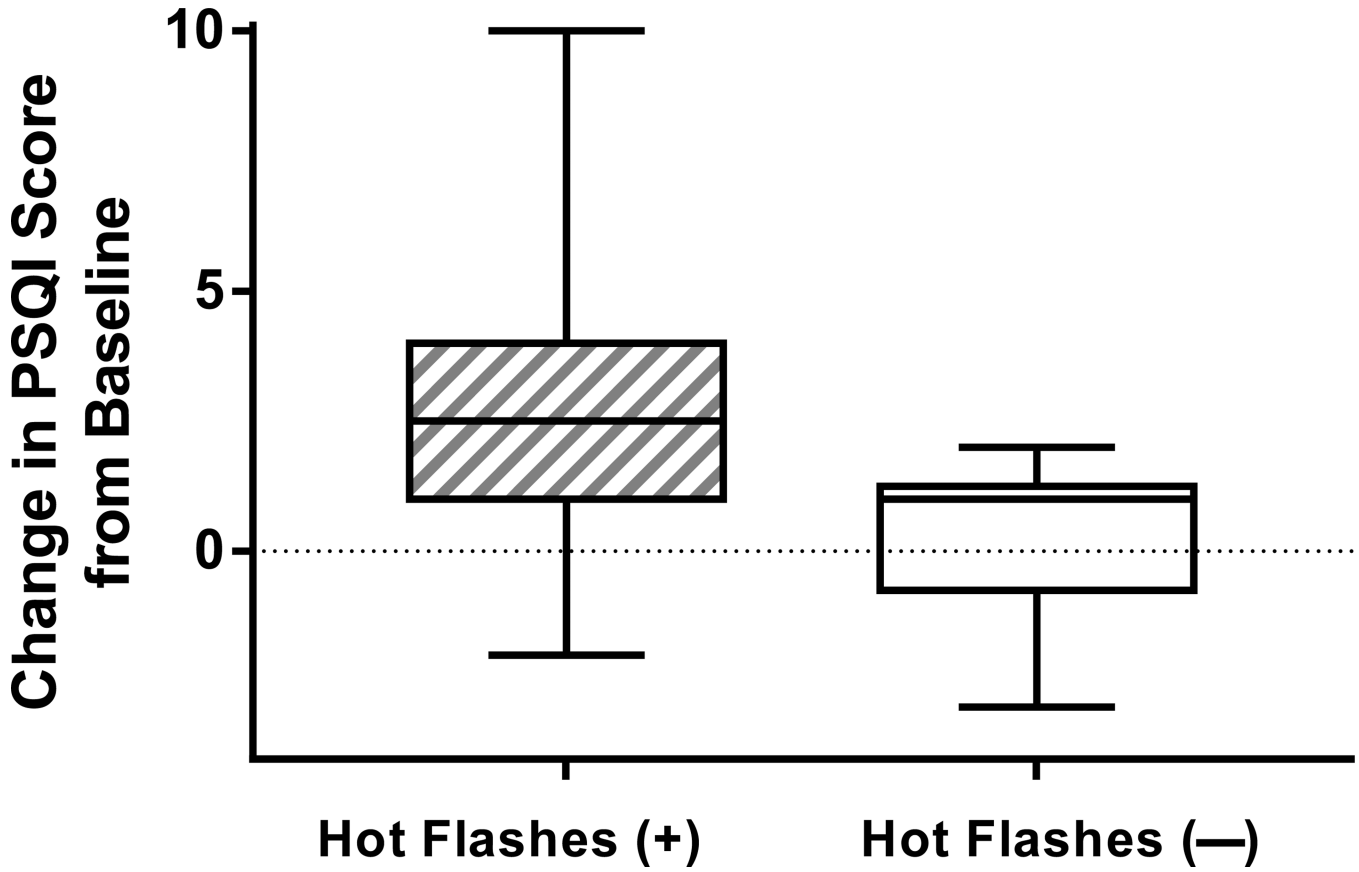

Figure 3.
Change in perceived sleep quality on the Pittsburgh Sleep Quality Index (PSQI) from before ("pre") to 4 weeks on treatment ("post") with the gonadotropin-releasing hormone agonist leuprolide in women who did and did not reported developing hot flashes (p=0.03). Increase in PSQI scores indicates worsening of perceived sleep quality.

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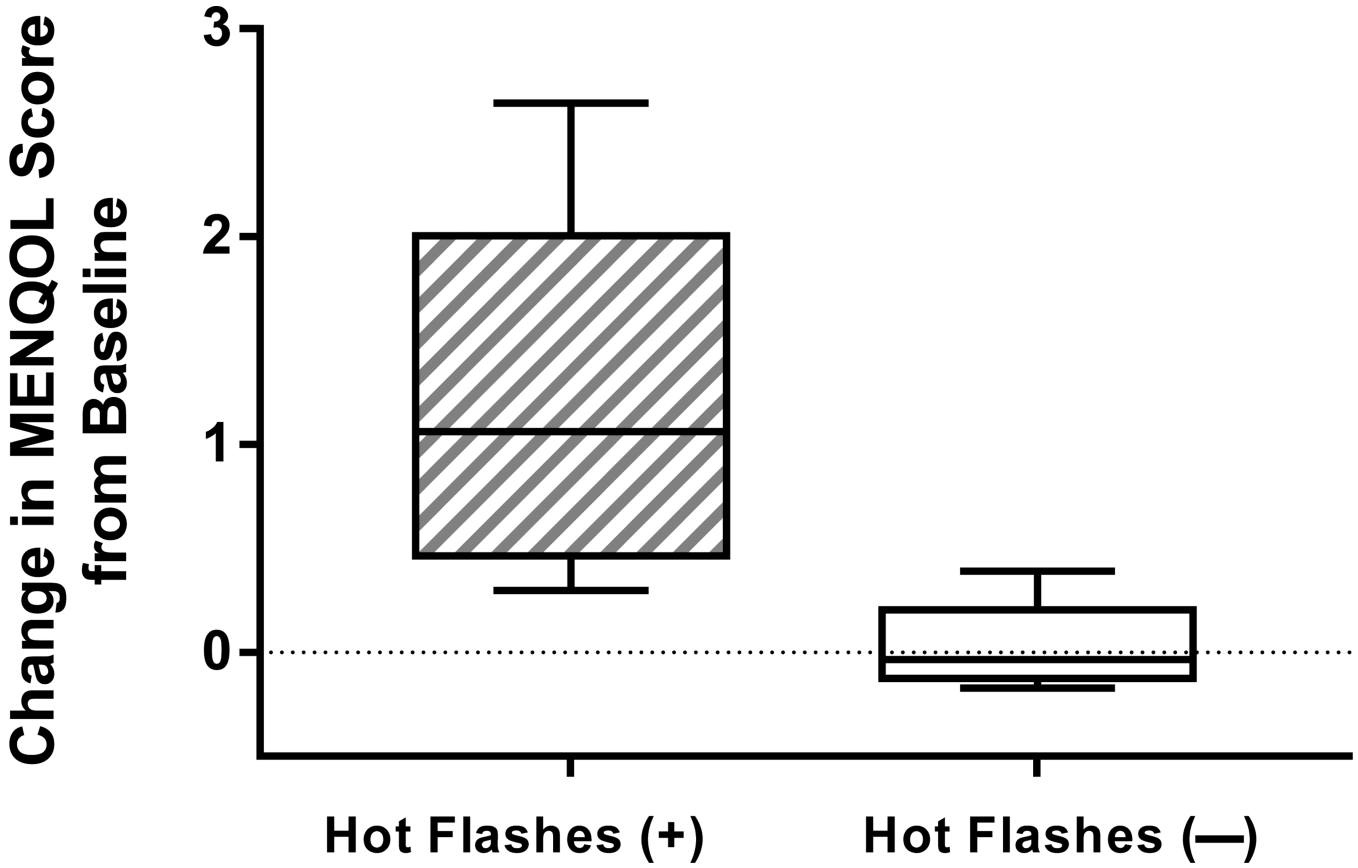

Figure 4.
Change in quality-of-life on the Menopause Quality of Life scale (MENQOL) from before ("pre") to 4 weeks on treatment ("post") with the gonadotropin-releasing hormone agonist leuprolide in women who did and did not report developing hot flashes ($p<0.001$). Increase in MENQOL scores indicates worsening of quality-of-life.

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Table 1

Data on association of subjectively reported and objectively recorded hot flashes with subjectively reported and objectively recorded sleep measures.

	Reported hot flashes	Recorded hot flashes
Reported sleep	↑ chronic insomnia diagnosis[3] ↓ sleep quality[1,2,4–8]	↓ sleep quality[8,10] No association[9]
Recorded sleep	Polysomnography studies No association[6, 15] Actigraphy studies ↑ wakefulness[7] ↑ sleep fragmentation[7,8] ↓ sleep efficiency[8]	Polysomnography studies ↑ wakefulness[11–14] ↓ sleep efficiency[12, 13] No association[10,16] Actigraphy studies ↓ sleep efficiency[8]

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Table 2

Study population characteristics at baseline according to subsequent development of subjectively reported hot flashes on gonadotropin-releasing hormone agonist.

	Subjective hot flash classification	
	Hot flashes reported (n=14)	**No hot flashes reported (n=6)**
Age, mean ± SD	32.8 ± 9.0	25.5 ± 6.7
BMI (kg/m^2)	27.3 ± 4.7	26.6 ± 4.7
Prior pregnancy, N (%)	7 (50.0%)	2 (33.3%)
Objective VMS, N (%)	12 (85.7%)	2 (33.3%)
Race		
Non-Hispanic White, N (%)	8 (57.1%)	3 (50.0%)
Hispanic or African-American, N (%)	6 (42.9%)	3 (50.0%)
Marital Status		
Married/living with partner	4 (28.6%)	0
Single/divorced/separated	10 (71.4%)	6 (100.0%)
Employment Status		
Working part time/full time	11 (78.6%)	3 (50.0%)
Student/Other	3 (21.4%)	3 (50.0%)
Education		
College graduate or higher	5 (35.7%)	2 (33.3%)
High school graduate/college student	9 (64.3%)	4 (66.7%)
	Median (interquartile range)	**Median (interquartile range)**
Baseline Objectively Measured Sleep Patterns		
Sleep Efficiency (%)	86.7 (85.1 to 90.4)	89.3 (80.6 to 92.2)
Latency (minutes)	13.8 (11.0 to 21.0)	14.5 (6.0 to 24.5)
WASO (minutes)	25.5 (20.0 to 42.0)	24.5 (19.0 to 32.5)
Baseline Perceived Sleep Quality		
PSQI Score	2.5 (1.0 to 3.0)	3.5 (2.0 to 5.0)
Baseline Menopause Quality-of-Life Measures		
MENQOL Overall	1.3 (1.2 to 1.4)	1.2 (1.1 to 1.3)
MENQOL Psychological	1.1 (1.0 to 1.6)	1.4 (1.0 to 2.0)
MENQOL Physical	1.2 (1.0 to 1.4)	1.3 (1.0 to 1.6)
MENQOL Sexual	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)
MENQOL Vasomotor	1.0 (1.0 to 2.0)	1.0 (1.0 to 1.0)
BDI Score	1.0 (0 to 2.0)	0 (0 to 1.0)
MADRS Score	1.0 (0 to 1.0)	0 (0 to 1.0)
ESS Score	6.5 (3.0 to 8.0)	3.5 (2.0 to 7.0)

Normally distributed data are presented as mean ± standard deviation, non-normal data are presented as median (interquartile range), and categorical data are presented as N (%).

WASO = wake-time after sleep-onset; PSQI = Pittsburgh Sleep Quality Index; MENQOL = Menopause Quality of Life; MADRS = Montgomery-Åsberg Depression Rating Scale; BDI = Beck Depression Inventory; ESS = Epworth Sleepiness Scale

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Table 3

Changes in objectively recorded sleep patterns, subjectively reported sleep quality, quality-of-life, and related domains from baseline to one month on gonadotropin-releasing hormone agonist therapy according to subsequent development of hot flashes, reported separately as medians (interquartile range) by (a) objectively recorded and (b) subjectively reported hot flashes, and (c) Spearman correlation with the number of hot flashes recorded or reported.

	(a) Objective hot flashes			(b) Subjective hot flashes		
	Hot flashes recorded (n=14)	**No hot flashes recorded (n=6)**	**(c) Spearman correlation with # of hot flashes recorded ‡**	**Hot flashes reported (n=14)**	**No hot flashes reported (n=6)**	**(c) Spearman correlation with # of hot flashes reported ‡**
Objectively recorded sleep						
Change in sleep efficiency †	−2.6 (−10.2 to −0.9) [a]	4.2 (0.8 to 7.5)	0.76 [a]	−1.8 (−7.7 to 1.2)	1.9 (−2.5 to 7.5)	0.47 [c]
Change in sleep-onset latency	7.0 (−0.5 to 16.5)	−1.3 (−4.0 to 3.0)	0.32	7.0 (−2.5 to 16.5)	3.0 (−3.0 to 3.0)	0.35
Change in WASO	2.0 (−5.0 to 9.0) [b]	7.3 (4.0 to 11.5)	0.32	3.5 (−5.0 to 11.0)	4.0 (0 to 10.0)	0.29
Subjectively reported sleep quality						
Change in PSQI	2.5 (1.0 to 4.0)	1.0 (1.0 to 2.0)	0.21	2.5 (1.0 to 4.0)[c]	1.0 (0 to 1.0)	0.53[c]
Quality-of-Life Questionnaires						
Change in overall MENQOL	1.1 (0.4 to 1.8)	0.3 (0 to 0.4)	0.11	1.1 (0.5 to 1.8)[d]	0 (−0.1 to 0.1)	0.82[d]
Change in BDI	0 (0 to 4.0)	0 (0 to 2.0)	0.04	0.5 (0 to 4.0)	0 (0 to 0)	0.44
Change in MADRS	2.0 (0 to 5.0)	1.0 (0 to 2.0)	0.15	2.0 (0 to 4.5)	0.5 (0 to 1.0)	0.68[d]
Change in ESS	0 (0 to 2.0)	0.5 (0.5 to 1.0)	0.11	0.5 (0 to 1.5)	0 (−0.5 to 1.0)	0.01

WASO = wake-time after sleep-onset; PSQI = Pittsburgh Sleep Quality Index; MENQOL = Menopause Quality of Life; BDI = Beck Depression Inventory; MADRS = Montgomery-Åsberg Depression Rating Scale; ESS = Epworth Sleepiness Scale

† Positive change score = worsening of symptoms from pre-treatment to post-treatment except for sleep efficiency, for which a negative change score = worsening of symptoms from pre-treatment to post-treatment.

‡ Correlations between number of hot flashes recorded (or reported) and worsening of the sleep or quality-of-life outcome.

[a] p≤0.005 and

[b] p=0.09 for differences using objectively recorded hot flash classification.

[c] p≤0.04 and

[d] p≤0.001 for differences using subjectively reported hot flash classification.