

## BRIEF REPORT

# Effects of perimenopausal transdermal estradiol on self-reported sleep, independent of its effect on vasomotor symptom bother and depressive symptoms

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### Abstract

**Objective:** The aim of this study was to determine the efficacy of transdermal estradiol (E<sub>2</sub>) plus intermittent progesterone (EPT) for improving self-reported sleep in perimenopausal women, after controlling for vasomotor symptoms (VMS) bother and depressive symptoms.

**Methods:** Using a double-blind, placebo-controlled design, 172 healthy women meeting STRAW+10 criteria for being in the menopausal transition or early postmenopause were randomized to 12 months of transdermal E<sub>2</sub> (0.1 mg/d) + 200 mg progesterone (12 d every 3 mo) or placebo. Using standard questionnaires, self-reported sleep, depression, and VMS bother were obtained at baseline and bimonthly postrandomization.

**Results:** Controlling for baseline levels, EPT (vs placebo) led to reductions in minutes to fall asleep (estimate = -0.12, *P* = 0.002) and number of awakenings (estimate = -0.24, *P* = 0.04) over the 12 months. Controlling for changes in VMS bother and depressive symptoms, EPT still predicted reductions in minutes to fall asleep (estimate = -0.28, *P* = 0.02) and number of awakenings (estimate = -0.11, *P* = 0.02) over the 12 months.

**Conclusions:** We extend existing research by demonstrating that hormone therapy (HT) in subjective sleep cannot be fully explained by improvements in VMS bother or depressive symptoms. Research to examine the mechanism(s) underlying HT's effects on sleep would have public health significance for perimenopausal women and also advance our general understanding of the pathophysiology of impaired sleep.

**Key Words:** Depression – Estrogen therapy – Menopausal transition – Sleep – Vasomotor symptoms.

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Disordered sleep is a public health concern linked to cardiovascular morbidity, the development of metabolic disorders (eg, glucose intolerance), deficits in immune function, reductions in quality of life, and the exacerbation of mood and anxiety symptoms. Sex differences in sleep problems are well established, such that women are more likely to report sleep problems compared with men.<sup>1</sup> More specifically, self-reported sleep problems increase by 2 to 3.5 times in women traversing the menopausal transition (MT)<sup>2,3</sup> and are reported by up to 56% of perimenopausal women, compared with 31% of older premenopausal women.<sup>4</sup> The MT is an aging process associated with pronounced fluctuations in estradiol (E<sub>2</sub>) that may influence sleep

quality.<sup>5</sup> Hormone therapy (HT) improves sleep for some, but not all, perimenopausal women with sleep problems. The mechanisms by which HT improves sleep remain unclear, partially due to co-occurring symptoms of the MT that are implicated in sleep disturbances and which respond to HT, including (1) vasomotor and (2) depressive symptoms.

Vasomotor symptoms (VMS) are experienced by up to 80% of women in the MT and cause sleep disturbances.<sup>6</sup> Women experiencing moderate-to-severe hot flashes are 3 times as likely to report nighttime awakenings, compared with women without hot flashes.<sup>7</sup> HT has been shown to effectively reduce VMS<sup>8</sup> and self-reported sleep disturbances.<sup>9</sup> A recent systematic review found that HT reduced self-reported sleep disturbances only for women with concomitant VMS, suggesting that HT indirectly improves self-reported sleep via reductions in VMS linked to nighttime awakenings.<sup>10</sup> A follow-up study confirmed relationships among HT, VMS, and self-reported sleep, such that reductions in sleep difficulties correlated with reductions in VMS after the administration of HT. Multivariate analyses, however, found that reductions in VMS did not fully account for reductions in sleep difficulties. These findings may be explained by improvements in depressive symptoms, which are prevalent

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in the MT and affect sleep, but were not examined in the aforementioned study.<sup>11</sup>

Depression risk increases for women in the MT, with rates of clinically significant symptoms doubling to tripling compared with premenopausal women.<sup>12</sup> Furthermore, depression and sleep are closely related, such that sleep disorders (eg, insomnia) increase the risk for depression<sup>13</sup> and depression increases self-reported sleep difficulties.<sup>14</sup> HT decreases depressive symptoms in the MT,<sup>15-17</sup> provides prophylactic mood benefits,<sup>18</sup> and improves self-reported sleep.<sup>5</sup> It has been suggested that improvements in self-reported sleep problems may be partially due to reductions in depressive symptoms.

The purpose of this study is to build upon the recent study by Cintron et al<sup>11</sup> and determine the efficacy of estrogen plus progestogen (EPT) in improving self-reported sleep problems, after controlling for improvements in self-reported VMS bother and depressive symptoms. Using a randomized, double-blind, placebo-controlled study design, we test the hypothesis that EPT will improve self-reported sleep and that these improvements will be explained by reductions in self-reported vasomotor bother and depressive symptoms. To date, we are unaware of any studies that have examined the influence of both self-reported vasomotor bother and depressive symptoms on the effects of HT for self-reported sleep difficulties in the MT.

## METHODS

### Participants

Participants were 172 women, 45 to 60 years ( $M = 51$  y;  $SD = 3.1$ ), medically healthy, and in the early MT, late MT, or early postmenopause (within 1 y of final menses) as defined by the Stages of Reproductive Aging Workshop criteria ( $-2$ ,  $-1$ , and  $+1a$ ) (see participant characteristics section in Results below). Menopausal staging was identified using self-reported bleeding patterns to determine STRAW+10 stage. Potential participants were self-referred via advertisements posted throughout the community and on social media. All women completed the Structured Clinical Interview for DSM-IV (SCID-IV) and were excluded if criteria were met for a history of the following: suicide attempts, bipolar disorder, psychotic disorders, severe substance use disorders (within the past 10 y), eating disorder, or posttraumatic stress disorder. At study enrollment, all participants were determined to be euthymic based on SCID-IV results. The study was approved by the University of North Carolina's IRB. Participants provided written, informed consent and received up to \$1,425 in compensation. Randomization scheme was determined by a study statistician and the UNC Hospitals Investigational Drug Services randomized and dispensed study medication in blinded form. The study design and methods are described in greater detail in previously published studies.<sup>18</sup>

### Study design

The Perimenopausal Estrogen Replacement Therapy Study (PERT) was designed to examine health benefits of transdermal  $E_2$  with intermittent progesterone in women traversing the MT and early postmenopause. The PERT study was also designed to

investigate additional mechanisms underlying the effects of  $E_2$ . The current article reports on the effects of EPT on depressive symptoms and VMS bother, in relation to self-reported sleep. The PERT study used a randomized, double-blind, placebo-controlled design to enroll and randomly assign participants to either patches of 0.1 mg of  $17\beta$ - $E_2$  or placebo (3 M Pharmaceuticals; St. Paul, MN) for 12 months. Oral micronized progesterone (200 mg/d for 12 d) was given every 2 to 3 months to women in the EPT group to protect the endometrium. An identical schedule of placebo pills was provided for women randomized to the placebo group. Study visits and self-report questionnaires were administered at baseline and months 1, 2, 4, 6, 8, 10, and 12. Visits were conducted monthly (as opposed to more frequently) to reduce participant burden and minimize attrition over the course of 12 months. To study the effects of  $E_2$  without the confound of progesterone, visits did not occur while women were taking progesterone. Each of the following measures was administered at each study visit.

### Measures

*Depressive symptoms* were measured with the *Center for Epidemiologic Studies-Depression Scale (CES-D)*.<sup>19</sup> The CES-D is a 20-item self-report measure assessing depressive symptoms within the past week (eg, I felt sad; I thought my life has been a failure) using a 4-point scale (0 = rarely or none of the time [ $<1$  d]; 3 = most or all of the time [5-7 d]). Total score can range from 0 to 60, with higher scores corresponding to more depressive symptoms. A CES-D score  $\geq 16$  indicates clinically significant depressive symptoms. In previous studies, elevated CES-D scores were sensitive to anti-depressive effects of HT in postmenopausal women.

*Vasomotor symptom bother* was measured with the *Greene Climacteric Scale-VMS subscale*.<sup>20</sup> The Greene-VMS subscale is a self-report measure assessing severity of climacteric symptoms using a 4-point scale (0 = not at all; 3 = extremely). The VMS subscale assesses symptom severity using two items: at the moment, how much are you bothered by (1) hot flushes and (2) sweating at night. Total score can range from 0 to 6, with higher scores corresponding to more vasomotor symptom bother.

*Sleep health* was measured with the *St. Mary's Sleep Questionnaire*.<sup>21</sup> This is a 14-item self-report measure, assessing total amount of time asleep (hours per night), sleep latency (number of minutes it takes to fall asleep), number of awakenings per night (how many times one wakes per night), and symptoms of daytime sleepiness and fatigue.

### Analytic plan

#### Data normalization

First, extreme outliers across baseline and follow-up time points (ie, any values 3 or more interquartile ranges lower than the first quartile or greater than the third quartile [SAS Institute Inc, 2011]) were identified and removed ( $n = 3$ ). Inspection of both sleep outcomes (time to fall asleep, number of awakenings) indicated strong right skew; in each case, a square root transformation was applied to both the baseline levels and the

repeated outcomes to normalize the distributions; this resulted in normal residuals in final analyses.

**Effect of treatment**

Unless otherwise specified, an intent-to-treat analysis was performed. First, we tested the main effect of treatment (placebo vs EPT) on our two outcomes: (1) time to fall asleep and (2) number of awakenings per night. Second, we tested the robustness of these effects after controlling for VMS change from baseline. Third, we tested the robustness of these effects after controlling for depressive symptom change from baseline. Finally, we tested the robustness of these effects after controlling for both current change from baseline in VMS bother and current change from baseline in depression symptoms, simultaneously.

All analyses were conducted using SAS, version 9.2 (SAS Institute Inc). To examine the effect of treatment (placebo vs EPT) on self-reported (1) time to fall asleep and (2) number of nighttime awakenings, two-level multiple regression analysis was conducted using PROC MIXED (for mixed models) with eight repeated measures (prerandomization [denoted visit – 1] and months 1, 2, 4, 6, 8, 10, and 12). In initial models, only baseline levels of the outcome and condition were included as predictors of follow-up scores. Controlling for baseline levels of the outcome alters the meaning of the repeated measures outcome, such that the outcome represents change over time adjusting for the individual’s baseline status.<sup>22</sup> In follow-up analyses, we included one or both of the following covariates: change in VMS bother relative to baseline levels, and change in depression (CES-D score) relative to baseline levels. A first-order autoregressive covariance structure was specified for within-person error. When they improved model fit, random effects of change in either VMS bother or depressive symptoms were retained (with an unstructured covariance structure). The Kenward–Roger method was used for computing degrees of freedom for tests of fixed effects. Because PROC MIXED does not delete missing data listwise, all

available data were used. A 2-sided value of  $P < 0.05$  was considered statistically significant.

**RESULTS**

**Participant characteristics**

One hundred seventy-two women entered the trial; women randomized to EPT and placebo did not differ significantly on baseline demographic, depression, VMS bother, reproductive staging, or sleep variables. Across all participants, 21% were early perimenopausal, 57.5% were late perimenopausal, and 21.5% were early postmenopausal. Forty participants withdrew from the study (17 from placebo; 23 from EPT). Seventy-six percent of participants attended all post randomization study visits, and 85% attended at least four visits (see Gordon et al for CONSORT information and baseline group difference tests).<sup>18</sup>

**Effect of treatment on sleep latency (minutes to fall asleep)**

Estimates from two-level multiple regression models predicting minutes to fall asleep are presented in Table 1. In the first level, we examined the impact of treatment (EPT vs placebo) on follow-up minutes to fall asleep after controlling for baseline levels. Women randomized to EPT reported a significantly lower sleep latency (fewer minutes to fall asleep) at follow-up visits relative to women randomized to placebo. In the second level, we control for changes (from baseline to the current follow-up time point) in VMS bother and depression symptoms. The beneficial impact of EPT on sleep latency remained significant (and in fact, was slightly increased) after controlling for change in VMS bother and depressive symptoms. Figure 1 presents the least squares follow-up means of this variable after controlling for baseline levels as well as vasomotor and depression symptom changes. Even after accounting for vasomotor and depression symptom changes, individuals on EPT had a significantly shorter sleep latency (minutes to fall asleep) compared with the placebo condition. Therefore, in this sample, the impact of EPT on sleep latency

**TABLE 1.** Estimates from multilevel regression models predicting changes in sleep latency and nighttime awakenings (N = 172)

	Outcome: change in time to fall asleep	Outcome: change in number of awakenings
<b>Treatment effects</b>		
Mean difference between treatment and placebo	–0.24 <sup>a</sup>	–0.12 <sup>b</sup>
Mean difference between treatment and placebo, <i>controlling for VMS Δ at the same visit</i>	–0.28 <sup>a</sup>	–0.10 <sup>a</sup>
Mean difference between treatment and placebo, <i>controlling for CES-D Δ at the same visit</i>	–0.24 <sup>a</sup>	–0.12 <sup>a</sup>
Mean difference between treatment and placebo, <i>controlling for VMS Δ and CES-D Δ at the same visit</i>	–0.28 <sup>a</sup>	–0.11 <sup>a</sup>
<b>Covariate associations</b>		
Correlation of VMS Δ with outcome Δ at the same visit, <i>controlling for treatment effect</i>	–0.05	0.03 <sup>b</sup>
Correlation of CES-D Δ with outcome Δ at the same visit, <i>Controlling for treatment effect</i>	0.004	–0.01
Correlation of CES-D Δ with outcome Δ at the same visit, <i>controlling for treatment effect and VMS Δ</i>	–0.05	0.03 <sup>b</sup>
Correlation of VMS Δ with time to outcome Δ at the same visit, <i>controlling for treatment effect and CES-D Δ</i>	0.004	0.004

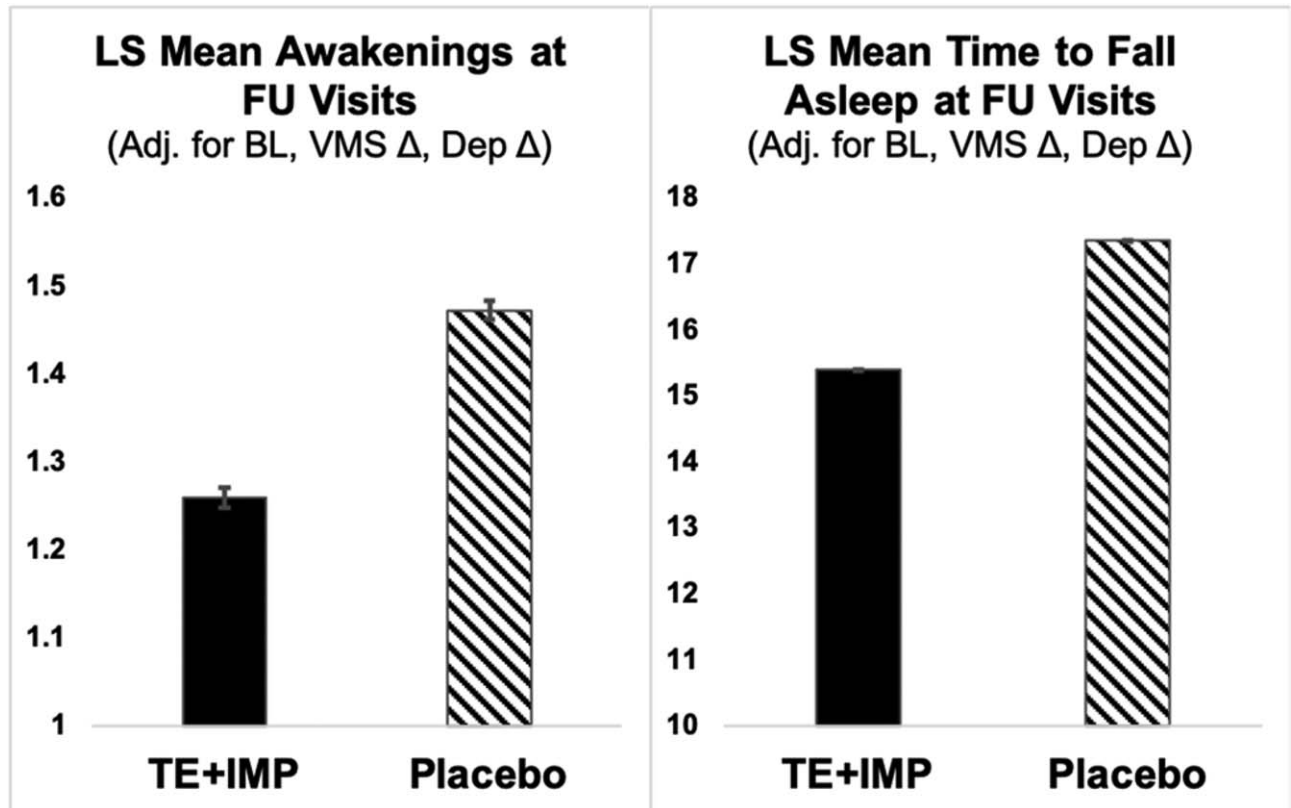
Δ and “Change” each refers to the change over the individual’s baseline value to follow-up (averaged across all follow-up visits). Outcomes have been square root transformed to achieve normal residual.

BL, baseline; CES-D, center for epidemiologic studies-depression scale; VMS, vasomotor symptoms.

<sup>a</sup> $P < 0.05$ .

<sup>b</sup> $P < 0.01$ .

<sup>c</sup> $P < 0.001$ .



**FIG. 1.** Effect of EPT (vs placebo) on mean time to fall asleep and mean awakenings at current follow-up visit after controlling for baseline time to fall asleep, current change in vasomotor symptoms relative to baseline, and current change in depression symptoms relative to baseline. BL, baseline value of the outcome;  $\Delta$ , change from baseline value of the outcome at that follow-up visit; Dep, center for epidemiological studies depression scale score; EPT, transdermal estradiol + intermittent micronized progesterone; FU, follow-up; LS, least squares; TE + IMP, transdermal estradiol plus intermittent progesterone; VMS, “Bother” item of the Greene Climacteric Scale.

could not be explained by improvements in hot flashes or depression.

#### Effect of treatment on reported number of awakenings per night

Estimates from two-level multiple regression models predicting number of awakenings per night are also presented in Table 1. In the first level, we examined the impact of treatment (EPT vs placebo) on follow-up number of awakenings per night after controlling for baseline levels. Women randomized to EPT reported significantly fewer awakenings per night at follow-up visits relative to women randomized to placebo. In the second level, we controlled for changes (from baseline to the current follow-up time point) in vasomotor symptom bother and depressive symptoms. The size of the beneficial impact of EPT on awakenings was reduced (from  $-0.12$  to  $-0.09$ ) after controlling for change in VMS bother and depressive symptoms; however, the beneficial impact of EPT remained significant. Figure 1 presents the least squares follow-up means of this variable after controlling for baseline levels as well as vasomotor and depression symptom changes. Therefore, as with sleep latency above, the impact of EPT on reducing the number of awakenings per night could not be fully explained by improvements in hot flashes or depression.

#### DISCUSSION

In a randomized, double-blind, placebo-controlled study, EPT improved self-reported sleep latency (fewer minutes to fall asleep) and number of awakenings (fewer nighttime awakenings)—two components of sleep quality particularly relevant to the MT.<sup>9</sup> We hypothesized that improvements in self-reported sleep disturbances would be explained by reductions in self-reported VMS bother and depressive symptoms. Improvements in self-reported sleep latency and reductions in number of awakenings associated with EPT, however, remained significant, even after accounting for improvements in vasomotor and depressive symptoms. The present study extends recent findings of Cintron et al<sup>11</sup> by concurrently studying depressive symptoms and VMS bother, instead of only VMS bother, to understand mechanisms by which HT improves self-reported sleep. Our findings suggest that HT likely improves self-reported sleep through mechanisms beyond improvements in both vasomotor *and* depressive symptoms. On the contrary, this is somewhat surprising, given the strong relationships among sleep disturbances, VMS bother, and depressive symptoms in the MT. On the contrary, it highlights that sleep problems in the MT are not a simple function of VMS bother or depression—rather, there may be additional mechanisms at play needing further evaluation.

Although speculative at present, one potential mechanism by which HT may improve sleep is through regulation of cortisol. Disruption in 24-hour cortisol rhythm contributes to sleep problems. Insomnia is associated with elevated 24-hour cortisol levels, with the greatest elevations occurring in the evening.<sup>23</sup> Cortisol secretion by the adrenal cortex is regulated by upstream release of corticotropin releasing hormone (CRH) in the paraventricular nucleus (PVN) of the hypothalamus, which is densely innervated with estrogen receptors. In rodents, ovariectomy reduces stress-induced corticosterone and ACTH secretion, which is reversed by systemic E<sub>2</sub> treatment.<sup>24</sup> Consequently, alternations between hyper- and hypoestrogenism, characteristic of the MT,<sup>25</sup> could exert a destabilizing effect on circadian cortisol synthesis and secretion, thereby disrupting sleep. HT, particularly transdermal E<sub>2</sub>, creates a relatively more stable E<sub>2</sub> profile in premenopausal ranges. Determining whether reductions in E<sub>2</sub> variability and/or its regulation of cortisol synthesis and secretion contributes to improved sleep in the MT awaits rigorous, controlled research.

The present study has a number of notable strengths. First, the study utilized a rigorous randomized, double-blind, placebo-controlled design and a relatively large sample size. Second, the study followed participants for a 12-month period, with eight time points for data collection, thereby increasing the reliability of measurement over time. The study design included assessment of history of psychiatric disorders, as diagnosed by the DSM-IV, and excluded participants with substance use and trauma-related disorders, which are associated with sleep problems. Participants with other comorbid health conditions that may impact sleep were, however, not excluded. Although not a limitation per se, the study relied solely on self-report measures of sleep and VMS bother. VMS bother has, however, been found to be more strongly associated with sleep disturbance than objective VMS frequency.<sup>26</sup> Furthermore, self-report measures of sleep are important to study because self-reported symptoms drive patients to seek care. Future studies may consider supplementing self-reported sleep measures with wrist actigraphy, and self-reported VMS with physiological measures detecting autonomic changes. In addition, understanding discrepancies between self-reported sleep problems and objectively measured sleep quality is an important avenue for future studies.

## CONCLUSIONS

The present study's findings suggest that EPT improves self-reported sleep parameters (number of nighttime awakenings and sleep latency), even after controlling for improvements in self-reported VMS bother and depression, building upon recent findings showing HT improves sleep after controlling for only self-reported VMS bother.<sup>11</sup> This suggests that there are additional biological mechanisms by which HT improves self-reported sleep. Given earlier demonstrations that beneficial effects of HT are seen most prominently in those with antecedent stressors,<sup>27</sup> the possibility that HT

improves sleep in part by reducing hypothalamic-pituitary-adrenal axis sensitivity and reactivity should be explored.

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