The Effects of Hormone Replacement Therapy on Sleep-Disordered Breathing in Postmenopausal Women: A Pilot Study

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Study Objectives: To evaluate the impact of estrogen and estrogen plus progesterone hormone-replacement therapy (HRT) on mild-to-moderate sleep-disordered breathing (SDB) in postmenopausal women.

Design and Setting: Within-subjects, progesterone placebo-controlled prospective HRT trial in a clinical laboratory.

Participants: Six postmenopausal women, diagnosed with mild-moderate SDB.

Intervention: Transdermal estradiol and oral micronized progesterone. Measurements and Results: Subjects underwent polysomnography (PSG) on four occasions: a screening/adaptation night; a baseline night on no HRT; and two nights on HRT: one night after 7 to 12 days on estrogen plus placebo followed by a second night after 7-13 days on estrogen plus progesterone. The PSG was performed with a Sandman130 computerized PSG system using a standard clinical montage. Modified sleep diaries were used in the baseline week and throughout the study period. Mood was measured with the 20-item version of the Positive and Negative Affect Schedule (PANAS). Estrogen monotherapy was associated with a significant reduction in the overall apnea-hypopnea index (AHI) (from a mean of 22.7 events per hour at baseline to a mean of 12.2 events per hour), but the AHI reduction on estradiol plus progesterone relative to baseline was not statistically significant (AHI=16.2 events per hour). Similar results were found for the percentages of total sleep time and of total non-rapid eye movement sleep time with oxygen saturation less than 90%. Estrogen, neither alone nor in combination with progesterone, significantly altered PSG- or diary-based measures of total sleep time, time to sleep onset, or time awake after sleep onset.

Conclusions: While the data are preliminary and based on a small number of subjects, estrogen appeared to have a substantial beneficial effect on measures of SDB in postmenopausal women. Overall, no additional benefit was seen with the addition of progesterone. In fact, progesterone attenuated the beneficial effects of estrogen in 4 out of the 6 participants.

Key Words: menopause, apnea, sleep-disordered breathing, estrogen, progesterone


INTRODUCTION

THE PREVALENCE OF SLEEP-DISORDERED BREATHING (SDB) INCREASES WITH MENOPAUSE, narrowing the well-documented high male-to-female ratio in the reported prevalence of SDB in younger cohorts.1 The prevalence of sleep apnea (defined by 10 or more apneas or hypopneas per hour plus daytime sleepiness) increases from 0.6% in premenopausal women to 2.7% in postmenopausal women who do not take hormone replacement therapy (HRT).2 The severity of SDB in postmenopausal women is, however, not related to the severity of vasomotor symptoms or to circulating estradiol levels.3 On the other hand, the prevalence of sleep apnea remains low (0.5%) for postmenopausal women who do take HRT.3 Past estimates suggested that a substantial proportion (34%) of postmenopausal women in the United States were taking HRT.4 Given the new findings from the Women’s Health Initiative (WHI) about risks associated with long-term use of HRT,5 estimates of the prevalence of future HRT are unavailable. Nevertheless, the American College of Obstetricians and Gynecologists (ACOG) does recommend short-term use of combination HRT for relief of menopausal symptoms.5 Therefore, it remains important to learn about the impact of HRT on breathing during sleep in postmenopausal women.

The paucity of data on the effects of estrogen and progesterone replacement therapy on sleep in menopause is particularly puzzling, in light of evidence that these two hormones have an impact on sleep in other contexts.6 Progesterone primarily affects non-rapid eye movement (NREM) sleep, whereas estrogen primarily affects REM sleep. Estrogen and progesterone act on the central nervous system, both through interaction with intracellular receptors that trigger genomically directed interactions in protein synthesis7 and through a more rapid nongenomic alteration of neuronal excitability through binding sites on neurotransmitter-gated ion channels such as the GABA_A receptor complex.8

Only one study has examined the effects of estrogen monotherapy on respiration during sleep.5 This study found improved respiration during sleep in postmenopausal women, including a reduction in respiratory disturbance index (RDI) and improved oxygenation. There is more evidence for the impact of progestins on breathing. Medroxyprogesterone acetate (MPA), a synthetic progestin, stimulates respiration during wakefulness,10-13 probably by its action on central carbon dioxide receptors.14,15 Its clinical utility in the treatment of SDB has been limited. Results from studies of the impact of MPA on breathing in normal male subjects during sleep are mixed, as are the results of studies of male SDB patients. Negative findings have been reported for morbidly obese apneic patients,16 for nonhypocapnic obstructive sleep apnea (OSA) patients,12 and for other OSA patients.17 Some studies that documented improvement in respiration with MPA during wakefulness did not find a similar improvement during sleep.11,12,18 Other studies, however, did find improvement with MPA in some aspects of SDB. One study found decreased daytime sleepiness, improved pedal edema, and decreased apnea index in 4 of 9 OSA patients.19 MPA also was found to improve oxygenation in alcohol-induced obstructive apneas, but it did not reduce the number or length of episodes.20 Combined estrogen and MPA reduces upper airway collapsibility in men,21 increases genioglossus...
muscletone in postmenopausal women,23 and elevates ventilation in pregnant women.16

We are unaware of any studies that have examined the impact of pro-
gestosterone monotherapy on the breathing of hypogonadal women with
SDB. There is, however, one placebo-controlled study that evaluated the
impact of MPA on respiration during sleep of healthy postmenopausal
women (21 participants).24 These authors found no significant group
differences between those treated with placebo and those treated with
MPA. They did, however, find that 6 of the 11 MPA-treated participants
who experienced a few respiratory events during the night did experience
a significant reduction in the “maximum duration of apnea.”24

There are also a few small studies addressing the impact of combined
estrogen and progestin on sleep in women. Administration of combined
MPA and estrogen improved respiration in two samples of OSA patients
who experienced spontaneous menopause25 and in a nonclinical sample of
5 women who had undergone ovariectomy or hysterectomy.26

Given the available literature, we hypothesized that postmenopausal
women with SDB will experience improvement relative to baseline in
respiration during sleep when treated with combined estrogen and pro-
gestosterone and that combined estrogen and progesterone will be more
beneficial than treatment with estrogen alone.

METHODS

Design

To test the hypotheses stated above, we used a within-subjects design,
in which respiratory indices and sleep architecture were evaluated
sequentially: at pretreatment/baseline (BL); during treatment with trans-
dermal estradiol plus placebo (E); and during treatment with transdermal
estradiol plus oral micronized progesterone (E+P). The design of the
study is depicted in Figure 1. We chose to assess the effects of progester-
one in the presence of estrogen rather than to directly compare proges-
terone with placebo because the effects of progesterone are enhanced
by estrogen. We chose a sequential design, without an intervening
washout period, in order to evaluate the impact of this common HRT
regimen on sleep.

Subjects

The participants were 6 women who had experienced a spontaneous
menopause. To qualify for the study, participants had to be between 45
and 65 years of age and had to meet established criteria for mild to mod-
erate OSAS,27 consisting of a complaint of excessive daytime sleepiness
and/or fatigue and an apnea hypopnea index (AHI) of at least 10 events
per hour. Postmenopausal status was determined by a history of cessa-
tion of menses at least 1 year before enrollment and was confirmed by
estrogen levels of 57 pg/mL, which is comparable to early follicular
ability (Vivelle®, Novartis). This dose yields average steady-state serum
estradiol levels of 30 pg/mL,28 participants were told that some of the capsules contained placebo and other capsules
had identical appearance. Participants were enrolled in the screening phase of
the study after providing written informed consent. The screening pro-
cess consisted of a semistructured clinical interview including (1) a sleep
history and a screening interview for psychiatric disorders (the Mini
International Neuropsychiatric Interview V5.0.0);28 (2) a screening
polysomnogram (PSG), which also served as a laboratory adaptation
night; and (3) a medical history and physical examination, including the
breasts and pelvis, and a review of results from mammography and a
Papanicolaou smear performed during the 12 months preceding study
enrollment. Following the screening phase, the 6 qualifying participants
entered a baseline week, during which they completed sleep-wake
diaries and had a baseline PSG. Participants then began HRT. HRT con-
sic of 2 weeks of estradiol patch plus placebo capsules (E) followed
by 2 weeks of estradiol plus micronized progesterone (E+P). Three sin-
gle-night laboratory PSGs were performed after the screening/adaptation
night: a baseline night, within 2 weeks after the screening night; an
estrogen night, after 7 to 12 days on estrogen plus placebo; and an estro-
gen plus progesterone night, after 7-13 days on estrogen plus proges-
terone. Participants were given a tray containing all capsules. The placebo
and progesterone capsules had identical appearance. Participants
were told that some of the capsules contained placebo and other capsules
contained progesterone and that they should, therefore, take the capsules
in the order indicated by the labels in the tray.

Treatment

Estradiol was administered through a transdermal matrix patch releas-
ing a daily dose of 50 mg of estradiol through skin of average perme-
ability (Vivelle®, Novartis). This dose yields average steady-state serum
estradiol levels of 57 pg/mL, which is comparable to early follicular
phase levels in young, menstruating women. A transdermal patch, rather
than an oral preparation of estradiol, was selected because it is not
associated with hepatic first-pass effects and it maintains the physiolog-
ic ratio of estradiol to estrone.29 In the present study, the average
evening serum estradiol levels on estrogen plus progesterone treatment
was 47.6±23.2 pg/mL. Serum estradiol levels on estrogen alone are not
available. Participants were instructed to change the estradiol patches
twice weekly (i.e. every 3.5 days). Progestrone and placebo were
administered orally using capsules of 200 mg of micronized proges-
terone and identically appearing capsules of lactose, both suspended in
olive oil. Participants were instructed to take the capsules 2 hours before
daytime sleep with a snack. Ingestion with food enhances absorption
of progesterone but does not alter time to peak levels.28 A progesterone
dose of 200 mg once daily has been approved for use in postmenopausal
HRT. The mean plasma level achieved with oral progesterone doses of
200 and 300 mg is comparable to low luteal phase levels. Participants
were not permitted to participate in any other experimental protocol or
to be on any medications that impact sleep or respiration or to receive
concomitant treatment for SDB while participating in the present study.

*The genioglossus is one of the major muscles responsible for dilation of the upper airway.

**Vivelle®, package insert 5989, Novartis
Measures

The PSG was performed with a Sandman™ computerized PSG system, using the standard clinical montage for the Stanford Sleep Disorders Clinic. This included five electroencephalogram (EEG) leads (C3/A2, C4/A1, Fz/A1+A2, O1/A2, O2/A1), two electrooculogram leads, a submentalis (surface) electromyogram (EMG), electrocardiogram (ECG), intercostal/diaphragmatic (surface) EMG, bilateral anterior tibialis EMG, pulse oximetry, airflow (nasal cannula linked to pressure transducer), and oral thermocouple respiratory efforts (uncalibrated inductive plethysmography). The EEG, ECG and EMG signals were recorded with a sampling rate of 1000 Hz; all other signals were digitized at 100 Hz. Appropriate bandpass filtering was used for all signals. Participants were scheduled in the laboratory according to their habitual sleep period and were told to maintain their habitual intake of caffeine and alcohol and their habitual nap behavior during the study. Sleep staging followed established criteria and respiratory events were scored based on the American Academy of Sleep Medicine criteria. A single scorer, who had no knowledge of the study hypothesis and was blind to the condition treatment of the participants, scored the PSG data.

Participants completed sleep diaries daily throughout the duration of the study. The diaries included a portion that was completed in the morning (logging bedtime, latency to sleep onset, time awake after sleep onset, wake-up time, and sleep quality) and a portion that was completed at bedtime (logging ratings of daytime mood, nap time, medication use, caffeine intake, alcohol intake, and occurrence of spotting or bleeding). Mood was measured with the 20-item version of the Positive and Negative Affect Schedule. It has two 10-item scales, the Positive Affect Scale and the Negative Affect Scale, that are largely uncorrelated. The subscales have high internal consistency (0.84 to 0.90) and are sensitive to fluctuation of mood. A low Positive Affect score reflects sadness and lethargy; a high Negative Affect score reflects subjective distress that subsumes aversive mood states such as anger, disgust, fear, and nervousness.

Adherence with treatment was measured via pill and patch counts and a review of daily logs in which participants recorded intake of study medications and times that the estradiol patch was changed. Plasma samples for estradiol and progesterone assays were collected 2 hours after progesterone ingestion and upon awakening on the PSG nights during treatment. Morning plasma data were available for 5 of the 6 participants, while evening plasma levels were available for 4 participants. Missing laboratory data were the result of laboratory errors and the unavailability of a phlebotomist on certain nights.

Statistical Analysis

Given the small sample size, we adopted a conservative analysis strategy and used nonparametric statistical tests. The nonparametric Wilcoxon signed rank test for related samples was used to compare sleep and respiratory measures at BL to those in the two treatment phases. Planned comparisons compared BL versus E, BL versus E+P, and E versus E+P. Cohen’s d effect sizes, expressing the difference between the means in terms of the estimated standard deviation units, are reported as well.

RESULTS

The age of the participants ranged from 47 to 63 (mean 56.0 ± 5.8), and their last menses occurred 1 to 12 years (mean 6.8 ± 4.5 years) before study entry. Mean BMI was 25.2 ± 3.43 kg/m². Individual participant characteristics are presented in Table 1. Baseline sleep and respiratory indices are summarized in Table 2. Estrogen therapy was associated with a significant reduction in the overall AHI compared to BL (Z = -2.20, p = 0.028), yielding an effect size of 0.8, but the reduction in AHI on E+P relative to BL was not statistically significant (Z = -1.36, p = 0.173, effect size 0.5). Means and standard deviations of respiratory indices across time are summarized in Table 2. An inspection of individual scores (Figure 2) reveals that the dramatic drop in AHI in one participant, from 45.3 at BL to 14.8 on E, accounted for a significant proportion of the decreased AHI in the group. Nonetheless, the reduction in AHI on E relative to BL remained statistically significant (Z = -2.02, p = 0.043) after excluding this participant from the analysis. Individual AHI scores across treatment conditions are presented in Figure 2a. Most of the improvement in the AHI on E therapy occurred during NREM sleep (Z=2.2, p=0.028). In contrast, improvement in AHI on E therapy during REM sleep was not significant (Z=-0.94, p=0.345). There was a statistical trend for improvement in oxygen saturation with E relative to baseline. The percent of total sleep time and of total NREM sleep time with oxygen saturation less than 90% was reduced on E treatment relative to BL (Z=1.83, p=0.068), a trend that was not present for E+P treatment relative to BL (p>0.100). Figure 2b shows individual scores across treatment condition for the percent of total sleep time in which oxygen saturation was <90%. Although overall minimum oxygen saturation levels were not significantly altered with either treatment, the treatments differentially impacted minimum oxygen saturation during NREM and REM sleep. Whereas E was associated with a trend to increased minimum oxygen saturation during REM sleep (Z=-1.75, p=0.080) and no change during NREM sleep, E+P

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Table 1—Participant Characteristics

<table>
<thead>
<tr>
<th>Subj</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Years From Last Menstruation</th>
<th>Daytime Sleepiness or Fatigue</th>
<th>Sleep Maintenance Insomnia</th>
</tr>
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<tr>
<td>1</td>
<td>47</td>
<td>25.7</td>
<td>1.6</td>
<td>Fatigue</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>26.6</td>
<td>12.0</td>
<td>Fatigue</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>29.3</td>
<td>1.5</td>
<td>Sleepy</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>25.5</td>
<td>8.0</td>
<td>Sleepy</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>25.3</td>
<td>8.0</td>
<td>Sleepy</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>18.9</td>
<td>10.0</td>
<td>Fatigue</td>
<td>+</td>
</tr>
<tr>
<td>Mean</td>
<td>56</td>
<td>25.2</td>
<td>6.8</td>
<td>—</td>
<td>—</td>
</tr>
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</table>

Table 2—Polysomnography Data and Respiratory Indices

<table>
<thead>
<tr>
<th>Sleep Architecture</th>
<th>Baseline</th>
<th>E+Pbo</th>
<th>E+Prog.</th>
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<tbody>
<tr>
<td>TST</td>
<td>381.3</td>
<td>391.1</td>
<td>356.2</td>
</tr>
<tr>
<td>SL</td>
<td>10.3</td>
<td>10.5</td>
<td>7.0</td>
</tr>
<tr>
<td>WASO (min)</td>
<td>83.9</td>
<td>91.8</td>
<td>83.5</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>80.9</td>
<td>79.3</td>
<td>78.5</td>
</tr>
<tr>
<td>Stage 1</td>
<td>7.0</td>
<td>7.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Stage 2</td>
<td>78.1</td>
<td>71.3</td>
<td>73.9</td>
</tr>
<tr>
<td>Stage 3 &amp; 4</td>
<td>1.3</td>
<td>2.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Stage REM</td>
<td>13.6</td>
<td>15.6</td>
<td>14.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measures of Respiration</th>
<th>Baseline</th>
<th>E+Pbo</th>
<th>E+Prog.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>22.7</td>
<td>12.2</td>
<td>16.2</td>
</tr>
<tr>
<td>NREM AHI</td>
<td>20.3</td>
<td>9.9</td>
<td>15.1</td>
</tr>
<tr>
<td>REM AHI</td>
<td>34.2</td>
<td>23.5</td>
<td>23.5</td>
</tr>
</tbody>
</table>

| Oxgenation              | Min O2 Sat (%) | 83.9 | 88.0 | 87.2 |
|                        | Min O2 Sat (%) | 84.0 | 88.6 | 88.6 |
|                        | Rem Min O2 Sat| 85.3 | 92.7 | 88.7 |
|                        | O2 Sat <90% (% of TST)| 6.7 | 0.6  | 2.9  |
|                        | NREM Sleep O2 Sat <90% | 7.1 | 0.4  | 8.3  |

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4Participants rate each evening the extent to which they have experienced each mood state on that day on a scale of 1 to 5: 1= very slightly or not at all; 2= a little; 3= moderately; 4= quite a bit; and 5= extremely.

5Baseline respiratory measurement were missing for two participants (S1 and S5) and were replaced by screening values.

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*S* p<0.05; *#* p<0.10
treatment was associated with a trend to increased minimum oxygen saturation during NREM sleep (Z=1.78, p=0.075) and no change during REM sleep.6

Treatment with E or E+P did not have a statistically or clinically significant impact on measures of sleep stage distribution or on PSG- or diary-based measures of sleep continuity. Means and standard deviations of PSG variables are summarized in Table 2 and those for diary-based sleep variables can be found in Table 3. Diary data revealed no significant change in daily mood, daytime sleepiness, or time spent napping. The two panels in Figure 3 display individual data on sleep-diary-based ratings of sleep quality and daytime sleepiness.

**DISCUSSION**

This progesterone placebo-controlled pilot study tested two hypotheses related to the impact of HRT on respiration during the sleep of postmenopausal women with SDB. The first hypothesis, that combined estrogen and progesterone is associated with a significant reduction in respiratory indices relative to BL, was partially supported. Treatment with E+P was associated an overall mean reduction of 8 respiratory events per hour of sleep, a moderate effect size (0.5). Absence of statistical significance was most likely a result of insufficient power to detect moderate effect sizes. Notably, half of the participants experienced significantly meaningful reduction in AHI on E+P, in that their AHI on E+P fell below the study entry criterion of 10 events per hour. Despite the documented soporific effects of micronized progesterone,6,37 administration of progesterone at bedtime did not result in increased daytime sleepiness in the present study.

The second hypothesis, that E+P is associated with a significantly lower AHI than E alone, was not supported by the data. To the contrary, AHI on E+P was higher than on E by an average of approximately 4 events per hour. In fact, the data revealed an unexpected robust decrease in AHI on E therapy. A statistically significant reduction in AHI relative to BL was observed with E treatment (effect size of 0.8). Estrogen also led to improvement in oxygenation during sleep, in that the percentage of time spent with oxygen saturation less than 90% was, on average, less than 1% on E treatment, compared with more than 6% at BL. This reduction, however, was not statistically significant, most likely because of insufficient power and because BL oxygen saturation was not very low. Overall, clinically meaningful improvements in SDB with E alone were observed in 3 of the 6 participants.

There are few published data on the impact of HRT on respiratory indices in postmenopausal SDB patients. Only one other published study has examined the impact of estrogen monotherapy on respiration during sleep.9 In this study, open-label treatment of 5 participants with estrogen alone resulted in reduced RDI relative to baseline.9 Similar to the present study, Keefe et al used a within-subjects design, in which participants were first treated with E alone for 3 to 4 weeks and then with E+P for 12 days. Unlike the present study, Keefe et al found a further reduction in AHI with the addition of a progestin in 4 of the 5 participants.8 Two methodologic differences likely explain the discrepancy in the observed impact of combined HRT relative to E alone. First, participants in the Keefe et al study had much higher BMI and greater disease severity. Secondly, the two studies used different treatment agents (i.e., medroxyprogesterone acetate vs. micronized progesterone and oral vs. transdermal estrogen). In addition, because both studies were based on very small sample sizes, the possibility needs to be considered that the results were specific to the samples. In particular, the continued reduction in AHI reported by Keefe and colleagues following the addition of a progestin was observed after one participant with a high AHI dropped out. The authors did not report the mean AHI for the remaining 4 participants when on E monotherapy, making it impossible to determine whether there was indeed a further reduction in AHI after a progestin was added to estrogen in these 4 women.

Data extracted from the study of Cistulli et al also suggest that respiration is improved by E+P.25 This group studied a mixed sample that included 9 women after spontaneous menopause, 4 of whom had an AHI above 80. Because their publication presented data from individual sub...

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**Table 3—Sleep Diary Data.**

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean</th>
<th>SD</th>
<th>E+Pbo Mean</th>
<th>SD</th>
<th>E+Prog. Mean</th>
<th>SD</th>
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<td><strong>Measures of Sleep</strong></td>
<td></td>
<td></td>
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<tr>
<td>Total sleep time (min)</td>
<td>435</td>
<td>20</td>
<td>443</td>
<td>18</td>
<td>437</td>
<td>23</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>8.6</td>
<td>7.0</td>
<td>11.0</td>
<td>6.3</td>
<td>17.6*</td>
<td>10.6</td>
</tr>
<tr>
<td>Number of awakenings</td>
<td>2.5</td>
<td>1.6</td>
<td>2.7</td>
<td>1.1</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>WASO (min)</td>
<td>23.8</td>
<td>24.7</td>
<td>28.1</td>
<td>17.9</td>
<td>19.3</td>
<td>16.8</td>
</tr>
<tr>
<td>Sleep quality (1-10)</td>
<td>5.9</td>
<td>2.2</td>
<td>4.6</td>
<td>1.9</td>
<td>6.3</td>
<td>1.6</td>
</tr>
<tr>
<td>How well rested (1-10)</td>
<td>5.2</td>
<td>2.9</td>
<td>4.6</td>
<td>2.1</td>
<td>5.7</td>
<td>1.4</td>
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<tr>
<td><strong>Mood Ratings</strong></td>
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<tr>
<td>PANAS Positive Affect</td>
<td>34.0</td>
<td>4.6</td>
<td>32.3</td>
<td>3.8</td>
<td>31.9</td>
<td>3.5</td>
</tr>
<tr>
<td>PANAS Negative Affect</td>
<td>12.4</td>
<td>1.0</td>
<td>11.6</td>
<td>3.7</td>
<td>12.6</td>
<td>3.9</td>
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<tr>
<td><strong>Daytime Sleepiness</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleepy Rating (1-5)</td>
<td>1.8</td>
<td>1.1</td>
<td>1.7</td>
<td>0.9</td>
<td>1.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Nap Time (min)</td>
<td>11.6</td>
<td>10.7</td>
<td>10.9</td>
<td>16.1</td>
<td>8.5</td>
<td>14.9</td>
</tr>
</tbody>
</table>

E+Pbo, estrogen plus pill placebo; E+Prog., estrogen plus progesterone; WASO = minutes awake after sleep onset; Sleep quality was measured on a 10-point Likert scale anchored at 1= very poor quality and 10= excellent quality; Rating of restfulness was measured on a 10-point Likert scale anchored at 1=very unfreshed and 10=very well rested; Sleepiness measured on a 5-point Likert scale anchored at 1=very, slightly or not at all sleepy and 5=extremely sleepy; PANAS (the Positive Affect and Negative Affect) was measured on a 5 point Likert scale. Positive Affect score is the sum of the 10 items on the Positive Affect Subscale and the Negative Affect score is the sum of the 10 items on the Negative Affect Subscale. *p<0.05.
jects, it was possible to extract the data for the remaining 5 participants with an AHI below 40. For this sub-sample, E+P treatment was associated with a reduction in the mean AHI, with an estimated effect size of approximately 0.8 relative to BL.

The clinical utility of HRT in the management of mild to moderate SDB in postmenopausal women is not clear. Unlike standard treatments for SDB, such as continuous positive airway pressure (CPAP) and bi-level therapy, HRT does not completely eliminate respiratory events during sleep. However, HRT does appear to markedly reduce AHI and to improve oxygenation during sleep. These benefits may have clinical significance in the management of patients with milder forms of SDB, who do not tolerate standard treatment with CPAP well. Each patients’ risk / benefit ratio will, however, need to be carefully evaluated given that the impacts of untreated SDB and of HRT on cardiovascular risk are in opposite directions. On the one hand, recent results from the WHI study indicate increased cardiovascular risk with continued treatment with HRT. On the other hand, there is increasing evidence that SDB is a risk factor for cardiovascular disease, and therefore its treatment might reduce this risk. These observations underscore the importance of making careful individualized decisions when considering the use of HRT.

There appear to be large individual differences in the impact of HRT on respiration in SDB patients during sleep. It has been reported that estrogen treatment increases the number of progesterone receptors in rats and, if it has a similar effect in humans, it might explain how variability in the bioavailability of estrogen might also influence the effect of combined estrogen and progesterone on respiration during sleep. Individual differences in the rate at which progesterone is converted into its active metabolites, pregnanolone and allopregnanolone, might also contribute to the observed difference in the impact of HRT on respiration during sleep. Individuals with an early peak of progesterone metabolism will have relatively little progesterone or its metabolites circulating in the latter part of the night when most REM-related apnea events occur. Progesterone’s muscle-toning effect is more likely to offset the effects of muscle atonia associated with REM in individuals with a later progesterone metabolite peak. It is for this reason important that future studies on the impact of HRT on sleep and respiration during sleep examine individual differences in the bioavailability of estrogen and progesterone prior to beginning the intervention. One limitation of the present study is the lack of complete plasma hormone data, which precluded examination of the relationship between bioavailability and the observed effect on respiration.

The mechanisms by which HRT might contribute to reduced AHI are not clear. Progesterone could exert its beneficial effects by reducing upper airway collapsibility by increasing genioglossus muscle tone and by its central action on CO2 receptors that can stimulate respiration during wakefulness. These physiologic effects, however, are unlikely to provide a sufficient explanation for the observed reduction in AHI during sleep on combined estrogen and progesterin, as studies on the impact of progesterone alone on respiration during sleep in SDB patients have yielded mixed results. There is evidence that estrogen’s effects on respiration in rats may be mediated indirectly through induction of progesterone receptors. If estrogen augments progesterone-receptor number in tissues involved in human respiration or in areas in the brain that control breathing during sleep, then this phenomenon might explain the observed trend towards improved respiration with E+P treatment relative to baseline. At the same time, the hypothesis that estrogen enhances progesterone’s effects on respiration would also predict that the E+P group would show a greater improvement than the E group. Analysis of our data indicates that this was not the case for any of the subjects, and indeed some subjects appeared not to do as well on E+P as they did on E alone. In short, we do not have a satisfactory explanation as to why estrogen was so powerful in reducing AHI and why the addition of progesterone attenuated the effects of estrogen. The challenge of future research, should these results be replicated, will be to increase our understanding of the effects of estrogen on respiration during sleep.

Several methodologic limitations need to be considered. One obvious limitation is the small sample size, which is particularly critical because of the large variability in the bioavailability of progesterone. Interpretations of the results need to take into account the fact that p-values and effect size estimates are less reliable with a small sample size. The small number of participants posed additional limitations. For example, it precluded controlling for treatment order effect through a counter-balance design. It is also important to note that because the study was designed to compare E alone with E+P, it did not include an estrogen placebo condition nor did it conceal from participants the fact that they were receiving an active treatment (estrogen). Consequently, it is impossible to discern the contribution of expectations of benefit and other non-specific therapeutic element to the observed benefit of estrogen. Together, these design issues limit the generalizability of our conclusion about the impact of estrogen alone on respiration during sleep. Finally, in order to avoid delay in the provision of standard treatment, this protocol was limited to one treatment cycle. It is, therefore, not clear whether the observed benefits of HRT on breathing during sleep will continue with long-term treatment. Future studies will need to address the important methodologic issues identified above, many of which can be resolved if a between-subjects design is used. Future research will need to study a sample large enough to allow exploration of the impact of individual dif-

![Figure 3a](image)

**Figure 3a**—Average subjective daily ratings of sleep quality across the four study phases. Ratings were done on a 1 to 10 Likert scale with 1=very poor and 10=excellent. BL=baseline, E+Pbo=estrogen plus pill placebo; E+Prog=estrogen plus progesterone. Baseline diary data are missing for S2.

![Figure 3b](image)

**Figure 3b**—Average subjective daily rating of daytime sleepiness across the four study phases. Ratings were done on a 1 to 5 scale as follows: 1=slightly or not at all; 2=slightly less; 3=moderately; 4=quite a bit; 5=extremely. BL=baseline, E+Pbo=estrogen plus pill placebo; E+Prog=estrogen plus progesterone. Baseline diary data are missing for S2.
ferences in the bioavailability of treatment on outcome and to monitor and control for the impact of sleep position on the severity of SDB at baseline and during treatment.

CONCLUSIONS

Further research on the impact of combined estrogen and progesterone on SDB is needed before its clinical utility can be determined. Beyond replication of the findings from this pilot study, future research should also examine the long term effects of HRT on respiration during sleep. Future research should also identify patients for whom HRT might be beneficial, with particular attention to issues related to hormone bioavailability.

REFERENCES