Effects of Continuous Positive Airway Pressure on Fatigue and Sleepiness in Patients with Obstructive Sleep Apnea: Data from a Randomized Controlled Trial

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Objectives: Complaints of fatigue are frequent in patients with obstructive sleep apnea (OSA); however, the impact of continuous positive airway pressure (CPAP) on fatigue remains unclear.

Methods: Fifty-nine men and women with OSA were randomly assigned to therapeutic or placebo CPAP in a double-blind fashion for a 3-week intervention period. Four outcome measures were assessed: (1) fatigue/vigor measured with the Multidimensional Fatigue Symptom Inventory—Short Form (MFSI-sf), the (2) fatigue and (3) vigor subscales of the Profile of Mood States—Short Form (POMS), and (4) the Epworth Sleepiness Scale (ESS). Data were analyzed using repeated-measures analysis of variance.

Results: Compared with patients receiving placebo CPAP, those patients treated with therapeutic CPAP showed significant reductions in the apnea-hypopnea index, as well as decreases in both measures of fatigue and increases in vigor (P values < 0.05). The beneficial effect of therapeutic treatment was most pronounced in patients with high levels of fatigue at study onset. Significant treatment effects in sleepiness scores were not observed in the entire sample (P > 0.05); however, in a subset of patients with excessive sleepiness at the onset of treatment, ESS scores were significantly reduced with use of therapeutic CPAP (P < 0.05).

Conclusions: Results suggest that 3 weeks of therapeutic CPAP significantly reduced fatigue and increased energy in patients with OSA. Therapeutic CPAP significantly reduced daytime sleepiness in patients who reported excessive sleepiness at the onset of treatment.

Keywords: Obstructive sleep apnea, continuous positive airway pressure, fatigue, vigor, energy, sleepiness

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to 50 kg/m². Potential participants were excluded if they had a history of heart, liver, or renal disease; diabetes; psychosis; narcolepsy; current alcohol or drug abuse; severe asthma; or cerebrovascular disease or were taking prescription medications. Women were excluded if pregnant. Patients who were taking hypertensive medications were withdrawn from their medications with permission of their physician and followed during a 3-week washout period while being monitored by a study physician. If blood pressure remained consistently below 170/105 mm Hg, subjects were entered into the study. The 2 subjects who were withdrawn from antihypertensive medications completed the washout period without incident.

Procedure
Potential participants contacted the lab and underwent an initial phone screening to determine eligibility. If it appeared that the subject met the inclusion criteria of the study, a preliminary OSA screening was conducted with an unattended home sleep study (Stardust home monitoring system, Respironics, Inc., Murrysville, PA). Subjects with an apnea-hypopnea index (AHI) of at least 10 were given a provisional diagnosis of OSA and were invited back to be assessed with a 1-night standard regimen of polysomnographic sleep monitoring conducted at the UCSD General Clinical Research Center Gillin Laboratory of Sleep and Chronobiology. Those participants who had an AHI of at least 10 on the in-laboratory study were diagnosed with OSA and randomly assigned to receive either therapeutic CPAP or the placebo CPAP in a double-blind fashion.

All participants then spent a second night in the sleep laboratory. Patients randomly assigned to receive therapeutic CPAP underwent standard CPAP titration. CPAP was started at a pressure of 4 cm H₂O and was increased by 1- to 2-cm H₂O increments based on the presence of apneas, hypopneas, snoring, or respiratory effort-related arousals. Titration was considered successful when all significant respiratory events stopped and the patient had spent at least 15 minutes of sleep in the final CPAP level.

Patients randomly assigned to the placebo-CPAP group underwent a mock-titration night. The placebo-CPAP system was a modified version of the sham CPAP. The placebo-CPAP consists of a modified nasal or full face (nasal oral) CPAP mask with 10 one-quarter-inch drill holes to allow free exchange of air during inhalation and exhalation, plus a pressure reducer placed in the CPAP tubing. With this system, the CPAP generator could be placed at any pressure to control for machine noise, but the pressure at the nose and mouth was 0.5 cm H₂O during exhalation and 0 cm H₂O during inhalation. Of importance to the placebo-CPAP blinding, the subject was able to feel a gentle breeze at the nose. To control for CPAP-blower noise, the pressure was set at 8 cm H₂O. In both treatment conditions, the CPAP systems were the same (ResMed S7 Elite CPAP with HumidAire 2i™ integrated heated humidifier; ResMed Corp. San Diego, CA). On the first night, the appropriate CPAP mask (therapeutic or placebo) was fitted, and the patient was trained on the use of the equipment.

After the titration night, patients in both groups were sent home with their assigned treatment equipment. Proper equipment use and setup was ensured by telephone calls and home visits by a sleep technician who was not involved in outcome assessments. The CPAP units each contained a hidden compliance clock that measured the amount of time the equipment was used at the designated pressure. Compliance data were downloaded by the sleep technician at the end of the treatment period and were used to determine the average number of hours CPAP was used over the study period.

Upon completion of the 3-week treatment period, patients returned to the sleep laboratory for a final polysomnogram, performed while the patients were using their assigned therapy. All questionnaires were also repeated at this time.

Sleep Monitoring
For all overnight polysomnography studies, electroencephalography, electrocardiography, electrooculography, chin and tibialis anterior electromyography, pulse oximetry, nasal-oral airflow by nasal cannula pressure transducer and thermistor, and thoracic and abdominal respiratory effort were recorded on a Grass Heritage digital polysomnograph (Model PSG36-2, Astro-Med, Inc., West Warwick, RI). Recordings were scored by a trained sleep technician according to criteria from Rechtschaffen and Kales. Apneas were defined as decrements in airflow of at least 90% from baseline for a minimum of 10 seconds. Hypopneas were defined as decrements in airflow of at least 50% but less than 90% from baseline for a minimum of 10 seconds. Significant oxyhemoglobin desaturations were defined as transient drops in oxyhemoglobin saturation by at least 3% from baseline. The total number of apneas and hypopneas per hour of sleep were calculated to yield the AHI. Participants with an AHI of 10 or more during the attended polysomnogram were considered to have OSA and were included in the study.

Sleepiness, Fatigue, and Vigor
Questionnaire data were obtained prior to study randomization and after the 3-week intervention period, prior to the final polysomnogram. Questionnaires were administered by a research coordinator who was blinded to treatment condition.

The Multidimensional Fatigue Symptom Inventory—Short Form
The Multidimensional Fatigue Symptom Inventory—Short Form (MFSI-sf) is a 30-item self-report measure designed to assess multidimensional aspects of fatigue. Items are rated on a 5-point scale, and respondents report how true each statement was for them during the previous week (0 = not at all; 4 = extremely). Scores are summed to obtain subscale scores that include general fatigue, emotional fatigue, physical fatigue, mental fatigue, and vigor. The vigor subscale score is subtracted from the sum of the 4 fatigue subscales to yield a total fatigue score. Subscale scores range from 0 to 24, and MFSI-sf total scores range from -24 to 96, with higher scores indicating more fatigue. MFSI-sf total scores above 0.85 represent significant fatigue. The MFSI-sf has been used extensively in multiple patient populations, including those with OSA. In this sample, it showed good internal consistency (α = 0.84).

The Profile of Mood States
The Profile of Mood States (POMS) is an established measure of psychological distress, which has shown high levels of
The Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a well-validated questionnaire that assesses the likelihood of falling asleep in a variety of common situations. The scale consists of 8 items that are self-rated on a 4-point scale (0 = would never doze to 3 = high chance of dozing). Scores range from 0 to 24, with higher scores indicating more sleepiness. In this sample, the scale showed good internal consistency (α = 0.88).

Data Analysis

A P value 0.05 or less was considered significant, and all testing was 2 tailed. Statistical analyses were performed using the SPSS statistical software package (SPSS for Windows 17.0; SPSS Inc.; Chicago, IL). Student t tests were used to compare groups on baseline characteristics with continuous outcome measures, χ² tests were used to compare multivariate outcome measures. Differences between the 2 groups over time were assessed using repeated-measures analysis of variance (ANOVA). This analysis allowed testing for a main effect of treatment (therapeutic CPAP vs placebo CPAP), a time effect (prior to treatment and after 21 days of treatment), and the interaction of time by treatment. A time effect alone implies that the treatment effects were nonspecific (i.e., placebo effects). A treatment-by-time interaction implies that subjects responded to a specific treatment over time with a significant response.

RESULTS

Recruitment Profile and Patient Characteristics

The recruitment profile is shown in Figure 1. Patient characteristics are presented in Table 1. A total of 59 patients (29 therapeutic CPAP and 30 placebo CPAP) completed treatment. The groups did not significantly differ on baseline characteristics, including age, body mass index, sex, race or ethnicity, daytime sleepiness, fatigue, vigor, or AHI. The groups also did not differ in the number of nights they used the CPAP treatment during the course of the study (therapeutic CPAP = 18.82 ± 1.98 vs placebo CPAP 18.73 ± 2.68; P = 0.89). However, there was a significant difference in how many hours the groups used the CPAP each night. The therapeutic CPAP group used the treatment for an average of 5.46 ± 1.09 hours per day over the 3-week treatment period. In contrast, the placebo-CPAP group used treatment for longer periods each night, an average of 6.59 ± 1.40 hours per day (P = 0.01).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 30)</th>
<th>Treatment (n = 29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.30 ± 9.04</td>
<td>48.14 ± 9.69</td>
<td>0.95</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.47 ± 3.89</td>
<td>30.57 ± 5.95</td>
<td>0.11</td>
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<td>Sex</td>
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<td>Male</td>
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</tr>
<tr>
<td>Female</td>
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<td>4</td>
<td></td>
</tr>
<tr>
<td>Race</td>
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<td>0.57</td>
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<td>Asian</td>
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<td>0</td>
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</tr>
<tr>
<td>Caucasian</td>
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<td>26</td>
<td></td>
</tr>
<tr>
<td>Other</td>
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<td></td>
</tr>
<tr>
<td>ESS baseline</td>
<td>10.93 ± 5.53</td>
<td>9.26 ± 5.11</td>
<td>0.26</td>
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<tr>
<td>MFSI-sf baseline</td>
<td>5.77 ± 14.96</td>
<td>8.76 ± 16.84</td>
<td>0.47</td>
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<tr>
<td>POMS Fatigue</td>
<td>6.27 ± 5.05</td>
<td>7.17 ± 6.30</td>
<td>0.54</td>
</tr>
<tr>
<td>POMS Vigor</td>
<td>15.33 ± 6.69</td>
<td>14.28 ± 7.39</td>
<td>0.57</td>
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<tr>
<td>AHI Baseline</td>
<td>31.67 ± 18.72</td>
<td>38.64 ± 24.28</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. CPAP refers to continuous positive airway pressure; BMI, body mass index; ESS, Epworth Sleepiness Scale; MFSI-sf, Multidimensional Fatigue Symptom Inventory—short form; POMS, Profile of Mood States; AHI, apnea-hypopnea index.
Effect of Treatment on Daytime Fatigue and Vigor

Significant time-by-treatment interactions were observed for the MFSI-sf total score (P = 0.02) and the POMS fatigue subscale (P = 0.03). When compared with the placebo-CPAP group, individuals in the therapeutic-CPAP group evidenced a significant reduction in MFSI-sf total scores (see Figure 2) and POMS fatigue scores (see Figure 3). A significant time-by-treatment interaction was also observed for vigor (P = 0.02), with the therapeutic-CPAP group reporting increased energy when compared with the placebo-CPAP group (see Figure 4).

We also investigated whether there were fatigue and energy changes in the placebo-CPAP group (i.e., a placebo effect). Significant reductions in fatigue were not observed in the placebo-CPAP group (P values > 0.36), nor did the placebo group demonstrate changes in energy/vigor (P = 0.20).

Effect of CPAP on Sleepiness

Significant time-by-treatment differences were not observed for the ESS scores (P > 0.05). Because the literature suggests that, the sleepier the patients feel before CPAP intervention, the greater their response to treatment, we split our sample using the ESS cutoff for excessive sleepiness (ESS ≥ 9). The therapeutic-CPAP and placebo-CPAP groups did not differ significantly in terms of the proportion of excessively sleepy (55.9%) versus not sleepy (44.1%) participants (χ² = 0.06, P = 0.82).
Table 2—Pretreatment and posttreatment data in patients with excessive sleepiness and fatigue at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo CPAP</th>
<th>Therapeutic CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Posttreatment</td>
</tr>
<tr>
<td>ESS (\text{a}^)</td>
<td>14.8 ± 4.0</td>
<td>14.1 ± 3.9</td>
</tr>
<tr>
<td>MFSI-sf (\text{b}^)</td>
<td>15.2 ± 12.5</td>
<td>12.5 ± 14.4</td>
</tr>
<tr>
<td>POMS fatigue (\text{c}^)</td>
<td>9.9 ± 4.0</td>
<td>9.0 ± 5.3</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. CPAP refers to continuous positive airway pressure; ESS, Epworth Sleepiness Scale; MFSI-sf, Multidimensional Fatigue Symptom Inventory—short form; POMS, Profile of Mood States. \(\text{a}^\)Time-by-treatment interaction \(P < 0.05.\)

EXPLORATORY ANALYSES

As noted above, CPAP was effective in reducing sleepiness in those subjects with high levels of sleepiness before commencing treatment. We next investigated whether this finding was also true with regard to fatigue. First, we investigated changes in the MFSI-sf, stratifying individuals as either fatigued or nonfatigued based on the MFSI-sf clinical cutoff score for fatigue (0.85). The proportion of excessively fatigued (59.3%) versus not fatigued (40.7%) participants did not differ significantly between therapeutic- and placebo-CPPA groups \((\chi^2 = 0.18, P = 0.67).\) To test for a specific effect of treatment in the high- and low-fatigued groups, we conducted a repeated-measure ANOVA with MFSI-sf scores as the outcome measure. There was a significant time-by-treatment effect in the fatigued group \((F_{1,21} = 4.42, P = 0.04, \eta^2 = 0.12);\) those who were treated with therapeutic CPAP had significantly reduced MFSI-sf scores, in comparison with those treated with placebo CPAP (see Table 2). The time-by-treatment interaction in the nonfatigued group was not significant \((F_{1,24} = 0.88, P = 0.36, \eta^2 = 0.04).\)

A similar story emerged when the POMS fatigue scale was used as the outcome measure. We performed a median split, breaking the groups into high (POMS ≥ 6) and low (POMS < 6) fatigue groups and conducting a repeated-measure ANOVA with POMS fatigue scores as the outcome measure. Again, therapeutic-CPAP and placebo-CPAP groups did not differ significantly in terms of the proportion of excessively fatigued (47.5%) versus not fatigued (52.5%) participants \((\chi^2 = 0.85, P = 0.36).\) Results of the ANOVA showed a significant time-by-treatment effect in the fatigued group \((F_{1,26} = 8.34, P < 0.01, \eta^2 = 0.24),\) whereby the therapeutic-CPAP group had significantly reduced POMS fatigue scores in comparison with the placebo group (see Table 2). In contrast, the time-by-treatment interaction in the nonfatigued group was not significant \((F_{1,29} = 0.60, P = 0.44, \eta^2 = 0.02).\)

DISCUSSION

Individuals with OSA experience significant sleepiness and fatigue. The aim of this study was to identify whether treatment with therapeutic CPAP was associated with improvement in sleepiness, fatigue, and vigor above and beyond nonspecific placebo effects. Findings revealed that, over a 3-week intervention period, treatment with therapeutic CPAP reduced fatigue and increased energy. In fact, at the end of treatment, mean scores from the therapeutic-CPAP group indicated that participants were no longer suffering from clinically significant levels of fatigue.\(^{14}\) The convergence of results, demonstrated by decreases in two independent measures of fatigue and an associated increase in vigor, lend support to the finding that CPAP treatment significantly decreases fatigue and increases energy in patients with OSA. We also observed that individuals who were excessively fatigued at the study onset received greater therapeutic benefit from treatment with CPAP, as compared with those who were not experiencing clinically significant levels of fatigue at study onset.

Several studies have shown large changes in sleepiness in patients with OSA treated with therapeutic CPAP. There are two main differences between those studies and our own. First, investigations that have observed significant reductions in sleepiness recruited participants who were excessively sleepy.\(^{7}\) Our patients’ ESS scores (mean = 10.2) were 35% to 40% lower than the scores of patients with OSA who have been recently studied.\(^{18-20}\) Second, studies that have observed reductions in sleepiness have generally employed a longer treatment protocol than did our study, raising the possibility that longer treatment may be necessary to reduce sleepiness.\(^{18-20}\) Although we could not lengthen our treatment protocol, we did investigate whether initial sleepiness level was predictive of treatment response. We found that excessively sleepy subjects treated with therapeutic CPAP showed a significant reduction in ESS scores, compared with those subjects treated with placebo CPAP. No significant changes in sleepiness were observed in participants who were not excessively sleepy at the start of treatment. These results lend support to previous work suggesting that, the sleepier patients are at the onset of treatment, the greater their sleepiness scores decline over time.

The groups were comparable in terms of days that they used CPAP during the study period, but the placebo group used the CPAP for more hours per night. This may have been a chance observation. On the other hand, one could also speculate that the CPAP group experienced such benefit from treatment that they did not feel it necessary to be as conscientious about compliance. Nonetheless, the compliance level in both groups was good, exceeding 4 hours per night.

We acknowledge several limitations of the current investigation. First, the population under study was free from other illnesses. Although all participants suffered from OSA, they may not represent the typical patients at a sleep medicine center, who are more likely to have comorbidities, such as diabetes or symptomatic coronary disease. Our patients, nonetheless, had unquestionable and moderately severe OSA (AHI > 30). Second, our treatment period of only 3 weeks was relatively short.

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Previous work from our group failed to discern a specific beneficial effect of CPAP treatment on fatigue levels after 1 and 2 weeks of treatment. On the other hand, this study found clear and compelling evidence that a 3-week CPAP intervention led to significant improvements of fatigue and sleepiness. The convergent validity of these observations is striking, given that they were supported by multiple measures (MFSI-sf fatigue, POMS fatigue, POMS vigor, and ESS). Current planned National Institutes of Health initiatives to examine long-term effects of CPAP in a double-blind fashion will be able to determine if these beneficial effects of CPAP persist in longer-term trials and in patients with OSA who have additional comorbidities.

Finally, we are left with questions about what mechanisms underlie the observed changes in fatigue. A possible theory is that CPAP reduces inflammation in patients with OSA, which thereby impacts fatigue. Patients with OSA have increased levels of local (upper airway) and systemic inflammation. Increases in inflammatory markers in individuals with OSA have been related to elevated fatigue. In turn, CPAP used continuously for more than 4 hours per night has been shown to reduce markers of inflammation. A logical next step in this research would involve extended studies focused on the long-term use of CPAP and associated measures of inflammation and fatigue.

In summary, patients with OSA who received therapeutic CPAP (vs placebo) had significant reductions in fatigue and reported improved vigor over a 3-week treatment period. CPAP appeared to be especially beneficial in reducing fatigue in those who were excessively fatigued or sleepy before treatment.

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DISCLOSURE STATEMENT
This was not an industry supported study. Dr. Ancoli-Israel has consulted for and/or been on the advisory board of Ferrering Pharmaceuticals, GlaxoSmithKline, Merck, NeuroVigil, Neurocrine, Pfizer, Respironics, Sanofi-Aventis, Separcor, and Schering-Plough. She has received research support from Separcor and Lifebook. Dr. Dimsdale has received research support from Separcor. The other authors have indicated no financial conflicts of interest.

REFERENCES