The Effect of CPAP in Normalizing Daytime Sleepiness, Quality of Life, and Neurocognitive Function in Patients with Moderate to Severe OSA

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Study Objectives: The study aimed to document the neurobehavioral outcomes of patients referred to and treated by a sleep medicine service for moderate to severe obstructive sleep apnea (OSA). In particular, we aimed to establish the proportion of patients who, while appearing to have optimal continuous positive airway pressure (CPAP) adherence, did not normalize their daytime sleepiness or neurocognitive function after 3 months of CPAP therapy despite effective control of OSA.
Design: Multicenter clinical-effectiveness study.
Setting: Three academic sleep centers in Australia.
Participants: Patients referred to a sleep medicine service with moderate to severe OSA (n = 174).
Intervention: CPAP.
Measurements and Results: Participants were assessed pretreatment and again after 3 months of CPAP therapy. At the beginning and at the conclusion of the trial, participants completed a day of testing that included measures of objective and subjective daytime sleepiness, neurocognitive function, and quality of life. In patients with symptomatic moderate to severe OSA (i.e., apnea-hypopnea index > 30/h), we found a treatment dose-response effect for CPAP in terms of Epworth Sleepiness Scale scores (P < 0.001). Several key indexes of neurobehavior (e.g., Functional Outcomes of Sleep Questionnaire, Epworth Sleepiness Scale) currently used to assess treatment response failed to normalize in a substantial group of patients after 3 months of CPAP treatment, even in those who were maximally compliant with treatment. Forty percent of patients in this trial had an abnormal Epworth Sleepiness Scale score at the conclusion of the trial. In addition, we showed no dose-response effect with the Maintenance of Wakefulness Test, raising doubts as to the clinical utility of the Maintenance of Wakefulness Test in assessing treatment response to CPAP in patients with OSA.
Conclusions: Our study suggests that a greater percentage of patients achieve normal functioning with longer nightly CPAP duration of use, but a substantial proportion of patients will not normalize neurobehavioral responses despite seemingly adequate CPAP use. It is thus crucial to adequately assess patients after CPAP therapy and seek alternate etiologies and treatments for any residual abnormalities.
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CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) HAS BEEN SHOWN TO REDUCE DAYTIME SLEEPINESS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA (OSA) and is widely accepted as the most efficacious therapy for OSA. Patel and colleagues performed a meta-analysis showing that CPAP reduced the Epworth Sleepiness Scale (ESS) score an average of 2.9 points more than did placebo (P < 0.001) in patients with OSA. Patients with moderate to severe OSA had a greater fall in ESS than did those with mild OSA.[1]

What is less well understood is the dose-response relationship of CPAP treatment in patients with OSA and the proportion of patients who return to normal neurobehavioral function after CPAP therapy. These are important questions because it is known that CPAP adherence varies widely among patients.[2] For

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example, in an early study, Weaver et al. reported that, among 32 patients using CPAP, half were consistent users, applying CPAP on more than 90% of nights for an average of 6.2 hours per night, whereas the other half were intermittent users who had a wide range of daily use, averaging 3.5 hours per night.[3] In addition, although many patients present with excessive daytime sleepiness (EDS), this is a relatively nonspecific symptom.[4] In the Sleep Heart Health study, the percentage of subjects with EDS, defined as an ESS score greater than 10, was increased from 21% in subjects with an AHI of less than 5 to 35% in those with an AHI of at least 30. Thus, many people without OSA were still subjectively reporting EDS.[5] It is likely that, in a proportion of patients with OSA, sleep apnea may not be the dominant cause of sleepiness, and, thus, CPAP therapy may only partially improve EDS. In a population-based study, Bixler and colleagues[6] found that depression was the most significant risk factor for EDS, followed by, in decreasing levels of importance, body mass index, age, typical sleep duration, diabetes, smoking, and finally OSA. The same group noted in an earlier study that obesity itself may be associated with EDS independent of OSA.[7-9]

Finally, recent evidence suggests that OSA may lead to permanent structural brain abnormalities.[9,10] If these abnormalities

contribute to the neurobehavior deficits found in patients with OSA, symptoms and cognitive function may not be fully reversible with CPAP therapy, even if adherence is optimal.

Weaver et al. assessed quality of life and subjective and objective sleepiness measurements before and after CPAP therapy in a group of patients with severe OSA. Neurocognitive tests were not part of their study design. They found a linear CPAP usage (dose) versus outcome response curve for objective and subjective sleepiness measures, but the curve flattened at CPAP use of 7 hours per night for quality-of-life measures. The authors also noted that, even among those patients using CPAP for more than 7 hours per night, at 3 months, only 30% of patients had normal results on the multiple sleep latency test (MSLT) and only 50% had normal results on the Functional Outcome of Sleep Questionnaire (FOSQ).[11] Thus, it appears that even the most optimally treated patients with OSA may not experience a complete reversal of daytime symptoms and functional abnormalities.[12] Zimmerman and colleagues[13] reported a similar finding with verbal memory. They found a dose-response relationship between the level of CPAP adherence and the extent of improvement in verbal memory scores after 3 months among 58 memory-impaired patients with OSA, but approximately a third of patients who had CPAP adherence levels greater than 6 hours per night did not have normal verbal memory scores.

Although dose-response relationships are expected, these data support that there are important differences in dose-response sensitivity to treatment and the degree of normalization among key clinical outcomes. It is also likely that some tests used to assess treatment outcomes in OSA are more sensitive to change than are others. Given that clinical decisions must ultimately be guided by a firm understanding of the dose-response relationships in the key clinical outcome measurements, such as EDS, quality of life, and neurocognitive performance the present study was designed to further explore the impact of CPAP adherence on clinical outcomes in OSA. We investigated patients with moderate to severe OSA, similar to the population studied by Weaver and colleagues, but expanded the number of daytime functional measures to include several tests of cognition and measures of general, as well as disease-specific, quality of life. We also explored the relationship between CPAP use and outcomes on the Maintenance of Wakefulness Test (MWT).

METHODS

The measurements reported in this study were obtained during the course of a randomized, controlled, open-label clinical trial, the main results of which have been reported previously.[14] Patients were recruited at 3 separate sleep medicine services, the Adelaide Institute for Sleep Health (Adelaide, SA, Australia), Alfred Hospital (Melbourne, Victoria, Australia), and John Hunter Hospital (Newcastle, NSW, Australia). Approval was granted by the ethics committee at each site, and the study was registered with the Australian Clinical Trials Registry (ID 012605000064606).

Participants

Referrals to the sleep medicine services at all 3 sites were reviewed. Patients referred with a clinical suspicion of OSA were interviewed to assess their eligibility for the trial. Inclusion criteria were (1) an ESS score of at least 8, (2) a history of snoring "most nights" or "every night," (3) age 18 to 75 years, and (4) the patient was willing to try CPAP. We excluded patients with (1) unstable cardiovascular diseases (e.g., recent unstable angina, myocardial infarction, stroke, or transient ischemic attack within the previous 6 months or severe left ventricular failure), (2) neuromuscular disease affecting or potentially affecting respiratory muscles, (3) moderate to severe respiratory disease (i.e., breathlessness affecting activities of daily living) or documented hypoxemia or awake SaO_2 less than 92%, or (4) psychiatric disease that limited the ability to give informed consent or complete the study. Patients were recruited between March 2004 and September 2006 and followed for 3 months after randomization to place.

Interventions

All patients who met these criteria and consented to participate in the study had overnight home oximetry (Masimo Radical oximeter, Masimo, Irvine, CA). The oximeter was set to average, acquire, and store finger SaO_2 data at 2-second intervals. Masimo oximetry data were downloaded using Download 2001 software (Stowood Scientific, Oxford, UK), and greater than 2%, greater than 3%, and greater than 4% O_2 desaturation dip rates were computed. Home oximetry was performed on all trial participants; the oximetry had been validated against in-laboratory polysomnography, as described in a previous study.[14] Patients were eligible for inclusion in this study if their SaO_2 desaturation rate exceeded twenty-seven > 2% dips per hour.

Polysomnography was performed on the 50% of patients, who were randomly selected for a sleep study, and included a standard sleep montage: electroencephalography, electromyography, electrooculography, and respiratory signals of thoracic and abdominal effort and their sum (inductance coils), nasal airflow (pressure transducer) and oximetry. Polysomnography records were transferred to the Adelaide site for scoring by a single BRPT-registered and experienced sleep technician. Sleep architecture was scored in the standard fashion,[15] and sleep apneas and hypopneas were scored using agreed-upon international standards and definitions.[16,17]

Polysomnography studies were conducted using Compumedics E Series equipment (Melbourne, Australia) at the Adelaide and Melbourne sites. The Newcastle site used Sensormedics equipment (Florida, USA) and transferred data to an EDF file to enable conversion to a Compumedics file for review.

The 2 arms of care in the trial were Model A (nurse led) and Model B (physician led). Detailed information about the protocols in Models A and B have been published previously.[14] Briefly, all patients had overnight oximetry, but only patients randomly assigned to Model B had polysomnography. All patients were treated with CPAP (S6 Elite lightweight, ResMed), with optional humidifier; records from both groups of patients were reviewed by an experienced nurse at 1 and 3 months. CPAP adherence was measured objectively by a built-in CPAP meter and daily average adherence calculated for the 3-month duration of the trial. The investigation and management of these 2 arms of care were conducted over equal time periods.

Outcome Measures

ESS scores were determined before and after 3 months of CPAP therapy.[18,19]

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Short Form 36

The Short Form 36 (SF-36) score has been used widely in OSA studies.[20-22] Subscales in the SF-36 of mental health and vitality were separately analyzed because these have been shown to be the most sensitive to CPAP therapy.[22]

The FOSQ

Patients completed the FOSQ before and after CPAP treatment. The FOSQ is a sleep-specific self-report questionnaire designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living. It has excellent internal validity and test-retest reliability.[23]

The MWT

The MWT[24] was performed only at the conclusion of the study. Normal values for the MWT were based on a study from our laboratory to establish normative values for a group of individuals from the community who did not have sleep disordered breathing and in whom the mean sleep latency to the first epoch of unequivocal sleep during the 40-minute trial (MWT) was 36.9 ± 5.4 minutes. The lower normal limit, defined as 2 SD below the mean, was therefore 26.1 minutes.[24] Specific details of the MWT testing procedure are detailed in the supplemental material.

Neurocognitive testing

Detailed neurocognitive testing before and after 3 months of CPAP was conducted using Brain Resource Company Integneuro testing via a touch-screen computer with a linked headphone set to provide instructions (BRC, Sydney, Australia). Because the testing process required some manual dexterity and significant comprehension of English, some patients were excluded from the neurocognitive testing on the basis of the following exclusion criteria: (1) previous significant head injury (loss of consciousness of more than 15 minutes in the last 5 years), (2) illicit drug or alcohol abuse (more than 8 standard drinks per day on most or all days of the week), (3) significant active psychiatric illness (e.g., major depression, active psychosis), (4) manual-dexterity problem (e.g., broken arm or hemiplegic and thus unable to perform tests), and (5) English not the primary language spoken at home.

Key data such as age, sex, and years of education were collected to enable comparison with a BRC database of matched controls.[25] The tests performed as part of the assessments of patient outcomes were different that the baseline tests to limit the potential for learning effects. Representative neurocognitive parameters from each domain of neurocognitive function were chosen as follows: verbal recall, choice reaction time, and executive maze errors and time to completion of the executive maze. More details regarding individual tests are presented in the supplemental material. These tests were selected from 58 available measurements because they are representative of the key neurocognitive domains previously reported to be affected by OSA,[26,27] namely, verbal memory, executive function, and vigilance. Overall pre-CPAP and post-CPAP results were compared with data from a control group matched for age, sex, and years of education; pre-CPAP and post-CPAP effects were examined as a function of CPAP compliance category for each of the selected tests.

All of the questionnaires and measurements were administered by research assistants who had no involvement in the clinical care of the patients.

Table 1— Characteristics of 174 patients at baseline

Characteristic	Results
Men	74.9
Age, y	50.1 ± 12.0
BMI, kg/m²	34.7 ± 6.8
Weight, kg	105.2 ± 22.0
Height, cm	174.1 ± 8.9
Neck circumference (cm)	44.1 ± 4.2
ODI, dips/h	
≥ 2%	50.9 ± 24.8
≥ 3%	36.2 ± 22.1
≥ 4%	28.0 ± 21.4
SaO$_2$ nadir, %	73.2 ± 13.8
ESS, score	13.4 ± 4.0
FOSQ, total score	14.9 ± 2.6
SF-36, total score	99.0 + 8.6
Nightly CPAP duration, h	4.3 ± 2.7

With the exception of the proportion of men in each group, all values are mean ± SD. BMI refers to body mass index; ODI, oxygen desaturation index; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; CPAP, continuous positive airway pressure.

Statistical Methods

Patients were grouped into average nightly CPAP compliance categories of 2 or fewer hours, more than 2 but less than 4 hours, at least 4 but less than 5 hours, at least 5 hours but less than 6 hours, at least 6 but less than 7 hours, and 7 or more hours per night. To test for differences in the distribution of patients between CPAP compliance categories in groups A versus B, χ^2 tests were used. Pre-CPAP versus post-CPAP treatment effects, and the effect of compliance category on the various outcome measures, were examined using analysis of variance for repeated measures, with treatment as a within-subject repeated factor and compliance category (grouped according to nightly hours of use) as a between-subject factor. Where applicable, treatment effects within compliance category subgroups were identified on the basis of non overlapping 95% confidence limits. Neurocognitive measures were compared between age, sex, and years of education-matched controls from a database of more than 5000 people[25] and patients with OSA before and after CPAP treatment using independent-sample t tests adjusted for multiple comparisons using the Dunn-Sidak procedure. Values are reported as mean ± SEM, unless otherwise indicated. P values if less than 0.05 were considered significant.

RESULTS

Baseline characteristics of the patients are shown in Table 1. Patients were generally obese, middle aged, and male and, thus, typical of clinical populations of patients with moderate to severe OSA. The oxygen desaturation index was consistent with moderate to severe OSA, and there was significant self-reported sleepiness. In the 95 patients who were randomly assigned to the specialist-led arm of the study, polysomnography revealed a mean (± SEM) apnea-hypopnea index (AHI) of 67.9 ± 2.8 events per hour.
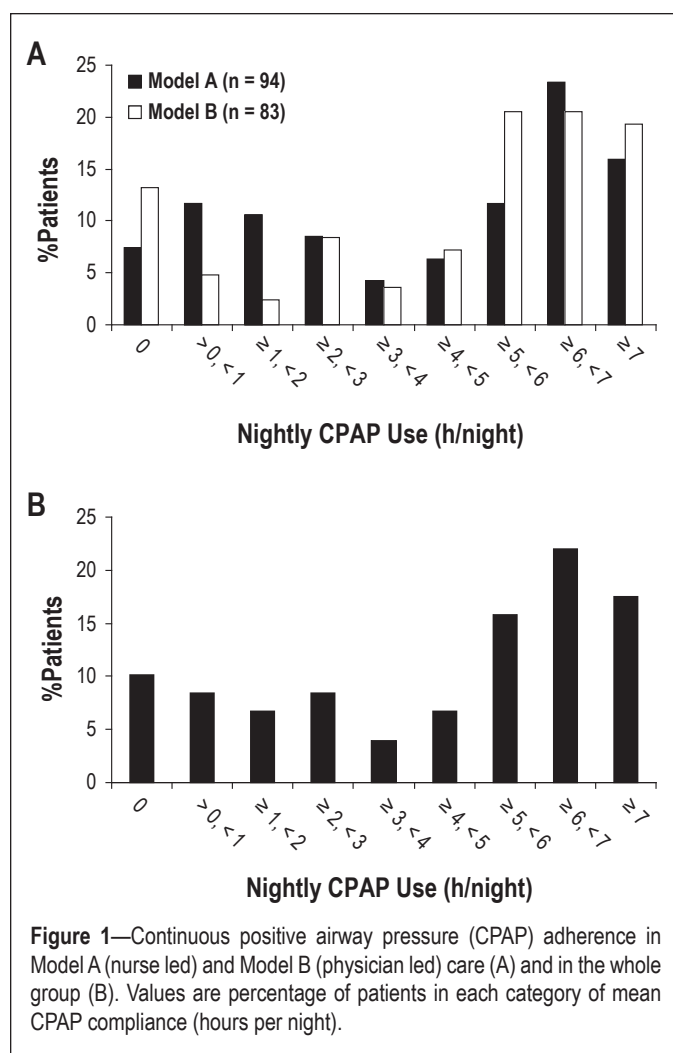
Figure 1—Continuous positive airway pressure (CPAP) adherence in Model A (nurse led) and Model B (physician led) care (A) and in the whole group (B). Values are percentage of patients in each category of mean CPAP compliance (hours per night).

CPAP Adherence

The percentages of patients within each hour of CPAP use per night category in the 2 models of care and in the total sample are shown in Figure 1. As might be expected, there was considerable variability in CPAP adherence, with a coefficient of variation of CPAP compliance in excess of 50%. There were no significant differences in CPAP compliance or in the distribution of patients between compliance categories between Model A (nurse led) and Model B (physician led), such that data from both groups were combined for all remaining analyses.

ESS Scores

The ESS showed substantial and dose-dependent improvement following CPAP treatment (P < 0.001, Figure 2A), with significantly greater improvement in more-adherent patients (compliance and treatment by compliance effects P = 0.018 and P = 0.004 respectively). Of the patients who used CPAP for more than 7 hours per night, 80.6% had a normal ESS score after treatment (Table 2), leaving 1 in 5 patients with abnormal ESS values despite optimal CPAP compliance. A smaller proportion (52.4%) of those using CPAP for between 2 and 4 hours per night reported normal ESS values after treatment. Across the whole patient cohort, only 59.5% exhibited a normal ESS score after treatment.

Among those who had abnormal ESS scores (≥ 10) before treatment, only 48% had normal ESS scores after 3 months of treatment, and only 66% of those who used CPAP for more than 5 hours per night over the 3 months and had abnormal ESS values at baseline had a normal ESS score at the conclusion of the trial (Figure 3 and Table 2).

The MWT

Approximately 70% of patients exhibited normal mean sleep latencies (> 26.1 min) on the MWT after treatment, and there was no effect of CPAP-adherence category on MWT results (P = 0.36, Figure 2B).

The FOSQ

The FOSQ scores showed significant improvements after treatment in all domains (activity, vigilance, intimacy, general productivity, social outcome, and total score, all P < 0.001). The FOSQ total and activity-level scores showed significant treatment-by-compliance interactions (P = 0.021 and P = 0.002 respectively, Figure 2C), indicating greater improvements in more-adherent patients. There was a similar trend in general productivity (P = 0.053) but no statistically significant compliance effects in other domains. In the absence of published normative data for the FOSQ,[11] a cutoff value of 17.9 or greater, as described by Weaver et al. (based on unpublished normative data), was used. Using this cutpoint, only 35% of all patients had normal FOSQ scores after treatment (Figure 3 and Table 2).

The SF-36

Of the SF-36 subscales, only vitality showed significantly greater improvements in more-adherent patients (treatment-by-compliance category interaction P = 0.006, Figure 2D), although role-physical and role-emotional approached statistical significance (P = 0.051 and P = 0.062, respectively).

Neurocognitive Data

Thirty three of 174 patients eligible were excluded as a result of the 5 additional exclusion criteria relevant to this aspect of the study, with a complete dataset collected in 141 patients. The most common reason for exclusion was that English was not the primary language spoken at home. Overall pretreatment and posttreatment results were compared with the control group matched for age, sex, and years of education (Table 3), and pretreatment versus posttreatment effects were examined as a function of CPAP-compliance category for each of the selected tests (e.g., Figure 4). Verbal memory and executive function tests showed significant improvement after 3 months of CPAP (all P < 0.001), but vigilance (as assessed by average reaction-time measurement) was not statistically significantly improved after CPAP (Table 3). Although there were statistically significant overall treatment effects in most of the neurocognitive measures examined, there were no adherence category or treatment-by-adherence category interaction effects in any measure.

DISCUSSION

The 2 main findings of this study are that (1) neurobehavioral responses to CPAP in patients with moderate to severe OSA varied markedly depending on the particular test used to measure the response and (2) although there was a treatment dose-
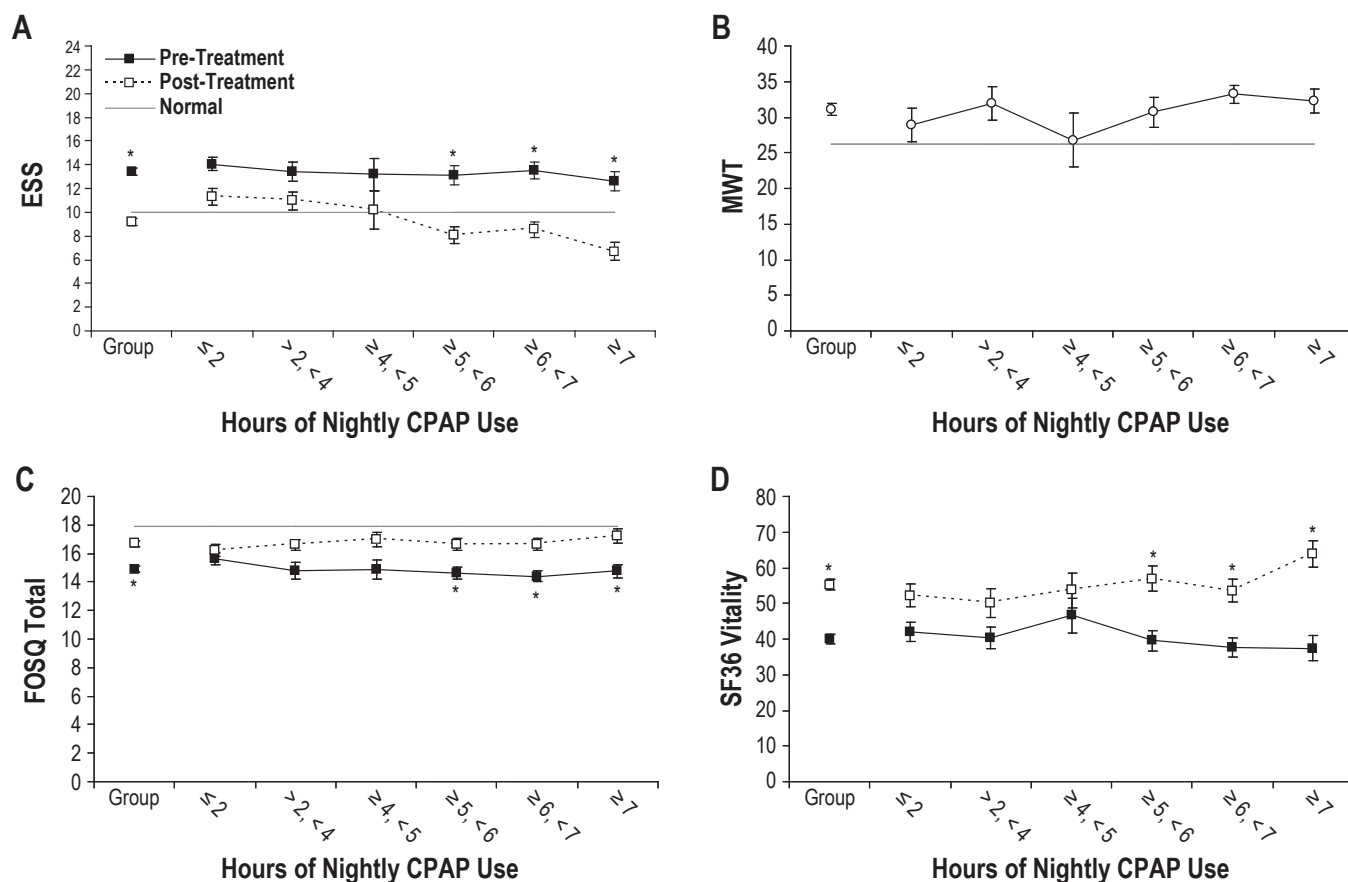
Figure 2—(A) Pretreatment and posttreatment Epworth Sleepiness Scale (ESS) scores, (B) posttreatment maintenance of wakefulness test (MWT, min) mean sleep latency, and pretreatment and posttreatment (C) total Functional Outcomes of Sleep Questionnaire (FOSQ) and (D) SF-36 vitality scores as a function of continuous positive airway pressure (CPAP) compliance category. Values are mean ± SEM. The unbroken ESS horizontal line indicates the cutoff of 10 usually used to distinguish normal from abnormal results.[18] The unbroken MWT horizontal line corresponds to the mean sleep latency cutoff value used to distinguish normal from abnormal results.[24] *Indicates $P < 0.05$ pretreatment vs posttreatment. A, C, D: Total n = 174 (≤ 2 n = 46; > 2, < 4 n = 21; ≥ 4, < 5 n = 12; ≥ 5, < 6 n = 26, ≥ 6, < 7 n = 39; ≥ 7 n = 30), C Total n = 123 (≤ 2 n = 23; > 2, < 4 n = 14; ≥ 4, < 5 n = 10; ≥ 5, < 6 n = 21, ≥ 6, < 7 n = 30; ≥ 7 n = 25).

Table 2—Percentage of patients with normal values before and after treatment and according to CPAP compliance

Measure (normal cutoff)	Patients with normal value before treatment, %	Post-treatment Mean CPAP hours per night						
		≤ 2	> 2 - < 4	≥ 4 - < 5	≥ 5 - < 6	≥ 6 - < 7	≥ 7	Total
ESS (≤ 10)	26.2 (44/168)	35.9 (14/39)	52.4 (11/21)	41.7 (5/12)	76.9 (20/26)	64.1 (25/39)	80.6 (25/31)	59.5 (100/168)
MWT (≥ 26.1 min)	-	60.9 (14/23)	71.4 (10/14)	60.0 (6/10)	61.9 (13/21)	80.0 (24/30)	68.0 (17/25)	68.3 (84/123)
FOSQ Total (≥ 17.9)	13.9 (23/166)	27.0 (10/37)	33.3 (7/21)	25.0 (3/12)	34.6 (9/26)	35.9 (14/39)	48.4 (15/31)	34.9 (58/166)
%Patients with abnormal pre-treatment values achieving normal values after treatment								
ESS (≤ 10)	26.2 (44/168)	25.0 (8/32)	41.2 (7/17)	12.5 (1/8)	70.6 (12/17)	58.6 (17/29)	71.4 (15/21)	48.4 (60/124)
FOSQ Total (≥ 17.9)	13.9 (23/166)	15.4 (4/26)	27.8 (5/18)	18.2 (2/11)	32.0 (8/25)	32.4 (12/37)	38.5 (10/26)	28.7 (41/143)

Values are presented as percentages with parenthetical numbers depicting the number of patients showing normal values versus the total number of patients within the relevant category.
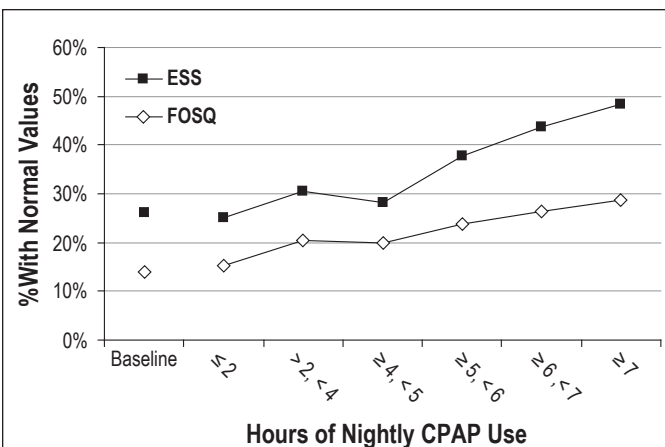
Figure 3—Total cumulative proportion of patients with abnormal baseline values achieving normal Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) values with increasing compliance derived from data within each compliance category shown in Table 2. Values are the percentage of patients returning to normal ESS and FOSQ scores with a given level of continuous positive airway pressure (CPAP) compliance. Total n = 174 (≤ 2 n = 46; > 2, < 4 n = 21; ≥ 4, < 5 n = 12; ≥ 5, < 6 n = 26, ≥ 6, < 7 n = 39; ≥ 7 n = 30).
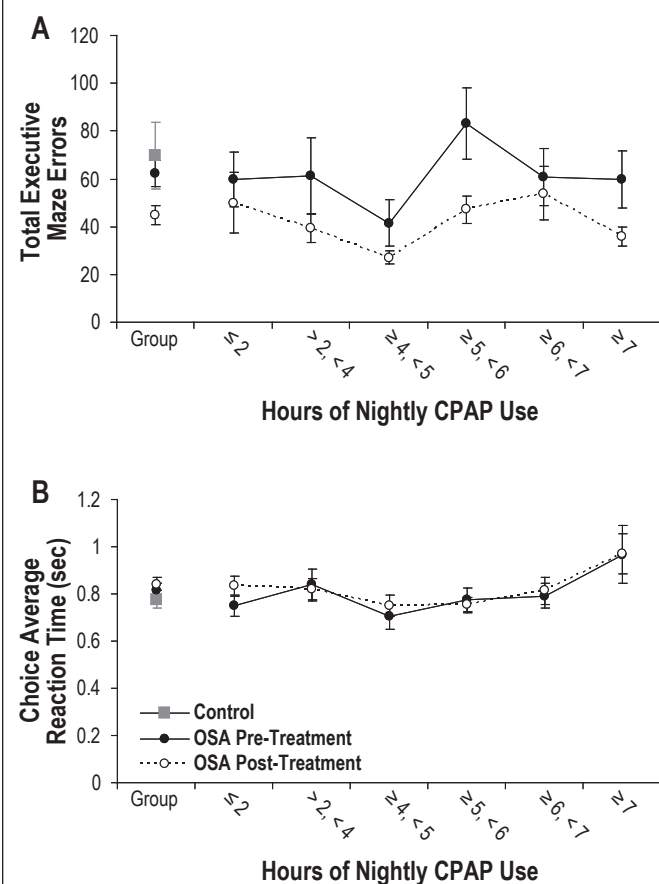
Figure 4—(A) Total executive maze errors and (B) choice reaction time as a function of adherence category before and after treatment with continuous positive airway pressure (CPAP). Values are mean ± SEM. One hundred thirteen control subjects; 143 subjects with obstructive sleep apnea (≤ 2 n = 36; > 2, < 4 n = 17; ≥ 4, < 5 n = 8; ≥ 5, < 6 n = 20, ≥ 6, < 7 n = 32; ≥ 7 n = 30).

response relationship observed for many, but not all behavioral measures, a substantial proportion of patients, even those who appeared to be optimally treated (i.e., CPAP compliance > 7 h/night), did not achieve normal functional status after 3 months of treatment.

The variation in response to CPAP among different tests of neurobehavioral function is well illustrated by the observation that 60% of patients had a normal ESS value after 3 months of CPAP, whereas only 35% had a normal FOSQ total score. Also, there were markedly different results for tests of subjective and objective sleepiness/vigilance. A clear dose-response relationship for CPAP therapy was evident in the posttreatment ESS results, whereas no dose-response relationship was evident for posttreatment MWT sleep latencies. By study design, a high proportion of patients were in the abnormal ESS range at baseline (74%), and this proportion decreased significantly, to 42%, after treatment. In contrast, the mean choice reaction time of patients with OSA to 1 of 4 targets activated at random, considered to be a more objective measure of vigilance, was not different from that control subjects before treatment and did not change as a result of CPAP treatment.

The failure of CPAP treatment to normalize ESS and FOSQ values in all patients might be due to a number of factors. The first and most obvious was the variable and generally low overall nightly CPAP use relative to the expected normal sleep time. However, even the 19% of patients with abnormal ESS pretreatment values in the subgroup that used CPAP for more than 7 hours per night failed to have normal ESS scores after treatment. Second, it is possible that treatment of OSA by CPAP was incomplete, perhaps as a result of incomplete control of upper airway obstruction or the development of "complex sleep apnea"[28] on CPAP. We consider these to be unlikely explanations, however, as the AHI averaged over 3 months was less than 10 per hour, as recorded by the CPAP machine and only 2 of the 95 patients in the in-laboratory CPAP-titration arm had a central apnea index of 5 or more per hour during the in-laboratory CPAP titration.[14] A third consideration is whether the normal values used were appropriate. There is no well-established normal range for the FOSQ. To enable our results to be compared with those of Weaver et al.,[11] we used the same normal cutoff value. The commonly used normal cutpoint for ESS of 10 was derived by Johns[18] in a study in a younger healthy population (mean age 36.4) in which the mean ± SD ESS score was 5.9 ± 2.2. However, a study by Bixler et al.[6] showed self-reported EDS to be twice as common in 20-year-olds as in 50-year-olds. Thus the age-appropriate normal ESS cutoff for the patient group we studied may have been lower than 10. However, this would have resulted in an even higher, rather than a lower, proportion of patients failing to have normal ESS values after CPAP therapy. A fourth possible explanation for failure of CPAP therapy to normalize ESS and FOSQ scores in all patients is that patients had other sleep disorders or comorbidities that contributed to EDS (e.g., sedating medications, depression, obesity itself, chronic sleep restriction) or that OSA causes hypoxic brain damage.[9,10] We found a very low prevalence of central sleep apnea and periodic limb movements in the patients enrolled in this study.[14] A current major depressive illness was an exclusion criterion, but lesser degrees of mood disturbance were not excluded. It will be important in future studies to sys-

tematically assess the contribution of mood disturbance and other medical comorbidities to the persistence of neurobehavioral disturbance following CPAP treatment.

The lack of a dose-response effect for CPAP on the mean sleep latency (as determined by the MWT) was surprising. Although it is a limitation that the MWT was only performed at the end of the trial, these results do raise some doubt as to the clinical utility of the MWT as a measure of sleepiness and treatment effects, particularly given that several other outcomes showed dose-response effects. In their meta-analysis of the effect of CPAP on daytime sleepiness, Patel et al.[1] pooled results from studies that had included the MSLT or MWT as part of their testing regimen and found a mean increase in mean sleep latency of 0.93 minutes across all studies (MSLT and MWT). Six of the 12 studies analyzed included patients with an AHI of more than 30 per hour. Given these small changes, use of the MWT as an objective marker of treatment effect on CPAP must be queried. There are several possible explanations for an apparent lack of a treatment effect in the MWT sleep latency in this and in previous studies. First, it may be that the test is not sufficiently sensitive to detect improvements in sleepiness after CPAP. Second, it is known that the MWT can be affected by patient motivation.[29] Our patients were referred to a sleep clinic and volunteered to participate in a research study. There may, therefore, have been subtle factors motivating subjects to try harder to stay awake (e.g., volunteers' willingness to please researchers or fear that the test result might have implications for driver licensing). A third possible explanation is that the subjective quality-of-life measures improve after CPAP because of a placebo effect, but more objective measures do not improve. Whatever the reason, our study findings bring into question the use of the MWT as a test to demonstrate CPAP treatment efficacy in OSA.

In the SF-36 subscales, only vitality showed significantly greater improvements in more-adherent patients. This is consistent with other published results showing the therapeutic effect size to be greatest for the vitality subscale of the SF36.[22,30] The bodily pain subscale improved the least, and, in both the study by Jenkinson et al.[30] and this study, there was no evidence of any dose-response effect.

There were significant improvements after CPAP across the neurocognitive domains of executive function and verbal memory, but no CPAP dose-response effect. This raises the possibility that some (or all) of the improvement seen after CPAP was related to patient-learning effects, although we attempted to minimize learning effects by administering different tests 3 months apart. The potential for practice effects was evaluated in a study by Cooper et al. using the same test battery and equipment used in the present study to assess dose-dependent effects of methylphenidate.[31] Participants completed the neurocognitive test battery 3 times per day, 1 day per week, for 6 weeks. None of the tests reported in the current study were shown to have a significant learning effect.[31]

Table 3—Selected Neurocognitive parameters before and after CPAP, and compared with a control group

Parameter	Control Subjects (n = 113)	Patients with OSA (n = 141)	
		Pretreatment	Posttreatment
Choice Average Reaction Time, msec	0.78 ± 0.25	0.81 ± 0.38	0.84 ± 0.29
Verbal recall, words recalled			
1	11.05 ± 1.35	9.62 ± 1.91[a]	10.82 ± 1.75[b]
7	6.78 ± 2.14	5.82 ± 2.37 [a]	6.52 ± 2.38[b]
Executive maze			
Time to complete, min	4.16 ± 2.38	4.87 ± 2.98 [a]	3.97 ± 2.61[b]
Total errors	69.67 ± 92.51	61.05 ± 64.91	43.83 ± 45.48 [a,b]

Values are mean ± SD. [a]$P < 0.05$ versus controls; [b]$P < 0.05$ vs pretreatment. Verbal Recall 1 and 7; ability to correctly recall a set of words given immediately after the words are given (1), and again at a later time (7).

We believe our results both complement and add to the report by Weaver et al.[11] Our sample population was remarkably similar with respect to age, sex distribution, body mass, sleep apnea severity, degree of baseline sleepiness (i.e., ESS score), sleep-related quality of life (FOSQ), and nightly CPAP compliance. Both studies report the results after 3 months of CPAP treatment. Our study differed in that patients were studied as part of a 3-center randomized controlled trial that compared 2 different OSA-management pathways (shown to have equivalent patient outcomes),[14] whereas Weaver et al. studied patients across 7 centers during routine clinical care. We found a CPAP dose-response curve for ESS similar to that reported by Weaver et al. However, whereas our mean pretreatment FOSQ scores were virtually identical to those of Weaver et al., we found that our patients had a flatter CPAP dose-response curve and that a smaller proportion of patients with abnormal baseline values had normal FOSQ scores after treatment (49% vs 72%).

To determine whether different results between this study and that of Weaver et al. may have been explained by the type of statistical analysis used, we undertook a posthoc analysis of posttreatment ESS and FOSQ in subjects with abnormal scores before treatment using piecewise linear regression,[32]as had been conducted by Weaver et al. Similar to Weaver et al., we found that posttreatment ESS score was optimally fit with a join point at 4.2 hours of CPAP use, but this did not provide a superior fit to that of linear regression, suggesting greater benefit with increasing CPAP use. In contrast with the findings of Weaver et al., piecewise regression did not provide a better fit of posttreatment FOSQ scores compared with linear regression ($F_{3,140} = 0.14$, $P = 0.936$), and the slope of the linear regression fit was also not statistically significant (0.149 SE = 0.08 change in FOSQ per hour of CPAP use, $P = 0.072$), such that there was little evidence for improvement in FOSQ scores with increasing CPAP use.

Some other notable differences between our study and that of Weaver et al.'s study include nearly twice as many patients in this study (174, compared with a range of 85-120 in the Weaver study) and the inclusion of objective neurocognitive measurements and MWT rather than MSLT performed on more subjects (123 vs 85). The MWT is frequently used to assess treatment response to CPAP and, thus, potentially has more clinical relevance than the MSLT. The American Academy of Sleep Medicine has determined that the MSLT is not routinely indicated in

the initial evaluation and diagnosis of OSA or in the assessment of change following treatment with nasal CPAP, whereas the MWT may be indicated in patients with EDS to assess response to treatment. Although evidence remains limited, in the US, the Federal Aviation Administration uses the MWT in the evaluation of pilots with OSA treated with CPAP. Our lack of dose-response effect on the MWT raises the question as to whether it is an appropriately sensitive test to be used in these circumstances.

The exclusion criteria applied by Weaver et al.[11] were more stringent than ours, with all psychiatric illness and all other sleep disorders excluded from their trial. Our cohort may, therefore, be more representative of a clinical sleep medicine service where psychiatric illness is a common comorbidity, reported to be present in up to 40% of patients referred to a sleep service for assessment of OSA and with nearly all (98%) receiving antidepressant medication.[33]

Methodologic Considerations

There are some important methodologic considerations relevant to this study. The study was designed as a randomized controlled trial to assess 2 arms of care, and thus, there was no control arm. It is likely that some of the positive responses to CPAP therapy reflect a placebo effect, and, had we had data from a placebo-control group, we would have been able to quantify this effect. As noted above, although participants in our study were referred to a sleep clinic, they were also willing to participate in a clinical trial and, thus, may not fully represent usual clinic patients. The MWT was performed only at the conclusion of the study because it was felt that to ask the patients to do this test also at the beginning of the study would have adversely affected recruitment, particularly given the other complexities of data collection. Only 50% of our patients had a full polysomnogram prior to therapy, but, given that patients were randomly assigned to 1 of the 2 arms of care after overnight oximetry testing and that there was no significant difference between the 2 groups in any baseline or outcome measurements, it seems unlikely that this study design would alter the main findings in any important way.

In conclusion, this study in patients with symptomatic (ESS ≥ 8) moderate to severe OSA (AHI > 30/h) showed that several key indexes of neurobehavior (e.g., FOSQ, ESS) currently used to assess treatment response failed to normalize in a substantial group of patients after 3 months of CPAP treatment, even in those who were maximally compliant. In future studies of cohorts of patients with OSA, detailed data collection of total sleep time, residual sleep disordered breathing, or prevalence of depression should be carefully assessed.

Although there were trends for improvement noted with increasing CPAP adherence, only the ESS, FOSQ, and some measures of neurocognitive function (verbal memory and executive function) showed significant improvement with greater CPAP adherence. Thus, some of the tests used clinically to assess response to treatment in OSA (MWT) and in research settings (SF-36) may not be sufficiently sensitive to make meaningful observations. It should be noted, however, that the SF-36 is a generic quality-of-life measurement tool and, thus, may be less responsive than a disease-specific instrument. Use of the subscales of the SF-36 (e.g., vitality) tests may overcome some of these limitations.

These data identify that careful thought and follow-up are needed when treating a patient with OSA. Other comorbidities frequently exist, and even optimal CPAP compliance may not normalize quality-of-life and EDS measures. It is important that the health professional assessing the patient does not rely simply on the numeric CPAP adherence value, because whether or not EDS and quality of life improve or normalize may depend on a number of other complex and often interrelated factors. Other comorbidities (e.g., depression) and treatments (e.g., sedating medication) should be considered, particularly in the setting of ongoing symptoms. It is also important to consider that OSA and EDS are both common problems that may coexist without necessarily a direct cause-and-effect relationship.

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