# Efficacy of Positive Airway Pressure and Oral Appliance in Mild to Moderate Obstructive Sleep Apnea

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**The efficacy of currently recommended treatments is uncertain in patients with mild to moderate obstructive sleep apnea (apnea–hypopnea index [AHI], 5–30). A group of 114 sleep clinic patients with an AHI of 5–30 have participated in a randomized controlled crossover trial of 3 months of treatment with each of nasal continuous positive airway pressure (CPAP), a mandibular advancement splint, and a placebo tablet. Outcomes were sleep fragmentation and hypoxemia, daytime sleepiness, quality of life, neurobehavioral function, and blood pressure. Both active treatments improved sleep outcomes, but positive airway pressure had a greater effect. The quality of life, symptoms, and subjective but not objective sleepiness improved to a similar degree with both treatments; however, many of the improvements seen in neuropsychologic function and mood were not better than the placebo effect. Some aspects of nocturnal blood pressure were improved with the splint but not with CPAP. This study has shown that although both CPAP and mandibular advancement splint effectively treated sleep-disordered breathing and sleepiness, the expected response in neurobehavioral function was incomplete. This may be due to the splint having a lesser therapeutic effect and CPAP being poorly tolerated and therefore used less in this patient group.**

**Keywords:** mandibular advancement; obstructive sleep apnea; positive pressure ventilation; randomized controlled clinical trials

Obstructive sleep apnea (OSA) syndrome is a common condition affecting at least 2% of adult females and 4% of adult males (1). It is characterized by repetitive obstruction of the upper airway during sleep, resulting in episodic hypoxemia and arousal, associated with symptoms, usually daytime sleepiness. There is now a considerable body of literature documenting the pathophysiology and consequences of more severe OSA; however, the morbidity, benefits of treatment, and optimal mode of management of mild to moderate OSA remain a clinical dilemma. It has been convincingly demonstrated that patients with an apnea–hypopnea index (AHI) of more than 30 have significant neuropsychological morbidity, which is improved by nasal continuous positive airway pressure (CPAP) therapy (2–6). A recent meta-analysis of studies of the neuropsychologic effects of OSA (7) concluded that there are insufficient data to assess adequately the impairment in subjects with mild OSA, particularly those with an AHI of less than 15. The therapeutic effect of CPAP on daytime sleepiness was examined in another recent meta-analysis (8). This study found an overall improvement in daytime somnolence with CPAP, but the authors concluded that there were too few subjects included with mild to moderate sleep apnea (AHI $\leqslant$ 30) to draw a valid conclusion for these subjects. These findings were supported by a recent Cochrane Review (9), which found that CPAP is effective in treating sleep-disordered breathing and in improving sleepiness and subjective health status; however, the data documenting the degree of morbidity and demonstrating the efficacy of CPAP in patients with mild to moderate disease (AHI, 5–30) remain inconclusive. There have been five randomized controlled trials of CPAP in subjects with mild to moderate OSA (10–14). These have showed a modest effect of CPAP, but there is a significant placebo effect, and treatment adherence is poor. Perhaps because of the poor treatment uptake, a significant disease load remains untreated by CPAP (3, 15), challenging sleep physicians to find alternative treatments for OSA.

Oral appliances are a relatively recent development and act to position the mandible in a protruded position during sleep. The mode of action is unclear but is probably multifactorial, involving both a structural change with enhancement of the caliber of the airway and also triggering of stretch receptors, which activate the airway support muscles (16). There are three published randomized, placebo-controlled trials assessing the efficacy of oral appliances in subjects with a wide range of OSA severity (17–19). All three studies showed that the device improves sleep-disordered breathing and sleep hypoxemia (in up to 63% subjects in the first two studies and one-third of the subjects in the third study). However, the first two studies did not measure neurobehavioral or blood pressure outcomes, and although snoring and daytime sleepiness showed a trend to improvement in the third, this did not reach statistical significance. Although two groups (20, 21) have shown that the potential improvement in sleep-disordered breathing with oral appliance use could be titrated and predicted from an overnight sleep study, no other outcomes were measured. Additionally, up to one-third of all subjects with OSA may have clinical or structural contraindications to the use of oral appliances (22), and up to one in four subjects may be unable to tolerate the device (23). Thus, although these devices have been recommended for use in patients with mild to moderate OSA or in those who have failed a trial of CPAP (24), there are inadequate placebo-controlled data to support this.

Six randomized but uncontrolled crossover studies have compared CPAP to oral appliances (25–30). Although five of these had small numbers (fewer than 30 subjects), they all found that treatment with the oral appliance resulted in an improvement in sleep-disordered breathing, albeit the effect was less than with CPAP. The largest study (51 subjects) also measured neurobehavioral outcomes (28) and found that although both treatments

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were effective, CPAP appeared superior to the oral appliance, and the treatment benefit extended to the subgroup of subjects with mild OSA (AHI, 5–15). This latter study was the only one of the six in which subjects preferred CPAP to the oral appliance.

There is an obvious need to define further the morbidity associated with mild to moderate OSA and for controlled data comparing the efficacy of CPAP with that of an oral appliance on clinically meaningful endpoints in these subjects. Some of the results of this study have been previously reported in the form of an abstract (31).

## METHODS

Full details of study design and methods used are provided in the online supplement. A randomized, three-way crossover trial was conducted in two Australian centers (Austin Health, Melbourne, Victoria, and Daw Park Repatriation General Hospital, Adelaide, South Australia) to investigate daytime sleepiness, neurobehavioral function, and blood pressure in sleep clinic patients with mild to moderate OSA (AHI, 5–30 per hour). The responses to 3 months of treatment with nasal CPAP (Sullivan Elite, ResMed, Australia), a mandibular advancement splint (Medical Dental Sleep Appliance, R. J. and V. K. Bird, Australia), and placebo tablet were compared.

Ethics committee approvals and informed subject consent were obtained. Randomization and subject eligibility were the same as our previously reported study of CPAP in patients with mild OSA (12), with the additional requirement of healthy and adequate dentition to enable use of the mandibular advancement splint (MAS).

At the beginning of the trial and at the end of each 3-month treatment period, all subjects underwent overnight polysomnography, comprehensive neurobehavioral testing (Table E1 in the online supplement), 24-hour ambulatory blood pressure, and echocardiography. Subjects were categorized as hypertensive using previous definitions (31) and as blood pressure dippers or nondippers (32). Height, weight, and neck, waist, and hip circumferences were recorded for each subject.

There was a 2-week washout between treatment periods; the first 18 subjects to complete the trial had additional polysomnography performed at the end of each washout period to confirm the return of sleep study variables to baseline (Figure 1).

Polysomnography (including analysis and scoring definition) and CPAP implementation were performed as previously described (12). The Maintenance of Wakefulness Test (MWT) was performed and analyzed according to standard guidelines (33) on the day after the overnight sleep study. Before each MWT nap, subjects completed the Stanford Sleepiness Scale (34) and a visual analog scale assessing subjective alertness and well-being (*see* Appendix 1 in the online supplement).

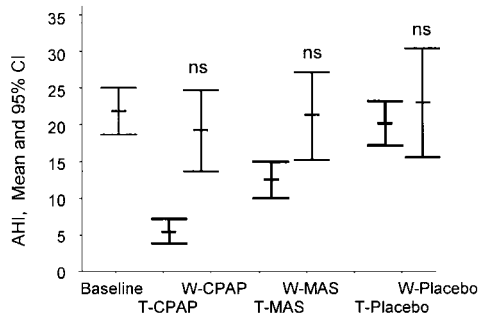


*Figure 1.* Apnea–hypopnea index (AHI) at baseline, on treatment, and at the end of each washout period. The AHI for each treatment at the end of the 2 week washout period has returned to baseline level, thus confirming the adequacy of the washout period for sleep variables. CI = confidence interval; W-CPAP = washout post-CPAP; W-MAS = washout post-MAS; W-Placebo = washout postplacebo; T-CPAP = post-CPAP treatment; T-MAS = post-MAS treatment; T-Placebo = postplacebo treatment. ns = no significant difference from baseline.

Protocols for overnight polysomnography, MWT, and neurobehavioral tests were standardized between the two centers. Interscorer reliability and intrascorer reliability were measured using intraclass correlation coefficients and paired *t* tests, which were within acceptable published limits (35).

CPAP use was measured objectively with an inbuilt "time at pressure" meter. Subjects kept a diary of their MAS use, and the remainder pills were counted to measure placebo use. At the conclusion of the study, each subject and their domestic partner were asked independently about treatment preference.

Subjects received a custom-made MAS which has a maximum protrusion of 12 mm, in 0.25-mm increments. In the wash-in period, it was advanced weekly by the study dentist as tolerated by subjects, until the maximum comfortable protrusion was reached, taking up to 4 weeks.

### Statistics

The Statistical Package for Social Sciences (SPSS Inc., version 11.0, 2001) program was used. Power and sample sizes were calculated (36) using the Epworth sleepiness scale (ESS) as the primary outcome variable. An intention-to-treat analysis of treatment response was performed, using repeated-measures analysis of variance with Bonferroni correction. Because of the large number of response variables, a two-stage factor analysis was also performed, and five significant factors were found. These were analyzed in the same way as the raw data, and additionally, the magnitude of the treatment response in each of the five factors was measured using effect sizes. Summing of these effect sizes gave an overview of the best treatment response. Results are given as mean ± SEM unless otherwise stated.

## RESULTS

### Subject Selection and Retention

One hundred four subjects with OSA were recruited, of whom 80 completed all three treatment arms (Figure 2). Only one subject was unable to tolerate CPAP, and two were unable to use the MAS. No subject complained of side effects from the placebo tablet. Baseline indicators and risk predictors for OSA severity (AHI, arousal index, sleep hypoxemia, sex, age, obesity) in those who completed and dropouts were the same. However,

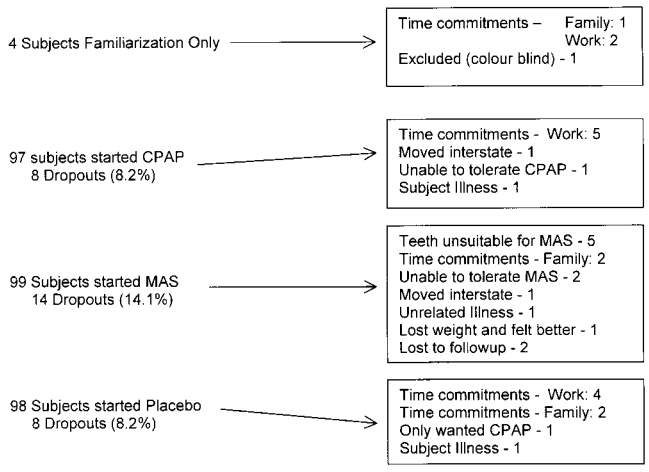


*Figure 2.* Of the 114 subjects recruited for the trial, 4 subjects did not attend for the baseline assessment. Similar numbers of subjects were offered each of the three treatments, and similar numbers failed to complete each treatment, mostly because of time commitments, either work or family. Additionally, five subjects were found to be ineligible for the mandibular advancement splint (MAS) because of poor dentition. Only one subject dropped out because of continuous positive airways pressure (CPAP) intolerance, and two subjects were unable to tolerate the MAS.

**TABLE 1. SUBJECT CHARACTERISTICS**

| | Entire Group | Completed Subjects | Dropout Subjects |
|---|---|---|---|
| Age, yr | 47.0 (0.9) | 46.4 (1.1) | 48.5 (1.9) |
| Sex, % male | 79.8 | 78.8 | 82.4 |
| BMI, kg/m$^2$ | 31.1 (0.5) | 31.0 (0.6) | 31.2 (0.9) |
| AHI, events/h | 21.3 (1.3) | 21.5 (1.6) | 21.1 (2.3) |
| Arousal Index, per h | 22.0 (1.2) | 22.2 (1.5) | 21.7 (2.3) |
| 4% $O_2$ desaturation | 12.4 (1.5) | 12.8 (1.9) | 11.6 (2.5) |
| Total sleep time, min | 321.1 (6.2) | 319.3 (8.0) | 325.3 (9.4) |
| ESS* | 10.7 (0.4) | 10.2 (0.5) | 11.9 (0.7) |
| FOSQ mean score* | 3.1 (0.1) | 3.2 (0.1) | 3.0 (0.1) |
| SASQ* | 64.7 (1.7) | 62.4 (2.0) | 70.2 (2.8) |
| NART-R | 107.5 (0.9) | 108 (1.1) | 106.0 (1.6) |

*Definition of abbreviations*: AHI = apnea–hypopnea index; BMI = body mass index; ESS = Epworth sleepiness scale; FOSQ = Functional Outcomes of Sleep Questionnaire; 4% $O_2$ desaturation = hourly rate of 4% oxygen desaturations; SASQ = Sleep Apnea Symptom Questionnaire; NART-R = National Adult Reading Test-Revised.

All data are mean (SEM).

* $p < 0.05$ completed vs. dropout subjects.

those subjects who dropped out had significantly worse self-assessment of their disease severity in terms of subjective sleepiness, quality of life, and symptoms compared with those who completed the trial (Table 1). There were six possible treatment orders. There were no significant carryover or period effects for any outcomes for these groups; therefore, the data were pooled. There was no difference in the mean duration of any treatment arm.

### Clinical Features

Subjects were middle aged (47.0 ± 0.9 years), predominantly male (80%), and overweight (interquartile range body mass index, 27.8–32.8 kg/m$^2$), with mild to moderate OSA (AHI, 5–30 per hour) (Table 1). Premorbid intelligence quotient (IQ) (as indicated by the National Adult Reading Test-Revised) showed that 98% of subjects with OSA were within 2 SDs of the normal population mean, validating our use and interpretation of the neuropsychologic tests. The initial problems encountered during CPAP therapy had all resolved by week 4 of treatment—several subjects required a different mask to the one with which they had been fitted at the CPAP implementation study; no subject required a pressure change on their CPAP pump. The wash-in period for the MAS ranged from 1 to 3 weeks; after this, there were no further changes in mandibular advancement, and no subject required an extra dental visit.

### Polysomnography

Compared with placebo, both CPAP and MAS improved the AHI and sleep hypoxemia, although the response was greater with CPAP than MAS (Table 2 and Table E2 in the online supplement). There was a significant reduction in stage 1 sleep and an increase in slow wave sleep (stages 3 and 4) with both CPAP and MAS but no significant change in total sleep time or sleep efficiency.

### Neurobehavioral Outcomes

***Sleepiness and symptoms.*** Subjects had significant subjective sleepiness at baseline; the ESS score was 10.7 ± 0.4, and 50.9% subjects had an ESS score greater than 10 (the cutoff for normal subjects) (37) (Table 2 and online supplement Table E3). However, their objective sleepiness was less pronounced, with MWT sleep latency of 30.7 ± 0.9 minutes, and 18.4% had a sleep latency shorter than 20 minutes (i.e., in the pathologically sleepy range) (38). Using an ESS cutoff of more than 10 and an MWT cutoff of less than 20 minutes to define normality, only 12 of 114 OSA subjects (10.5%) were both objectively and subjectively sleepy, and 51 (44.7%) had neither objective nor subjective sleepiness. The Sleep Apnea Symptom Questionnaire score was high at 64.7 ± 1.7 compared with reported normal values (39).

Compared with placebo, both CPAP and MAS significantly improved subjective daytime sleepiness (ESS, $p < 0.001$) and the symptom score ($p < 0.001$). They did not differ in treatment effectiveness. There was no improvement in objective sleepiness (MWT) with treatment. The visual analog scale assessment of alertness improved significantly with CPAP ($p < 0.001$) but not with MAS, and there was no difference in the feeling of well-being with any treatment.

***Neuropsychologic function and mood.*** A broad range of neuropsychological function was assessed (Table 2 and online supplement Tables E1 and E4). CPAP increased vigilance (i.e., decreased Psychomotor Vigilance Task lapses), and both CPAP and MAS were superior to placebo in improving executive cognitive function (Paced Auditory Serial Addition Task [PASAT 1.2]). No other treatment effects on neurocognitive function were observed.

Clinically significant depression (Beck Depression Inventory [BDI]) was present in 40.4% subjects with OSA. Compared with placebo, CPAP resulted in improvements in four domains of the Profile of Moods States and the total mood disorder score. MAS treatment produced improvement in the tension–anxiety domain only. The Beck Depression score responded equally to all three treatments (suggesting a placebo effect).

***Quality of life.*** Compared with placebo, MAS treatment improved quality of life as measured by the Functional Outcomes of Sleep Questionnaire mean score and social outcome domain and by the sf36 overall health score (Table 2 and the online supplement Table E5). CPAP treatment was effective with respect to Functional Outcomes of Sleep Questionnaire overall score and activity level, as well as the sf36 mean score and well-being.

### Blood Pressure and Echocardiography

Of the 110 subjects with OSA who had baseline 24-hour ambulatory blood pressure measurement, 16 were hypertensive (BP systolic > 140 and/or BP diastolic > 90), and 44 were nondippers (Table 2). After controlling for age, sex, and body mass index, there was a significant but weak correlation ($R = 0.20$, $p = 0.04$) between baseline AHI and 24-hour systolic BP, but not with any other blood pressure measures. Treatment with MAS showed a significant improvement in nighttime diastolic blood pressure,

**TABLE 2. POLYSOMNOGRAM, NEUROBEHAVIORAL, AND BLOOD PRESSURE OUTCOMES**

| | Baseline | CPAP | MAS | Placebo |
|---|---|---|---|---|
| AHI | 21.3 (1.3) | 4.8 (0.5)*†‡ | 14.0 (1.1)*† | 20.3 (1.1) |
| Arousal index | 22.0 (1.2) | 18.3 (0.9)†‡§ | 23.8 (1.2) | 25.2 (1.1) |
| 4% Oxygen desaturation | 12.4 (1.5) | 1.6 (0.2)*†‡ | 8.1 (1.3)*† | 12.5 (1.6) |
| Minimum oxygen saturation % | 86.7 (0.6) | 91.9 (0.3)*†‡ | 87.8 (0.4)† | 85.4 (0.6) |
| Epworth sleepiness scale | 10.7 (0.4) | 9.2 (0.4)*† | 9.2 (0.4)*† | 10.2 (0.4) |
| MWT, min | 30.7 (0.9) | 30.0 (0.9) | 29.6 (0.9) | 28.0 (0.9)§ |
| SASQ | 64.7 (1.7) | 52.9 (1.7)*† | 54.9 (1.6)*.** | 60.1 (1.5)§ |
| Digit span backward | 4.4 (0.1) | 4.6 (0.1) | 4.6 (0.1) | 4.8 (0.1)¶ |
| Trailmaking B | 85.9 (4.4) | 73.3 (3.3)* | 76.0 (3.7)¶ | 74.2 (3.6)* |
| Digit symbol substitution task | 46.4 (0.4) | 47.3 (0.4)¶ | 47.5 (0.4)§ | 46.8 (0.4) |
| COWAT | 43.2 (1.1) | 46.5 (1.2)* | 46.3 (1.1)* | 46.3 (1.0)* |
| PVT lapses | 2.5 (0.3) | 2.1 (0.2)‖ | 2.2 (0.2) | 2.7 (0.3) |
| Stroop color association test | 4.8 (0.8) | 9.3 (0.9)* | 10.3 (0.9)* | 9.2 (0.9)* |
| PASAT-1.2 | 3.4 (0.2) | 2.9 (0.1)¶**‡ | 2.6 (0.03)*† | 3.4 (0.1) |
| POMS-total mood disorder | 15.5 (2.0) | 6.3 (1.7)*.** | 9.7 (2.1)¶ | 11.8 (2.1) |
| Beck Depression Inventory | 9.2 (0.5) | 6.7 (0.5)* | 6.9 (0.5)* | 7.7 (0.6)§ |
| FOSQ mean score | 3.1 (0.1) | 3.3 (0.1)* | 3.3 (0.1)*‖ | 3.3 (0.1)§ |
| sf36 mean score | 69.4 (1.3) | 74.1 (1.2)*‖ | 73.7 (1.2)* | 71.4 (1.4) |
| Blood pressure, mm Hg | | | | |
| 24-Hour mean systolic | 126.5 (1.0) | 127.3 (1.2) | 126.7 (1.0) | 128.2 (1.2) |
| 24-Hour mean diastolic | 76.3 (0.8) | 76.7 (0.8) | 76.3 (0.7) | 77.3 (0.7) |
| Night diastolic | 69.4 (0.9) | 69.9 (0.9) | 67.2 (0.8)‡,§,‖ | 68.9 (0.8) |

*Definition of abbreviations*: AHI = apnea hypopnea index; CPAP = continuous positive airway pressure; COWAT = controlled oral word association task; FOSQ = Functional Outcomes of Sleep Questionnaire; MAS = mandibular advancement splint; MWT = Maintenance of Wakefulness Test, latency to sleep; 4% Oxygen desaturation = hourly rate of oxygen desaturations of at least 4%; PASAT-1.2 = paced auditory serial addition task at the 1.2 second speed, time per response; POMS = profile of moods states; PVT lapses = psychomotor vigilance task, the number of responses more than 500 ms; SASQ = Sleep Apnea Symptom Questionnaire; sf36 = 36-item Medical Outcomes Study questionnaire.

* $p < 0.001$ compared with baseline.
† $p < 0.001$ compared with placebo.
‡ $p < 0.05$ CPAP vs. MAS.
§ $p < 0.01$ compared with baseline.
¶ $p < 0.05$ compared with baseline.
‖ $p < 0.05$ compared with placebo.
** $p < 0.01$ compared with placebo.

but there were no other significant changes with either MAS or CPAP. In particular, there was no significant response in the hour-by-hour mean systolic or diastolic blood pressure with either MAS or CPAP (Figure E1). The lack of a CPAP treatment response held when these analyses were repeated in the subgroups of 16 hypertensive subjects and in the 44 nondippers. With MAS treatment, a significant proportion of nondipper subjects regained their normal nocturnal dip in blood pressure, but not with either CPAP or placebo (Figure 3).

Transthoracic echocardiography is technically challenging in obese subjects, and complete measurements were not possible in all subjects with OSA. The method used to measure pulmonary artery pressure required a regurgitant tricuspid jet; therefore, baseline pulmonary artery pressure measurements were available in only 35 subjects with OSA. The pulmonary artery pressure in these subjects was 20.5 ± 0.9 mm Hg, and there was no significant change with any treatment. Left ventricular mass measurements were available in 89 subjects. The calculated left ventricular mass was 225.1 ± 5.2 g, and again, there was no significant change with any treatment.

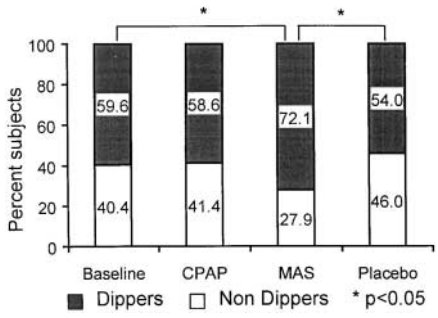


***Figure 3.*** The proportion of subjects who had a normal nocturnal dip in blood pressure was significantly improved with MAS but showed no response to CPAP.

### Factor Analysis

Factor 1 described the severity of the sleep-disordered breathing and comprised mainly sleep oxygenation (oxygen nadir and 4% desaturation) and AHI. There was a significant improvement from baseline with both CPAP and MAS, no placebo effect, and CPAP was more effective than MAS (Figure 4A). Factor 2 described symptoms of sleep apnea and sleepiness, including the ESS, the Sleep Apnea Symptom Questionnaire, and the Functional Outcomes of Sleep Questionnaire. Both CPAP and MAS treatment resulted in significant improvements, with neither being better than the other (Figure 4B). Factor 3 described neurocognitive function and summarized the Trails B test, Digit Symbol Substitution Task, and Controlled Oral Word Association Test results. There was a significant placebo response, and neither of the active treatments was better than this (Figure 4C). Factor 4 described vigilance, mainly the psychomotor vigilance task. Again, neither of the active treatments was better than placebo (Figure 4D). Factor 5 described mood and self-assessment and comprised mainly the Beck Depression Index, Profile

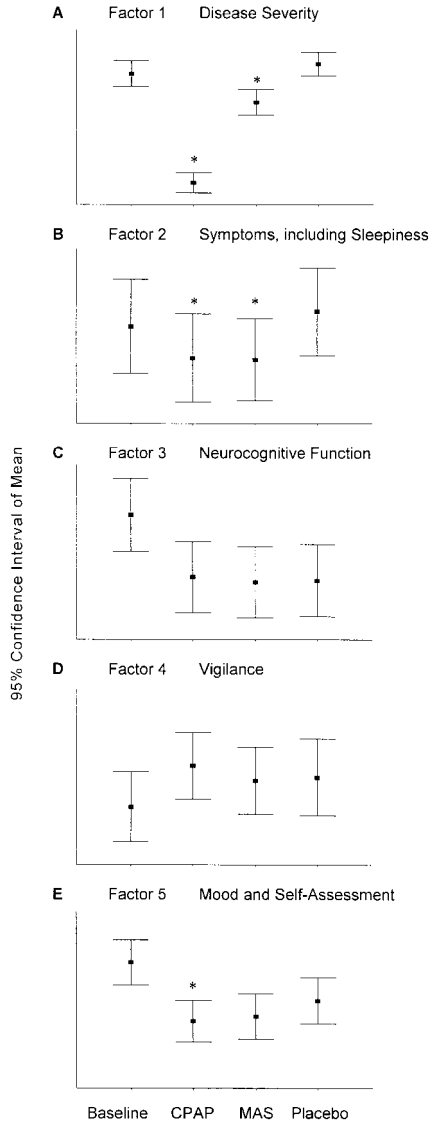


*Figure 4.* Factor results for obstructive sleep apnea (OSA) and control subjects and at each treatment level for OSA subjects. OSA subjects have worse outcomes than control subjects for factors 1, 2, and 5. There is a significant treatment effect (*) for both CPAP and MAS for factors 1 and 2 and with CPAP only for factor 5.

of Mood States Total Mood Disorder score, and the sf36. Only CPAP was more effective than placebo (Figure 4E).

***Overall assessment of response.*** To obtain a measure of the clinical response to treatment, effect sizes were calculated for each of the five factors, as well as the proportion of subjects who achieved a response of at least moderate size (Table 3). These results were quite consistent with the statistical analysis, showing that both CPAP and MAS improved sleep-disordered breathing and symptoms; there was only a placebo response for neuropsychologic function and vigilance, but in addition to a CPAP response in mood, almost two-thirds of the subjects responded to MAS. The only factor in which CPAP was more effective than MAS was for improvement of sleep-disordered breathing. These effect sizes were then summed to give an overall score, which indicated the clinical improvement with each treatment. Almost two-thirds of the subjects had their best response to CPAP; one-fourth responded best to MAS, and placebo had the greatest effect in 10% of subjects.

### Treatment Adherence

CPAP use was measured objectively by an inbuilt meter, which measured time at pressure. MAS use was assessed subjectively with a subject diary, and the placebo tablets were counted at the end of the treatment period to determine the percent of treatment nights they were taken. Of the 88 subjects for whom we had CPAP adherence data, the CPAP pump was used for $4.2 \pm 0.3$ nights per week and for an average of $3.6 \pm 0.3$ hours per night over the entire treatment period. Complete MAS diary data were available for 49 of the 85 subjects who completed the MAS treatment arm; the reported use was $5.3 \pm 0.3$ nights per week for $5.5 \pm 0.3$ hours per night over the entire treatment period. All subjects returned their placebo pill bottles; they took the placebo tablets for $94.3 \pm 1.2\%$ treatment nights. It has been proposed (2) that effective CPAP treatment of OSA requires use for at least 4 hours per night on at least 70% nights; by this criterion, 38 of 88 (43%) subjects treated with CPAP received adequate treatment, and 37 of 49 (76%) subjects treated with MAS (for whom we have usage data) received adequate treatment (Figure 5). It should be noted, however, that on the night before the neurobehavioral assessment, adherence was 100% for each treatment.

Subjects were categorized according to whether they had used the prescribed treatment for at least 4 hours per night on 70% nights ("users" and "nonusers"), and the treatment response for the five factors was repeated separately for each group. For CPAP, this was not different from the entire group analysis, suggesting that the CPAP response extends to low usage levels. For MAS, there was also no difference from the treatment response of the entire group except in factor 2 (sleepiness and symptoms) where the response was limited to users only.

### Treatment Preference

Both subjects with OSA and their domestic partners felt that the placebo tablet was easiest to use, but that CPAP worked best (56% subjects and 53% partners) and was the overall preferred treatment for 44% subjects and 40% partners (Figure E2). MAS was the overall preferred treatment for 30% of the subjects and 36% of the domestic partners.

### Mandibular Advancement Splint Fitting and Response

Mandibular advancement with the MAS was $10.3 \pm 0.3$ mm and ranged between 1–13 mm. Seventy-seven percent of subjects achieved at least 70% of maximum possible protrusion. With this degree of protrusion, 56.1% subjects achieved a reduction in the AHI of at least five events per hour (range, 5.1–48.0); 14% had an AHI increase of at least five events per hour (range 5.2–20.1), and 29.9% subjects changed by less than five events per hour.

In addition to the primary analysis, we measured the improvement in sleep-disordered breathing with the MAS using response definitions that have been used in similar studies (17). A complete response is defined as a reduction in the AHI to below 10, and a partial response is a fall of at least 50% in the AHI but not below 10, with an improvement in symptoms; the remainder of subjects is classified as treatment failures. By these criteria, 49.1% subjects had a complete response to the MAS, and a further 6.1% had a partial response.

### Response in Mild Subjects

A planned post hoc analysis of the 47 subjects with a baseline AHI of 15 or less was performed. Both CPAP ($p < 0.001$)

**TABLE 3. FACTOR ANALYSIS**

| | Effect Sizes % Subjects ⩾ 0.5 | | | Comparison to Placebo p Values | | | CPAP vs. MAS p Values |
|---|---|---|---|---|---|---|---|
| | CPAP | MAS | Placebo | Baseline | CPAP | MAS | |
| Factor 1, disease severity | 80.7 | 37.7 | 18.4 | NS | * | * | * |
| Factor 2, symptoms and sleepiness | 50.7 | 35.1 | 22.8 | NS | † | † | NS |
| Factor 3, neuropsychologic function | 51.8 | 60.5 | 51.8 | * | NS | NS | NS |
| Factor 4, vigilance | 35.1 | 36.8 | 35.1 | NS | NS | NS | NS |
| Factor 5, mood and quality of life | 60.5 | 61.4 | 22.8 | * | ‡ | NS | NS |
| Best overall response to treatment, % of subjects | 64.7 | 25.0 | 10.3 | | | | |
| No response to treatment, effect size ⩽ 0.2, % of subjects | 2.6 | 2.6 | 6.1 | | | | |

*Definition of abbreviations*: CPAP = continuous positive airway pressure; MAS = mandibular advancement splint.
Effect sizes: ⩾ 0.2 is small, ⩾ 0.5 is moderate, ⩾ 0.8 is large.
* $p < 0.001$.
† $p < 0.01$.
‡ $p < 0.05$.

and MAS ($p = 0.002$) were significantly better than placebo in improving sleep-disordered breathing (AHI and 4% desaturation rate). All but 4 (8.5%) subjects had at least a moderate effect size response to CPAP, and 25 (53%) subjects achieved the MAS treatment target of AHI of 10 or less. The best effect size response was similar to the group as a whole, with 66% of the subjects having their best response to CPAP, 26% with MAS, and 8% with placebo. These mild OSA subjects had an improvement with both CPAP and MAS that was significantly better than placebo ($p \leq 0.05$) in symptoms, ESS, Functional Outcomes of Sleep Questionnaire, and sf36. Neither treatment was superior to the other. Although there was some improvement in neuropsychologic function, it was not better than placebo. In this group, 28% preferred CPAP, 41% preferred MAS, and 31% preferred placebo.

### Sleepy Versus Nonsleepy Subjects

Our subject group comprised 53 "sleepy" patients with an ESS of 11 or more, and 61 "nonsleepy" subjects with an ESS of 10 or less. Nonsleepy subjects had a significantly better baseline Functional Outcomes of Sleep Questionnaire mean score than sleepy subjects ($p = 0.001$), but there were no other baseline differences. There was no difference from the group as a whole in the treatment responses of nonsleepy subjects in any of the outcomes measured, either the raw data outcomes or the factor analysis.

## DISCUSSION

This randomized controlled trial has compared the treatment efficacy of CPAP and the medical dental sleep appliance (MDSA) oral appliance in 114 subjects with mild to moderate OSA (AHI, 5–30). We have shown that these subjects have a significant disease burden with respect to sleep quality, sleep hypoxemia, quality of life, daytime sleepiness, symptoms, neurobehavioral function, and blood pressure. With intention-to-treat analysis, it was found that both CPAP and MAS were more effective than placebo in treating obstructive sleep breathing events, sleep fragmentation, and hypoxemia, but CPAP was superior to MAS in this regard. Both treatments were more effective than placebo in improving quality of life, symptoms, and subjective but not objective sleepiness, with neither treatment being better than the other. When compared with placebo, CPAP improved vigilance, complex cognitive function, and several mood subscales, whereas MAS improved the complex cognitive function task. Many of the neurobehavioral tests showed a significant improvement after placebo, emphasizing the importance of placebo-controlled studies. There was no response in blood pressure to CPAP; however, MAS improved the nocturnal diastolic blood pressure and significantly increased the proportion of subjects with a normal night-time dip in blood pressure.

Self-reported adherence to the MAS was greater than the (objectively) measured CPAP use. It is a significant limitation of this study that whereas CPAP adherence was measured covertly and objectively, the MAS adherence was by self-report diary, and responses were obtained in only 60% of subjects who completed the MAS arm. It is to be expected that this has overestimated the actual use of the MAS device. For those patients who completed MAS diaries, use was not correlated with objective efficacy but was correlated with improvements in subjective sleepiness and symptoms. Thus, as might be expected, those subjects who felt that they gained a benefit from the splint used it the most. However, this was not reflected in any objective benefit. CPAP use did not correlate with neurobehavioral improvement, despite supervised CPAP use on the night before neurobehavioral testing. Although subjects reported that CPAP was the most difficult treatment to use, they felt that it was the most effective and overall preferred it to the MAS, which was in turn preferred to the placebo.

Another potential limitation of this study was the dropout

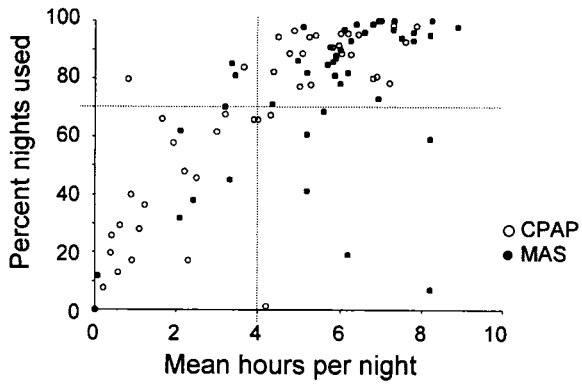


***Figure 5.*** Adherence to CPAP and MAS by hours used per night and percentage of nights used. Forty three percent of the subjects used CPAP for at least 4 hours for at least 70% of nights, and 71% used the MAS for at least 4 hours for at least 70% of nights.

rate, with 30% of subjects failing to complete all three treatment arms. However, given the significant time commitment of participants (four overnight sleep studies, 4 full days of testing plus at least 7 half days of other appointments) over 11–12 months, this dropout rate was expected. The dropout rate was the same in each treatment arm, and there was no effect of treatment order; therefore, we do not believe that the dropouts have influenced the study results. The only baseline difference between dropouts and those who completed was in subjective assessment of disease consequences (quality of life, symptoms, and sleepiness). Subjects who completed the study had milder disease than those who dropped out. The possible consequence of this bias is that the magnitude of the treatment response would have been greater had the dropouts continued.

Previous studies comparing the efficacy of oral appliances and CPAP in the treatment of subjects with a wide range of OSA severity (25–30) have shown that although both CPAP and oral appliances improved sleep fragmentation and hypoxemia, CPAP was more effective. Our study supports these findings and additionally has shown benefits over placebo in quality of life, symptoms, and daytime sleepiness for both CPAP and MAS. CPAP was markedly more effective than MAS in improving sleep fragmentation and hypoxemia at the final sleep study; yet when compared with placebo, CPAP treatment resulted in no greater improvement than MAS in some measures of daytime function (sleepiness, executive function, quality of life) or was found to have only a very slight advantage (mood). This apparent discrepancy may relate to differences in treatment adherence over the 3-month treatment periods with an otherwise superior CPAP treatment response being moderated by relatively poor adherence. An exception to this is the observation that alertness (measured by visual analog scale as the state rather than trait of alertness), vigilance (Psychomotor Vigilance Task lapses), and complex cognitive function (PASAT 1.2 seconds) were significantly better after CPAP than after MAS or placebo on the mornings after the sleep studies. This may be due to a superior acute treatment effect from CPAP when the treatment use was supervised.

Two randomized, placebo-controlled trials have compared MAS and CPAP treatment responses in subjects with mild to moderate OSA. Engleman and colleagues (28) performed a subgroup analysis on 18 subjects with AHI of 15 or less and failed to find a statistically significant improvement in AHI with the oral appliance used, whereas we have now shown that both the CPAP and MAS responses extend to subjects with mild disease. The lack of the MAS response may be due to the small subject numbers in the Edinburgh trial (i.e., a type II error). Our results with respect to beneficial responses in symptoms, quality of life, and sleepiness in mild disease concur with this group, but we found a smaller improvement in neuropsychologic function. This may be partially explained by the uncontrolled design of the Edinburgh trial, in that many of our subjects derived a significant benefit in neuropsychologic function from the placebo tablet. The other study of Randerath and colleagues (29) recruited 20 subjects with an AHI of 5–30 and found a significant improvement in sleep fragmentation and hypoxemia with CPAP but not with the oral device. The oral devices were set at a fixed 66% protrusion rather than being adjusted to suit the individual subject, which may partially explain the lack of response, and again, there may be a type II error with the small subject numbers. Two recent meta-analyses concluded that there was insufficient evidence to show that CPAP improves sleepiness (8) or general health and quality of life (9) in patients with mild to moderate OSA. The results of this study help close this knowledge gap. We have shown that in this patient group, CPAP significantly improves subjective but not objective daytime sleepiness, as well as a wide range of other neurobehavioral sequelae of OSA (8, 9).

Our results do not concur with those of Barbé and colleagues (40), who found that subjects who are not subjectively sleepy during the day do not respond to CPAP. Despite having milder disease (mean [SEM] AHI 20.3 [1.9] in our study vs. 54 [3] and 57 [4] for the two groups in the Barbé study) and less impairment in terms of neuropsychologic function and quality of life, our nonsleepy subjects had the same CPAP response as our sleepy subjects; additionally, the MAS treatment was less effective in nonsleepy subjects only for vigilance and subjective sleepiness. The subjects of Barbé and colleagues were treated for only 6 weeks, which may be insufficient time to see a full treatment response.

Previous studies have shown that the severity of OSA is independently associated with systemic hypertension (41) in a linear fashion (42, 43) and that treatment of hypertensive subjects with OSA with CPAP results in an improvement in blood pressure (44–48). Additionally, patients with OSA have been shown to have pulmonary hypertension (49), right (50), and left (51) ventricular hypertrophy (51) and left ventricular systolic dysfunction, which respond to CPAP therapy (52–54). We are unaware of any published study that has measured or documented a response in blood pressure or cardiac function to an oral appliance. The significant association found between AHI and systemic hypertension confirms previous work from our group (41), but we found no association between AHI and the echocardiographic measures we have used to reflect right (pulmonary artery pressure) and left (left ventricular wall thickness and mass) heart strain due to OSA. This may reflect a type II statistical error due to the small number of observations.

The blood pressure response to MAS in our subjects was not seen with CPAP treatment. There are four published randomized controlled trials of CPAP treatment on blood pressure in OSA (46, 48, 55, 56). The first parallel-design trial enrolled 31 subjects and showed the same small fall in blood pressure with 1 week of effective CPAP as with 1 week of sham CPAP. However, the sham CPAP in this trial reduced the respiratory disturbance index from a mean of 41.7 to 28.1, a lesser effect than CPAP, but perhaps enough to have a small effect on blood pressure. Alternatively, 1 week of CPAP treatment may have been inadequate to achieve a blood pressure response. The second study was a crossover trial and enrolled 71 nonhypertensive patients with an AHI of 15 or more and showed a statistically significant (although probably clinically insignificant) improvement with CPAP of 1.5 mm Hg in the 24-hour diastolic blood pressure compared with an oral placebo. The analysis was repeated in a subgroup of 14 subjects with more than 20 4% oxygen desaturations per hour, and significant improvements were seen in 24-hour systolic, 24-hour diastolic, and mean arterial blood pressure. The third study, also a parallel design, enrolled 118 men and showed a significant improvement in ambulatory blood pressure of between 3.0 and 4.2 mm Hg in those who used CPAP compared with those using sham CPAP. However, in those subjects who were below the median of 33 episodes of more than 4% oxygen desaturation per hour, the blood pressure difference was only 1.1 mm Hg ($p = 0.4$). The most recent study was also a parallel design, comparing subtherapeutic (3–4 cm $H_2O$) to therapeutic CPAP. This group used a Portapres to measure ambulatory blood pressure and found blood pressure falls of 10.3–12.6 mm Hg. These studies enrolled all eligible sleep clinic subjects, who had much more severe sleep-disordered breathing than our own group of subjects and thus potentially more severe hypertension and therefore a greater chance of response. Both the Edinburgh (48) and Oxford (46) groups looked separately at the more severe subjects in their groups and found a much greater benefit for CPAP in those subjects. Additionally, the

Oxford group found no benefit for those subjects with a 4% oxygen desaturation rate below 33; only nine of our subjects had a 4% desaturation rate of 33 or greater. It is likely therefore that the severity of sleep-disordered breathing in our group of subjects with mild to moderate OSA would have only a small effect on blood pressure, and this may explain the lack of response to CPAP. Nonetheless, the blood pressure response to MAS was greater than that to CPAP and raises the possibility that some aspect of CPAP treatment may mitigate against a lowering of blood pressure in the mild OSA severity range. To our knowledge, there have been no other published controlled trials of the effect on blood pressure of treating subjects with OSA with CPAP, and none with an oral appliance.

There has been concern that vertical dimension opening of an oral appliance may result in posterior movement of the tongue and soft palate with consequent reduction of the posterior airway space (57) and worsening of sleep-disordered breathing. The AHI increase in uncontrolled oral appliance trials has been attributed to a problem with the design of the oral appliance; however, we found that significantly fewer subjects had an AHI increase with MAS than with placebo; therefore, this increase is probably a failure of treatment rather than a consequence of treatment. One recent study has supported this and has shown that vertical dimension of opening has no effect on device efficacy (58).

We have conclusively shown in this large and complex randomized controlled study that CPAP and MAS are effective in treating sleep-disordered breathing in subjects with an AHI of 5–30, although CPAP appears to be superior to the oral appliance. They are both also effective in alleviating symptoms, improving daytime sleepiness, quality of life, and some aspects of neurobehavioral function, with CPAP use being less than self-reported MAS use. Nevertheless, more subjects and their domestic partners felt that CPAP was the most effective treatment, although MAS was easier to use. Nocturnal systemic hypertension was shown to improve with MAS but not CPAP, although the changes are small.

Despite these positive responses for both treatments, there remain significant residual neurobehavioral deficits, perhaps related to poor usage of CPAP and lesser efficacy of MAS. An ongoing challenge for sleep physicians is to develop treatment options that are as effective as CPAP and that are widely acceptable to patients and their families.

***Conflict of Interest Statement***: M.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.D.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; N.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.G.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; N.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.J.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript

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