

TITLE PAGE

Title: Efficacy of Positive Airways Pressure and Oral Appliance in Mild to Moderate Obstructive Sleep Apnea

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Sources of Financial Support:

National Health and Medical Research Council of Australia provided funding for the project and a post-graduate scholarship for Dr. Maree Barnes

ResMed Australia (Sydney) supplied the CPAP pumps

RJ & VK Bird (Melbourne) supplied the mandibular advancement splints

Running Head: CPAP and Oral Appliance for Sleep Apnea

Subject Category: 111. Sleep-disordered breathing: treatment

This article has an online data supplement, which is accessible from this issue's Table of Contents online at www.atsjournals.org

ABSTRACT

The efficacy of currently-recommended treatments is uncertain in patients with mild to moderate obstructive sleep apnea (apnea-hypopnea index 5-30). A group of 114 sleep clinic patients with apnea-hypopnea index 5-30 have participated in a randomized controlled crossover trial of 3 months treatment with each of nasal continuous positive airways pressure, 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 airways pressure had a greater effect. 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 neuropsychological function and mood were not better than the placebo effect. Some aspects of nocturnal blood pressure were improved with the splint but not with continuous positive airways pressure. This study has shown that although both continuous positive airways pressure 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 continuous positive airways pressure being poorly tolerated and therefore used less in this patient group.

Key Words: Sleep Apnea, Obstructive

Controlled Clinical Trials, Randomized

Mandibular Advancement

Positive Pressure Ventilation

INTRODUCTION

Obstructive sleep apnea (OSA) syndrome is a common condition affecting at least 2% adult females and 4% adult males¹. 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 remains a clinical dilemma. It has been convincingly demonstrated that patients with apnea hypopnea index (AHI) >30 have significant neuropsychological morbidity, which is improved by nasal continuous positive airways pressure (CPAP) therapy²⁻⁶. A recent meta-analysis of studies of the neuropsychological effects of obstructive sleep apnea⁷ concluded that there are insufficient data to adequately assess the impairment in subjects with mild OSA, particularly those with AHI < 15. The therapeutic effect of CPAP on daytime sleepiness was examined in another recent meta-analysis⁸. 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 ≤ 30) to draw a valid conclusion for these subjects. These findings were supported by a recent Cochrane Review⁹ 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) remains inconclusive. There have been five randomized controlled trials of CPAP in subjects with mild to moderate OSA¹⁰⁻¹⁴. These have showed a modest effect of CPAP, but there is a significant placebo effect and treatment adherence is poor. Perhaps due to 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 probably multi-factorial, involving both a structural change with enhancement of the calibre of the airway and also triggering of stretch receptors which activate the airway support muscles¹⁶. There are three published randomized placebo controlled trials assessing the efficacy of oral appliances in subjects with a wide range of OSA severity¹⁷⁻¹⁹. 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 1/3 subjects in the third study). However the first two studies did not measure neurobehavioral or blood pressure outcomes, and while 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 usage could be titrated and predicted from an overnight sleep study, no other outcomes were measured. Additionally, up to one-third of all OSA subjects may have clinical or structural contra-indications to the use of oral appliances²², and up to 1 in 4 subjects may be unable to tolerate the device²³. 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 CPAP²⁴, there are inadequate placebo-controlled data to support this.

Six randomised but uncontrolled crossover studies have compared CPAP to oral appliances²⁵⁻³⁰. 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 outcomes²⁸ and found that while both treatments 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 6 in which subjects preferred CPAP to the oral appliance.

There is an obvious need to further define 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 abstract³¹.

METHODS

Word Count for this section: 544

Full details of study design and methods used are provided in the Online Data Supplement.

A randomized three-way crossover trial was conducted in two Australian centres (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 obstructive sleep apnea (AHI 5-30/hour). The responses to 3 months treatment with nasal CPAP (Sullivan Elite, ResMed, Australia), a mandibular advancement splint (Medical Dental Sleep Appliance, RJ & VK Bird, Australia) and placebo tablet were compared.

Ethics Committee approvals and informed subject consent were obtained. Randomisation and subject eligibility were the same as our previously reported study of CPAP in mild OSA patients¹², with the additional requirement of healthy and adequate dentition to enable MAS usage.

At the beginning of the trial and at the end of each 3-month treatment period all subjects underwent overnight polysomnography (PSG), comprehensive neurobehavioral testing (Table E1), 24-hour ambulatory blood pressure and echocardiography. Subjects were categorised as hypertensive using previous definitions³¹ and as blood pressure dippers or non-dippers³². 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 PSG performed at the end of each washout period to confirm the return of sleep study variables to baseline.

PSG (including analysis and scoring definition) and CPAP implementation were performed as previously described¹². The Maintenance of Wakefulness Test (MWT) was performed and analysed according to standard guidelines³³ on the day following the overnight sleep study. Prior to each MWT nap, subjects completed the Stanford Sleepiness Scale³⁴ and a visual analog scale assessing subjective alertness and well-being (Appendix 1, Online Supplement). Protocols for overnight PSG, MWT and neurobehavioral tests were standardized between the two centers. Inter- and intra-scorer reliability were measured using intraclass correlation co-efficients and paired T-tests, which were within acceptable published limits³⁵.

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

Subjects received a custom-made MAS which has a maximum protrusion of 12mm, in 0.25mm 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 calculated³⁶ using the Epworth Sleepiness Scale (ESS) as the primary outcome variable. An intention to treat analysis of treatment response was performed, using repeated measures ANOVA with Bonferroni correction. Due to the large number of response variables, a two-stage factor analysis was also performed, and five significant factors were found. These were analysed 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 \pm SEM unless otherwise stated.

RESULTS

Subject Selection and Retention

114 OSA subjects were recruited, of whom 80 completed all three treatment arms (Fig 1). 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, gender, age, obesity) in those who completed and dropouts were the same. However, 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 to 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 Table 1.

Subjects were middle-aged (47.0 ± 0.9 years), predominantly male (80%) and overweight (interquartile range BMI 27.8-32.8kg/m²), with mild to moderate obstructive sleep apnea (AHI 5-30/h). Pre-morbid IQ (as indicated by the NART-R) showed that 98% of OSA subjects were within 2 standard deviations of the normal population mean, validating our use and interpretation of the neuropsychological 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; following this, there were no further changes in mandibular advancement and no subject required an extra dental visit.

Polysomnography Table 2 and Online Supplement Table E2.

The results of sleep studies performed at the end of the washout period in the first 18 subjects to complete the study showed that after 2 weeks without treatment, sleep-disordered breathing had returned to baseline pre-treatment levels (Fig 2), confirming the adequacy of the washout period for sleep-disordered breathing.

Compared with placebo, both CPAP and MAS improved the AHI and sleep hypoxemia, although the response was greater with CPAP than MAS. There was a significant reduction in stage one 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 Table 2 and Online Supplement Table E3.

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 subjects³⁷). 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 (ie in the pathologically sleepy range³⁸). Using an ESS cutoff of >10 and a MWT cutoff of <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 or subjective sleepiness. The Sleep Apnea Symptom Questionnaire score was high at 64.7 ± 1.7 compared to reported normal values³⁹.

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.

Neuropsychological Function and Mood

Table 2 and Online Supplement Table E4.

A broad range of neuropsychological function was assessed (Table E1). CPAP increased vigilance (ie decreased PVT lapses) and both CPAP and MAS were superior to placebo in improving executive cognitive function (PASAT 1.2). No other treatment effects on neurocognitive function were observed.

Clinically significant depression (BDI) was present in 40.4% OSA subjects. Compared with placebo, CPAP resulted in improvements in 4 domains of the POMS 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

Table 2 and the Online Supplement Table E5.

Compared to placebo, MAS treatment improved quality of life as measured by the FOSQ mean score and social outcome domain, and by the sf36 overall health score. CPAP treatment was effective with respect to FOSQ overall score and activity level, as well as the sf36 mean score and well-being.

Blood Pressure and Echocardiography

Table 2

Of the 110 OSA subjects who had baseline 24-hour ambulatory blood pressure measurement, 16 were hypertensive (BP systolic >140 and/or BP diastolic >90), and 44 were non-dippers. After controlling for age, gender and BMI, 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, 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 (Fig 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 non-dippers. With MAS treatment, a significant proportion of non-dipper subjects regained their normal nocturnal dip in blood pressure, but not with either CPAP or placebo (Fig 3).

Transthoracic echocardiography is technically challenging in obese subjects and complete measurements were not possible in all OSA subjects. The methodology used to measure pulmonary artery pressure (PAP) required a regurgitant tricuspid jet, therefore baseline PAP measurements were available in only 35 OSA subjects. The PAP in these subjects was 20.5 ± 0.9 mmHg, 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.

Factor Analysis

Factor One 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 (fig 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 (fig 4B). Factor Three described neurocognitive function and summarised 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 (fig 4C). Factor Four described vigilance, mainly the psychomotor vigilance task. Again, neither of the active treatments was better than placebo (fig 4D). Factor Five described mood and self-assessment, and comprised mainly the Beck Depression Index, Profile of Mood States total mood disorder score and the sf36. Only CPAP was more effective than placebo (fig 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 neuropsychological function and vigilance, but in addition to a CPAP response in mood, almost 2/3 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 $\frac{2}{3}$ subjects had their best response to CPAP, $\frac{1}{4}$ responded best to MAS and placebo had the greatest effect in 10% subjects.

Treatment Adherence

CPAP usage was measured objectively by an inbuilt meter which measured time at pressure, MAS usage 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 ± 0.3 nights per week and for an average of 3.6 ± 0.3 hours per night over the whole treatment period. Complete MAS diary data was available for 49 of the 85 subjects who completed the MAS treatment arm; the reported use was 5.3 ± 0.3 nights per week for 5.5 ± 0.3 hours per night over the whole 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 proposed² that effective CPAP treatment of OSA requires usage 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 (71%) subjects treated with MAS (for whom we have usage data) received adequate treatment (fig 5). It should be noted however, that on the night prior to the neurobehavioral assessment, adherence was 100% for each treatment.

Subjects were categorised according to whether or not 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 whole 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 whole group except in factor 2 (sleepiness and symptoms) where the response was limited to users only.

Treatment Preference

Both OSA subjects 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 (Fig E2). MAS was the overall preferred treatment for 30% subjects and 36% domestic partners.

Mandibular Advancement Splint Fitting and Response

Mandibular advancement with the MAS was 10.3 ± 0.3 mm, and ranged between 1-13mm. 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 5 events per hour (range 5.1 – 48.0), 14% had an AHI increase of at least 5 events per hour (range 5.2-20.1), and 29.9% subjects changed by less than 5 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 studies¹⁷. 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 are 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 baseline AHI ≤ 15 was performed. Both CPAP ($p < 0.001$) 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%) of subjects achieved the MAS treatment target of AHI ≤ 10 . The best effect size response was similar to the group as a whole, with 66% subjects having their best response to CPAP, 26% with MAS and 8% to 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, FOSQ and sf36. Neither treatment was superior to the other. Although there was some improvement in neuropsychological function, it was not better than placebo. In this group, 28% preferred CPAP, 41% preferred MAS and 31% preferred placebo.

Sleepy vs. Non-sleepy Subjects

Our subject group comprised 53 ‘sleepy’ patients with an ESS ≥ 11 , and 61 ‘non-sleepy’ subjects with ESS ≤ 10 . Non-sleepy subjects had a significantly better baseline FOSQ 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 non-sleepy 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 MDSA oral appliance in 114 mild to moderate OSA subjects (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 sub-scales, while MAS improved the complex cognitive function task. Many of the neurobehavioral tests showed a significant improvement following placebo, emphasising 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 usage. 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 over-estimated the actual

use of the MAS device. For those patients who completed MAS diaries, usage was not correlated with objective efficacy, but was correlated with improvements in subjective sleepiness and symptoms. So 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 usage did not correlate with neurobehavioral improvement, despite supervised CPAP usage on the night prior to 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 rate, with 30% subjects failing to complete all three treatment arms. However given the significant time commitment of participants (4 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 severity²⁵⁻³⁰ have shown that while 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 analogue scale as the state rather than trait of alertness), vigilance (PVT lapses) and complex cognitive function (PASAT 1.2sec) 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 *et al*²⁸ performed a sub-group analysis on 18 subjects with $AHI \leq 15$ 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 (ie 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 neuropsychological 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 neuropsychological function from the placebo tablet. The other study of Randerath *et al*²⁹ recruited 20 subjects with AHI 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

sleepiness⁸ or general health and quality of life⁹ in patients with mild to moderate OSA. The results of the present 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 *et al*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 2 groups in the Barbé study) and less impairment in terms of neuropsychological function and quality of life, our non-sleepy subjects had the same CPAP response as our sleepy subjects; additionally, the MAS treatment was less effective in non-sleepy subjects only for vigilance and subjective sleepiness. The subjects of Barbé *et al* 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 obstructive sleep apnea is independently associated with systemic hypertension⁴¹ in a linear fashion^{42, 43} and that treatment of hypertensive OSA subjects with CPAP results in an improvement in blood pressure⁴⁴⁻⁴⁸. Additionally, patients with OSA have been shown to have pulmonary hypertension⁴⁹, right⁵⁰ and left⁵¹ ventricular hypertrophy⁵¹ and left ventricular systolic dysfunction which respond to CPAP therapy⁵²⁻⁵⁴. We are unaware of any published study which 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 group⁴¹, 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 obstructive sleep apnea. 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 thirty-one 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, one week of CPAP treatment may have been inadequate to achieve a blood pressure response. The second study was a crossover trial, and enrolled seventy-one non-hypertensive patients with AHI \geq 15, and showed a statistically significant (although probably clinically insignificant) improvement with CPAP of 1.5mmHg in the 24-hour diastolic blood pressure, compared to an oral placebo. The analysis was repeated in a subgroup of 14 subjects with more than twenty 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 4.2mmHg in those who used CPAP compared to those using sham CPAP. However in those subjects who were below the median of 33 episodes of >4% oxygen desaturation per hour, the blood pressure difference was only 1.1mmHg (p=0.4). The most recent study was also a parallel design, comparing sub-therapeutic (3-4cmH₂O) to therapeutic CPAP. This group used a Portapres to measure ambulatory blood pressure, and found blood pressure falls of 10.3-12.6mmHg. 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 Edinburgh⁴⁸ and Oxford⁴⁶ 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 9 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 obstructive sleep apnea 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 OSA subjects 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 space⁵⁷ 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 shown that vertical dimension of opening has no effect on device efficacy⁵⁸.

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 AHI 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 usage being less than self-reported MAS usage. 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 which are as effective as CPAP and which are widely acceptable to patients and their families.

ACKNOWLEDGEMENTS

The authors would like to thank the sleep laboratory staff at both institutions for their advice, help and good humor; and Dr Andrew Russell and Mr Brian Dunn, Cardiographics, at Repatriation General Hospital Daw Park and Ms. Jann Lauri at the Austin Hospital for their assistance with the ambulatory blood pressure measurements.

REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230-1235.
2. Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, Redline S, Henry JN, Getsy JE, Dinges DF. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Resp Dis* 1993;147:887-95.
3. Naegele B, Pepin J-L, Levy P, Bonnet C, Pellat J, Feuerstein C. Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. *Sleep* 1998;21:392-397.
4. Engleman HM, Martin SE, Kingshott RN, Mackay TW, Deary IJ, Douglas NJ. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. *Thorax* 1998;53:341-5.
5. Ballester E, Badia JR, Hernandez L, Carrasco E, de Pablo J, Fornos C, Rodriguez-Roisin R, Montserrat JM. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999;159:495-501.

6. Jenkinson C, Davies R, Mullins R, Stradling J. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. *Lancet* 1999;353:2100-05.
7. Beebe DW, Goesz L, Wells C, Nichols A, McGee K. The neuropsychological effects of obstructive sleep apnea: A meta-analysis of norm-referenced and case-controlled data. *Sleep* 2003;26:298-307.
8. Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous Positive Airway Pressure Therapy for Treating Sleepiness in a Diverse Population With Obstructive Sleep Apnea: Results of a Meta-analysis. *Arch Intern Med* 2003;163:565-571.
9. White J, Cates C, Wright J. Continuous positive airways pressure for obstructive sleep apnoea . The Cochrane Library 2003.
10. Redline S, Adams N, Strauss ME, Roebuck T, Winters M, Rosenberg C. Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. *Am J Respir Crit Care Med* 1998;157:858-865.
11. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep Apnea/Hypopnea syndrome. *Am J Resp Crit Care Med* 1999;159:461-7.
12. Barnes M, Houston D, Worsnop CJ, Neill AJ, Mykityn IJ, Kay AJ, Trinder J, Saunders NA, McEvoy RD, Pierce RJ. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. *Am J Respir Crit Care Med* 2002;165:773-780.
13. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. *Thorax* 1997;52:114-9.
14. Monasterio C, Vidal S, Duran J, Ferrer M, Carmona C, Barbe F, Mayos M, Gonzalez-Mangado N, Juncadella M, Navarro A, Barreira R, Capote F, Mayoralas LR, Peces-Barba G, Alonso J, Montserrat JM. Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med* 2001;164:939-943.
15. Lamphere J, Roehrs T, Wittig R, Zorick F, Conway W, Roth T. Recovery of alertness after CPAP in apnea. *Chest* 1989;96:1364-1367.
16. Ng AT, Gotsopoulos H, Qian J, Cistulli PA. Effect of Oral Appliance Therapy on Upper Airway Collapsibility in Obstructive Sleep Apnea. *Am. J. Respir. Crit. Care Med.* 2003;168:238-241.
17. Mehta A, Qian J, Petocz P, Darendeliler MA, Cistulli PA. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. *Am J Respir Crit Care Med* 2001;163:1457-1461.
18. Gotsopoulos H, Chen C, Qian J, Cistulli PA. Oral appliance therapy improves symptoms in obstructive sleep apnea: A randomized, controlled trial. *Am J Respir Crit Care Med* 2002;166:743-748.
19. Johnston C, Gleadhill I, Cinnamond M, Gabbey J, Burden D. Mandibular advancement appliances and obstructive sleep apnoea: a randomized clinical trial. *Eur J Orthod.* 2002;24:251-62.
20. Tsai WH, Vazquez J-C, Oshima T, Dort L, Roycroft B, Lowe AA, Hadjuk E, Remmers JE. Remotely Controlled Mandibular Positioner Predicts Efficacy of Oral Appliances in Sleep Apnea. *Am J Resp Crit Care Med* 2004;Epub ahead of print:200310-1446OC.
21. Petelle B, Vincent G, Gagnadoux F, Rakotonanahary D, Meyer B, Fleury B. One-Night Mandibular Advancement Titration for Obstructive Sleep Apnea Syndrome . A Pilot Study. *Am J Respir Crit Care Med* 2002;165:1150-1153.
22. Petit F-X, Pepin J-L, Bettiga G, Sadek H, Raphael B, Levy P. Mandibular Advancement Devices: Rate of Contraindications in 100 Consecutive Obstructive Sleep Apnea Patients. *Am J Respir Crit Care Med* 2002;166:274-278.
23. Marklund M, Stenlund H, Franklin KA. Mandibular Advancement Devices in 630 Men and Women With Obstructive Sleep Apnea and Snoring: Tolerability and Predictors of Treatment Success. *Chest* 2004;125:1270-1278.
24. American Sleep Disorders Association. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. *Sleep* 1995;18:511-516.
25. Ferguson K, Ono T, Lowe A, Keenan S, Fleetham J. A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. *Chest* 1996;109:1269-1275.
26. Ferguson K, Ono T, Lowe A, al-Majed S, Love L, Fleetham J. A short-term controlled trial of an adjustable oral appliance for the treatment of mild to moderate obstructive sleep apnoea. *Thorax* 1997;52:362-368.

27. Clark G, Blumenfeld I, Yoffe N, Peled E, Lavie P. A crossover study comparing the efficacy of continuous positive airway pressure with anterior mandibular positioning devices on patients with obstructive sleep apnea. *Chest* 1996;109:1477-1483.
28. Engleman HM, McDonald JP, Graham D, Lello GE, Kingshott RN, Coleman EL, Mackay TW, Douglas NJ. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. *Am J Respir Crit Care Med* 2002;166:855-859.
29. Randerath WJ, Heise M, Hinz R, Ruehle K-H. An individually adjustable oral appliance vs continuous positive airway pressure in mild-to-moderate obstructive sleep apnea syndrome. *Chest* 2002;122:569-575.
30. Tan Y, L'Estrange P, Luo Y, Smith C, Grant H, Simonds A, Spiro S, Battagel J. Mandibular advancement splints and continuous positive airway pressure in patients with obstructive sleep apnoea: a randomized cross-over trial. *Eur J Orthod* 2002;24:239-49.
31. Barnes M, McEvoy R, Pierce R. Neurobehavioural impairment in mild sleep apnea patients compared to control subjects. *Sleep* 2001;24S:A276.
32. Ancoli-Israel S, Stepnowsky C, Dimsdale J, Marler M, Cohen-Zion M, Johnson S. The effect of race and sleep-disordered breathing on nocturnal BP "dipping": analysis in an older population. *Chest* 2002;122:1148-1155.
33. Mitler M, Gujavarty K, Browman C. Maintenance of wakefulness test: a polysomnographic technique for evaluation treatment efficacy in patients with excessive somnolence. *Electroencephalogr Clin Neurophysiol* 1982;53:658-61.
34. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement W. Quantification of sleepiness: a new approach. *Psychophysiology* 1973;10:431-6.
35. Shahar E, Whitney C, Redline S, Lee E, Newman AB, Javier Nieto F, O'Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered breathing and cardiovascular disease. Cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;163:19-25.
36. Bach L, Sharpe L. Sample size for clinical and biological research. *Aust N Z J Med* 1989;19:64-68.
37. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-5.
38. Mitler M, Doghramji K, Shapiro C. The maintenance of wakefulness test: normative data by age. *J Psychosom Res* 2000;49:363-5.
39. Goudge R, Goh N, Barnes M, Howard M, Worsnop C. Validation Of A Sleep Apnoea Symptom Questionnaire. *Am J Respir Crit Care Med* 2001;163:A933.
40. Barbe F, Mayoralas L, Duran J, Masa J, Maimo A, Montserrat J, Monasterio C, Bosch M, Lalaria A, Rubio M, Rubio R, Medinas M, Hernandez L, Vidal S, Douglas N, Agusti A. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. a randomized, controlled trial. *Ann Intern Med* 2001;134:1015-23.
41. Worsnop CJ, Naughton MT, Barter CE, Morgan TO, Anderson A, Pierce RJ. The prevalence of obstructive sleep apnea in hypertensives. *Am J Respir Crit Care Med* 1998;157:111-115.
42. Hla KM, Young TB, Bidwell T, Palta M, Skatrud JB, Dempsey J. Sleep apnea and hypertension. A population-based study. *Ann Intern Med* 1994;120:382-388.
43. Grote L, Hedner J, Peter JH. Sleep-related breathing disorder is an independent risk factor for uncontrolled hypertension. *J Hypertens* 2000;18:679-85.
44. Naughton M, Pierce R. Effects of nasal continuous positive airway pressure on blood pressure and body mass index in obstructive sleep apnoea. *Aust N Z J Med* 1991;21:917-9.
45. Hla KM, Skatrud JB, Finn L, Palta M, Young T. The Effect of Correction of Sleep-Disordered Breathing on BP in Untreated Hypertension. *Chest* 2002;122:1125-1132.
46. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 2002;359:204-10.
47. Wilcox I, Grunstein RR, Hedner JA, Doyle J, Collins FL, Fletcher PJ, Kelly DT, Sullivan CE. Effect of nasal continuous positive airway pressure during sleep on 24-hour blood pressure in obstructive sleep apnea. *Sleep* 1993;16:539-44.
48. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med* 2001;163:344-348.

49. Sajkov D, Wang T, Saunders NA, Bune AJ, Neill AM, McEvoy RD. Daytime pulmonary hemodynamics in patients with obstructive sleep apnea without lung disease. *Am J Respir Crit Care Med* 1999;159:1518-1526.
50. Guidry UC, Mendes LA, Evans JC, Levy D, O'Connor GT, Larson MG, Gottlieb DJ, Benjamin EJ. Echocardiographic features of the right heart in sleep-disordered breathing . The Framingham Heart Study. *Am J Respir Crit Care Med* 2001;164:933-938.
51. Niroumand M, Kuperstein R, Sasson Z, Hanly PJ. Impact of obstructive sleep apnea on left ventricular mass and diastolic function. *Am J Respir Crit Care Med* 2001;163:1632-1636.
52. Sajkov D, Wang T, Saunders NA, Bune AJ, McEvoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2002;165:152-158.
53. Cloward TV, Walker JM, Farney RJ, Anderson JL. Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with nasal continuous positive airway pressure. *Chest* 2003;124:594-601.
54. Laaban J, Pascal-Sebaoun S, Bloch E, Orvoen-Frija E, Oppert J-M, Huchon G. Left ventricular systolic dysfunction in patients with obstructive sleep apnea syndrome. *Chest* 2002;122:1133-1138.
55. Dimsdale JE, Loredó JS, Profant J. Effect of continuous positive airway pressure on blood pressure : a placebo trial. *Hypertension* 2000;35:144-147.
56. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 2003;107:68-73.
57. L'Estrange P, Battagel J, Harkness B, Spratley M, Nolan P, Jorgensen G. A method of studying adaptive changes of the oropharynx to variation in mandibular position in patients with obstructive sleep apnoea. *J Oral Rehabil* 1996;23:699-711.
58. Pitsis AJ, Darendeliler MA, Gotsopoulos H, Petocz P, Cistulli PA. Effect of vertical dimension on efficacy of oral appliance therapy in obstructive sleep apnea. *Am J Respir Crit Care Med* 2002;166:860-864.

FIGURE LEGENDS

Figure 1. 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 due to time commitments, either work or family. Additionally, five subjects were found to be ineligible for MAS due to poor dentition. Only 1 subject dropped out because of CPAP intolerance and 2 subjects were unable to tolerate the MAS.

Figure 2. Apnea Hypopnea Index 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.

Abbreviations: CI = Confidence Interval; W-CPAP = washout post CPAP; W-MAS = washout post MAS; W-Placebo = washout post placebo; T-CPAP = Post CPAP treatment; T-MAS = Post MAS treatment; T-Placebo = Post placebo treatment.

ns = no significant difference from baseline

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.

Figure 4. Factor results for 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.

Figure 5. Adherence to CPAP and MAS by hours used per night and percentage of nights used. 43% 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.

TABLE 1 SUBJECT CHARACTERISTICS

	Whole Group	Completed Subjects	Dropout Subjects
Age (years)	47.0(0.9)	46.4(1.1)	48.5(1.9)
Gender (% 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/hr)	21.3(1.3)	21.5(1.6)	21.1(2.3)
Arousal Index, per hr	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 (mins)	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)

All data are mean(SEM)

*p<0.05 Completed vs. Dropout Subjects

Abbreviations: BMI = Body Mass Index; AHI = Apnea Hypopnea Index; 4% O₂ desaturation = hourly rate of 4% oxygen desaturations; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; SASQ = Sleep Apnea Symptom Questionnaire; NART-R = National Adult Reading Test - Revised

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, minutes	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 Backwards	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 (mmHg)				
– 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)

All data are mean(SEM)

Definition of Abbreviations: AHI = Apnea Hypopnea Index; 4% Oxygen Desaturation = Hourly rate of oxygen desaturations of at least 4%; MWT = Maintenance of Wakefulness Test, latency to sleep; SASQ = Sleep Apnea Symptom Questionnaire; COWAT = Controlled Oral Word Association Task; PVT lapses = Psychomotor Vigilance Task, the number of responses > 500mseconds; PASAT – 1.2 = Paced Auditory Serial Addition Task at the 1.2 second speed, time per response; POMS = Profile of Moods States; FOSQ = Functional Outcomes of Sleep Questionnaire; sf36 = 36-item Medical Outcomes Study questionnaire

	p<0.05	p<0.01	p<0.001
Compared to baseline	*	†	‡
Compared to placebo	§	¶	¶
CPAP vs. MAS	**		

TABLE 3 FACTOR ANALYSIS

	Effect Sizes			Comparison to Placebo			CPAP vs. MAS
	CPAP	MAS	Placebo	Baseline	CPAP	MAS	p values
Factor One - Disease Severity	80.7	37.7	18.4	ns	‡	‡	‡
Factor Two - Symptoms and Sleepiness	50.7	35.1	22.8	ns	†	†	ns
Factor Three - Neuropsychological Function	51.8	60.5	51.8	‡	ns	ns	ns
Factor Four - Vigilance	35.1	36.8	35.1	ns	ns	ns	ns
Factor Five – Mood and Quality of Life	60.5	61.4	22.8	‡	*	ns	ns
Best Overall Response to Treatment (% subjects)	64.7	25.0	10.3				
No Response to Treatment (Effect size ≤0.2, % subjects)	2.6	2.6	6.1				

Effect Sizes: ≥ 0.2 is small, ≥ 0.5 is moderate, ≥0.8 is large.

*p<0.05 † p<0.01 ‡p<0.001

Figure 1

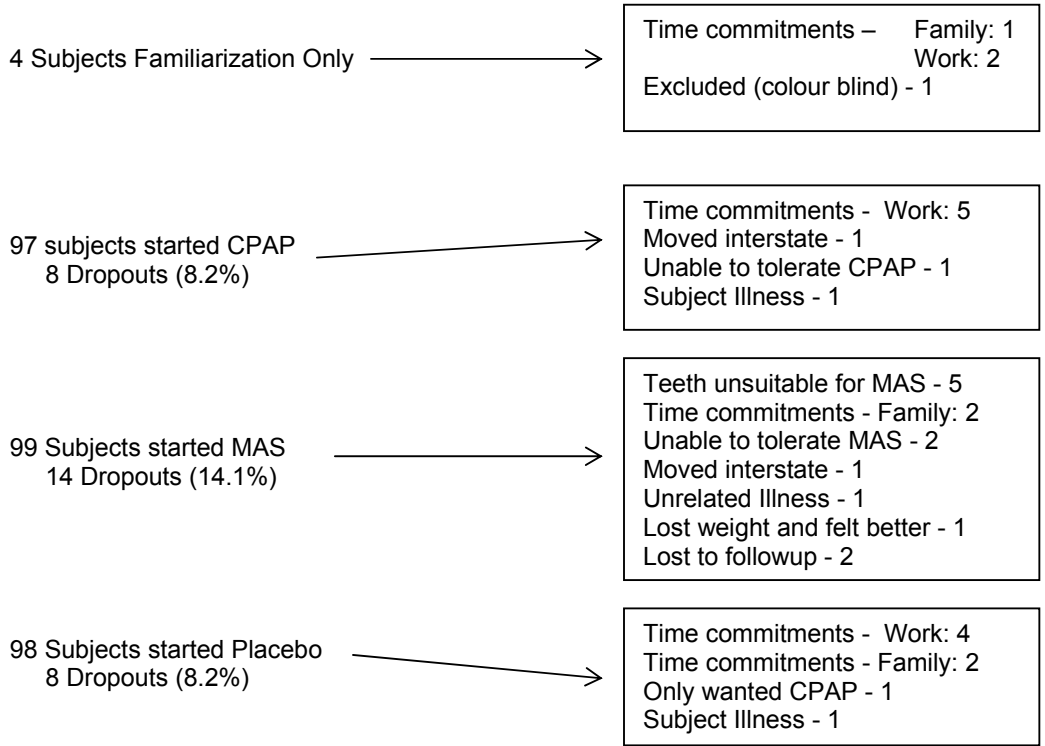


Figure 2

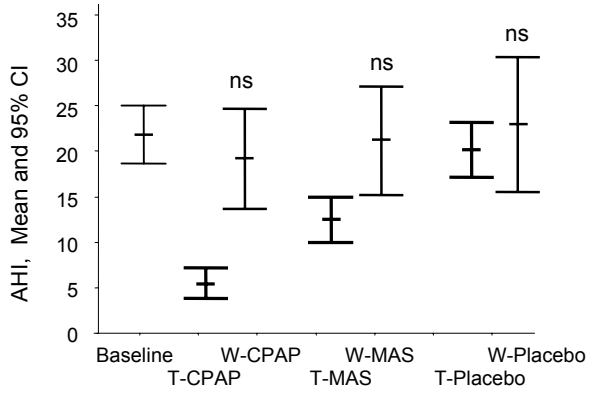


Figure 3

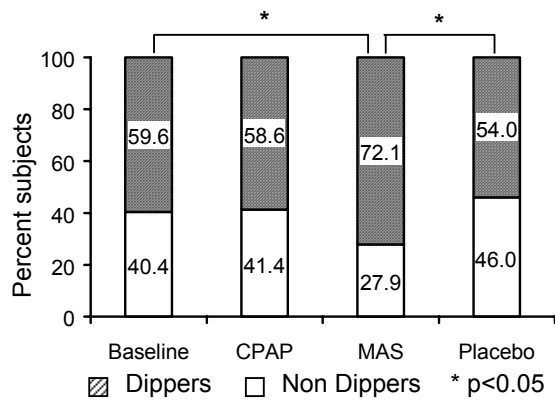
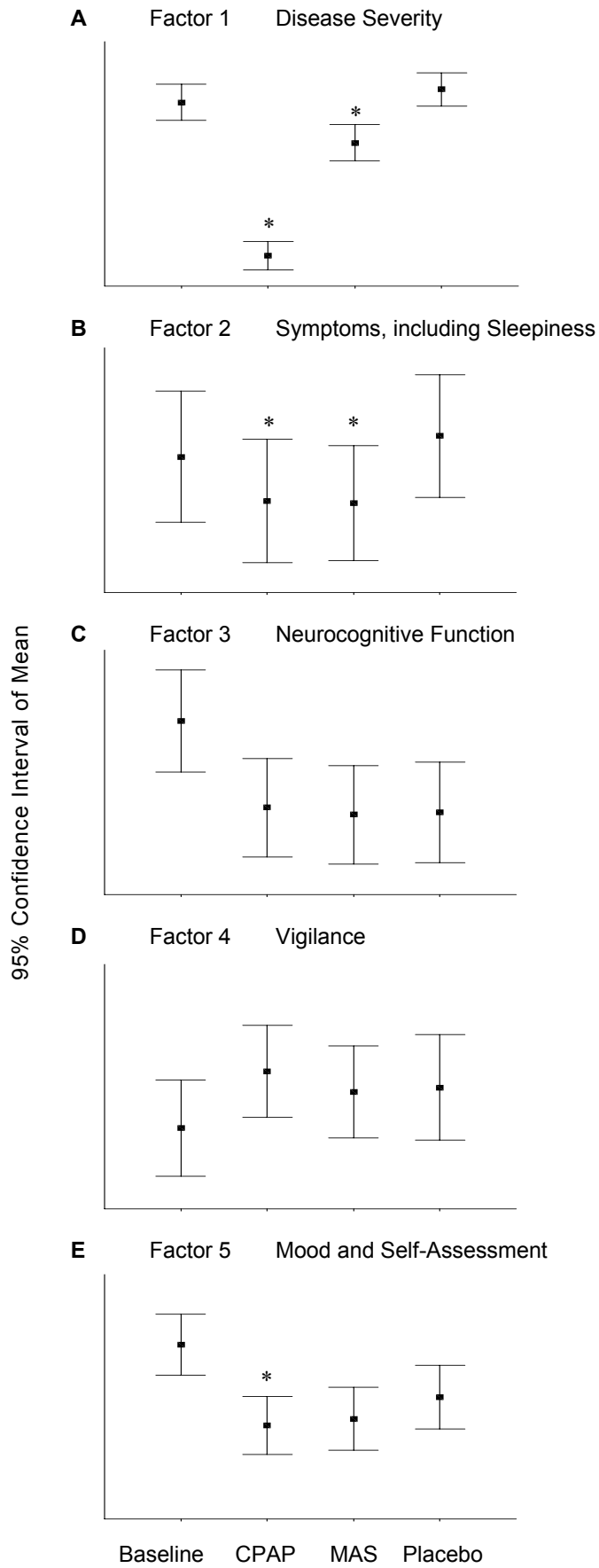


Figure 4



* p<0.05 treatment response

Figure 5

