

Oral Appliance Therapy Improves Symptoms in Obstructive Sleep Apnea

A Randomized, Controlled Trial

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The aim of this study was to evaluate the effect of a mandibular advancement splint (MAS) on daytime sleepiness and a range of other symptoms in obstructive sleep apnea (OSA). Using a randomized crossover design, patients received 4 weeks of treatment with MAS and a control device (inactive oral appliance), with an intervening 1-week washout. At the end of each treatment period, patients were reassessed by questionnaire, polysomnography, and multiple sleep latency test. Fifty-nine men and 14 women with a mean (\pm SD) age of 48 ± 11 years and proven OSA experienced a significantly improved mean (\pm SEM) sleep latency on the multiple sleep latency test (10.3 ± 0.5 versus 9.1 ± 0.5 minutes, $p = 0.01$) and Epworth sleepiness scale score (7 ± 1 versus 9 ± 1 , $p < 0.0001$) with the MAS compared with the control device after 4 weeks. The proportion of patients with normal subjective sleepiness was significantly higher with the MAS than with the control device (82 versus 62%, $p < 0.01$), but this was not so for objective sleepiness (48 versus 34%, $p = 0.08$). Other OSA symptoms were controlled in significantly more patients with the MAS than with the control device. MAS therapy improves a range of symptoms associated with OSA.

Keywords: sleep apnea; obstructive; orthodontic appliances

Obstructive sleep apnea (OSA) is a prevalent disorder, particularly among the middle-aged (1). It is marked by recurring partial or complete occlusion of the upper airway during sleep, resulting in oxyhemoglobin desaturation and arousal. The associated excessive daytime sleepiness (EDS) and nocturnal symptoms such as snoring, witnessed apneas, and sleep disruption can lead to emotional, marital, social, occupational, and road safety impairment (2, 3). The management of OSA is primarily targeted toward the relief of such debilitating symptoms (4). Although the gold standard of treatment for the disorder is nasally applied continuous positive airway pressure (nCPAP) (5), suboptimal patient compliance rates attributed mainly to its side effects and obtrusive nature have driven the search for a suitable alternative (6).

Mandibular advancement splint (MAS) therapy is gaining increasing recognition as a treatment option for a substantial number of patients with OSA (4, 7–14). These removable oral devices are believed to act by maintaining the mandible in a protruded position during sleep, thereby preventing pharyngeal collapse (15). Despite being less effective in controlling sleep-disordered breathing compared with nCPAP, they

are preferred by patients due to their user-friendliness and fewer side effects (8–10, 13). To date, however, reports on the effect of MAS therapy on symptoms associated with OSA have been predominantly based on findings from uncontrolled case series with small study populations and often a sparse description of study procedures (7, 12). Moreover, the impact of this treatment on EDS has been confined to either subjective evidence alone (7–11, 13, 14) or limited objective evidence from uncontrolled trials (16, 17). Hence, the aim of this study was to further elucidate the clinical role of MAS therapy by systematically assessing its effect on objective and subjective daytime sleepiness and on a range of other symptoms commonly linked with OSA.

METHODS

Study Participants

The present study formed part of a larger trial investigating the effect of MAS therapy on a range of health outcomes in OSA, including blood pressure and neurocognitive function. Consecutive patients who were referred for assessment and treatment of OSA to a multidisciplinary clinic for sleep disorders in a teaching hospital were recruited. Inclusion criteria were (1) evidence of OSA on polysomnography (respiratory disturbance index [RDI] ≥ 10 /hour) and at least two of the following symptoms: daytime sleepiness, snoring, witnessed apneas, or fragmented sleep; (2) age more than 20 years; and (3) the ability to protrude the mandible by at least 3 mm. Exclusion criteria were (1) predominant central sleep apnea on sleep study; (2) psychiatric disease, use of narcotics, sedatives, or psychoactive medications; (3) insufficient teeth to permit adequate splint retention; (4) periodontal disease or dental decay; or (5) an exaggerated gag reflex. Approval was obtained from the institutional Ethics Committee, and all subjects gave their written informed consent.

Study Treatment

The MAS was custom-made for individual patients, as illustrated in Figure 1. The control device consisted of the upper appliance alone, which had no protrusive effect on the mandible. Patients were informed that the aim of the study was to examine the efficacy of oral appliance therapy for OSA by comparing two appliances. With ethics approval, patient blinding to active and control treatments was achieved by concealing the likely inactive nature of the control device.

Study Design

A randomized, controlled, two-period crossover trial (AB/BA) was performed. At baseline, patients completed the Epworth sleepiness scale (ESS) questionnaire and a symptom questionnaire and underwent overnight polysomnography. This was followed by a period of acclimatization to the MAS, during which the mandible was incrementally advanced until the maximum comfortable limit was reached. The purpose of acclimatization was solely to permit adaptation to the MAS, to ensure an adequate therapeutic trial during the subsequent crossover phases of the study. Symptomatic response was specifically not assessed during this period so as to avoid potentially unblinding patients. Patients then underwent a washout period of 1 week, after which they were randomized to receive either active or control treatment for a period of 4 weeks, followed by the alternate treatment for 4 weeks with an interven-

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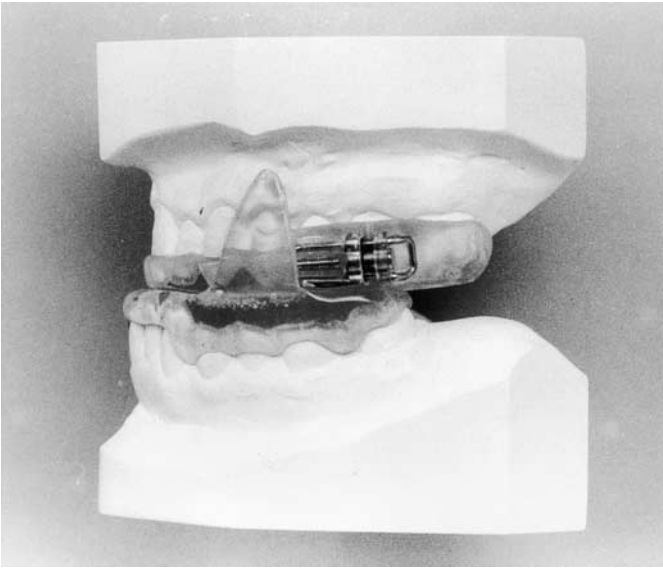


Figure 1. Photograph of the MAS mounted on study models. Design features of the MAS were (1) separate upper and lower acrylic appliances anchored onto the dental arches and covering the occlusal surfaces of all teeth. (2) Two acrylic flanges situated bilaterally on the buccal surface of the lower appliance in the molar region. These fit against a slot on the upper appliance in the same region, thus allowing engagement of the two appliances. The length and angle of the flanges were used to guide the mandible forward and maintain advancement. (3) Two 10-mm "Lewa" screw devices (Rocky Mountain Orthodontics, Denver, CO) to enable advancement of the slots; this permits incremental protrusion of the mandible. The vertical height of the MAS was kept to a minimum (the average thickness of each upper and lower appliance was between 1.5 and 2.0 mm).

ing washout period of 1 week. At the end of each 4-week period, subjects completed the ESS questionnaire and a symptom questionnaire and underwent overnight polysomnography with the appliance, followed by a multiple sleep latency test (MSLT) the next day.

Outcome Measures

Questionnaires. Subjective assessment of sleepiness was performed using the ESS, a reliable and validated, self-administered questionnaire (18). Patients were deemed to be sleepy when they had an ESS score greater than 10 (18). A self-administered, detailed, in-house questionnaire was used to document the frequency and intensity of a range of nocturnal and daytime symptoms and treatment-related side effects and satisfaction. Treatment compliance was monitored by diary completion.

Polysomnography. Nocturnal sleep studies were performed by a trained sleep technician in a standard fashion (19). Respiration and snoring sound measurement techniques and the definition of arousal have been reported previously (14, 20). Sleep recordings were scored by an experienced polysomnographer who was blinded to patient clinical status.

Treatment outcome. A complete response (CR) to treatment was defined as a reduction in RDI to less than five per hour (21). A partial response (PR) was defined as a reduction of 50% or more in RDI compared with baseline, but with the RDI remaining at five or more per hour. Treatment failure was defined as less than 50% reduction in RDI compared with baseline. OSA severity was defined according to the RDI: mild, 5 to less than 15 per hour; moderate, 15 to 30 per hour; and severe, greater than 30 per hour (21).

Multiple sleep latency test. Objective daytime sleepiness was assessed by the MSLT, according to the standard research protocol (22). A polysomnographer blinded to patient clinical status and treatment allocation performed and manually scored the MSLT. Resolution of EDS was defined as a return of the mean sleep latency (MSL) to normal;

TABLE 1. STUDY SAMPLE CHARACTERISTICS AT BASELINE*

Variable	Group I (AB) (n = 36)	Group II (BA) (n = 37)	Total (n = 73)
Sex	30 M, 6 F	29 M, 8 F	59 M, 14 F
Age, yr	48 ± 11	48 ± 11	48 ± 11
BMI, kg/m ²	28.4 ± 5.2	29.6 ± 4.1	29.0 ± 4.7
Neck circumference, cm	39.9 ± 3.2	40.7 ± 3.1	40.3 ± 3.2
Waist:hip	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
RDI, per h	28.3 ± 17.3	25.9 ± 13.2	27.1 ± 15.3
MinSao ₂ , %	85 ± 6	86 ± 5	86 ± 6
Arousal index, per h	35.0 ± 14.7	34.9 ± 12.3	35.0 ± 13.5
ESS score	11 ± 5	11 ± 5	11 ± 5

Definition of abbreviations: BMI = body mass index; ESS = Epworth Sleepiness Scale; F = female; M = male; MinSao₂ = minimum arterial oxygen saturation; RDI = respiratory disturbance index.

* Groups compared using Student's two-sample *t* test. Data are presented as mean ± SD.

i.e., more than 10 minutes (23). Pathologic sleepiness was defined as an MSL of less than 5 minutes (23).

Statistical considerations. Data were stored and analyzed on SPSS (version 10.0; SPSS Inc., Chicago, IL). The response to treatment, period effects, and interactions between treatment and period were determined using two-way analysis of variance (ANOVA), with treatment order as a between-subject factor and treatment as a within-subject factor (24). A two-sided significance level of 0.1 was considered significant for carryover (25). Univariate ANOVA was used to assess the relationship between daytime sleepiness treatment response (within-subject differences between the MAS and the control) and potential prognostic variables, after adjustment for regression to the mean. Categorical data were analyzed by the chi-squared test. Descriptive statistics are presented as mean ± SD and estimated means as mean ± SEM. Differences in estimated means are presented with 95% confidence intervals (CI). All probability values were calculated from two-tailed tests of statistical significance. A 0.05 significance level was maintained throughout these analyses.

RESULTS

Study Population

A total of 85 patients were eligible for study participation. Twelve patients withdrew from the study due to the following reasons: refusal to participate after initial recruitment (chose and received nCPAP) (n = 1); work interference (n = 3); permanent relocation interstate (n = 2); extended overseas trip (n = 1); self-perception during acclimatization that any treatment was not required (n = 1); unrelated health problems (n = 3); and refusal to continue with alternate treatment due to a self-perceived improvement in OSA symptoms with the MAS during Phase 1 (n = 1). Comparison of those who withdrew with those who completed the study revealed that the two groups did not differ in sex distribution, age, or ESS scores. However, there was a significant difference in body mass index (BMI) and RDI, with study patients having both a lower mean BMI (29.0 ± 0.5 versus 34.0 ± 1.9 kg/m², *p* < 0.01) and mean RDI (27.1 ± 1.8 versus 39.5 ± 6.7/hour, *p* < 0.05).

The 73 patients who were randomized and followed for the duration of the study period consisted of 59 men and 14 women and, as a group, were middle-aged and overweight. OSA severity subgroups revealed a predominance of moderate and severe OSA, with 41 patients (56%) and 21 patients (29%) in each subgroup, respectively. Thirty-eight patients (52%) were considered to be subjectively sleepy according to the ESS. The baseline characteristics were comparable for the two sequence groups (Table 1). Considering the small proportion of women included in the trial cohort and the lack of significant difference between

TABLE 2. NOCTURNAL POLYSOMNOGRAPHY AT BASELINE, WITH MANDIBULAR ADVANCEMENT SPLINT AND WITH CONTROL DEVICE

Variable	Baseline (n = 73)	MAS (n = 73)	Control (n = 73)
Respiratory			
RDI, per h*	27 ± 2	12 ± 2	25 ± 2
MinSao ₂ , %*	86 ± 1	89 ± 1	86 ± 1
Sleep architecture			
TST, min†	349 ± 8	370 ± 7	366 ± 7
TST in REM, min	66 ± 3	68 ± 3	63 ± 3
TST in NREM, min‡	283 ± 6	299 ± 6	303 ± 6
TST in REM, %	18 ± 1	18 ± 1	17 ± 1
TST in NREM, %	82 ± 1	81 ± 1	83 ± 1
Sleep efficiency, %	81 ± 1	84 ± 1	82 ± 2
Arousal index, per h*	35 ± 2	25 ± 2	33 ± 2
Snoring			
Snoring frequency, per h*	NA	207 ± 20	366 ± 21
Mean snoring intensity, dB*	NA	48 ± 1	51 ± 1
Maximum snoring intensity, dB§	NA	67 ± 1	70 ± 1

Definition of abbreviations: MAS = mandibular advancement splint; MinSao₂ = minimum arterial oxygen saturation; NA = not available; NREM = nonrapid eye movement; RDI = respiratory disturbance index; REM = rapid eye movement; TST = total sleep time.

MAS and control treatments compared using two-way analysis of variance. Baseline and control treatment compared using paired *t* test. Data are presented as mean ± SEM.

* *p* < 0.0001, MAS versus control.

† *p* < 0.05, baseline versus control.

‡ *p* < 0.01, baseline versus control.

§ *p* < 0.01, MAS versus control.

sex groups in baseline and outcome measures, results were pooled for men and women.

Acclimatization Phase

The mean period of acclimatization to the MAS was 8 ± 4 weeks (range, 2–22 weeks). The mean advancement of the mandible with the MAS was 7 ± 2 mm (range, 3–13 mm), representing 80 ± 9% (range, 50–95%) of maximum jaw protrusion.

Study Outcomes

Objective daytime sleepiness. The MAS resulted in a significantly longer MSL of 10.3 ± 0.5 minutes on the MSLT, compared with 9.1 ± 0.5 minutes for the control device (*p* = 0.01). The mean difference was estimated as 1.2 minutes (95% CI; 0.3, 2.1). Thirty-five patients (48%) showed a normal MSL with active treatment, compared with 25 patients (34%) with the control treatment (*p* = 0.08). Of those who remained objectively sleepy with the MAS, five (7%) were pathologically sleepy. Eleven (29%) of the patients whose MSLT was not in the normal range with active treatment achieved a CR and 10 (26%) achieved a PR.

Subjective daytime sleepiness. The MAS resulted in a small but highly significant reduction in the mean ESS score compared with the control device (7 ± 1 versus 9 ± 1, *p* < 0.0001). The difference in estimated means was two points (95% CI; 1, 3). Subjective sleepiness with the control treatment was significantly less than at baseline (9 ± 1 versus 11 ± 1, *p* < 0.01). Active treatment produced a normal ESS score in 60 patients (82%), compared with 45 patients (62%) on the control treatment (*p* < 0.01).

Polysomnographic markers of OSA. Findings for treatment effects on polysomnography are detailed in Table 2. The MAS produced a 52% reduction in mean RDI and a significantly higher mean minimum arterial oxygen saturation (MinSao₂) compared with the control device. Twenty-six patients (36%) showed a CR to the MAS, whereas 20 patients (27%) showed

a PR. Twenty-seven patients (37%) were treatment failures. The control device had no statistically significant effect on baseline RDI, MinSao₂, or other sleep variables (Table 2). Whereas the MAS resulted in a highly significant reduction in the mean arousal index compared with the control device, there was no significant difference in mean total sleep time (TST), mean sleep efficiency, or sleep stage distribution between appliances. Active treatment resulted in a highly significant reduction in objective snoring frequency and in both average and maximum snoring intensity in comparison with the control treatment.

There was no statistically significant treatment-by-period interaction or period effect for MSL on the MSLT, ESS score, or polysomnographic variables.

Other subjective outcomes. There was a highly significant reduction in both the reported frequency and intensity of snoring with the MAS compared with the control device (*p* < 0.0001) (Figure 2). Whereas significantly more patients reported improved sleep quality with active treatment (*p* < 0.0001) (Figure 3), sleep fragmentation did not differ between appliances in terms of the reported average number of nights woken per week or the average number of times woken per night (*p* > 0.05). The main reason specified for waking up with each appliance was nocturia. However, at baseline, patients reported waking up mainly due to nocturia, the bed partner who was disturbed by the patient's snoring, or a dry mouth. Six patients (8%) reported witnessed apneas with the MAS compared with 20 patients (27%) using the control device (*p* > 0.05). The proportion of patients reporting nocturnal choking episodes did not differ between active and control treatments. A significantly higher proportion of patients experienced side effects with the MAS than with the control device; namely, jaw discomfort (*p* < 0.0001), tooth tenderness (*p* < 0.0001), and excessive salivation (*p* < 0.05). The majority of patients who complained of side effects reported them to be generally mild in nature and to last for the duration of the relevant treatment phase.

Significantly greater treatment satisfaction was achieved with the MAS (*p* < 0.0001). Active and control treatments were found to be very satisfactory in controlling subjective OSA symptoms in 30 patients (41%) versus 5 patients (7%), satisfactory in 40 patients (55%) versus 25 patients (34%), and not satisfactory in 3 patients (4%) versus 43 patients (59%), respectively. At the end of the relevant treatment phase, 72 patients (99%) expressed a desire to continue with active treatment, compared with 36 patients (49%) who wished to continue with the control (*p* < 0.0001).

Self-reported compliance. Self-reported treatment compliance during each 4-week treatment period was high and did not differ between appliances. Patients reported wearing both the MAS and the control device for an average duration of 6.7 ± 0.1 hours per night. There was no difference in reported mean percentage of nights the MAS and control device were used during the 4 weeks (97 ± 1 versus 96 ± 1%).

Prognostic variables. The BMI, neck circumference, and the average number of hours patients reported sleeping per night during each treatment phase did not differ significantly between the MAS and the control device (Table 3). However, the mean percentage of TST spent supine during overnight polysomnography with the MAS was significantly higher compared with that when using the control device (Table 3). Drugs known to produce sleepiness were not detected on urine drug screening at the end of each MSLT. Univariate ANOVA revealed that the within-subject change in objective daytime sleepiness between the MAS and control was unrelated to age, sex, BMI, RDI, OSA severity subgroup, MinSao₂, arousal index, ESS score, or subjective sleepiness status at baseline. Similarly, no significant associations were found with measures of protrusion or concurrent changes in

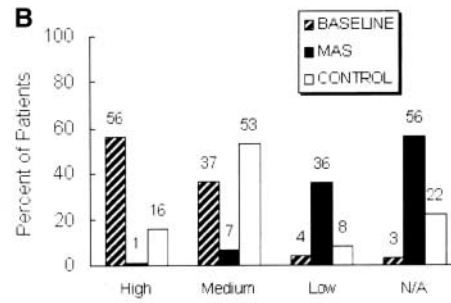
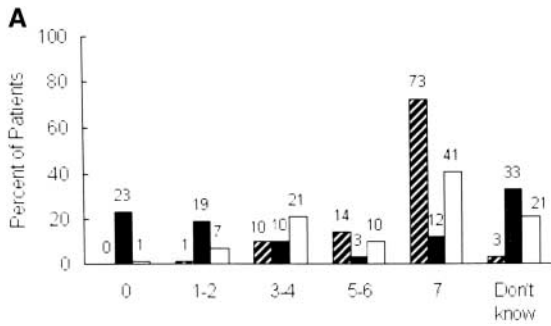


Figure 2. Relative frequency distribution of (A) snoring frequency (nights per week) and (B) snoring intensity with the MAS and the control device. n = 73. Percentages may not add up to 100 due to rounding. p Values are less than 0.0001 for both (A) snoring frequency and (B) snoring intensity (MAS versus control device). Don't know = snoring status unknown; N/A = nonsnorer or snoring status unknown.

RDI, MinSao₂, arousal index, time spent in rapid eye movement sleep and nonrapid eye movement sleep, sleep efficiency, or ESS score. The change in within-subject subjective daytime sleepiness between treatments was not associated with any of the aforementioned variables. However, a trend was evident for an association with respiratory treatment outcome, although this was not statistically significant (p = 0.06).

DISCUSSION

The key symptoms of OSA have an adverse impact on both the individual and the wider community. The results of this randomized, controlled, crossover trial in patients with mild to severe OSA demonstrate significant objective and subjective evidence of improvement in such symptoms with MAS therapy. To our knowledge, this is the first systematic study to show a significant objective reduction in daytime sleepiness with a MAS. The mean MSL with the active appliance after 4 weeks of treatment was in the range of MSL scores achieved by normal adult volunteers (26). In the only other study assessing the effect of oral appliance therapy on objective daytime sleepiness in OSA, Menn and colleagues (17) showed a marked improvement in MSL on the maintenance of wakefulness test of 7 minutes in 13 patients with MAS treatment, 10 of whom achieved a normal sleep latency. Although these improvements were substantially greater than in the present study, they were based on a patient subgroup favoring responders with moderate to severe OSA from a case series agreeable to testing after treatment with the MAS for 3 months. Furthermore, results from the two different tests may not be comparable as they may measure different abilities (27).

The efficacy of the MAS in resolving objective sleepiness in comparison with nCPAP remains uncertain. Interestingly, a randomized, controlled, crossover study of nCPAP for OSA

with patient entry criteria similar to those used in our study also showed an improvement in mean MSL on MSLT of approximately 1 minute with active therapy, compared with a tablet placebo after 4 weeks of treatment, but the improved sleep latencies remained within the abnormal range (28). A similar study performed in patients with moderate to severe OSA reported an increase of 2.4 minutes with nCPAP, with scores reaching normal limits (29). A parallel group study in patients with an ESS score greater than 10 at baseline showed a 7-minute improvement in median maintenance of wakefulness test time with therapeutic nCPAP versus subtherapeutic nCPAP after 4 weeks of treatment (30). The mean test time after therapeutic treatment was similar to the mean in healthy people. A randomized, controlled trial of MAS therapy against nCPAP in patients with OSA would be required to make a valid comparison of the efficacy of the two treatments in resolving objective sleepiness.

Whereas the magnitude of improvement in subjective sleepiness with the MAS in our study sample was highly significant, the two-point decrease in the ESS score may not be clinically important. Case review studies of oral appliances for OSA (7) and a study by Menn and coworkers (17) found that a self-reported improvement in sleepiness occurred in the majority of patients after treatment. However, unlike the present study, these investigators did not use a validated and reliable instrument to assess subjective sleepiness. Nevertheless, our findings must be considered with the knowledge that the main limitation of the ESS, as with any subjective report, is that it is open to response bias. Two randomized, crossover trials by Ferguson and coworkers (10) and Bloch and coworkers (11) reported study samples with a mean ESS score at baseline similar to ours and showed significant reductions in the mean ESS score of 5.6 points and in the median ESS score of 4.5 points, respectively. However, these improvements were in comparison with no treatment. Interestingly, subjective sleepiness with the control was found to be significantly less than at baseline in the current study, sug-

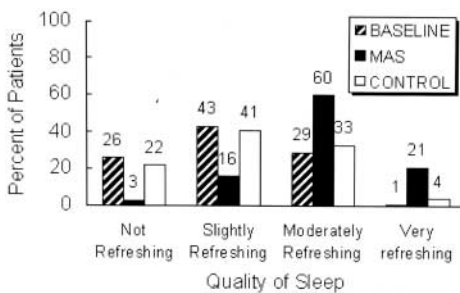


Figure 3. Relative frequency distribution of sleep quality with the MAS and the control device. n = 73. Percentages may not add up to 100 due to rounding. p < 0.0001 (MAS versus control device).

TABLE 3. POTENTIAL CONFOUNDERS AND EFFECT MODIFIERS WITH MANDIBULAR ADVANCEMENT SPLINT AND CONTROL DEVICE

Variable	MAS	Control
BMI, kg/m ²	30.0 ± 0.6	30.0 ± 0.6
Neck circumference, cm	39.8 ± 0.4	39.7 ± 0.4
TST spent supine, %*	50 ± 3	42 ± 3
Time slept per night during treatment phase, h	7.0 ± 0.1	7.1 ± 0.1

Definition of abbreviations: BMI = body mass index; MAS = mandibular advancement splint; TST = total sleep time.

Comparison made using paired t test. Data are presented as mean ± SEM. * p < 0.05.

gesting the possibility of regression to the mean or a placebo effect and hence highlighting the importance of using a “sham” control to establish the true treatment effect of such a physical therapy. Randomization assured the validity of our study by ensuring that treatment groups were similar on average and by controlling for regression to the mean, period effects, learning effects, treatment order effects, and placebo effects. It is interesting to note that similar reductions in ESS scores have been shown with sham (subtherapeutic) nCPAP in some randomized, controlled trials (30, 31, 32) but not in others (33).

The absence of a relationship between the ESS score and MSL on the MSLT in the present trial is consistent with findings from previous studies in patients with OSA (34, 35). A poor correlation has also been demonstrated between the complaint of sleepiness and the MSLT score (36, 37). Furthermore, improvements in reported sleepiness after treatment for OSA have not always been reflected in MSLT results (37).

Although a significant improvement was found in both objective and subjective sleepiness with the MAS, a significant proportion of patients did not respond to treatment and some patients experienced only a partial recovery. There are several possible explanations for this. OSA was either not improved or was not optimally controlled with the MAS in 55% of the patients with a persistently abnormal MSL, and this is a likely explanation for any lack of improvement in EDS. Although the mean arousal index was significantly reduced for the 73 patients, it did not reach normal levels (38). This raises the possibility that although the MAS improves sleep-disordered breathing, upper airway resistance may persist (39) and could account for sleepiness among complete responders. Furthermore, the prescribed treatment period of 4 weeks may not have been sufficient to correct chronic EDS in all patients. The allocated treatment period was chosen on the basis of previously reported improvement in EDS with nCPAP after an equivalent treatment interval (29). An additional explanation may be the presence of residual sleepiness, as has been suggested for persistent sleepiness in patients treated with nCPAP (40).

The present study found significant improvements with active treatment in respiratory and sleep variables as previously reported (7, 9–11, 14, 17). The mean percentage of TST spent supine during nocturnal polysomnography was significantly higher with the MAS than with the control device and hence may have led to an underestimate of the benefit of active therapy. The mean snoring frequency was significantly reduced by 43%, and both the mean snoring intensity and maximum snoring intensity by 3 dB, similar to the study by Mehta and coworkers (14). O’Sullivan and colleagues (41) found an 18% reduction in snoring frequency and a 15.8% reduction in snoring intensity reflected by the proportion of snores of 50 dB or more. Bloch and coworkers (11) found that time spent snoring during polysomnography did not change; however, the snoring index with their Herbst and Monobloc devices was reduced by 36 and 58%, respectively, compared with no treatment. Significantly more patients reported a reduction in snoring frequency and intensity with the MAS as in previous studies of such oral appliances that assessed subjective snoring outcomes (7, 9–11, 14). However, only a small proportion of patients (23%) reported an absence of snoring with the MAS, which is also in agreement with previous results (10, 11, 14, 41).

Although the proportion of patients who reported improved sleep quality was significantly greater with the MAS than with the control device, our study found no statistically significant difference in the number of patients who reported sleep fragmentation and choking episodes or witnessed apneas between treatments. Three randomized, controlled trials (8–10) have shown

that both oral appliance therapy and nCPAP improve a range of OSA symptoms.

Patient acceptance of the MAS was very high, with almost all (99%) expressing a desire to continue with such treatment. Short-term treatment-related side effects were generally mild and transient, similar to those reported previously (7–10). Interestingly, 30 patients (41%) believed that the control treatment was either very satisfactory or satisfactory in controlling their symptoms, and 36 patients (49%) wished to continue with the control. This further highlights the need for objective evidence of clinical improvement with the MAS. Although dropouts had a significantly lower mean BMI and RDI, all but one was unrelated to treatment, and hence it is unlikely that the intervention itself would have acted as a major source of bias. High acceptance rates of the MAS have also been reported by others (9–11, 14).

The objective and subjective treatment effect in daytime sleepiness with the MAS was not significantly associated with any potential prognostic factors; however, there was a trend for subjective sleepiness improvement to be associated with better respiratory treatment outcomes. Similar observations have been made with respect to nCPAP treatment (28, 29).

A particular strength of this study stems from the use of an inactive control oral appliance. Although use of a matched placebo control in any randomized trial would be ideal to eliminate the placebo effect and to ensure double blinding, this is not achievable with a physical therapy such as MAS. A viable solution to this important issue is the use of a control device that is physically comparable to the device being evaluated but does not produce any changes in OSA. Such an approach has been adopted by a number of investigators by using nCPAP at subtherapeutic pressures (sham nCPAP) as the control device (30–33). We believe that we have achieved a similar effect in our study. Despite a difference in the anteroposterior position of the mandible between the MAS and the control device, patients were kept blind to active and control treatments as a result of the physical similarity between the two oral appliances and by concealment of the inactive nature of the control. The comparable compliance with the two appliances during each treatment phase suggests that patients were equally interested in the two treatments. Similarly, the improved subjective daytime sleepiness with the control treatment and the reported desire to continue treatment with the control device by a significant proportion of patients indicate an effective blinding process. The *a priori* assumption of the inactive nature of the upper appliance alone was confirmed on finding that OSA severity, determined by the RDI and $\text{MinSa}_{\text{O}_2}$, did not differ significantly between the control treatment and baseline. This is in accordance with our previous study in which the control device consisted of a single lower plate (14), and confirms the importance of advancement in achieving a positive therapeutic effect.

The final MAS setting ranged from 50 to 95% of maximal jaw protrusion, indicating the wide variability in tolerance between patients. The lack of significant association between measures of sleepiness with the MAS and measures of protrusion do not make it possible to draw conclusions as to the optimal advancement for resolution of EDS with such appliances. Whereas most randomized, controlled trials of MAS therapy for OSA have reported advancing the mandible with the MAS by a set amount for all patients (9, 10, 41), the present study chose the maximum comfortable limit of advancement as the stopping point to account for between-subject tolerance to mandibular protrusion and to maintain patient blinding.

In conclusion, this study has shown that 4 weeks of MAS therapy improves daytime sleepiness and a range of other symptoms associated with OSA. This study extends our previous findings, confirming the efficacy of MAS therapy in controlling

OSA in a substantial number of patients, including those with moderate and severe OSA. However, it remains unclear which patients benefit and what factors predict this improvement. Improvement in sleepiness with treatment does not appear to equate solely with the extent of resolution of sleep-related abnormalities. These findings support suggestions by others (35, 36) for the need to develop better and more responsive tests for sleepiness and to identify clinically important variables that relate better to sleepiness.

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