Randomized Crossover Trial of Two Treatments for Sleep Apnea/Hypopnea Syndrome

Continuous Positive Airway Pressure and Mandibular Repositioning Splint

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Mandibular repositioning splints (MRSs) and continuous positive airway pressure (CPAP) are used to treat the sleep apnea/hypopnea syndrome (SAHS). There are some data suggesting that patients with milder symptoms prefer MRS, but there are few comparative data on outcomes. Therefore, we performed a randomized crossover trial of 8 weeks of CPAP and 8 weeks of MRS treatment in consecutive new outpatients diagnosed with SAHS (apnea/hypopnea index [AHI] $\geq$ 5/hour, and $\geq$ 2 symptoms including sleepiness). Assessments at the end of both limbs comprised home sleep study, subjective ratings of treatment value, sleepiness, symptoms, and well-being, and objective tests of sleepiness and cognition. Forty-eight of 51 recruited patients completed the trial (12 women; age [mean $\pm$ SD], 46 $\pm$ 9 years; Epworth 14 $\pm$ 4; median AHI, 22/hour; interquartile ratio [IQR], 11–43/hour). Significant ($p \leq 0.01$) differences between MRS and CPAP were observed for 7 of 21 variables (effect sizes, 0.3–0.6 SDs), all favoring CPAP, including AHI (15 $\pm$ 16 and 8 $\pm$ 6/hour, respectively), effectiveness rating, symptoms, Epworth (12 $\pm$ 5 and 8 $\pm$ 5, respectively), functional outcomes of sleepiness questionnaire, short-form 36 health survey mental component, and health transition scores. Objective sleepiness, cognitive performance, and preference for treatments were not different. In patients experiencing a mild form of the syndrome (AHI $<$ 15, n = 18), symptoms, treatment efficacy and satisfaction, and subjective sleepiness were also better with CPAP than with MRS (effect sizes, 0.7–1.1 SDs). These results do not support these MRS devices as first-line treatment for sleepy patients with SAHS.

Keywords: positive pressure ventilation; intraoral device; sleep apnea syndromes; randomized controlled trial

Recent systematic reviews of treatments for the sleep apnea/hypopnea syndrome (SAHS) (1, 2) have found high-level, randomized and controlled evidence for only two treatments—continuous positive airway pressure (CPAP) and mandibular repositioning splints (MRSs). CPAP is the best-evaluated treatment for SAHS (1, 2), with a growing high-level evidence base of its efficacy in preventing breathing pauses during sleep and its clinical effectiveness for symptoms during longer-term home treatment (3–6). Thus, CPAP, together with weight loss and alcohol awareness, represents the treatment of choice in SAHS. However, CPAP is an obtrusive therapy that is declined or discontinued by a significant proportion of patients (7, 8), thus producing a clinical need for alternative treatment modalities for SAHS. Among the best-studied alternative treatments for SAHS are MRSs (1, 2, 9), intraoral appliances designed to hold the mandible in protrusion during sleep. A recent controlled study shows that MRSs improve apnea/hypopnea index (AHI), nocturnal saturation, and arousals from sleep (10). Uncontrolled intervention studies of MRS indicate that many patients obtain good results for objective efficacy and subjective effectiveness (9, 11–24) and that efficacy for breathing pauses may be higher among patients with SAHS with lower levels of sleep-disordered breathing (9, 11–13). Follow-up studies have identified some drawbacks of MRS therapy, such as excessive salivation, occlusive changes, and temporomandibular joint or dental pain, but these appear to be tolerated by the majority of patients in case series (14, 15).

Systematic reviews (1, 2) have also included three recent trials (16–18) of MRS treatment against CPAP for SAHS. All were crossover trials, and two were randomized (17, 18). These reported greater patient satisfaction and preference (16–18) and lower side effects (18) for MRS over CPAP, despite the inferior effectiveness of MRS for AHI (16–18) and for nocturnal (17) or daytime symptoms (18). Objective effectiveness of MRS showed greater variability than that of CPAP, and in the study by Clark and coworkers (16), better efficacy was linked with lower initial AHI. Previous crossover trials (16–18) have not included objective sleepiness, cognitive function, or validated symptom scales as outcomes, excluding the study by Ferguson and coworkers (18), which incorporated the Epworth sleepiness scale. All have studied 30 or fewer patients, with their sample sizes reduced further by withdrawals.

The primary aim of the current study was to conduct a direct prospective comparison of the clinical effectiveness of long-term home treatment with CPAP and MRS, analyzed on an intention-to-treat basis in a mixed-severity group of patients with SAHS. Assessments would include validated objective and subjective measures where available and examine drawbacks as well as benefits of treatments. A subanalysis was planned in patients with lower AHI to assess any differential treatment response among these patients. A secondary analysis would aim to identify prospective markers of patients' preference for CPAP or MRS treatment.

METHODS

Consecutive new patients aged 18–70 years with AHI of 5 or more and two or more symptoms of SAHS, including sleepiness (Epworth score [4–7] of 8 or greater or reported sleepiness while driving), were recruited after giving written informed consent to the study, which was approved by the local Ethics Committee. Patients with fewer than four teeth remaining in either arch, coexisting narcolepsy or periodic limb movements of more than 10 per hour, major medical illness, shift work, or

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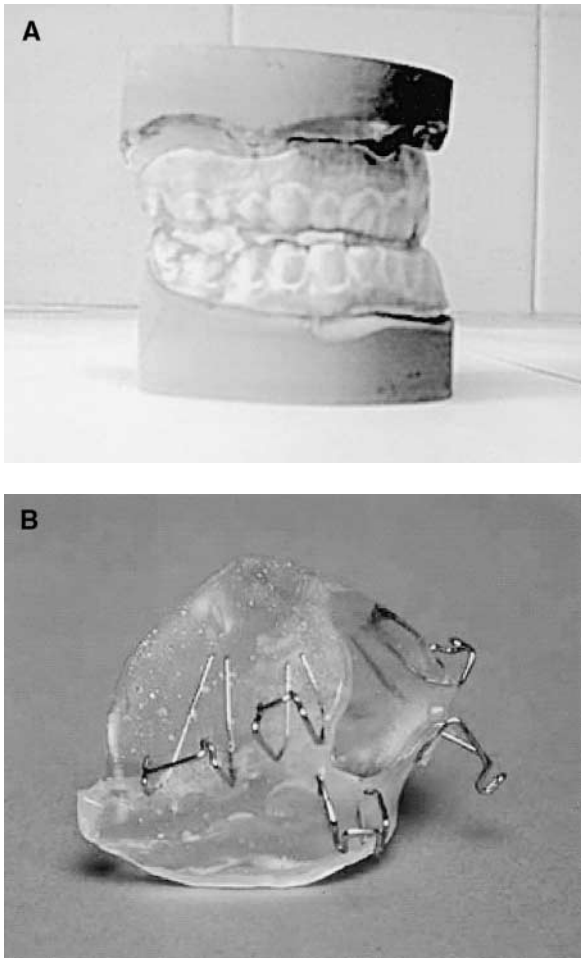

Figure 1. Mandibular repositioning splints (*A*) with occlusal coverage and (*B*) without occlusal coverage.

living more than 50 miles away from Edinburgh were excluded. Patients were randomized to treatment order using balanced blocks of four, stratified for separate severity (AHI $\geq$ 15 per hour or $<$ 15 per hour). Patients underwent a baseline assessment (Table E1 in the online data supplement), all-night CPAP titration, and custom-fitting of MRS before randomization. MRS devices were individually manufactured and fitted to produce 80% of maximal comfortable mandibular protrusion, with 2–4 mm of interdental clearance. Patients were randomized to one of two MRS constructions (Figures 1A and 1B). The first consisted of two mouthguards providing complete occlusal coverage, constructed from Kombiplast hard/soft (Dreve, Frankfurt, Germany), an ethylene-methylacrylate/polystyrene material, and the two units were sealed in protrusion. Retention was by engagement of undercuts by the flexible material. The second was manufactured from less-flexible 1MEDL dual laminate material, molded to fit the interior contours of the hard palate and frontal dentition during mandibular protrusion and affixed to the dentition with metal Adams clasps, holding the mandible in protrusion.

Patients were asked to use each treatment for 2 months, during which adjustments to CPAP pressure and MRS protrusion could be made by the staff supervising treatments, aiming to optimize comfort and benefits and abolish snoring.

Outcomes (Table E1 in the online data supplement) were to be measured in the final 10 days of each treatment, after at least 6 weeks on treatment. Patients were asked to undergo a limited home sleep study (Edentrace II; Edentec Ltd., Pleasanton, CA) (25) and ambulatory neurophysiologic recording (Compumedics P-series) for 1 day to identify daytime sleep episodes. On another day, objective sleepiness and cognition were measured, and subjective ratings based on their second month's treatment were obtained. All sleep data were scored by an observer blinded to treatment. At the end of the study, patients selected their preferred treatment.

Analysis

Analysis was conducted on an intention-to-treat basis. The primary statistical analysis assessed between-treatment differences with Wilcoxon tests and the binomial test for treatment preference. The likelihood of false-positive statistical errors from the 21 outcomes was reduced by adopting p values of 0.01 or less for statistical significance in this primary analysis. The clinical relevance of changes was estimated by calculating effect sizes (26) (score difference/SD of difference). A subanalysis of treatment effects in patients with mild SAHS was planned prospectively. With sample sizes of n = 48 (all patients) and n = 18 (patients with mild SAHS), powers of 99 and 65%, respectively, were provided to detect a 1 SD difference between treatment scores.

Secondary analyses were conducted to seek predictors of treatment preference. These adopted a significance level of p values of 0.05 or less. Putative prospective determinants were identified by Mann–Whitney comparisons of baseline scores in MRS- and CPAP-preferrers. Significant variables from the Mann–Whitney analysis were then entered as covariates in a conditional forward logistic regression with entry at p values of 0.2 or less. All analyses were by SPSS for Windows (27).

RESULTS

Subject Recruitment and Assessment

Ninety-seven consecutive patients meeting entry criteria were approached for study participation, of whom 51 were recruited after obtaining written consent from them. Reasons for declining study participation are detailed in Figure E1 in the online data supplement. Four decliners had first undergone a CPAP titration study, but none had completed all MRS fittings.

Of the 51 patients, 3 (6%) irretrievably withdrew from the study after starting treatment. One has been uncontactable since his first CPAP limb and gave no reason for withdrawal. Two others commenced new jobs during their first treatment limb (one on CPAP, one on MRS) and were no longer able to spare time for tests. Outcome is unknown for the defaulting patient, and in the other two, one is using no treatment and the other is a verified continuing CPAP user. Forty-eight patients (12 women) completed the trial, with median AHI of 22 (interquartile ratio [IQR] 11–43) per hour (mean $\pm$ SD, 31 $\pm$ 26), mean $\pm$ SD age of 46 $\pm$ 9 years, and an Epworth score of 14 $\pm$ 4 at baseline. Of these, 24 patients started on CPAP and 24 on MRS.

Only 12 patients were willing to undergo daytime electroencephalographic portable recordings. Objective laboratory test scores (maintenance of wakefulness test and cognitive battery) for final assessments were lost in two patients, one unable to spare time for the full assessment protocol and one rapidly transferred to CPAP after a sleep-related road traffic accident while on MRS treatment. The former also did not have a home sleep study. Both completed questionnaires, and these data are included in the analysis. To prevent withdrawal from the trial, treatment was shortened and assessments brought forward to 1 month at the request of four patients, three of these on MRS and one on CPAP.

Intertreatment Differences

Treatment effectiveness, usage, satisfaction, and preference. Effectiveness of CPAP was significantly better both by objective AHI during sleep study and by patients' treatment effectiveness rating (effect size [ES] 0.4 SDs, $p \leq 0.01$). AHI during the home study was reduced to 5 or less per hour for nine patients (19%) on MRS and 16 patients (34%) on CPAP. Twenty-two (47%) and 31 (66%) patients showed an AHI of 10 or less per hour for MRS and CPAP, respectively (Table 1).

Ratings of average treatment use, satisfaction, and acceptability did not differ between treatments. Neither treatment was

TABLE 1. INTERTREATMENT SCORE DIFFERENCES

	All Patients (*n = 48*)					
	Direction of Improvement	MRS (*Mean ± SD*)	CPAP (*Mean ± SD*)	Effect Size†	p Value (*CPAP versus MRS*)	Patients with Mild SAHS Effect Size (*n = 18*)†
Rx use & effectiveness						
Reported Rx use, hours per night	+	5.0 ± 2.3	4.9 ± 2.4	−0.04	0.569	0.25
Edentec AHI, hours slept	−	15 ± 16	8 ± 6	0.45*	0.001	0.34
Effectiveness	+	5 ± 3	7 ± 3	0.46*	0.004	1.14*
Acceptability	+	6 ± 3	6 ± 3	−0.01	0.933	0.30
Satisfaction	+	5 ± 3	6 ± 3	0.23	0.118	0.68
Side effects	−	21 ± 15	17 ± 13	0.20	0.292	0.58
Preferred treatment		n = 19	n = 25		0.194	
Symptoms & sleepiness						
In-house symptom questionnaire	−	17 ± 8	11 ± 7	0.58*	< 0.001	0.98*
Epworth score	−	12 ± 5	8 ± 5	0.57*	< 0.001	0.96*
MWT sleep onset latency, min	+	22 ± 12	24 ± 12	0.16	0.460	0.21
FOSQ score	+	13 ± 3	14 ± 2	0.51*	0.001	0.86*
Daytime sleep time, %	−	3 ± 3	4 ± 6	−0.26	0.594	—
Well-being						
SF-36 health transition score	−	2.9 ± 0.8	2.4 ± 0.8	0.52*	0.001	0.62
SF-36 physical component score	+	45 ± 10	47 ± 10	0.35	0.023	0.46
SF-36 mental component score	+	48 ± 11	52 ± 10	0.34*	0.008	0.69*
HADS anxiety score	−	6 ± 4	6 ± 6	0.05	0.160	0.49
HADS depression score	−	5 ± 5	4 ± 3	0.31	0.064	0.59
Cognitive performance						
Performance IQ decrement score	−	−2 ± 14	−1 ± 14	−0.10	0.549	−0.21
Trailmaking B, s	−	64 ± 28	59 ± 21	0.27	0.106	0.25
SteerClear (cows hit)	−	50 ± 44	49 ± 60	0.03	0.266	−0.17
PASAT 2s correct	+	39 ± 10	40 ± 11	0.25	0.064	0.61

Definition of abbreviations: AHI = apnea+hypopnea index; CPAP = continuous positive airway pressure; FOSQ = functional outcomes of sleepiness questionnaire; HADS = hospital anxiety and depression scale; MRS = mandibular repositioning splint; MWT = maintenance of wakefulness test; PASAT = paced auditory serial addition test; Rx = prescription medication; SF-36 = short-form 36 health survey.

* Considered statistically significant.

† Positive values favor CPAP and negative values favor MRS.

significantly preferred by the patients, 19 preferring MRS and 25 preferring CPAP ($p > 0.1$). There were no differences in use, satisfaction, effectiveness, acceptability, or side effect outcomes between the two MRS devices ($p > 0.11$).

Symptoms and sleepiness. Symptom score and subjective sleepiness scores (Epworth and functional outcomes of sleepiness questionnaire) were better with CPAP compared with MRS (ES 0.5–0.6 SDs). Objective daytime sleepiness measured by maintenance of wakefulness and home portable sleep time were not different.

Well-being. Short-form 36 health survey (SF-36) scores for health transition and mental component were significantly better with CPAP (ES 0.5 and 0.3 SDs, respectively). There were no significant differences between treatments in scores for SF-36 physical component or hospital anxiety and depression scale.

Cognitive performance. There were no significant differences in cognitive scores between the two treatments.

Adverse events. Adverse events or difficulties with treatment were common both for MRS and CPAP treatment (Table 2). The severity of adverse events did not differ across treatments. Whereas some reported problems were treatment-specific (e.g., dental pain or salivation with MRS and stuffy nose or mask problems with CPAP), others were common under both regimens (difficulties initiating or maintaining sleep, awakening to find equipment removed) (Table 2). Patients reporting low treatment use (⩽ 3 hours/night) comprised a significant minority for both treatments. Patients free of problems that limited use were also in the minority for both treatments. One patient experienced a sleep-related road traffic accident while on MRS.

Subanalysis in patients with mild SAHS (AHI, 5–15). A subanalysis in patients with milder symptoms (n = 18: last column of Tables 1 and E2) showed significantly better ratings for symptoms, treatment efficacy and satisfaction, Epworth, functional outcomes of sleepiness questionnaire, and SF-36 mental component scores (effect sizes, 0.7–1.1 SDs; $p \leqslant 0.01$) with CPAP. The preferred treatment for 14 of 18 patients was CPAP ($p = 0.03$).

Predictors of Treatment Preference

Mann–Whitney tests of baseline scores in MRS- and CPAP-preferrers associated eventual CPAP preference with higher body mass index and greater daytime impairments (larger symptom and Epworth scores, longer trailmaking B time, and smaller functional outcomes of sleepiness questionnaire and SF-36 physical component scores) ($p \leqslant 0.05$; Table 3). No significant differences in age, AHI, or sex proportion were observed.

Of prospective determinant variables, independent predictors of CPAP preference identified were higher body mass index, symptom score, and trailmaking delay and more impaired SF-36 physical component score (all $p \leqslant 0.06$). This four-variable model explained 57% of variance in treatment preference and correctly predicted 74 and 83% of patients, respectively, preferring MRS and CPAP.

Objective CPAP use, downloadable during early follow-up, was added as a further predictor of potential clinical use in predicting eventual treatment preference. This second model contained the same significant determinants as the first model (all $p \leqslant 0.1$), with CPAP use as an additional significant independent predictor of eventual CPAP preference. The second model explained 11% more variance (68%) in treatment preference than the prospective-only model and showed slightly improved accuracy in identifying eventual preferrers of MRS (83%) or CPAP (90%).

TABLE 2. ADVERSE EVENTS AND SIDE EFFECTS OF TREATMENTS

MRS	Frequency	CPAP	Frequency
Pain in teeth, gums, or jaw	33 (69%)	Sleep disruption	16 (33%)
MRS is removed or comes off in sleep	19 (40%)	Leaky or painful mask	11 (23%)
Sleep disruption	12 (25%)	Stuffy nose	8 (17%)
Excessive salivation	9 (19%)	Mask is removed in sleep	7 (15%)
Dental crown damaged	3 (6%)	Cold airstream	7 (15%)
		Noise/inconvenience	6 (13%)
		Dry upper airway	5 (10%)
Reported use ⩽3 hours per night (second month)	10 (21%)	Reported use ⩽3 hours per night (second month)	13 (27%)
No problems limiting use (second month)	13 (27%)	No problems limiting use (second month)	15 (31%)

Definition of abbreviations: CPAP = continuous positive airway pressure; MRS = mandibular repositioning splint.

In the prospective model, a fivefold increase in probability of preferring CPAP was associated with a 4 kg/m^2 increase in body mass index (β exp = 1.3), a 4-second delay in trailmaking completion time (β exp = 1.1) a rise in symptom score (β exp = 1.2), or a drop in physical component score (β exp = 0.9) of four points apiece. The second model's estimate associated an additional hour per night of use with near double the likelihood of eventual CPAP preference (β exp = 1.8).

DISCUSSION

This study showed significantly better effectiveness with CPAP in comparison with MRS treatment for objective AHI on sleep study and subjective ratings of effectiveness, symptoms, sleepiness, sleepiness-specific functional status, and generic health transition and mental health status. Whereas the majority of variables did not differ significantly between the treatments, all but 4 of 21 had a positive polarity signifying a bias in favor of CPAP. There were no significant advantages favoring MRS over CPAP, including in satisfaction, acceptability, or side effect scores. The statistically significant CPAP-biased effects were of magnitudes (0.3–0.6 SDs) suggestive of small and moderate clinical significance (26). These effect sizes are more notable for a between-treatments trial such as this, with smaller expected differences than in a placebo versus treatment trial (3–7).

TABLE 3. BASELINE VARIABLES IN PATIENTS PREFERRING MANDIBULAR REPOSITIONING SPLINT AND CONTINUOUS POSITIVE AIRWAY PRESSURE

	MRS (*n = 19*)	CPAP (*n = 29*)	p Value
Age, yr	45 ± 9	47 ± 8	0.342
AHI, per hour	30 ± 21	32 ± 29	0.387
Sex	3F	9F	0.199
BMI, kg/m^2	28 ± 4	31 ± 5	0.012*
Symptom score	20 ± 5	24 ± 6	0.029*
Epworth score	13 ± 4	15 ± 3	0.015*
FOSQ score	12 ± 2	10 ± 3	0.028*
SF-36 physical component score	49 ± 6	40 ± 11	0.006*
SF-36 mental component score	45 ± 12	42 ± 12	0.327
HADS anxiety score	7 ± 4	7 ± 4	0.656
HADS depression score	5 ± 4	7 ± 5	0.101
IQ decrement score	4 ± 12	9 ± 12	0.221
Trailmaking B, s	59 ± 14	74 ± 21	0.018*
SteerClear (cows hit)	82 ± 83	106 ± 96	0.330
PASAT 2s (correct sums)	35 ± 8	33 ± 11	0.680

Definition of abbreviations: AHI = apnea+hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; FOSQ = functional outcomes of sleepiness questionnaire; HADS = hospital anxiety and depression scale; IQ = intelligence quotient; MRS = mandibular repositioning splint; PASAT = paced auditory serial addition test; SF-36 = short-form 36 health survey.

* Considered statistically significant.

This study did not confirm previous observations (16–18) of comparable efficacy and greater patient preference for MRS amongst patients with milder SAHS. Results from a planned subanalysis in patients with AHI of 5–15 (last column, Tables 1 and E2) were congruent with those of the full sample. Despite reduced statistical power for the 18 patients with mild SAHS, five subjective ratings among the 21 outcomes (treatment effectiveness, symptoms, sleepiness, sleepiness-specific functional status, and generic mental health status) were better ($p \leqslant 0.01$) with CPAP than with MRS. In the mild SAHS subgroup, the polarity of effect sizes favored CPAP for 19 of 21 outcomes.

The conflict between the current and previous findings (16–18) may be explained by differences in patient selection procedures or in CPAP or MRS practice between studies. Our patients were of similar polysomnographic severity to those of a previous randomized controlled trial comparing CPAP and MRS (18), and achieved a reduction in AHI similar to that in previous studies (9, 10–14, 16–24). However, all our patients, including the mild SAHS group, were deliberately enriched for sleepiness, with Epworth score of 8 or more or driving impairment as an entry criterion. Epidemiologic studies show that perhaps five times as many people have irregular breathing during sleep as those having irregular breathing plus sleepiness (28). However, evidence of benefit of treatment is restricted to symptomatic patients (1), and thus, we have focused on symptomatic patients for this study. Selection pressure for sleepiness may also explain why sleepiness was identified as a univariate (Table 3) but not as an independent determinant of treatment preference.

The types of CPAP and MRS used may have been another factor in the differences in our results. The treatments we assessed were those in current local clinical use, consisting of fixed-pressure CPAP and custom-fitted MRS. A high level of support was offered for each, with adjustments to CPAP pressures and interfaces, and MRS refittings made. Our MRSs were not expressly adjustable by design, although they were remade in cases of poor comfort or effectiveness. The randomized controlled trial with best findings for MRS (18) employed an adjustable appliance. It is therefore possible that the use of an adjustable device might have produced better results for the MRS group, but this remains to be tested. Indeed, there are few objective studies comparing MRS devices. In one recent randomized comparison of two custom-fitted MRS devices, the simpler model (similar to those used in the current trial) achieved better efficacy (19).

The costs of MRS manufacture, exclusive of clinician time, were estimated at £40 to £80 per device, with an expected life of 6 months to 1 year. A fixed-pressure CPAP unit, with life expectancy of 10 years, has an estimated capital cost of £280, with replacement of accessories (mask and hose) costing a further £50 per year. Thus, the local costs of MRS (£800) and CPAP (£770) over 10 years appear comparable.

A limitation of the current and previous studies of MRS devices (16–18) has been the lack of objective data on patients' use of MRS, as is available for CPAP (3–8). We tried to produce a thermal device built into our MRSs to measure patient use objectively but failed to achieve this for this study. This is the reason that reported use was adopted as the common metric across MRS and CPAP treatments. Although we cannot know how much of the relative ineffectiveness of MRS related to inadequate use rather than to failure of the device, reported use times during the home sleep study nights were not different (MRS 5.6 ± 2.0 hours, CPAP 6.1 ± 1.9 hours; $p > 0.17$). Similarly, CPAP treatment was at a fixed pressure, whereas newer "intelligent" CPAP units can provide adjustable pressure as required.

CPAP preference in this sample of sleepy patients with AHI of 5 or more, who had MRS treatment available, was independently associated with higher weight and worse symptoms, physical health status, and psychomotor performance. Treatment preference was not independently related to AHI, age, or sleepiness. This array of determinants has plausible interpretations within biomedical and social-cognition models of treatment adherence (29). With a prospective, intention-to-treat methodology, this study may have better predictive value than studies with retrospective or selective methods. All the independently predictive tests (body mass index, symptom and SF-36 questionnaires, and trailmaking tests) can be administered in a waiting or consulting room equipped with pen and desktop within 30 minutes, with age-stratified norms for trailmaking times available in Lezak (30). Additional determinants of treatment preference may include individual experiences of treatments and the success of interventions to improve comfort. Problems with and discontinuation of MRS (14, 15, 17) and CPAP (1–8) have been previously reported and were also observed in both treatments in this study (Table 2), where treatment use was closely associated with side effect score ($r = -0.6$ MRS, -0.8 CPAP).

In conclusion, this study did not support the use of these MRS devices as a first-line treatment for symptomatically sleepy patients with SAHS, even those with mild AHI (5–15/hour), as better outcomes were achieved with CPAP in both the full group and patients with milder SAHS. However, the observed advantages of CPAP were limited to objective breathing pauses during sleep and subjective ratings of daytime function, with no differences between treatments in objective measures of sleepiness or cognition or in patient preference. Whereas problems with both MRS and CPAP treatments were frequent, preference for MRS treatment was independently predicted by lesser obesity and symptoms and greater functional status. These data support CPAP as a first-line treatment for symptomatic patients with SAHS, although some patients with milder SAHS can be expected to transfer to MRS due to CPAP intolerance. Future treatment recommendations may also vary with the current rapid changes in both MRS and CPAP technology.

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