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Original Article

A custom-made mandibular repositioning device for obstructive sleep apnoea–hypopnoea syndrome: the ORCADES study

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ABSTRACT

Background: Mandibular repositioning devices (MRDs) are usually recommended as the first therapy option in patients with mild-to-moderate obstructive sleep apnoea (OSA). However, data on the long-term efficacy of MRDs are limited, not only in OSA patients who are noncompliant with continuous positive airway pressure (CPAP) but also in those with more severe OSA. The ORCADES study aimed to prospectively determine the long-term efficacy and tolerability of two custom-made Narval™ MRDs for obstructive sleep apnoea–hypopnoea syndrome (OSAHS) patients. The interim 3- to 6-month data are reported.
Methods: Eligible patients had OSAHS and had refused or were noncompliant with prescribed CPAP. Outcome measurements after gradual mandibular advancement titration included: apnoea–hypopnoea index (AHI), oxygen saturation, sleepiness, symptoms, quality of life, side effects and compliance.
Results: A total of 369 patients were included. Overall, MRD treatment was successful (≥50% decrease in AHI) in 76.2% of the participants; complete response (AHI <10/h) was achieved in 63.5%. Severe OSAHS was effectively treated (AHI <15/h) in about 60% of the participants; 38% had complete symptom resolution. Mandibular repositioning devices significantly decreased subjective sleepiness, eliminated symptoms and improved quality of life. They were well tolerated and compliance was excellent. Only 8% of the participants stopped MRD treatment due to side effects.
Conclusion: Custom-made Narval™ MRDs are effective for mild to severe OSA in patients who refuse or are noncompliant with CPAP. They are well tolerated and have excellent compliance.

1. Introduction

The consensus definition of obstructive sleep apnoea–hypopnoea syndrome (OSAHS) states that it is characterised by repetitive episodes of complete or partial upper airway obstruction during sleep and is usually associated with snoring, intermittent hypoxaemia and

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sleep fragmentation [1]. Excessive daytime sleepiness is frequent and increases the risk for vehicle crashes and occupational accidents [2]. Obstructive sleep apnoea–hypopnoea syndrome is associated with significant comorbidities and impaired quality of life (QOL) [3–5], and is considered to be a major public health problem.

Treatment of behavioural consequences such as fatigue, sleepiness, and memory problems are important but not sufficient enough to cure OSA. Upper airway surgery is only indicated in a small subset of OSAHS patients who have a specific aetiology [6]. The most widely used disease-specific therapies for treating OSAHS symptoms are: continuous positive airway pressure (CPAP) and mandibular repositioning devices (MRDs). Continuous positive airway pressure has been shown to be a very effective treatment; it reduces sleepiness, road accidents, cardiovascular risk and mortality [7–9]. However, good adherence is needed to realise treatment benefits [10] and 20–50% of OSAHS patients are unable or unwilling to comply with CPAP [11].

Mandibular repositioning devices enlarge the upper airway during sleep by holding the mandible in a forward position. They are efficacious treatment alternatives for patients with mild-to-moderate [12] or supine-position-dependent [13] OSAHS, or in those who are noncompliant with CPAP. The effects of MRDs on sleep-disordered breathing are usually inferior to CPAP, especially for apnoea–hypopnoea index (AHI) reductions, but patient acceptability may be better [14], with similar QOL and symptom effects.

Guidelines recommend MRDs as first-line therapy for patients with mild-to-moderate obstructive sleep apnoea (OSA) [15,16]. However, few studies have specifically assessed the long-term efficacy of MRDs in OSA patients who are noncompliant with CPAP. Discontinuation rates for MRD therapy in the literature are 14–63% after four to five years [17–19].

These uncertainties about the long-term clinical benefits of MRD therapy resulted in the French Health Technology Assessment agency (Haute Autorité de Santé) to request that each MRD manufacturer provide additional clinical data on both the efficacy and side effects of their MRD devices over five years of treatment. The prospective, multicentre, observational ORCADES study determined the efficacy of two custom-made Narval™ MRDs in real-life conditions over five years in a cohort of OSAHS patients who refused or were noncompliant with CPAP. This paper presents the interim 3- to 6-month follow-up results.

2. Methods

2.1. Subjects

Patients with newly diagnosed OSAHS were recruited from 28 sleep centres across France. Inclusion criteria were: age ≥18 years; OSAHS (AHI >30/h or AHI 5–30/h on polysomnography (PSG) or cardiorespiratory polygraphy [PG]); excessive daytime sleepiness assessed by the clinician and/or an Epworth Sleepiness Scale (ESS) score >10; and refusal of or noncompliance with CPAP (pressure or mask intolerance, compliance <3 hours/night). Patients were excluded if they had received previous MRD treatment or any of the following characteristics: central apnoea index ≥5/h; AHI <30/h with severe sleep comorbidities other than OSAHS; or coexisting psychiatric disease. Patients with contraindications for MDR that had been assessed by a dental specialist investigator were also excluded. All patients gave written informed consent to participate in the study, which had ethics committee approval and was conducted according to the Declaration of Helsinki principles (ClinicalTrials.gov identifier: NCT01326143).

2.2. Intervention

The Narval™ devices used in this study were bi-block MRDs that were made with semi-rigid plastic materials (biocompatible polymer) and customised using either a high-precision computer-aided design (CAD)/computer-aided manufacturing (CAM) (ResMed, Narval CC™) or non-CAD/CAM process (ResMed, Narval™) (Fig. 1). Devices manufactured using non-CAD/CAM processes are reserved for patients with tooth morphology that is unsuitable for CAD/CAM technology (eg, short teeth or removable appliance leading to inadequate retention with CAD/CAM device). The MRDs were gradually adjusted to provide mandibular advancement over a 15-mm range. Each MRD was fitted by a dental specialist with an initial advancement of 67 ± 18% of maximal jaw protrusion. During titration, mandibular advancement was adjusted at the discretion of the dental sleep specialist until the best benefit–risk ratio between symptom resolution and tolerability was achieved.

Fig. 1. Examples of: (A) a non-computer-aided design/computer-aided manufacturing mandibular repositioning device and (B) a computer-aided design/computer-aided manufacturing mandibular repositioning device.

2.3. Endpoints

The primary endpoint used to assess the success of MRD therapy was the proportion of patients with a ≥50% decrease in AHI from baseline to follow-up (three to six months). This threshold is commonly used in clinical trials and was selected for this study because of the evaluation of MRD as a second-line treatment in the absence of another alternative therapy [16].

Secondary endpoints included: complete response to MRD treatment (using AHI cut-off values of <5/h or <10/h), mean AHI decrease, evolution of other respiratory criteria, OSAHS symptoms, QOL, compliance and tolerability. Additional pre-planned subgroup analyses were conducted in subgroups of patients according to AHI severity, previous CPAP therapy, diagnosis method (PG or PSG), and MRD type.

2.4. Assessments

Sleep and/or respiratory parameters were recorded during sleep at baseline and the 3-month follow-up visit using the same PG or PSG device used to diagnose OSAHS. If MRD therapy was suboptimal (AHI decrease of <50% and/or persistent symptoms), PSG/PG was performed again at a 6-month follow-up visit after additional mandibular advancement. The PSG/PG recordings were manually scored according to the American Academy of Sleep Medicine (AASM) guidelines [20]. Obstructive apnoea was defined as a ≥10-s cessation of airflow on the pressure nasal cannula, with or without association with an oro-nasal thermal sensor. Hypopnoea was defined as a ≥50% reduction in airflow, or a <50% airflow reduction on the nasal pressure cannula accompanied by a ≥3% decrease in arterial oxyhaemoglobin saturation (SpO_2) recorded using finger pulse oximetry or an arousal. The oxygen desaturation index (ODI) describes the average number of desaturation episodes per hour, with desaturation defined as a ≥3% decrease in SpO_2 from the average value. Other recorded parameters were: the lowest value of SpO_2 (nadir SpO_2) and the total time that SpO_2 was <90% (SpO_2 <90%). Objective data on snoring were obtained from PSG, including snoring duration (as a percentage of total sleep time (TST)) and the number of snoring events per hour of sleep.

At follow-up, investigators recorded self-reported clinical symptoms, including: snoring (daily snoring/loud snoring/bothersome snoring); nocturnal polyuria; libido disorders; and nocturnal mouth breathing. Sleep quality, state on waking and morning headache were recorded by the patient at baseline and follow-up on a visual analogue scale (VAS) from 0 to 10. Subjective sleepiness, assessed using the Epworth Sleepiness Scale (ESS score), QOL (Quebec Sleep Questionnaire [21]) and fatigue (Pichot scale [22]), was also determined at baseline and the 3- to 6-month follow-up visits. Office blood pressure (BP) was measured after 10 min of rest in the supine position at baseline and during follow-up.

During the clinical examination at each follow-up visit, the treating physician subjectively determined, by patient self-report, compliance with the MRD (number of hours used per night and number of nights used per week). Comprehensive data on MRD-related side effects were also collected at follow-up visits. The sleep and dental sleep physicians determined the severity of side effects and their impact on MRD treatment.

2.5. Statistical analysis

In this prospective study based on pre- and post-treatment evaluations of the same subjects, the sample size was determined by the accuracy required to estimate the primary endpoint with a confidence interval (CI) of 95%; a minimum sample size of n = 323 was determined. It was also estimated that about 10% of participants

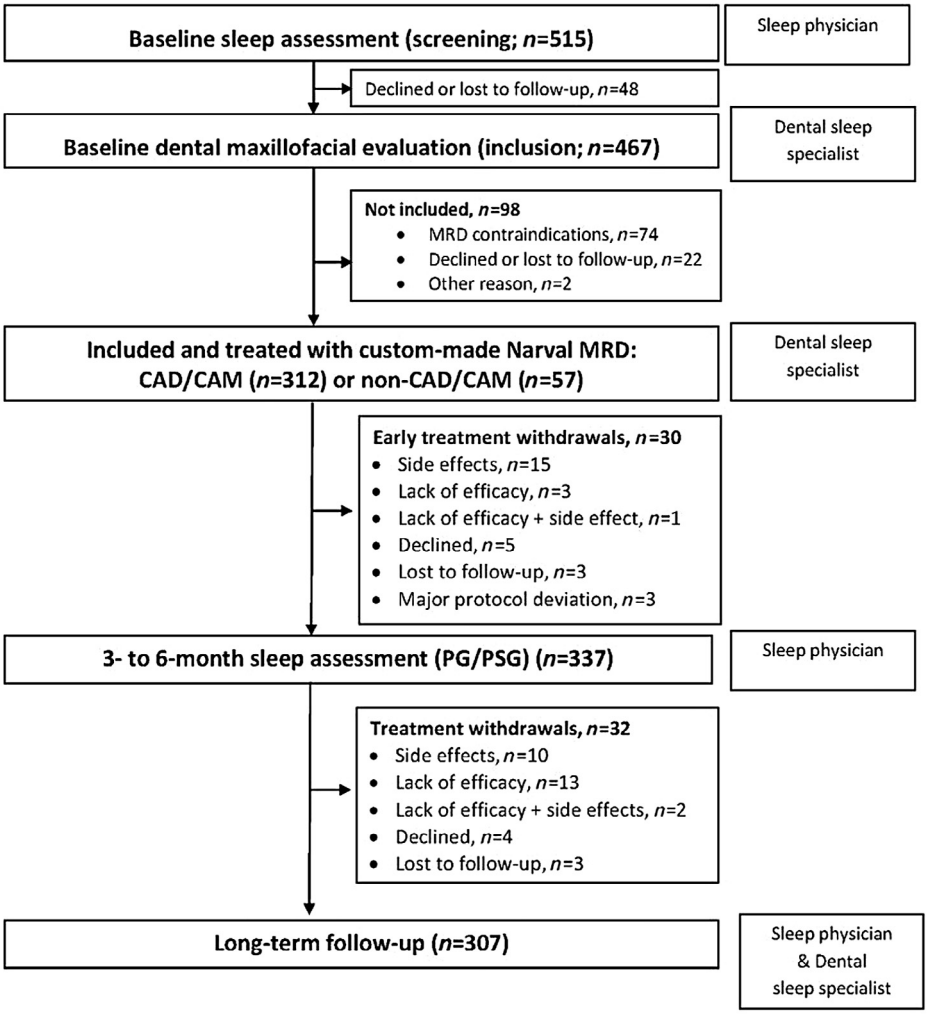

Fig. 2. Flow of participants through the study. CAD/CAM, computer-aided design/computer-aided manufacturing; MRD, mandibular repositioning device; PG, polygraphy; PSG, polysomnography.

would be lost to follow-up, resulting in a target sample size of 360 patients.

Quantitative changes from baseline to the 3- to 6-month follow-up visits were presented as mean values, with standard deviation, minimum, maximum, median and quartile values, and compared using unpaired or paired Student's t-test or the Wilcoxon–Mann–Whitney nonparametric test according to normality of distribution and group comparison. Qualitative changes were described using frequency distribution and compared using Fisher's exact test or Chi-squared test. Comparisons between patient subgroups were assessed using the Student's t-test, ANOVA or Wilcoxon–Mann–Whitney test. Statistical analyses were performed using SAS version 9.

A logistic procedure with backward stepwise regression analysis was used to determine the independent factors associated with treatment success and complete response after selection of variables, with a p-value of <0.10 on univariate analysis. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Population

A total of 515 eligible patients were screened between May 2011 and September 2013. One hundred and forty six were not recruited into the study according to the following main reasons: 74 had maxillofacial contraindications to MRD therapy (temporomandibular joint disorders, craniofacial dimorphism, poor dental or periodontal status) and 72 declined to participate. Therefore, 369 eligible patients were included and treated with a CAD/CAM (n = 312) or non-CAD/CAM (n = 57) MRD (Fig. 2). Overall, 50% of the participants had previously received CPAP (median duration 11 months; median therapy pressure 11 cmH_2O (Q1–Q3: 9–12 cmH_2O)). Thirty MRD-treated participants withdrew from the study before the 3-month follow-up, mainly because of side effects (n = 16). The PG/PSG follow-up data were available for 337 participants. Eleven participants without PG/PSG follow-up for either no valid reason (n = 7) or early study withdrawal for subjective lack of efficacy (n = 4) were classified as treatment failures. Therefore, the primary endpoint was assessed in 348 participants. Baseline participant demographic and clinical data are shown in Table 1.

Table 1
Participant demographic, respiratory and clinical data at baseline.

	Total (n = 369)
Male, n (%)	273 (74.0)
Age, years	52.6 ± 11.3
Body mass index, kg/m^2	27.2 ± 4.3
Overweight, n (%)	171 (46.7)
Obese, n (%)	80 (21.9)
Waist circumference, cm	97.4 ± 12.4
Neck circumference, cm	39.7 ± 3.8
Systolic blood pressure, mmHg	127.2 ± 12.5
Diastolic blood pressure, mmHg	78.3 ± 10.3
AHI, /h	29.5 ± 15.2
Supine AHI, /h	37.0 ± 22.4
AI, /h	12.7 ± 12.9
HI, /h	16.8 ± 10.3
cAI, /h	0.5 ± 1.2
SpO_2, %	93.7 ± 2.0
Minimum SpO_2, %	81.7 ± 7.6
Median time SpO_2 <90%, min	7
ODI, /h	21.7 ± 18.4
Dental status, n (%)	
Good	301 (82.2)
Acceptable	65 (17.8)
Periodontal status, n (%)	
Good	294 (80.3)
Acceptable	72 (19.7)
Dental mobility, n (%)	
None	342 (93.4)
Low and limited	24 (6.6)
Angle malocclusion, n (%)	
Type 1	236 (66.7)
Type 2	102 (28.8)
Type 3	16 (4.5)

Values are mean ± standard deviation or number of patients (%), unless otherwise stated.
AHI, apnoea–hypopnoea index; AI, apnoea index; cAI, central apnoea index; HI, hypopnoea index; MRD, mandibular repositioning device; ODI, oxygen desaturation index; SpO_2, oxygen saturation.

3.2. MRD titration

In 84% of participants, at least one MRD titration visit was required (median 2, range 0–4); 25% required additional titration after the first PG/PSG control and were evaluated at the 6-month follow-up visit. Mean mandibular advancement after the last titration was 7.3 ± 2.1 mm (85 ± 26% of maximal, Q1-Q3: 73–100%) irrespective of the type of MRD.

3.3. Efficacy

3.3.1. Primary endpoint

Mandibular repositioning device treatment success was achieved in 76.2% of the participants (95% CI 71.4–80.3%).

3.3.2. Secondary endpoints

The complete response rates were 35.9% (AHI <5/h) and 63.5% (AHI <10/h). An AHI <15/h was achieved in 78% of participants during MRD therapy. Correction of AHI was greater in mild-to-moderate vs severe OSAHS (Fig. 3). However, more than half of all participants with severe OSAHS achieved an AHI of <15/h.

Treatment success was equivalent, irrespective of OSAHS severity at baseline (Fig. 3), previous CPAP therapy and diagnosis method. However, the treatment success rate was higher in those using a CAD/CAM vs non-CAD/CAM MRD (79.1% (95% CI 74.1–83.4%) vs 60.7% (95% CI 47.6–72.4%); p = 0.0031). The complete response rate with AHI <10/h was also higher in the CAD/CAM subgroup (66.2% (60.5–71.5%) vs 49.1% (36.1–62.1%); p = 0.017).

3.3.2.1. Other respiratory criteria. Mandibular repositioning device therapy had significant beneficial effects on AHI, apnoea index (AI), hypopnoea index (HI), and ODI. Changes from baseline were significantly greater in participants with severe OSAHS at baseline vs those with mild or moderate disease (Table 2). Mandibular repositioning device therapy had no significant effect on mean SpO_2, but nadir values significantly increased from baseline to follow-up, and time with SpO_2 <90% significantly decreased during MRD therapy (Table 2). Based on PSG assessment, the number of snoring events decreased by 50% and the duration of snoring decreased by 75% compared with baseline during MRD therapy (Fig. 4A).

3.3.2.2. PSG data. Baseline and follow-up PSG data were available for 142 participants. There were no significant changes from baseline in total sleep time (TST) (417.1 ± 72.3 vs 411.9 ± 73.9 min), sleep latency (–2.7 ± 39.0 min) and sleep stage durations (stage 1–2 non-rapid eye movement (NREM): –2.8 ± 14.4% of TST; stage 3–4 NREM: +1.7 ± 11.9% of TST; REM: +1.2 ± 8.4% of TST) during MRD therapy. The number of arousals per hour decreased, irrespective of OSAHS severity, from 24.2 ± 17.5 at baseline to 16.1 ± 12.1 at follow-up (p < 0.0001). Although there was no overall change, participants with severe OSAHS showed a significant decrease in stage 1–2 NREM sleep (median 6% decrease; p = 0.014) in favour of an increase in REM sleep (median 3% increase; p = 0.023), without change in TST. Supine and non-supine AHI were significantly reduced from 37.0 ± 22.2 to 12.2 ± 16.0/h of TST (p < 0.001) and from 18.0 ± 17.5 to 6.3 ± 10.9 of

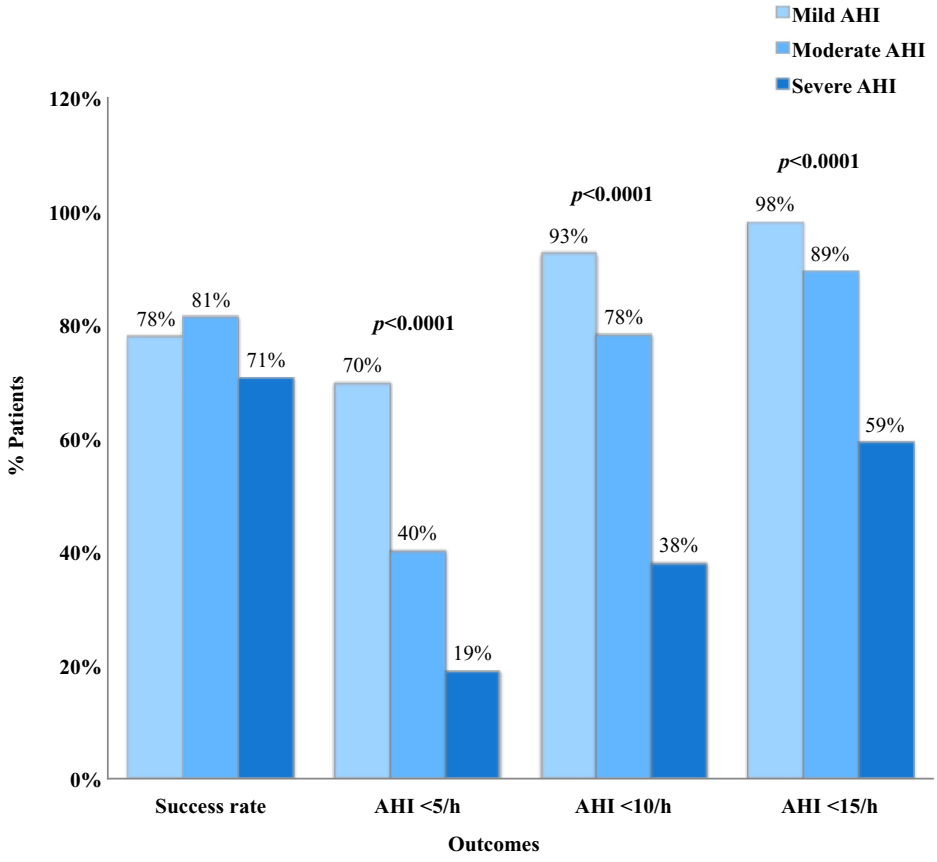

Fig. 3. Mandibular repositioning device efficacy by obstructive sleep apnoea–hypopnoea syndrome severity at 3- to 6-month follow-up. AHI, apnoea–hypopnoea index; Success rate, percentage of patients with a ≥50% decrease in AHI from baseline to follow-up.

TST ($p < 0.001$), respectively; TST in the supine (197.6 ± 109.5 vs 208.8 ± 115.4 min) or non-supine (226.0 ± 121.1 vs 212.9 ± 116.0 min) position was unchanged.

3.3.2.3. Daytime sleepiness. The ESS score decreased from 11.2 ± 4.8 at baseline to 7.8 ± 4.3 during MRD therapy; $p < 0.0001$). Overall, 62% of participants with excessive sleepiness at baseline had complete symptom resolution.

3.3.2.4. Clinical symptoms. Most clinical symptoms significantly improved during MRD therapy. Data on reductions in objective and subjective snoring are shown in Fig. 4A and B, respectively. Nocturnal polyuria and libido disorders resolved in 64% and 81% of participants affected by these problems at baseline and there was a significant reduction in the percentage of those with moderate or severe OSAHS who had nocturnal mouth breathing ($p = 0.0001$). Improvements in polyuria were seen across disease severity subgroups ($p < 0.0001$), but libido disorders only improved in those with severe OSAHS ($p < 0.01$). Visual analogue scale scores for sleep, state on waking, and morning headache significantly improved from baseline to follow-up ($p < 0.0001$).

3.3.2.5. Quality of life. Significant improvements from baseline (+24%) were documented in all five domains of the Quebec Sleep Questionnaire during MRD therapy (Fig. 5), irrespective of OSAHS severity. The Pichot score significantly decreased from 14.1 ± 7.8 at baseline to 9.0 ± 7.2 at follow-up ($p < 0.0001$).

3.3.2.6. Blood pressure and body weight. There were no changes in body weight, mean office systolic or diastolic BP, or heart rhythm from baseline to 3-month follow-up.

3.3.3. Tolerability

Fifty per cent of participants reported side effects during MRD therapy (Table 3). The most common events were temporomandibular joint or dental pain, and feelings of dental occlusion change. The majority of side effects were of mild severity and the investigators classified only 14% as severe. Pain was usually transitory and resolved within a median of 10 min of MRD removal in the morning. Twenty-eight participants (8%) prematurely discontinued MRD therapy because of side effects, which were similar across OSAHS severity subgroups, and there were no differences between the two types of MRD.

3.3.4. Compliance

Mean subjective compliance was 6.7 ± 1.3 hours/night, 6.7 ± 0.9 nights/week. The majority of participants (96.1%) used the MRD for ≥4 h/night, ≥4 days/week, and 86% used the device every night. Compliance results were similar regardless of OSAHS severity or MRD type.

3.3.5. Factors predictive of MRD efficacy

Univariate analysis identified a number of statistically significant factors at a threshold of 10% to predict a ≥50% decrease in AHI from baseline (Table 4). In an adjusted multivariate analysis, five factors remained as statistically significant predictors of a ≥50% decrease in AHI: use of a CAD/CAM MRD (odds ratio (OR) 3.02, 95%

Table 2
Changes in respiratory parameters from baseline to follow-up based on severity of obstructive sleep apnoea–hypopnoea syndrome in participants treated with a mandibular repositioning device.

	OSAHS severity at baseline			p (between-group comparison)
	Mild (n = 61)	Moderate(n = 150)	Severe (n = 158)	
AHI, /h				
Baseline	11.1 ± 2.8	22.5 ± 4.4	43.3 ± 12.3	
Three months	4.0 ± 3.7*	7.1 ± 6.1*	17.9 ± 17.2*	
Difference	−7.0 ± 4.0	−15.1 ± 6.7	−25.0 ± 16.4	<0.0001
AI, /h				
Baseline	4.4 ± 3.5	7.7 ± 6.4	20.7 ± 15.1	
Three months	1.0 ± 1.6*	2.0 ± 3.5*	7.9 ± 13.3*	
Difference	−3.3 ± 3.5	−5.6 ± 5.9	−13.5 ± 15.4	<0.0001
HI, /h				
Baseline	6.8 ± 3.4	14.8 ± 6.5	22.5 ± 11.5	
Three months	2.9 ± 2.8*	5.1 ± 4.2*	10.1 ± 8.9*	
Difference	−3.8 ± 3.6	−9.6 ± 7.4	−11.4 ± 12.6	<0.0001
Supine AHI, /h				
Baseline	20.2 ± 13.5	32.1 ± 17.5	49.4 ± 23.1	
Three months	5.5 ± 5.7*	9.7 ± 10.7*	20.6 ± 23.4*	
Difference	−14.9 ± 12.5	−20.9 ± 18.3	−26.9 ± 29.0	0.011
Mean SpO_2, %				
Baseline	94.6 ± 1.7	93.9 ± 1.8	93.1 ± 2.1	
Three months	94.6 ± 1.5	94.0 ± 1.8	93.5 ± 2.0	
Difference	−0.1 ± 1.6	0.1 ± 1.5	0.2 ± 2.1	NS
cAI, /h				
Baseline	0.2 ± 0.4	0.4 ± 0.8	0.8 ± 1.6	
Three months	0.2 ± 0.3	0.3 ± 1.1#	0.8 ± 2.6	
Difference	−0.04 ± 0.36	−0.03 ± 1.05	0.04 ± 2.9	NS
Nadir SpO_2, %				
Baseline	84.6 ± 6.0	82.3 ± 6.7	80.0 ± 8.6	
Three months	86.9 ± 8.0*	84.9 ± 9.1*	83.5 ± 8.0**	
Difference	2.1 ± 10.4	2.8 ± 10.0	3.5 ± 7.9	NS
$TSpO_2$ <90%, min (median (Q1, Q3))				NS
Baseline	2 (0, 7)	6 (1, 17)	12.5 (2, 42.5)	
Three months	0 (0, 1)***	0.9 (0, 8)*	4.0 (0, 23)***	
Difference	−1 (−22.8, 1.5)	−2 (−12, 0)	−1 (−4, 0)	
ODI, /h				
Baseline	10.9 ± 8.3	16.3 ± 13.1	30.9 ± 21.1	
Three months	4.4 ± 6.8*	8.2 ± 9.7*	14.2 ± 16.1*	
Difference	−5.9 ± 10.7	−8.6 ± 14.3	−15.4 ± 23.2	0.003

Values are mean ± standard deviation, unless stated otherwise.
AHI, apnoea–hypopnoea index; AI, apnoea index; cAI, central apnoea index; HI, hypopnoea index; mild, AHI 5/h to <15/h; moderate, AHI ≥15/h to <30/h; NS, not significant; ODI, oxygen desaturation index; OSAHS, obstructive sleep apnoea–hypopnoea syndrome; severe, AHI ≥30/h; $TSpO_2$ <90%, time with oxygen saturation <90%; SpO_2, oxygen saturation; Success, ≥ 50% decrease in AHI.
* p < 0.0001 vs baseline.
** p < 0.001 vs baseline.
*** p < 0.01 vs baseline.
\# p < 0.05 vs baseline.

CI 1.44–6.33; p = 0.0035); waist circumference (OR 0.97, 95% CI 0.94–0.99; p = 0.0072); dental overbite (OR 1.22, 95% CI 1.03–1.45; p = 0.022); maximal jaw protrusion (OR 1.18, 95% CI 1.03–1.35; p = 0.015); and baseline AI (OR 0.97, 95% CI 0.95–0.99; p = 0.016).

There were also a number of significant univariate predictors of complete response (AHI <10/h) during MRD therapy (Table 4). On adjusted multivariate regression analysis, four factors were significant independent predictors of complete response: use of CAD/CAM MRD (OR 2.99, 95% CI 1.42–6.29; p = 0.0039); baseline AI (OR 0.89, 95% CI 0.87–0.92; p < 0.0001); maximal jaw protrusion (OR 1.21, 95% CI 1.07–1.37; p = 0.0018); and baseline HI (OR 0.93, 95% CI 0.90–0.95; p < 0.0001). Age, body mass index, and supine AHI were not identified as predictive factors of MRD efficacy.

4. Discussion

This prospective observational study described the treatment of 369 patients with OSAHS and with an MRD. Although MRDs have a place in the management of OSAHS, it is believed that, to date, there are few comparative studies looking at the efficacy and tolerability of different oral appliances [23]. Available data suggest that custom-made and adjustable devices are more effective than prefabricated, fixed, thermoplastic appliances [24,25]. In the absence of direct comparative trials, multiple factors can make comparing data from different studies difficult, including: heterogeneity in OSAHS severity, variety in MRD type, and use of varying treatment success definitions [26].

This study had a number of strengths. These included its multicentre real-life design, the large sample (369 participants), objective titration with PSG/PG at the end of final titration, re-evaluation of suboptimal efficacy after optimisation of mandibular advancement, and a multidisciplinary approach involving sleep physicians and sleep dental specialists. Primary and efficacy endpoints were assessed in more than 90% of participants and the proportion lost to follow-up was very low (<2%). In addition, the study identified some predictive factors of efficacy and showed that MRD therapy can be successful in some patients with severe OSAHS and/or obesity.

Participants were carefully selected, based on oral conditions as recommended by current guidelines. However, the proportion of screened patients who were not selected by a dental specialist for MRD therapy (15%) was lower than expected. Other data show that MRD contraindications could be present in up to 34% of patients, mainly due to dental problems [27]. Furthermore, participants in

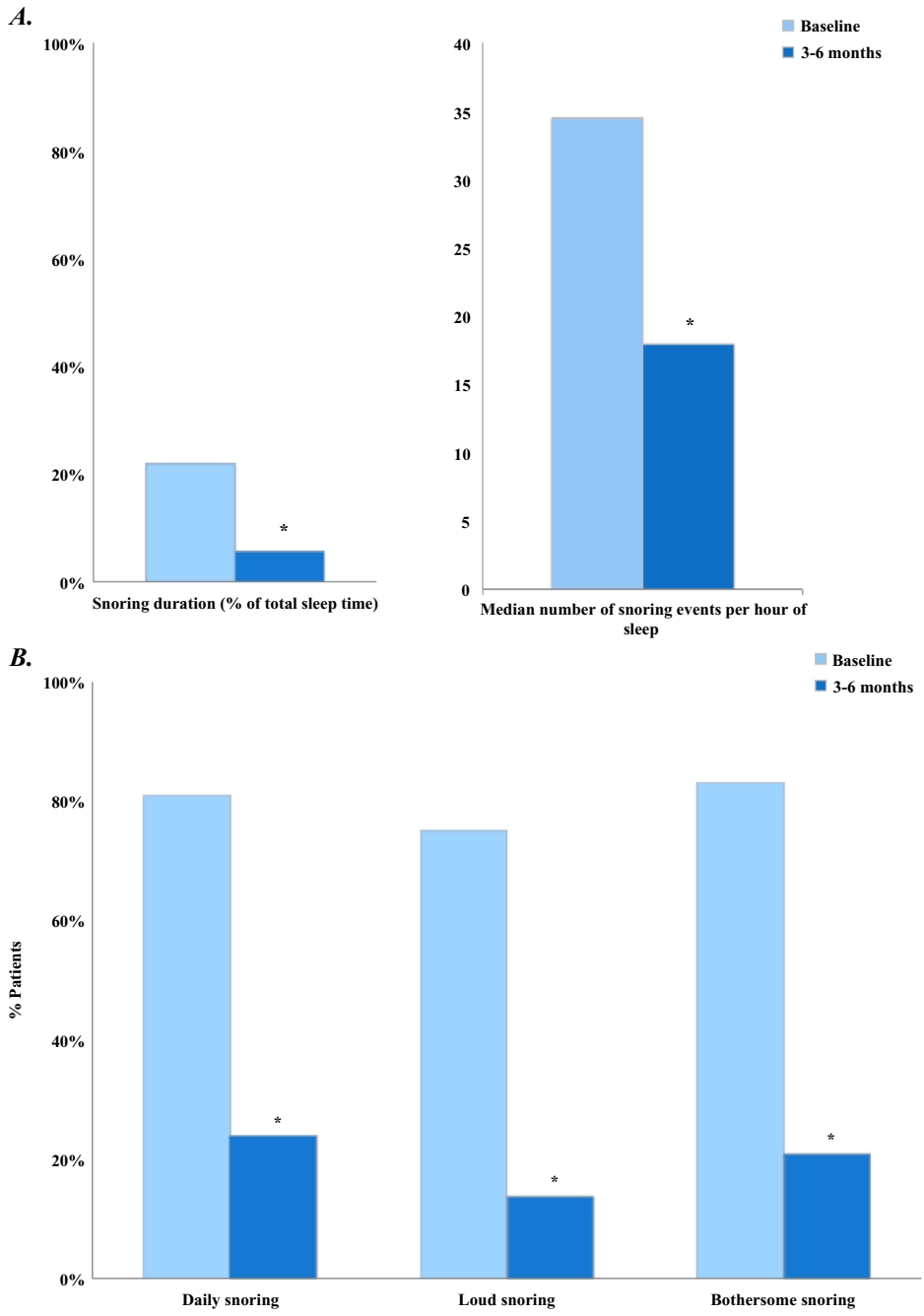

Fig. 4. Effects of mandibular repositioning device therapy on snoring: (A) based on polysomnology data or (B) patient self-report (*$p < 0.0001$ vs baseline).

this study were not excluded for criteria that were previously identified to influence MRD effectiveness (eg, AHI, BMI, sex, age) in other studies. The present results suggest that MRDs may be indicated for the majority of patients who are noncompliant with CPAP therapy. Moreover, 25% of participants received additional titration after the first 3-month PG/PSG control to achieve optimal efficacy, showing that objective measurement of AHI is essential for controlling MRD therapy and that proper individualised titration is probably as important as patient selection.

Improvements in snoring in this study were not only subjectively assessed but also objectively determined using PSG/PG, which confirmed that the MRD-related improvements reported by patients and partners are consistent with existing data [28]. Reported reductions in daytime sleepiness and the incidence of excessive sleepiness were also of a similar magnitude to previously reported changes [28–31] and similar to those achieved with CPAP [29]. Furthermore, this study documented significantly improved QOL after MRD therapy using the Quebec Sleep Questionnaire. Not many previous studies have explored QOL after MRD treatment [30,32–34].

Subjectively assessed MRD compliance in this study was excellent (95.8%). Previous reports of self-assessed compliance with MRD therapy have ranged from 76 to 95% [29]. Recent data suggest that there is good similarity between subjective and objective

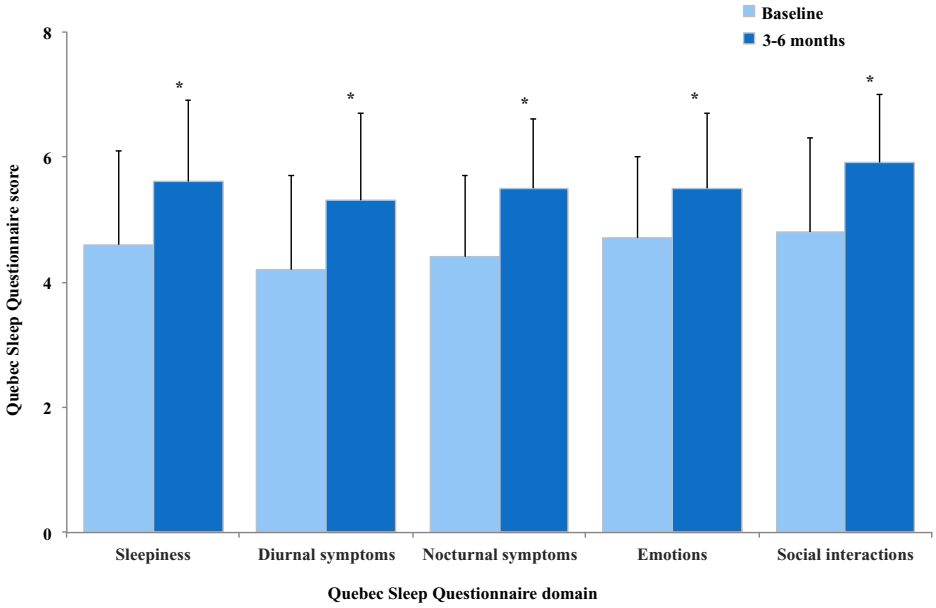

Fig. 5. Effect of mandibular repositioning device on quality of life (Quebec Sleep Questionnaire) (*$p < 0.0001$ vs baseline).

long-term compliance rates with MRD therapy [35,36]. Thus, even though CPAP remains the treatment of choice in severe OSA, better long-term compliance with MRD therapy could minimise actual differences between the effectiveness of MRD and CPAP in clinical practice [16,35].

MRD therapy is currently recommended for the treatment of patients with mild or moderate OSAHS (level A recommendation) [15,16,29,37]. A large subgroup of participants (42.8%) in the current study had severe OSAHS (AHI >30/h) and MRD was able to significantly reduce AHI, despite high mean baseline AHI values (43 ± 12/h). Thus, while an MRD might be less effective for resolving severe OSAHS compared with mild/moderate disease, a significant number of patients with severe OSAHS have been effectively treated with an MRD [16,38].

Table 3
Side effects reported during mandibular repositioning device therapy.

	Side effects during MRD therapy, n (%)		
	Minor, n (%)	Severe, n (%)	Requiring treatment withdrawal
TMJ pain	49 (13.3)	13 (3.5)	2 (0.5)
Dental pain	46 (12.5)	8 (2.2)	8 (2.2)
Occlusion change	50 (13.6)	1 (0.3)	2 (0.5)
Gingival bleeding	26 (7.1)	3 (0.8)	3 (0.8)
Periodontal pain	23 (6.3)	6 (1.6)	3 (0.8)
Dental mobility	19 (5.1)	1 (0.3)	1 (0.3)
Mouth dryness	18 (4.9)	0	0
Hypersalivation	14 (3.8)	1 (0.3)	1 (0.3)
Gingival pain	11 (3.0)	3 (0.8)	1 (0.3)
Jaw pain	10 (2.8)	2 (0.5)	2 (0.5)
Teeth clenching	10 (2.7)	0	1 (0.3)
TMJ disorders	7 (1.9)	3 (0.8)	0
Gingivitis	5 (1.3)	5 (1.4)	2 (0.5)
Broken MRD	5 (1.3)	4 (1.1)	4 (1.1)
Dental fracture	2 (0.5)	4 (1.1)	0
Mild tooth migration	6 (1.6)	0	0
Jaw stiff	6 (1.6)	0	0
Local inflammatory reaction	1 (0.3)	1 (0.3)	1 (0.3)
Prosthesis loosening	2 (0.5)	0	0

MRD, mandibular repositioning device; TMJ, temporomandibular joint.

The results of this 'real-life' study show that a custom-made Narval™ MRD is effective and well tolerated in OSAHS patients who refuse or do not tolerate CPAP. Significant improvements were documented in AHI, SpO_2, clinical symptoms and QOL in mild-to-moderate and severe OSAHS. The Narval™ MRD device is custom-made with flexible biocompatible polyamide; such soft acrylic materials have been shown to be better tolerated and to have better efficiency than thermoplastic monobloc or hard acrylic MRDs [23,29]. Moreover, the traction-based triangle and connector articulations enable mandibular advancement in parallel to the occlusion plane. This vector of advancement reduces stress on muscles and TMJ contact force [39], and may be a possible explanation for the good tolerance of MRD in the present cohort. MRD therapy was well tolerated in this study and most participants expressed a desire to continue using the MRD.

Treatment success (76%) and complete response (64%) rates with Narval™ MRD in this study were at the upper end of the range reported in previous studies of MRD devices in OSAHS. Data from randomised, controlled trials have shown mean decreases in the frequency of respiratory disturbances of 14–80% with MRD therapy [28,29] and complete response rates of 50–70% [28,32]. In parallel with AHI improvements, MRD therapy significantly increased minimal SpO_2, significantly decreased time spent with SpO_2 <90% and the ODI to a similar extent, as previously reported [29,40].

In the present study, use of a CAD/CAM MRD device was also a significant independent predictor of treatment success, suggesting that the type of MRD may have an important influence on the outcome of therapy. Waist circumference was found to be an independent predictor of MRD efficacy, and a much stronger predictor than BMI. Moreover, in univariate analysis, success rate and complete response in obese patients were 58.1% and 44.3%, respectively. Consistent with existing data, other results have suggested that MRD efficacy is not affected by supine-dependent OSAHS [41]. Greater overbite was a significant predictor of treatment success, which may predispose patients with mandibular retrognathia, especially those with class II division 2 malocclusions, to a high success rate, in accordance with previous data on MRDs. The associations that were found between MRD treatment outcome and both functional and morphological factors should be taken into account in therapeutic decision-making.

Table 4
Univariate predictors of treatment success and complete response for mandibular repositioning device therapy.

Variable	Yes	No	OR (95% CI)	p
Treatment success (≥50% decrease in AHI)				
Type of device, % participants				
Non-CAD/CAM	60.7	39.3	Reference	
CAD/CAM	79.1	20.9	2.45 (1.34–4.49)	0.0031
Sex: M/F, % participants	73.6/83.3	26.4/16.7	1.79 (0.96–3.33)	0.063
Neck circumference, cm	39.2 ± 3.6	40.8 ± 3.7	0.89 (0.82–0.96)	0.0022
Waist circumference, cm	95.7 ± 11.9	101.9 ± 12.7	0.96 (0.94–0.98)	0.0001
BMI, % participants				
Normal	86.0	14.0	Reference	
Overweight	78.5	21.5	0.60 (0.31–1.16)	NS
Obese	58.1	41.9	0.23 (0.11–0.46)	<0.0001
Malocclusion dental class, % participants				
I	74.8	25.2	Reference	
II	85.4	14.6	1.98 (1.04–3.76)	0.067
III	66.7	33.3	0.68 (0.22–2.06)	NS
Dental overbite, mm	3.0 ± 2.0	2.2 ± 1.9	1.27 (1.09–1.49)	0.0004
Maximum jaw protrusion, mm	9.1 ± 2.5	8.2 ± 2.1	1.20 (1.07–1.34)	0.0019
Dental overjet, mm	3.1 ± 1.8	2.3 ± 1.8	1.31 (1.11–1.55)	0.0013
Mandibular advancement, %	85.6 ± 26.0	91.1 ± 26.4	0.990 (0.980–0.999)	0.009
Baseline AHI, /h	28.3 ± 13.9	33.8 ± 18.3	0.98 (0.96–0.99)	0.028
Baseline AI, /h	11.6 ± 12.3	17.6 ± 14.3	0.97 (0.95–0.99)	0.0001
Supine AHI, /h	35.6 ± 21.2	41.9 ± 25.6	0.99 (0.98–1.00)	0.098
Mouth breathing: yes/no, % participants	73.1/82.3	26.9/17.7	1.72 (0.95–3.09)	0.070
Complete response (AHI <10/h)				
Type of device, % participants				
Non-CAD/CAM	49.1	50.9	Reference	
CAD/CAM	67.5	32.5	2.16 (1.20–3.91)	0.010
Sex: M/F, % participants	60.5/76.5	39.5/23.5	2.12 (1.21–3.73)	0.0078
Neck circumference, cm	38.9 ± 3.6	40.9 ± 3.5	0.84 (0.78–0.91)	<0.0001
Waist circumference, cm	94.5 ± 12.1	101.5 ± 11.3	0.95 (0.93–0.97)	<0.0001
BMI, % participants				
Normal	77.9	22.1	Reference	
Overweight	64.7	35.3	0.52 (0.30–0.92)	<0.0001
Obese	44.3	55.7	0.23 (0.12–0.44)	<0.0001
Dental overbite, mm	3.0 ± 2.0	2.5 ± 2.0	1.16 (1.02–1.31)	0.0066
Maximum jaw protrusion, mm	9.2 ± 2.4	8.6 ± 2.4	1.12 (1.02–1.24)	0.028
Dental overjet, mm	3.1 ± 1.8	2.5 ± 1.7	1.23 (1.07–1.41)	0.0047
Mandibular advancement, %	83.0 ± 25.4	88.3 ± 26.4	0.99 (0.98–1.00)	0.040
Baseline AHI, /h	23.7 ± 11.4	39.1 ± 15.8	0.92 (0.90–0.94)	<0.0001
Baseline AI, /h	8.9 ± 9.4	20.5 ± 15.7	0.92 (0.90–0.95)	<0.0001
Baseline HI, /h	14.9 ± 8.9	18.6 ± 10.2	0.96 (0.94–0.98)	0.0012
Supine AHI, /h	31.5 ± 18.3	46.9 ± 25.2	0.97 (0.96–0.98)	<0.0001
ESS score, % participants				
≤10	58.3	41.7	Reference	
>10	69.0	31.0	1.59 (0.99–2.55)	0.054
Mouth breathing: yes/no, % participants	61.4/73.0	38.6/27.0	1.70 (1.01–2.86)	0.044

AHI, apnoea–hypopnoea index; BMI, body mass index; CAD, computer-aided design; CAM, computer-aided manufacturing; CI, confidence interval; ESS, Epworth Sleepiness Scale; NS, not significant; OR, odds ratio.

As mentioned briefly above, outcomes in the present study appeared to be better for participants treated with a CAD/CAM MRD. In most studies, greater protrusion was associated with better improvement in AHI, nocturnal oxygen desaturations, and pharyngeal collapsibility [23,32,42,43]. The same gradual titration procedures were followed with the two MRD devices, but results with the non-CAD/CAM device were comparable to recent published data from a study with no systematic MRD titration [26]. The present results suggest that the better efficacy of the CAD/CAM device may be due to its specific design and/or different manufacturing process compared with the non-CAD/CAM device. There are several potential explanations for this, including: differences in material plasticity, shape and thickness of splints, and the degree of vertical dimension of occlusion provided. It has been shown that vertical opening may have a significant effect on pharyngeal collapse in some patients [44] and may, therefore, reduce MRD efficacy. The manufacturing process for the CAD/CAM Narval™ device allows accurate adjustment of the vertical opening compared to the non-CAD/CAM device. This may be one mechanism that contributed to the higher efficacy seen with CAD/CAM device in this study. What is important is that use of a titratable and adjustable MRD device is essential, and that effective and individualised mandibular titration plays a key role in therapy success [16,30,45].

Although MRD therapy had no significant effects on blood pressure in the overall study population, there was an indication that greater reductions in blood pressure from baseline were observed in those with pre-existing hypertension. This is something that warrants further investigation in future clinical trials.

The present study had some limitations. There was no control group, but the primary aim was to assess long-term MRD efficacy and tolerability in a large real-life cohort of severe and/or symptomatic OSAHS patients who were noncompliant with CPAP and required mandatory treatment. Compliance data were based on subjective reports, but because previous data have shown good concordance between subjective and objective compliance assessments [34], this is unlikely to have influenced the findings.

The results of this study, which show good efficacy, tolerability and adherence with MRD therapy, support the use of this intervention in OSAHS patients who refuse or do not tolerate CPAP, including those with severe disease. Long-term follow-up is continuing and further assessments, including PSG/PG, will be performed after two and five years, which will allow additional data

analysis and more precise determination of factors predicting the success of therapy.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.05.020.

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