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SCIENTIFIC INVESTIGATIONS

Mandibular advancement device use in obstructive sleep apnea: ORCADES study 5-year follow-up data

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Study Objectives: Mandibular advancement devices (MADs) are an alternative to continuous positive airway pressure for the management of obstructive sleep apnea (OSA). The ORthèse d'avanCée mAndibulaire dans le traitement en DEuxième intention du SAHOS sévère (ORCADES) study is investigating the long-term effectiveness of MAD therapy in patients with OSA who refused or were intolerant of continuous positive airway pressure. Five-year follow-up data are presented.

Methods: Data were available in 172 of 331 patients treated with a custom-made computer-aided design/computer-aided manufacturing biblock MAD (Narval CC; ResMed, Saint-Priest, France). The primary end point was treatment success ($\geq 50\%$ decrease in apnea-hypopnea index from baseline).

Results: Five-year treatment success rates were 52% overall and 25%, 52%, and 63%, respectively, in patients with mild, moderate, or severe OSA. This reflects a decline over time vs 3–6 months (79% overall) and 2 years (68%). Rates declined in all patient subgroups but to the greatest extent in patients with mild OSA. The slight worsening of respiratory parameters over time was not associated with any relevant changes in sleepiness and symptoms. Moderate or severe OSA at baseline, treatment success at 3–6 months, and no previous continuous positive airway pressure use were significant independent predictors of 5-year treatment success on multivariate analysis. No new safety signals emerged during long-term follow-up. The proportion of patients using their MAD for ≥ 4 h/night on ≥ 4 days/wk was 93.3%; 91.3% of patients reported device use of ≥ 6 h/night at 5 years. At 5-year follow-up, 96.5% of patients reported that they wanted to continue MAD therapy.

Conclusions: Long-term MAD therapy remained effective after 5 years in $>50\%$ of patients, with good levels of patient satisfaction and adherence.

Keywords: obstructive sleep apnea, mandibular advancement device, apnea-hypopnea index, adherence

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Continuous positive airway pressure is the gold standard therapy for obstructive sleep apnea, but suboptimal long-term adherence can limit the clinical effectiveness of therapy. Mandibular advancement devices offer an alternative treatment solution for patients with obstructive sleep apnea, but there are limited data on the long-term use of these devices.

Study Impact: Although there was a tendency for control of the apnea-hypopnea index to decline over time, mandibular advancement device therapy remained effective in $>50\%$ of patients after 5 years, with ongoing symptom control, good quality of life, and high levels of adherence and patient satisfaction.

INTRODUCTION

Obstructive sleep apnea (OSA) affects almost 1 billion individuals aged 30–69 years worldwide¹ and represents a significant global health burden. Nasal continuous positive airway pressure (CPAP) is the first-choice treatment for severe OSA, but long-term adherence is often suboptimal.^{2,3} Oral appliances offer an alternative option for managing OSA, the most common of which are mandibular advancement devices (MADs).

MADs bring the mandible forward, advance the tongue and enlarge the retropalatal airway via an increase in its lateral diameter, thereby increasing upper airway volume, decreasing upper airway closing pressure, and reducing the tendency of the upper airway to collapse.^{4,5} A better response to MAD therapy may occur in patients with OSA with better passive upper airway collapsibility and/or anatomy and those with a more stable respiratory control system (ie, low loop gain).^{6,7}

MADs are recommended as a first-line therapy for mild-to-moderate OSA and for severe OSA where patients are intolerant of, or refuse, CPAP.⁸ Advantages of MADs over CPAP include simplicity, portability, and patient acceptance. Although the efficacy of MADs for reducing the frequency of obstructive events is lower than that of CPAP, their overall effectiveness is similar because of better adherence to treatment.^{9,10} Improvements in symptoms and quality of life after 12 months of treatment are similar for MADs and CPAP.¹¹

The prospective multicenter ORthèse d'avanCée mAn-dibulaire dans le traitement en DEuxième intention du SAHOS sévère (ORCADES) study investigated the long-term effectiveness of MAD therapy in patients with CPAP-naïve OSA who refused CPAP therapy and in CPAP-treated patients who were intolerant of CPAP therapy. ORCADES study data from 6-month and 2-year follow-ups showed that use of a custom-made MAD was associated with significant reductions in the apnea-hypopnea index (AHI) and OSA symptoms and was more effective than a non-custom-made device.^{12,13} This analysis presents ORCADES study 5-year follow-up data for patients with OSA treated with a custom-made computer-aided design/computer-aided manufacturing (CAD/CAM) biblock MAD.

METHODS

Study design

The ORCADES study was conducted in 28 centers in France (NCT01326143). The protocol was approved by the relevant ethics committees, and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Patients

Eligible patients were aged ≥ 18 years, had OSA on polysomnography or cardiorespiratory polygraphy (AHI > 30 events/h or AHI 5–30 events/h with excessive daytime sleepiness and/or an Epworth Sleepiness Scale [ESS] score > 10), and refused or were noncompliant with (use < 3 h/night) CPAP therapy.^{12,13} Those who had previous MAD treatment, severe sleep comorbidities other than OSA (idiopathic hypersomnia, narcolepsy with or without cataplexy, restless legs syndrome), coexisting psychiatric disease, or contraindications for MAD use were excluded.

Treatment and follow-up

Patients included in this analysis were treated with a CAD/CAM MAD (Narval CC; ResMed, Saint-Priest, France). In France, at the time of the study, the Narval CC MAD device was approved for the first-line treatment of snoring and mild to moderate OSA and for the second-line treatment of severe OSA after CPAP failure, intolerance, or refusal. MAD was fitted and gradually adjusted by a dental specialist. During titration, mandibular advancement was adjusted to achieve the best balance between symptom resolution and tolerability. Patients attended the dental clinic annually for follow-up with a dental specialist. Sleep study and consultation with the sleep physician took place after 3 months and 2 and 5 years of follow-up, and patients were

contacted by telephone in between sleep specialist follow-up visits (ie, at 1, 3, and 4 years of follow-up).

End points

The primary end point was treatment success (percentage of patients with a $\geq 50\%$ decrease in AHI from baseline). Secondary end points were as follows: absolute change in AHI from baseline, percentage of patients with complete response (AHI < 5 events/h) and partial responses (AHI < 10 or < 15 events/h), overall and in baseline OSA severity subgroups; mean AHI decrease; evolution of other respiratory parameters; OSA clinical symptoms; quality of life; compliance; and tolerability.

Assessments

AHI was determined using polygraphy or polysomnography; the same method was used consistently for each patient at each follow-up evaluation. Polysomnography/polygraphy recordings were manually scored using American Academy of Sleep Medicine guidelines.¹⁴ Obstructive apnea was defined as a ≥ 10 -second cessation of airflow on the pressure nasal cannula, with or without association with an oro-nasal thermal sensor. Hypopnea was defined as a $\geq 50\%$ reduction in airflow or a $< 50\%$ airflow reduction on the nasal pressure cannula accompanied by a $\geq 3\%$ decrease in arterial oxygen saturation on finger pulse oximetry or an arousal. Clinical evaluation at 5-year follow-up was identical to that performed at the 3- to 6-month and 2-year follow-up visits.^{12,13} Somnolence was evaluated using the ESS, and self-reported data on snoring, nocturia, and libido disorders were recorded. Patients rated sleep quality, state on waking, and morning headache on nongraduated 10-cm visual analog scales, from “very bad” to “excellent” (sleep quality/state on waking) or from “absence of pain” to “maximal pain” (morning headache). Quality of life was evaluated using the Quebec Sleep Questionnaire and Pichot fatigue scale questionnaire. The occurrence and severity of MAD-related side effects were determined by sleep and dental sleep physicians. MAD compliance data (h/night; nights/wk) were obtained by patient self-report.

Statistical analysis

Quantitative changes from baseline to 5 years are presented as mean and standard deviation or median and interquartile range (IQR) and compared using unpaired or paired Student *t* test or Wilcoxon-Mann-Whitney nonparametric test as appropriate based on normality of distribution and group comparison. Qualitative changes were described using frequency distribution and compared using Fisher's exact test or χ^2 test. Changes over time in AHI, 3% oxygen desaturation index, time with oxygen saturation $< 90\%$, ESS score, clinical symptoms, and Quebec Sleep Questionnaire and Pichot fatigue scores were determined using repeated-measures analysis of variance; if significant, this was followed by a Tukey's test to compare visits 2 by 2. Comparisons between subgroups based on baseline OSA severity, sex, and body mass index were assessed using Student *t* test, analysis of variance, or Wilcoxon-Mann-Whitney test. Compliance analysis included patients who completed the 5-year follow-up.

Three logistic models were created, and backward stepwise regression analysis was used to determine factors independently associated with the following end points: treatment success

($\geq 50\%$ AHI decrease), model 1; having an AHI < 10 events/h (in patients with 5-year AHI data), model 2; and treatment continuation, model 3. Variables with $P < .10$ in univariate analysis were entered in the stepwise logistic regressions, and those with $P < .05$ were retained in the final multivariate models. Statistical analyses were performed using SAS v9.

RESULTS

Population

A total of 331 patients were treated with a CAD/CAM MAD; 5-year follow-up data were available in 172 patients (Figure 1). Median follow-up was 61 months (IQR, 60–64). Most patients were male (75%), and 21% were obese (Table 1). Weight remained stable over 5 years in all OSA severity subgroups ($P = .25$). However, patients in the mild OSA group showed an increase in neck and waist circumferences from baseline to 5 years (from 38.1 ± 3.8 to 39.7 ± 4.5 cm [$P = .022$] and from 91.7 ± 13.0 to 97.8 ± 5.1 cm [$P = .0030$], respectively). Patients underwent 2.0 (IQR, 1.0–4.0) MAD titrations before initial efficacy assessment; mandibular advancement after titrations (just before to the 3- to 6-month efficacy evaluation) was 6 mm (IQR, 5.0–7.0), representing 70% (IQR, 58%–80%) of maximal protrusion. At 5-year follow-up, total mandibular advancement had increased to 8 mm (IQR, 7.0–10.0; $P = .0001$ vs after advancement at 3–6 months); this was driven mainly by a significant increase in mandibular advancement in patients with moderate OSA ($P = .0001$), with no significant change in patients with mild ($P = .66$) or severe ($P = .41$) OSA.

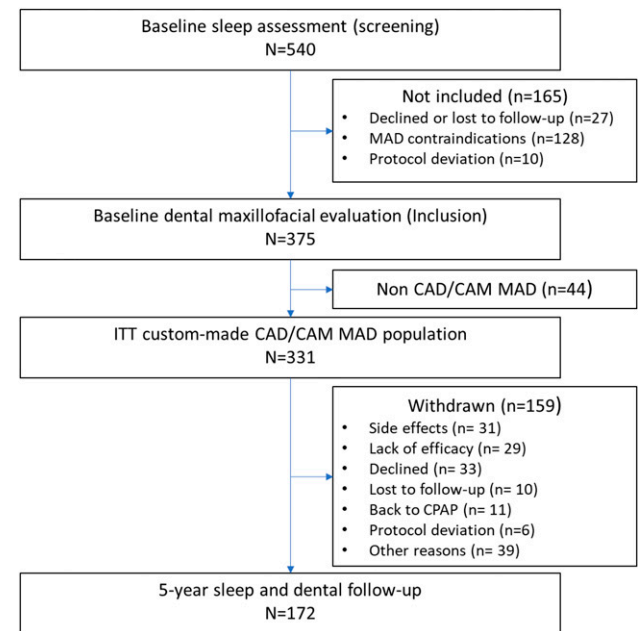
Main reasons for withdrawal before 5-year follow-up were side effects ($n = 31$), lack of efficacy ($n = 29$), and withdrawal of consent ($n = 33$; Figure 1), with no difference by baseline OSA severity or sex. Withdrawal because of lack of efficacy was more common in patients with severe vs mild or moderate OSA ($P = .008$) and in obese vs nonobese patients ($P = .032$). Most withdrawals (56.6%) occurred during the first year of treatment; side effect–related withdrawals were most common in the first 2 years of treatment (74.3% occurred within the first 24 months).

Respiratory and sleep data

Overall treatment success rates declined significantly over time, with the greatest decline seen in patients with mild OSA; success rates in patients with severe OSA were relative stable throughout 5 years of MAD therapy (Figure 2A). Five-year treatment success rates were significantly higher in patients with moderate or severe vs mild OSA ($P < .022$ and $P < .002$, respectively; Figure 2A). Five-year treatment efficacy rates at the AHI < 5 events/h threshold did not differ significantly by AHI severity, whereas there were significant differences between patient subgroups based on baseline OSA severity at the < 10 and < 15 events/h thresholds, with efficacy rates generally decreasing as OSA severity increased (Figure 2B). The proportion of patients with a response at the < 10 events/h threshold was significantly higher in patients with mild or moderate vs severe OSA (67% and 52% vs 28%, $P = .0015$ and $P = .0087$, respectively; Figure 2B).

Median (IQR) AHI decreased from 26.4 events/h (17.70–37.10) at baseline to 11.05 events/h (6.10–17.30) at 5-year

Figure 1—Study flowchart.



*Other reasons for withdrawal from the study were as follows: patients who did not decline the therapy or withdraw their consent but declined to return to follow-up visits at the hospital (these patients could not be considered as lost to follow-up because they answered phone calls; $n = 19$); MAD-treated patients who did not withdraw their consent but moved out of the area during the follow-up period ($n = 7$); patients effectively treated with an MAD but who preferred surgery or other therapy to treat their OSA during follow-up ($n = 6$); patients who stopped MAD because of another pathology (eg, cancer, depression; $n = 3$); patients who stopped MAD therapy because of weight loss that resolved their OSA ($n = 1$); death ($n = 1$); patient with dental treatment not linked to MAD therapy who did not want to resume study treatment ($n = 1$); and patient file lost by center ($n = 1$). CAD/CAM = computer-aided design/computer-aided manufacturing, CPAP = continuous positive airway pressure, ITT = intention-to-treat, MAD = mandibular advancement device.

follow-up (median [IQR] change: -50.3% [-72.7 to -24.2]; $P < .0001$; Figure 3). A significant decrease in AHI was seen during MAD use, irrespective of baseline OSA severity, but was greatest in those with moderate or severe OSA (-10 events/h [-17.5 to -4.3], -50.5% ; and -22.3 events/h [-30.8 to -13.8], -60.1% , respectively; Figure 3). Significant reductions from baseline were also seen in the apnea index (AI), hypopnea index, supine AHI, and oxygen desaturation index over 5 years of MAD therapy, although the magnitude of benefit decreased over time (Table 2). There were also statistically significant improvements from baseline in nadir oxygen saturation and time with oxygen saturation $< 90\%$ (Table 2).

The number of microarousals and sleep latency decreased significantly (median [IQR] change: -8 events/h [-19 to 2], $P = .0008$ and -5 minutes [-23 to 6], $P = .027$, respectively). Sleep duration also decreased from 407.30 ± 76.68 minutes at baseline to 393.31 ± 62.71 minutes at 5-year follow-up ($P = .018$).

Daytime sleepiness, clinical symptoms, and quality of life

Relevant and statistically significant reductions in the ESS score from baseline (median [IQR] 11 [8 – 15]) were seen after

Table 1—Patient demographic and clinical characteristics at baseline.

	Patients (n = 331)
Male, n (%)	249 (75.2)
Age, y	53.0 [45.0–61.0]
BMI, kg/m ²	26.7 [24.6–29.4]
BMI > 30 kg/m ² , n (%)	70 (21.3)
Weight, kg	81.5 [73.0–90.0]
Waist circumference, cm	97.0 [90.0–105.0]
Neck circumference, cm	40.0 [38.0–42.0]
Previously treated with CPAP, n (%)	165 (49.8)
ESS score	11.0 [8–15]
ESS score > 10, n (%)	195 (59)
AHI, events/h	26.4 [17.7–37.1]
OSA severity, n (%)	
Mild	52 (16)
Moderate	142 (43)
Severe	137 (41)
ODI, /h	17.0 [9.0–29.0]
Dental status, n (%)	
Good	272 (83)
Acceptable	56 (17)
Periodontal status, n (%)	
Good	266 (81)
Acceptable	63 (19)
Dental mobility, n (%)	
None	309 (94)
Low and limited	20 (6)
Angle malocclusion, n (%)	
Type 1	221 (69)
Type 2	85 (27)
Type 3	13 (4)

Values are median [interquartile range] or number of patients, (%). AHI = apnea-hypopnea index, BMI = body mass index, CPAP = continuous positive airway pressure, ODI = oxygen desaturation index, OSA = obstructive sleep apnea.

3–6 months (7 [5–10]; $P < .0001$) and were sustained over 5 years (6 [4–10]; $P < .0001$; **Figure 4**). The Pichot Fatigue Scale (**Figure S1** in the supplemental material) and Quebec Sleep Questionnaire (**Figure 5**) scores showed the same sustained reductions from baseline. This was also the case for morning headache visual analog scale scores, whereas sleep quality and state on waking visual analog scale scores showed marked and sustained improvements during MAD therapy (**Figure S2** in the supplemental material). At 5 years, 75.5% of patients had an ESS score < 10. Subjective snoring, nocturia, and libido disorders had disappeared in 44.7%, 62.9%, and 74.4% of patients, respectively, at the 5-year follow-up.

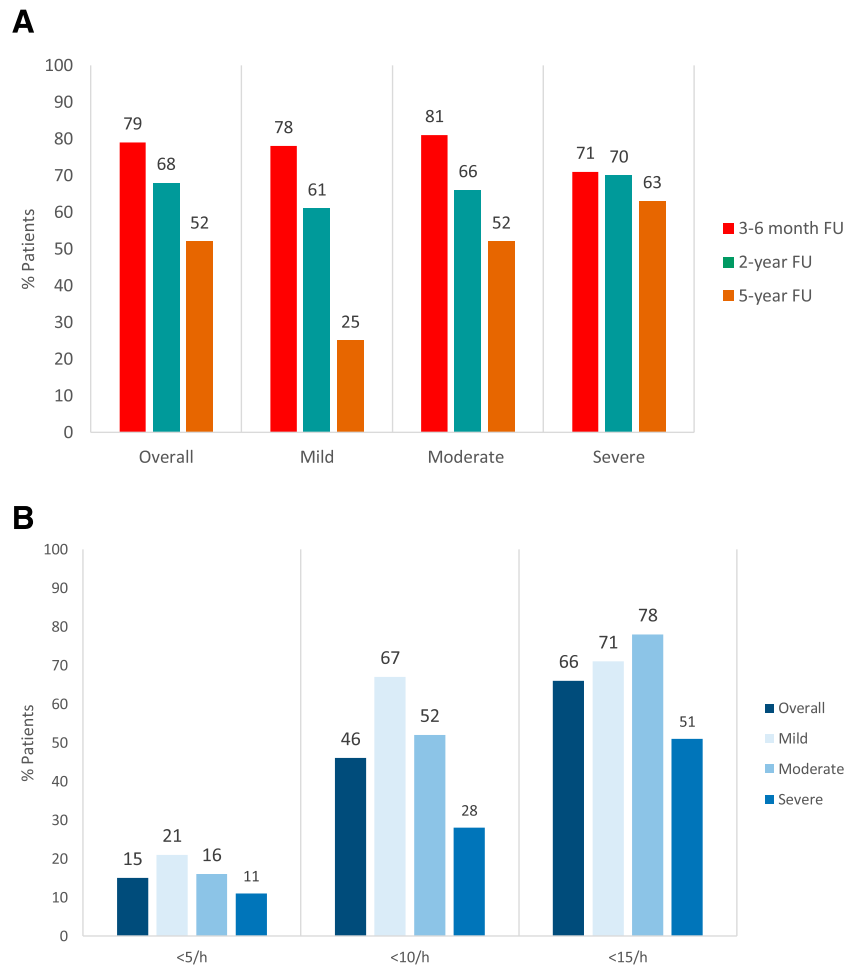
Compliance

At 5-year follow-up, 82.8% of patients were using their MAD on 7 nights/wk and 91.3% of patients reported device use

of ≥ 6 h/night, with no differences between OSA severity subgroups. The proportion of patients who used their MAD for ≥ 4 h/night on ≥ 4 days/wk was 93.3%, irrespective of sex and body mass index.

Tolerability and comfort

At least 1 adverse event was reported by 69.2% of the 331 patients treated with a CAD/CAM MAD (**Table 3**). Of the 706 adverse events reported over 5 years, 44.3% were reported within the first 6 months, 56.4% within the first year, and 70.7% before the 2-year follow-up. Only 70 events (9.9%) were considered severe (**Table 3**). MAD treatment was stopped early because of side effects in 31 of 331 patients (9.4%). At 5 years, 91.7% of patients reported “not feeling occlusion change at wake up,” similar to the rate at 3–6 months (83.3%, $P = .08$). Treatment comfort and patient satisfaction ratings remained high throughout the study (visual analog scale scores 8–9).

Figure 2—Treatment success rate and 5-year efficacy of mandibular advancement device therapy.

(A) Treatment success rate (percentage of patients with a $\geq 50\%$ reduction in the AHI from baseline) during mandibular advancement device therapy in patients with OSA, overall and in patient subgroups based on baseline OSA severity (mild: AHI 5– ≤ 15 events/h; moderate: AHI 15– ≤ 30 events/h; severe: AHI > 30 events/h). Overall: $P = .0159$ for the difference between 3- to 6-month FU and 2-year FU; $P < .001$ for the difference between 3- to 6-month FU and 5-year FU; and $P = .034$ for the difference between 2-year FU and 5-year FU. **(B)** Five-year efficacy of mandibular advancement device therapy, defined as the proportion of patients achieving an AHI of < 5 , < 10 , or < 15 events/h at 5-year follow-up, in the overall population and in patient subgroups based on baseline OSA severity (mild: AHI 5– ≤ 15 events/h; moderate: AHI 15– ≤ 30 events/h; severe: AHI > 30 events/h). AHI < 5 events/h: no statistically significant difference between patient subgroups; AHI < 10 events/h: $P = .0015$ for the difference between the mild and severe OSA subgroups and $P = .0087$ for the difference between the moderate and severe OSA subgroups. AHI < 15 events/h: $P = .0025$ for the difference between the moderate and severe OSA subgroups. AHI = apnea-hypopnea index, FU = follow-up, OSA = obstructive sleep apnea.

At the 5-year follow-up, 96.5% of patients reported that they wanted to continue MAD therapy.

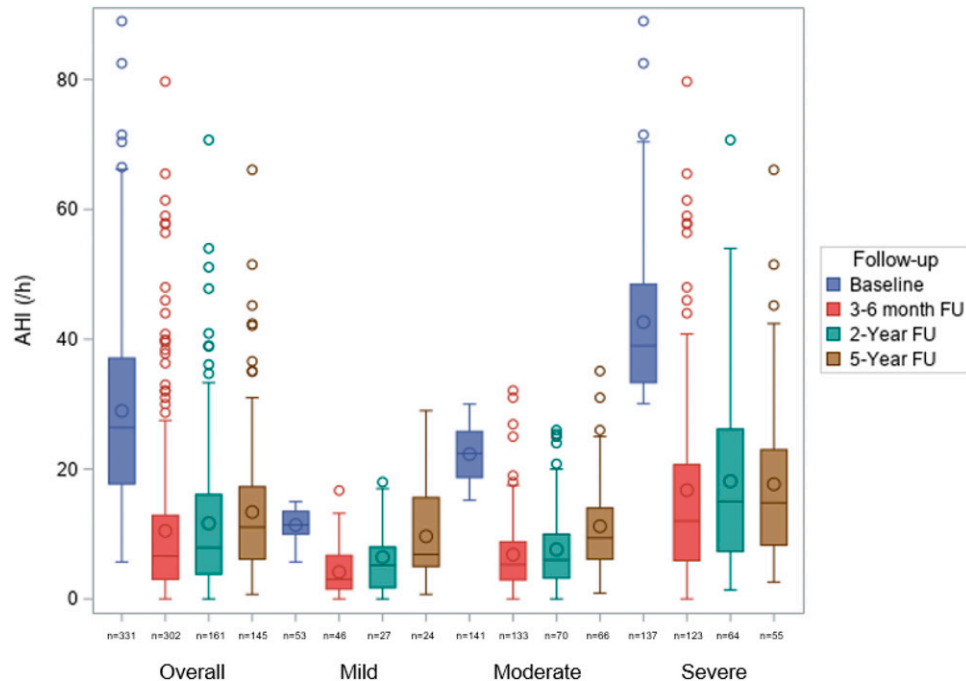
Predictors of efficacy and treatment continuation

The following parameters were identified as significant independent predictors of treatment success at 5 years in model 1: moderate OSA at baseline, severe OSA at baseline, treatment success at 3–6 months, and no previous CPAP use (Table 4). In model 2, baseline AI and higher baseline body weight were significant predictors of a lower complete response rate during MAD therapy, whereas patients in dental class II vs I at baseline had a much higher rate of complete response. In model 3, self-reported sleep duration of 7–8 hours and MAD device renewal were significant predictors of better long-term therapy continuation (Table 4).

DISCUSSION

These data show that MAD treatment remained effective over 5-year follow-up in patients with mild to severe OSA who were intolerant of, noncompliant with, or refused CPAP. Efficacy in terms of AHI reduction did decline over time, but most of this attenuation of effect was evident by 2 years of follow-up, consistent with existing data.^{15–20} Despite the slight worsening of respiratory parameters over time, sleepiness and symptoms (eg, fatigue, morning headache) remained well controlled, and sleep quality and state on waking showed marked and sustained improvements during long-term MAD therapy. These findings suggest that measurement of AHI alone might not provide an accurate picture of the long-term benefits associated with MAD therapy, particularly in patients with mild OSA for

Figure 3—Change in the AHI over time in the overall population and in patient subgroups based on baseline OSA severity (mild: AHI 5–≤15 events/h; moderate: AHI 15–≤30 events/h; severe: AHI > 30 events/h).



Overall: $P < .0001$ for the difference between baseline and each FU visit; $P = .0187$ for the difference between 3- and 6-month FU and 2-year FU and $P < .0001$ for the difference between 3- and 6-month FU and 5-year FU; Mild OSA: $P < .0001$ for the difference between baseline and 3- to 6-month FU; $P = .0002$ for the difference between baseline and 2-year FU; and $P < .0001$ for the difference between 3- to 6-month FU and 5-year FU. Moderate OSA: $P < .0001$ for the difference between baseline and each FU visit; $P < .0001$ for the difference between 3- to 6-month FU and 5-year FU; and $P = .0004$ for the difference between 2-year FU and 5-year FU. Severe OSA: $P < .0001$ for the difference between baseline and each FU visit. AHI = apnea-hypopnea index, FU = follow-up, OSA = obstructive sleep apnea.

Table 2—Sleep and respiratory parameters over time.

	Baseline	Mandibular Advancement Device		
		3–6 Months	2 Years	5 Years
Apnea-hypopnea index, events/h	26.4 [17.7–37.1]	6.6 [3.0–12.9] ^a	7.9 [3.8–16.1] ^{a,b}	11.1 [6.1–17.3] ^{a,d}
Apnea index, /h	8.3 [3.4–18.0]	1.0 [0.2–3.6] ^a	1.1 [0.3–3.8] ^{a,b}	2.0 [0.4–5.8] ^{a,c}
Hypopnea index, /h	15.0 [9.2–22.4]	5.0 [2.0–9.7] ^a	5.5 [2.4–10.9] ^{a,d}	7.3 [4.0–13.0] ^{a,e}
Supine AHI, events/h	32.9 [20.5–49.9]	8.0 [3.0–16.6] ^a	11.8 [3.2–21.6] ^{a,b}	14.0 [5.8–25.0] ^{a,e}
Nadir SpO ₂ , %	84 [78–87]	87 [83–90] ^f	87 [84–89] ^{b,f}	86 [82–88] ^{c,f}
Time with SpO ₂ < 90%, min	6 [1–22]	1 [0–9] ^f	1 [0–6] ^f	2 [0–11] ^{f,g}
ODI > 3%, /h	17 [9–29]	5 [2–11] ^a	8 [3–15] ^{a,d}	11 [5–17] ^{a,e}

Values are median [interquartile range]. ^a $P < .0001$ vs baseline. ^b $P < .05$ vs 3–6 months. ^c $P < .05$ vs 2 years. ^d $P < .001$ vs 3–6 months. ^e $P < .001$ vs 2 years. ^f $P < .01$ vs baseline. ^g $P < .01$ vs 2 years. AHI = apnea-hypopnea index, ODI = oxygen desaturation index, SpO₂ = oxygen saturation.

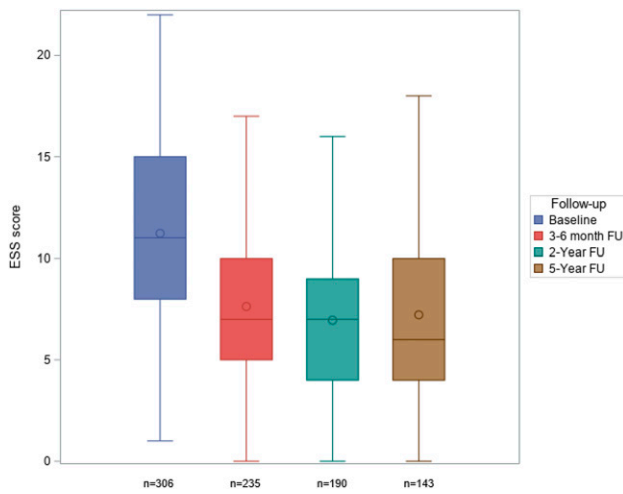
whom improvement in symptoms, especially diurnal sleepiness, might be more clinically relevant than substantial reductions in the AHI. Therefore, both objective and self-reported assessments should be included in the evaluation of MAD therapy, especially over the longer term.

After 5-year follow-up in our prospective cohort study, 52% of the initial cohort remained on MAD therapy. The decline in the number of patients using an MAD after 5 years in the current study is relatively comparable to that 30%–64% of patients previously reported to have been compliant with MAD therapy after approximately 5 years of follow-up in the

limited number of studies that have undertaken long-term follow-up of MAD treatment.^{21–23} It is also similar to the dropout rate reported in studies of long-term CPAP use.^{24,25} Longer-term follow-up of MAD use for ≥10 years indicates that 21%–58% of patients remain on therapy.^{18,26,27} Taken together, our study and existing data suggest that MAD use decreases over time, highlighting the difficulty in maintaining patients in a clinical pathway of chronic therapy, as previously described.²⁸

Treatment with an MAD for 5 years was associated with sustained and clinically relevant improvements in AHI, oxygen

Figure 4—Change in ESS score during 5 years of mandibular advancement device therapy ($P < .0001$ for comparison with baseline at each FU visit).



ESS = Epworth Sleepiness Scale, FU = follow-up.

saturation, clinical symptoms, and quality of life, irrespective of baseline OSA severity, consistent with the findings of previous long-term MAD studies.^{16,21,27,29} We defined treatment success as a $\geq 50\%$ reduction in AHI from baseline. This definition has been widely used in other studies and allows comparison between trials.^{10,30} The overall 5-year success rate in our study was 52%, but this was higher in those with more severe OSA at baseline and lowest in patients with mild OSA. One potential explanation could be the greater increase in neck and waist circumference seen in the mild OSA subgroup during follow-up. In contrast, neck and waist circumference did not change significantly in patients with moderate or severe OSA. On univariate analysis, patients for whom MAD therapy was effective had a smaller neck circumference than other patients ($P = .017$). In addition, waist circumference increased to a smaller extent in those with vs without MAD treatment success (1.75 ± 15.77 vs 3.04 ± 6.36 cm; $P = .05$). It is also possible that patients with mild OSA whose symptoms resolved during use of an MAD would not have had any further titration of mandibular advancement after the 3- to 6-month follow-up, which could explain the low number of patients with effective treatment at 5 years in this group.

Having moderate or severe OSA at baseline was a significant independent predictor of treatment success on multivariate analysis in our study. Although a higher baseline AHI allows for a greater absolute decrease, these findings highlight the potential for MAD therapy beyond mild OSA. Other significant predictors of treatment success were no previous CPAP use and early treatment success. Half of the patients in our study had tried CPAP before the MAD, and this may have reduced the effectiveness of therapy, whereas the importance of early treatment success was highlighted by a previous long-term study.²¹

Baseline AI was a significant predictor of achieving AHI < 10 events/h at 5 years. Each unit increase in AI decreased the

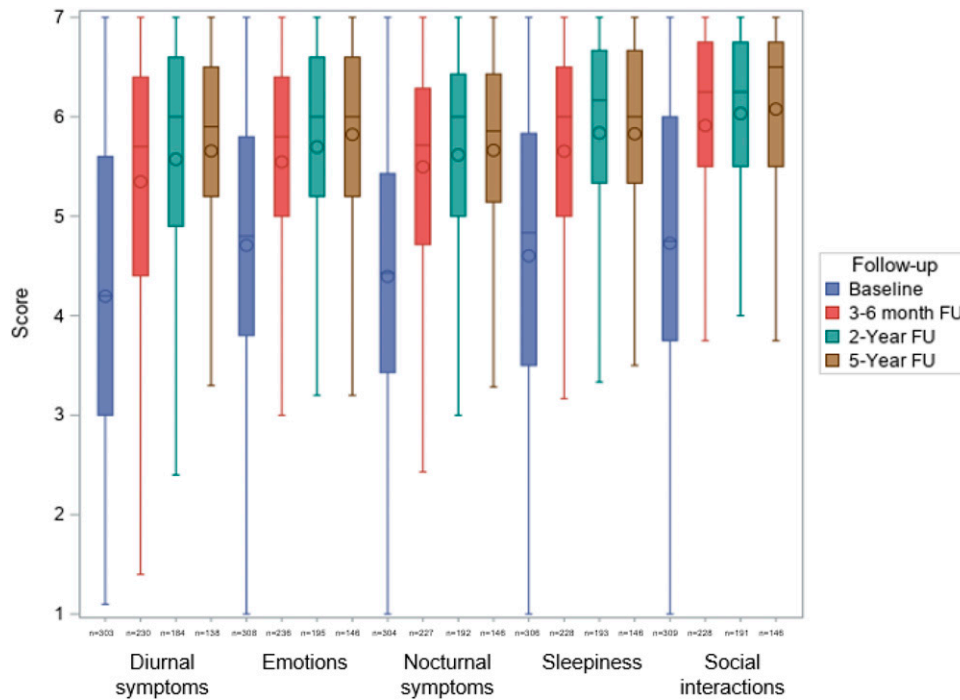
probability of treatment response by 5.8%. We had identified baseline AI as a predictor of complete response as early as 3–6 months after MAD therapy initiation¹³ and as a contributor to the differential short-term efficacy of MAD therapy in men vs women, as previously described.³¹ Patients with type 2 angle malocclusion were also significantly more likely to achieve complete response during MAD therapy. Greater overjet has already been described as a significant predictor of MAD therapy success,³² and retrognathia was predictive of a favorable response after 1 year of MAD treatment.³³ An increase in body weight was a significant negative predictor of complete response during 5 years of MAD therapy, consistent with previous data.^{27,34–36} Therefore, weight control and waist and neck circumference are important aspects of patient follow-up during MAD therapy. These factors highlight the importance of careful patient selection for MAD therapy and the need for careful and regular monitoring to ensure good short-term outcomes, as recommended in current guidelines.⁸

Response rates in this study used 3 different residual AHI thresholds. Residual AHI < 10 events/h is related to long-term control of symptoms, and AHI < 15 events/h has been associated with a reduction in the risk of new-onset hypertension.³⁷ At 5-year follow-up, 46% of patients had an AHI < 10 events/h and 66% had an AHI < 15 events/h. Corresponding rates patients with severe OSA at baseline were 28% and 51%, respectively. These findings suggest that long-term MAD therapy is a feasible option for some patients with severe OSA.

We identified 2 significant independent predictors of treatment continuation: self-reported sleep duration of 7–8 vs ≤ 6 hours and MAD renewal. Patients who renewed their MAD during the study were >4.5 times more likely to continue therapy. In our cohort, a low proportion ($n = 86$; 26% of the population) renewed their MAD (the average lifespan of an MAD is ≈ 3 years).³⁸ This could have contributed to patient withdrawal from the study. It has previously been shown that patients who have their devices replaced or adjusted have better long-term effects than those still using their original device.²¹ In addition, greater mandibular advancement is associated with greater improvement in the AHI.⁶ Therefore, in routine practice, it is important to ensure that MAD devices are regularly adjusted or replaced.

Long-term MAD therapy was well tolerated, and patients were very satisfied with treatment. Side effects during treatment with the custom-made CAD/CAM MAD in our study were consistent with previous data,³⁹ and observed dental changes were small and considered clinically insignificant.⁴⁰ Dental or gingival pain and temporomandibular joint discomfort were the most frequent events, but pain was usually transient and should not be a contraindication for MAD.³⁹ However, persistence of side effects such as mouth dryness and tooth or jaw discomfort may lead to treatment discontinuation.¹⁰ In addition, self-perceived side effects are a contributing factor to cessation of MAD therapy.⁴¹ Therefore, patients may need time to become accustomed to the device.¹⁶ Furthermore, increasing age with a decrease in upper airway dilator strength and soft tissue advancement, with skeletal and bite changes over time, are factors that may alter MAD effectiveness, highlighting the need for long-term dental follow-up to optimize ongoing effectiveness.^{17,18,42,43}

Figure 5—Change in Quebec Sleep Questionnaire scores during 5 years of mandibular advancement device therapy ($P < .0001$ for comparison with baseline at each FU visit).



FU = follow-up.

Table 3—Adverse events in all patients treated with a custom-made computer-aided design/computer-aided manufacturing biblock mandibular advancement device (n = 331).

	Adverse Events (n = 706), Number of Events (%)		Patient Withdrawal, Number of Patients (%)
	All Events	Severe Events	
Temporomandibular joint disorders	162 (22.9)	21 (3.0)	7 (2.1)
Gingival pain or gingivitis	124 (17.6)	18 (2.5)	5 (1.6)
Occlusion change	107 (15.1)	1 (0.1)	2 (0.6)
Dental pain	87 (12.3)	9 (1.3)	8 (2.4)
Tooth migration or dental mobility	69 (9.8)	5 (0.7)	0 (0)
Mouth dryness or hypersalivation	51 (7.2)	0 (0)	1 (0.3)
Discomfort	47 (6.6)	2 (0.3)	1 (0.3)
Mouth pain or irritation	29 (4.1)	3 (0.4)	2 (0.6)
Dental fracture or prosthesis loosening	11 (1.6)	7 (1)	2 (0.6)
Nausea or vomiting	9 (1.3)	2 (0.3)	1 (0.3)
Mouth ulcer	6 (0.8)	1 (0.1)	0 (0)
Suspected allergy	4 (0.6)	1 (0.1)	2 (0.6)

Objective data on MAD adherence are limited, with 1 study reporting objective MAD use of 6.7 ± 1.3 h/night over a 3-month period, maintained at >6 h/night after 1 year.⁴⁴ Our results confirmed excellent compliance at 5 years with device use of ≥ 6 h/day in nearly 91% of patients. Self-reported compliance, as assessed in our study, has been shown to correlate well with objective measures, although a difference of 44 minutes between objective and self-reported compliance was reported.⁴⁵

In addition, all those still using the MAD after 5 years wanted to continue therapy.

This study had several strengths including the number of patients overall (n = 331) and 5 years of MAD use (n = 172). Patients were selected and followed up by a multidisciplinary team of specialists, and the MAD device was custom made, allowing individualized mandibular titration and control of mouth opening, which are important predictors of efficacy.⁴⁶

Table 4—Significant predictors of therapy success (percentage of patients with a $\geq 50\%$ decrease in AHI from baseline, model 1), complete response (AHI < 10 events/h, model 2), and long-term treatment continuation (model 3) on multivariate analysis.

	Odds Ratio (95% CI)	P
Model 1		
Baseline AHI 15 to ≤ 30 events/h (moderate OSA vs mild OSA)	3.49 (1.26–9.64)	.0190
Baseline AHI ≥ 30 events/h (severe OSA vs mild OSA)	4.74 (1.59–14.11)	.0190
No previous CPAP therapy	2.47 (1.25–4.88)	.0161
Treatment success after 3- to 6-month follow-up	3.99 (1.57–10.14)	.0161
Model 2		
Body weight change (per 1-kg increase)	0.88 (0.82–0.96)	.0033
Dental class II (vs class I)	5.61 (2.25–14.01)	.0011
Baseline apnea index (per 1-event/h increase)	0.95 (0.90–0.99)	.0188
Model 3		
Self-reported sleep duration 7–8 h (vs ≤ 6 h)	1.96 (1.12–3.45)	.0285
MAD device renewal (yes vs no)	4.65 (2.24–9.66)	<.0001

AHI = apnea-hypopnea index, CI = confidence interval, CPAP = continuous positive airway pressure, MAD = mandibular advancement device, OSA = obstructive sleep apnea.

Some limitations also need to be taken into account. The study has an observational, registry-based design, without random allocation to treatment, but is representative of a large real-life cohort in routine clinical practice. Patient dropout might have influenced the findings because 48% of initially enrolled patients withdrew from the study before the 5-year evaluation, although this was accounted for in the multivariate analysis of treatment continuation. During the study, the same assessment device (polygraphy or polysomnography) was consistently used in the same patient, but agreement in event scoring between these 2 types of devices was not assessed, and the possibility for some discrepancies needs to be acknowledged.

In conclusion, long-term MAD therapy was effective in patients with OSA, regardless of baseline disease severity. Although there was a tendency for control of AHI to decline over time, symptoms remained well controlled, and patients reported good quality of life throughout the long-term follow-up. Several factors predicting long-term treatment success and therapy continuation were identified. These can be used to inform precision medicine and personalized medicine strategies for patients with OSA that maximize the use and effectiveness of MAD therapy, with the goal of improving patient outcomes.

ABBREVIATIONS

AHI, apnea-hypopnea index
 AI, apnea index
 CAD/CAM, custom-made computer-aided design/computer-aided manufacturing
 CPAP, continuous positive airway pressure
 ESS, Epworth Sleepiness Scale
 IQR, interquartile range
 MAD, mandibular advancement device
 OSA, obstructive sleep apnea

REFERENCES

- Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):687–698.
- Askland K, Wright L, Wozniak DR, Emmanuel T, Caston J, Smith I. Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2020;4:CD007736.
- Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2019;15(2):335–343.
- Chan AS, Sutherland K, Schwab RJ, et al. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. *Thorax*. 2010;65(8):726–732.
- Kato J, Isono S, Tanaka A, et al. Dose-dependent effects of mandibular advancement on pharyngeal mechanics and nocturnal oxygenation in patients with sleep-disordered breathing. *Chest*. 2000;117(4):1065–1072.
- Edwards BA, Andara C, Landry S, et al. Upper-airway collapsibility and loop gain predict the response to oral appliance therapy in patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2016;194(11):1413–1422.
- Vena D, Azarbarzin A, Marques M, et al. Predicting sleep apnea responses to oral appliance therapy using polysomnographic airflow. *Sleep*. 2020;43:zsaa004.
- Ramar K, Dort LC, Katz SG, et al. Clinical Practice Guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. *J Clin Sleep Med*. 2015;11(7):773–827.
- Almeida FR, Henrich N, Marra C, et al. Patient preferences and experiences of CPAP and oral appliances for the treatment of obstructive sleep apnea: a qualitative analysis. *Sleep Breath*. 2013;17(2):659–666.
- Sutherland K, Vanderveken OM, Tsuda H, et al. Oral appliance treatment for obstructive sleep apnea: an update. *J Clin Sleep Med*. 2014;10(2):215–227.
- Schwartz M, Acosta L, Hung YL, Padilla M, Enciso R. Effects of CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: a systematic review and meta-analysis. *Sleep Breath*. 2018;22(3):555–568.
- Attali V, Vecchierini MF, Collet JM, et al.; ORCADES Investigators. Efficacy and tolerability of a custom-made Narval mandibular repositioning device for the treatment of obstructive sleep apnea: ORCADES study 2-year follow-up data. *Sleep Med*. 2019;63:64–74.

13. Vecchierini MF, Attali V, Collet JM, et al; ORCADES Investigators. A custom-made mandibular repositioning device for obstructive sleep apnoea-hypopnoea syndrome: the ORCADES study. *Sleep Med*. 2016;19:131–140.
14. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep*. 1999;22(5):667–689.
15. Marklund M. Long-term efficacy of an oral appliance in early treated patients with obstructive sleep apnea. *Sleep Breath*. 2016;20(2):689–694.
16. Marklund M, Verbraecken J, Randerath W. Non-CPAP therapies in obstructive sleep apnoea: mandibular advancement device therapy. *Eur Respir J*. 2012;39(5):1241–1247.
17. Rose EC, Barthlen GM, Staats R, Jonas IE. Therapeutic efficacy of an oral appliance in the treatment of obstructive sleep apnea: a 2-year follow-up. *Am J Orthod Dentofacial Orthop*. 2002;121(3):273–279.
18. Uniken Venema JAM, Doff MHJ, Joffe-Sokolova D, et al. Long-term obstructive sleep apnea therapy: a 10-year follow-up of mandibular advancement device and continuous positive airway pressure. *J Clin Sleep Med*. 2020;16(3):353–359.
19. Walker-Engström ML, Tegelberg A, Wilhelmsson B, Ringqvist I. 4-year follow-up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea: a randomized study. *Chest*. 2002;121(3):739–746.
20. Sharples LD, Clutterbuck-James AL, Glover MJ, et al. Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. *Sleep Med Rev*. 2016;27:108–124.
21. Marklund M, Sahlin C, Stenlund H, Persson M, Franklin KA. Mandibular advancement device in patients with obstructive sleep apnea: long-term effects on apnea and sleep. *Chest*. 2001;120(1):162–169.
22. de Almeida FR, Lowe AA, Tsuiki S, et al. Long-term compliance and side effects of oral appliances used for the treatment of snoring and obstructive sleep apnea syndrome. *J Clin Sleep Med*. 2005;1(2):143–152.
23. Marklund M. Predictors of long-term orthodontic side effects from mandibular advancement devices in patients with snoring and obstructive sleep apnea. *Am J Orthod Dentofacial Orthop*. 2006;129(2):214–221.
24. Gagnadoux F, Le Vaillant M, Goupil F, et al; IRSR Sleep Cohort Group. Influence of marital status and employment status on long-term adherence with continuous positive airway pressure in sleep apnea patients. *PLoS One*. 2011;6(8):e22503.
25. Schoch OD, Baty F, Niedermann J, Rüdiger JJ, Brutsche MH. Baseline predictors of adherence to positive airway pressure therapy for sleep apnea: a 10-year single-center observational cohort study. *Respiration*. 2014;87(2):121–128.
26. Mintz SS, Kovacs R. The use of oral appliances in obstructive sleep apnea: a retrospective cohort study spanning 14 years of private practice experience. *Sleep Breath*. 2018;22(2):541–546.
27. Wiman Eriksson E, Leissner L, Isacson G, Fransson A. A prospective 10-year follow-up polygraphic study of patients treated with a mandibular protruding device. *Sleep Breath*. 2015;19(1):393–401.
28. Attali V, Chaumereuil C, Arnulf I, et al. Predictors of long-term effectiveness to mandibular repositioning device treatment in obstructive sleep apnea patients after 1000 days. *Sleep Med*. 2016;27-28:107–114.
29. Gong X, Zhang J, Zhao Y, Gao X. Long-term therapeutic efficacy of oral appliances in treatment of obstructive sleep apnea-hypopnea syndrome. *Angle Orthod*. 2013;83(4):653–658.
30. Fukuda T, Tsuiki S, Kobayashi M, Nakayama H, Inoue Y. Selection of response criteria affects the success rate of oral appliance treatment for obstructive sleep apnea. *Sleep Med*. 2014;15(3):367–370.
31. Vecchierini MF, Attali V, Collet JM, et al; ORCADES Investigators. Sex differences in mandibular repositioning device therapy effectiveness in patients with obstructive sleep apnea syndrome. *Sleep Breath*. 2019;23(3):837–848.
32. Milano F, Billi MC, Marra F, Sorrenti G, Gracco A, Bonetti GA. Factors associated with the efficacy of mandibular advancing device treatment in adult OSA patients. *Int Orthod*. 2013;11(3):278–289.
33. Lam B, Sam K, Lam JC, Lai AY, Lam CL, Ip MS. The efficacy of oral appliances in the treatment of severe obstructive sleep apnea. *Sleep Breath*. 2011;15(2):195–201.
34. Palotie T, Riekkii S, Mäkitie A, Bachour A, Arte S, Bäck L. The effect of mandible advancement splints in mild, moderate, and severe obstructive sleep apnea—the need for sleep registrations during follow up. *Eur J Orthod*. 2017;39(5):497–501.
35. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep*. 2006;29(2):244–262.
36. Marklund M, Stenlund H, Franklin KA. Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. *Chest*. 2004;125(4):1270–1278.
37. Wee JH, Lim JH, Gelera JE, Rhee CS, Kim JW. Comparison of success criteria based on long-term symptoms and new-onset hypertension in mandibular advancement device treatment for obstructive sleep apnoea: observational cohort study. *BMJ Open*. 2018;8(5):e021644.
38. Ho-A-Yun JA, Sharma PR. The 'lifespan' of mandibular repositioning appliances. *Br Dent J*. 2019;227(6):470–473.
39. Doff MH, Finnema KJ, Hoekema A, Wijkstra PJ, de Bont LG, Stegenga B. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on dental side effects. *Clin Oral Investig*. 2013;17(2):475–482.
40. Kerbrat JB, Navailles B, Attali V, et al. Déplacements dentaires sous orthèse d'avancée mandibulaire (OAM) sur mesure dans le traitement du SAOS: résultats à long terme de l'étude ORCADES. *Med Sommeil*. 2018;15(1):20.
41. Dieltjens M, Vanderveken O. Oral appliances in obstructive sleep apnea. *Healthcare (Basel)*. 2019;7(4):141.
42. Marklund M. Update on oral appliance therapy for OSA. *Curr Sleep Med Rep*. 2017;3(3):143–151.
43. Sutherland K, Cistulli P. Mandibular advancement splints for the treatment of sleep apnea syndrome. *Swiss Med Wkly*. 2011;141:w13276.
44. Vanderveken OM, Dieltjens M, Wouters K, et al. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. *Thorax*. 2013;68(1):91–96.
45. Dieltjens M, Braem MJ, Vroegop AVMT, et al. Objectively measured vs self-reported compliance during oral appliance therapy for sleep-disordered breathing. *Chest*. 2013;144(5):1495–1502.
46. Marklund M, Braem MJA, Verbraecken J. Update on oral appliance therapy. *Eur Respir Rev*. 2019;28(153):190083.

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