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Original Article

Predictors of long-term effectiveness to mandibular repositioning device treatment in obstructive sleep apnea patients after 1000 days

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ABSTRACT

Objective/background: In obstructive sleep apnea (OSA), long-term adherence to treatment is crucial. This prospective single-center study investigated factors associated with long-term adherence to mandibular repositioning device (MRD) therapy.
Patients/methods: All OSA patients who had MRD treatment initiated in the previous year were prospectively contacted to evaluate long-term effectiveness and compliance. Long-term adherence was based on continuation of treatment (yes/no). Predictors of long-term adherence were analyzed using an adjusted multivariate analysis.
Results: Median follow-up was 1002 days (interquartile range: 668–1345) in 279 patients (age 58 [50–64] years); 63% of patients were continuing MRD treatment with a good efficacy, tolerability and compliance over time. In some patients, relapse of nocturia was observed while efficacy was maintained for snoring and somnolence. In adjusted multivariate analysis, significant predictors of continuing MRD treatment were early ≥50% reduction in AHI (odds ratio [OR] 2.73, 95% confidence interval [CI] 1.466–5.10; p = 0.0002) and complete symptom resolution (OR 3.83, 95% CI 1.74–8.48; p = 0.0014). In the 37% of patients who stopped MRD treatment, median treatment duration was 351 (174–752) days. The main reasons for late stopping of treatment were inefficacy (26.2%), discomfort (25.2%) and side effects (21.4%).
Conclusions: After three years, MRD was effective for the two-thirds of OSA patients who continued treatment. Relapse of nocturia might be an early signal of MRD wear that may explain long-term cessation of treatment in some patients. Short-term control of OSA by MAD was predictive of long-term efficiency. The major criteria were a ≥50% reduction in AHI and complete symptom resolution at short-term evaluation.

1. Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent collapse of the upper airway during sleep. Obstructive apneas and hypopneas lead to oxygen desaturation, sleep fragmentation and increased sympathetic tone, which in turn induce a variety of systemic consequences [1]. OSA has been associated with cardiovascular morbidity [2], sleepiness-related accidents [3] and cognitive

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dysfunction, particularly in memory, attention and executive function [4]. The rate of cardiovascular events can be significantly reduced by treatment with continuous positive airway pressure (CPAP), which is considered the standard of care. However, more than 40% of patients do not tolerate CPAP or use it irregularly [5].

Mandibular repositioning devices (MRDs) protrude the mandible and tongue, and enlarge and stabilize the upper airways during sleep [6]. Over the short term, MRDs are less efficient than CPAP at reducing respiratory events, but are associated with better long-term compliance and similar efficacy on symptoms and quality of life (QOL) [7], making MRDs a viable alternative to CPAP for the treatment of OSA [8,9]. Two long-term studies, both based on observational follow-up of initially randomized trials, compared MRD to CPAP and reported smaller reductions in the apnea-hypopnea index (AHI) but similar effects on symptoms compared with CPAP, akin to findings over the shorter term [10,11]. Possible side effects of long-term MRD use include dental adverse events, such as occlusal changes [12], which may lead to poor compliance [12–14]. Practical considerations may also limit long-term compliance. In fact, there is a lack of data on the long-term clinical effects of MRDs, and particularly on long-term compliance with therapy. The main objective of this study was to provide long-term data on MRD use in a large cohort of OSA patients treated in routine clinical practice, and to evaluate if some factors could help physicians predict long-term adherence.

2. Methods

This observational, single-center study was conducted at the Pitié-Salpêtrière Hospital, France, was in accordance with Declaration of Helsinki principles, and consisted of a long-term evaluation of MRD effects based on one prospective contact. In addition, baseline data, titration process and short-term evaluation of MRD were extracted from patient's medical records at the time of the study. The Pitié-Salpêtrière Hospital is a large (n = 2146 beds) clinical and university center where OSA management is based on integrated care. Around 400 OSA patients per year are newly diagnosed (on 700 polysomnographies for OSA suspicion) and treated by either CPAP or MRD. The majority of patients that are treated by CPAP and MRD treatment represent around 15–20% of treatment indications. In this study, a dedicated dental specialist managed MRD treatment of OSA patients and worked closely with sleep specialists; MRD treatment and collection of data about efficacy, tolerability and compliance were procedure-based. Ethics Committee approval and data processing authorization were obtained for the study (CCTIRS, Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé; CNIL, Commission Nationale de l'Informatique et des Libertés). All patients were provided with information about the study and were free to refuse participation.

2.1. Patients and eligibility to MRD treatment

Eligibility for MRD treatment in this study was based on the sleep specialist's evaluation (clinical evaluation and polysomnography) followed by the dental specialist's evaluation (clinical evaluation and panoramic X-ray). All OSA patients referred to the dental specialist by the sleep specialist with an indication for an MRD were screened. All patients having been treated by MRD for at least one day and who had started treatment at least one year previously (those who were still using the device at the time of the prospective contact for our study and patients who had stopped treatment in the period between initiation and our prospective contact) and consented to take part in the study were included in the analysis. Patients who did not initiate the MRD treatment were screened but not included. Indication of MRD treatment, was based on French indications in OSA (patients with an AHI >30/h or ≤30/h with severe excessive sleepiness in patients intolerant to or refusing CPAP; OR 5/h ≤ AHI ≤ 30/h, mild to moderate excessive sleepiness and without severe cardiovascular morbidity). The dental specialist confirmed or disconfirmed the indication of MRD. He performed an in-depth clinical evaluation (number of teeth, dental mobility, periodontal and temporomandibular evaluations) and a radiological evaluation based on a panoramic X-ray to detect any other dental or periodontal diseases. For all patients, measurements of mandibular advancement from end to end in maximum protrusion, maximal jaw propulsion, dental overjet and dental overbite, were completed. Contraindications were less than eight healthy teeth per jaw, periodontal disease, and temporomandibular joint disease. A cephalometric evaluation was not required even if some patients had this evaluation (not collected in this study).

2.2. Data file collection for baseline data, titration process and short-term evaluation

Baseline variables, MRD-related data (treatment initiation date, type of MRD and titration), short-term clinical and AHI evaluation, tolerability and compliance data were obtained from patient medical records. For PSG data, American Academy of Sleep Medicine (AASM) guidelines [15] were used to define respiratory events. Apnea was defined as absence of airflow for at least 10 s, hypopnea as a reduction of airflow by at least 30% associated with a decrease in oxygen saturation of three percent or more, or with arousal.

2.3. Prospective long-term follow-up

Prospective long-term follow-up consisted of phone contact to obtain record of MRD effects. The first question determined whether the MRD was still being used or not. In patients who stopped MRD treatment, the cessation date, main reasons for MRD discontinuation and therapeutic changes were recorded. In patients continuing MRD treatment, global clinical efficacy (answer yes/no to the following question: “Is your device efficient on OSA symptoms?”), OSA symptoms, the Epworth Sleepiness Scale (ESS) score, MRD-related side effects, MRD-related compliance (use time per night, number of nights/week with use and reasons for low use) and patient satisfaction with MRD therapy were assessed. Satisfaction over the preceding four weeks of treatment was determined based on three general items (global satisfaction, quality of sleep, treatment manageable) scored on a scale from zero (very bad) to ten (excellent) and four items compared with CPAP (comfort, reduction in symptoms, compliance, social life) scored on a scale from zero (MRD worse than CPAP) to ten (MRD very superior to CPAP).

2.4. Statistical analysis

Measures are presented as median and interquartile range for quantitative variables and number and percentage for qualitative variables. Comparison between patients with vs. without continuation of treatment was performed as follows: group description was performed using mean ± standard deviation (SD) for quantitative variables and percentages for qualitative variables. Univariate comparisons were performed using Student's t tests for quantitative variables and Chi-square tests for qualitative variables. Two logistic models were created to determine predictors of treatment continuation, the first including the whole study population and the second including only patients with a short-term PSG evaluation. Variables with a p-value lower than 0.10 in the univariate analysis were entered in the stepwise logistic regressions, and

variables with a p-value lower than 0.05 using the Wald test were retained in the final models. All computations were performed using SAS V9.3 (SAS Institute Inc, Cary, NC, USA). Cessation of MRD treatment over time was estimated by the Kaplan-Meier method.

3. Results

3.1. Baseline data, titration and short-term evaluation

A total of 458 OSA patients were screened for MRD treatment, including 309 (67.5%) who were treated with an MRD, which represents a 15–20% estimated prevalence, regarding OSA treatment in this center. This estimation was based on the number of OSA patients newly diagnosed per year in this center and treated by either CPAP or MRD (n = 400), and a time interval of four to five years for our study (total number of patients = 1600–2000). Non-treatment reasons were mostly (n = 83) dental or periodontal contraindications to MRD use (less than eight healthy teeth per jaw, periodontal disease and temporomandibular joint disease). Others were lost to follow-up (n = 55) or were finally treated by CPAP (n = 11). The 309 MRD-treated patients were prospectively contacted and 279 were included in the study (eight patients were lost to follow-up and 22 refused to participate) (Fig. 1). For the whole population, the median time from treatment initiation to the start of long-term follow-up was 1002 days (668, 1345). Median time between the first visit with a sleep specialist and treatment initiation was 162 days (First quartile, third quartile; 89, 282 days) and was less than three months in 26% of patients. All patients were effectively selected for MRD treatment following the center procedures (see Section 2.1) and all had an evaluation by both sleep and the dental specialist before treatment, and a panoramix X-ray. Baseline clinical and demographic data, and dental parameters evaluated by the dental specialist (dental status, dental mobility, periodontal status, mandibular advancement from end to end in maximum protrusion, maximal jaw propulsion, dental overjet and dental overbite) of the 279 included patients are shown in Table 1.

3.1.1. MRD titration

Only custom-made titratable and adjustable MRD devices approved by the French Health Technology Assessment Agency (Haute Autorité de Santé) for OSA treatment were used. The majority of patients (86.7%) were treated with the Narval CC™ (ResMed), a bi-block MRD made with semi-rigid plastic materials (biocompatible polymer) and customized using high-precision computer-aided design/computer-aided manufacturing (CAD/CAM). Others were treated either with Somnodent™ (SomnoMed Ltd) or Orthosom (SomnoMed Ltd), or Narval™ (ResMed) for patients with tooth morphology unsuitable for use of the CAD/CAM technology (eg, short teeth or removable appliance leading to inadequate retention with CAD/CAM device). All patients had at least one titration visit and the median number of titration visits was two. Titration was performed in the supine position, step by step, by replacing the connecting rod for the Narval CC™, Narval™ and Orthosom, or advancing the screw by 1 mm for the Somnodent™, starting at 50% of the patient's maximum mandibular protrusion. Mandibular advancement was adjusted at each visit at the discretion of the dental sleep specialist until the best benefit–risk ratio between symptom resolution and tolerability was achieved (only clinically based). At each titration visit, mandibular advancement was continued for as long as the patient was comfortable and there was an absence of pain. At the end of titration, the dental specialist had referred all patients to the sleep specialist for a clinical and polysomnographic evaluation (short-term evaluation). Some patients had more than one polysomnography (repeated after MRD adjustment if efficacy was not complete on AHI), however only the last one (very end of titration)

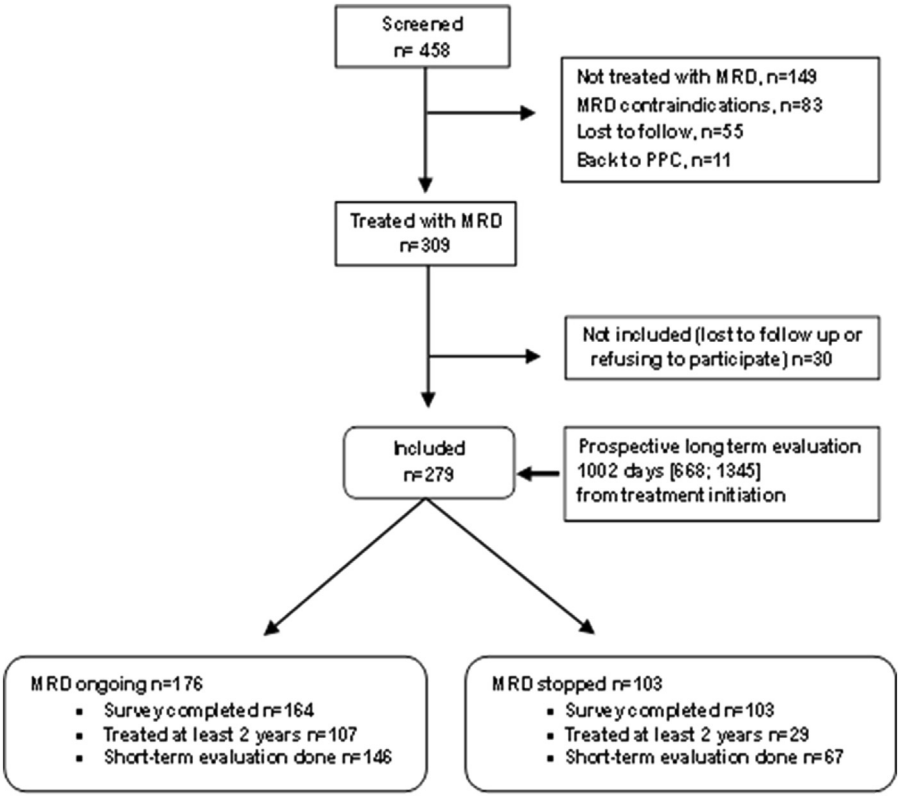

Fig. 1. Patient flow through the study.

Table 1
Patient demographic and clinical characteristics at baseline.

	Patients (n = 279)
Age, years	58 (50, 64)
Female, n (%)	81 (29.0)
BMI, kg/m^2	26.4 (23.9, 30.0)
BMI ≥30 kg/m^2, n (%)	71 (25.5)
Comorbidities, n (%):	
Diabetes	25 (89.6)
Arterial hypertension	94 (33.7)
Cardiovascular	53 (19.0)
Not previously treated with CPAP, n (%)	119 (42.7)
Inside network, n (%)	240 (86.0)
ESS score (0–24)	11 (7, 14)
ESS score >10, n (%)	145 (52.0)
AHI,/h	26 (19, 36)
Severity of OSA, n (%)	
AHI >30/h	109 (39.1)
Mild-to-moderate AHI plus ESS >10	77 (27.6)
Mild-to-moderate AHI plus ESS ≤10	93 (33.3)
Dental status, n (%):	
Good	177 (63.4)
Acceptable	96 (34.4)
Bad	6 (2.2)
Periodontal status, n (%)	
Good	194 (69.5)
Acceptable	84 (30.1)
Bad	1 (0.4)
Dental mobility, n (%)	
None	217 (77.8)
Low and limited	62 (22.2)
Overbite, mm	3.0 (2.0, 4.0)
Overjet, mm	3.0 (2.0, 4.0)
Pa, mm	4.0 (3.0, 5.0)
Maximum protrusion, mm	8.0 (6.0, 10.0)
MRD type, n (%):	
Narval CC (CAD/CAM)	242 (86.7)
Narval (non-CAD/CAM)	15 (5.4)
Somnomed	13 (4.7)
Orthosom	9 (3.2)
Mandibular advancement at the end of titration, mm	7.0 (6.0, 8.0)
Number of MRD titrations, n	2.0 (1.0, 2.0)

Values are median (quartiles) or number of patients (%).
BMI, body mass index; AHI, apnea-hypopnea index, per hour; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale, MRD, mandibular repositioning device, OSA, obstructive sleep apnea, CAD/CAM, computer-aided design/computer-aided manufacturing; Pa, mandibular advancement from end to end in maximum protrusion.

was collected for this study. MRD data (type, mandibular advancement at the end of titration and number of titrations) are shown in Table 1.

3.1.2. Short-term evaluation extracted from patient's medical record

All patients were clinically evaluated at short-term, three to six months after initiation of MRD therapy. At this short-term evaluation, 237 patients (85%) reported good global clinical efficacy with MRD treatment and 120 (43%) had complete resolution of symptoms. The ESS score had decreased from 11 (7, 14) at baseline to eight (5, 12) ($p < 0.0001$). Overall, 44% of those who had excessive sleepiness (defined as an ESS score >10) at baseline had an ESS score of <10 at this evaluation. Regarding tolerability, 142 patients (51%) did not report any side effects of MRD therapy; the majority of side effects reported by the remaining patients were of mild severity and did not require treatment discontinuation.

PSG data were available for 213 patients (76% of those treated), with a median time between treatment initiation and evaluation of 104 (63, 174) days. Baseline characteristics for patients with available PSG data were similar to those in the overall population (age 59 [50, 65] years; body mass index 26.4 [23.8, 30.0] kg/m^2; AHI 28 [20, 36]/h; AHI ≥30/h 43% of patients). Short-term PSG evaluation was pending in 66 patients (24%) treated for 845 (506, 1210) days, but had been cancelled or delayed by the patient. A ≥50% reduction in AHI was achieved in 67% of patients, irrespective of baseline OSA severity, and the AHI during MRD therapy was nine (five, 16)/h ($p < 0.0001$ vs. baseline). Individual values for AHI and ESS scores at inclusion and at short-term evaluation in the 213 patients with PSG data are shown in Fig. 2. The efficacy of the MRD, determined as reductions in AHI to <5/h, <10/h and <15/h and by severity of OSA is provided in Fig. 5 (supplemental appendix). Immediately after the short-term evaluation, 15 patients (5%) discontinued MRD use, seven for inefficacy, four because of side effects (dental, periodontal or articular pain, and one patient for dental migration) and four without any specific reason.

3.2. Long-term follow-up

At the time of the study, 176 patients (63%) were still continuing MRD treatment and 103 (37%) had stopped previously. In the 176 patients who continued MRD therapy, median treatment duration was 928 (584, 1341) days. Long-term evaluation of efficacy, tolerability and compliance was complete for 164 patients (12 patients refused to complete the clinical evaluation survey); 107/164 patients had been treated for more than two years. Long-term subjective compliance was excellent, with median MRD usage of seven (six, eight) h/night on seven (six, seven) nights/week. The majority of participants (88%) used the MRD for ≥4 h/night, ≥4 days/week, and 73% used the device every night. The ESS score decreased from 11 (seven, 14) at baseline to five (two, eight) ($p < 0.00001$). There were significant reductions in almost all OSA symptoms (snoring, mouth opening, headache, sleepiness, unrefreshing sleep, tiredness), excluding nocturia and libido disorder. Efficacy over time was maintained for snoring, sleepiness and ESS score, but there was a mild reduction in MRD efficacy over time with respect to nocturia, mouth opening, headache, unrefreshing sleep and tiredness. Symptoms at inclusion and short-term and long-term evaluations are shown in Fig. 3. MRD use was well tolerated. Overall, 106 patients (65%) did not report any side effects. Those reported by other patients were generally of mild intensity and manageable (dental, articular or periodontal pain [27% of patients], tooth mobility or migration [7%], joint malfunction or occlusion [9%], and bleeding or irritation [17%]). MRD efficacy and tolerability was similar for patients treated for <2 or ≥2 years. Patient satisfaction with MRD therapy was excellent; global satisfaction score was 7.6 ± 1.6, comfort score 7.2 ± 1.8, quality of sleep score 7.3 ± 2 and treatment manageable score 9.5 ± 1.1. We compared these results with CPAP scores: comfort 9.4 ± 1.6, reduction of symptoms 8.3 ± 2.4, compliance 9.3 ± 1.5 and social life 6.8 ± 2.4. Clinical efficacy, side effects and compliance at baseline and at short-term evaluation (all included patients, n = 279) and at long-term evaluation (for those who were continuing at the time of the study, n = 164), are shown in Table 3. For the long-term evaluation, results are shown for the whole group (n = 164, all patients were treated for more than six months) and by subgroups for several duration of treatment, subgroup of patients treated more than two years (n = 107), subgroup of patients treated more than three years (n = 60) and subgroup of patients treated more than four years (n = 30).

In the 103 patients who stopped MRD treatment, median treatment duration was 351 (174, 752) days (29 patients were treated for six months or less, 23 patients for six months to one year, 22 patients for one to two years, 21 patients for two to three years, seven patients for three to four years, and one patient for more than four years). Four patients had died at the time of the prospective contact. All were males and had stopped their MRD treatment for intolerance prior to their death, which was secondary to oesophageal cancer ([patient age 82 years], amyotrophic lateral sclerosis [age 57 years], dementia [age 87 years, and sudden death [age 77

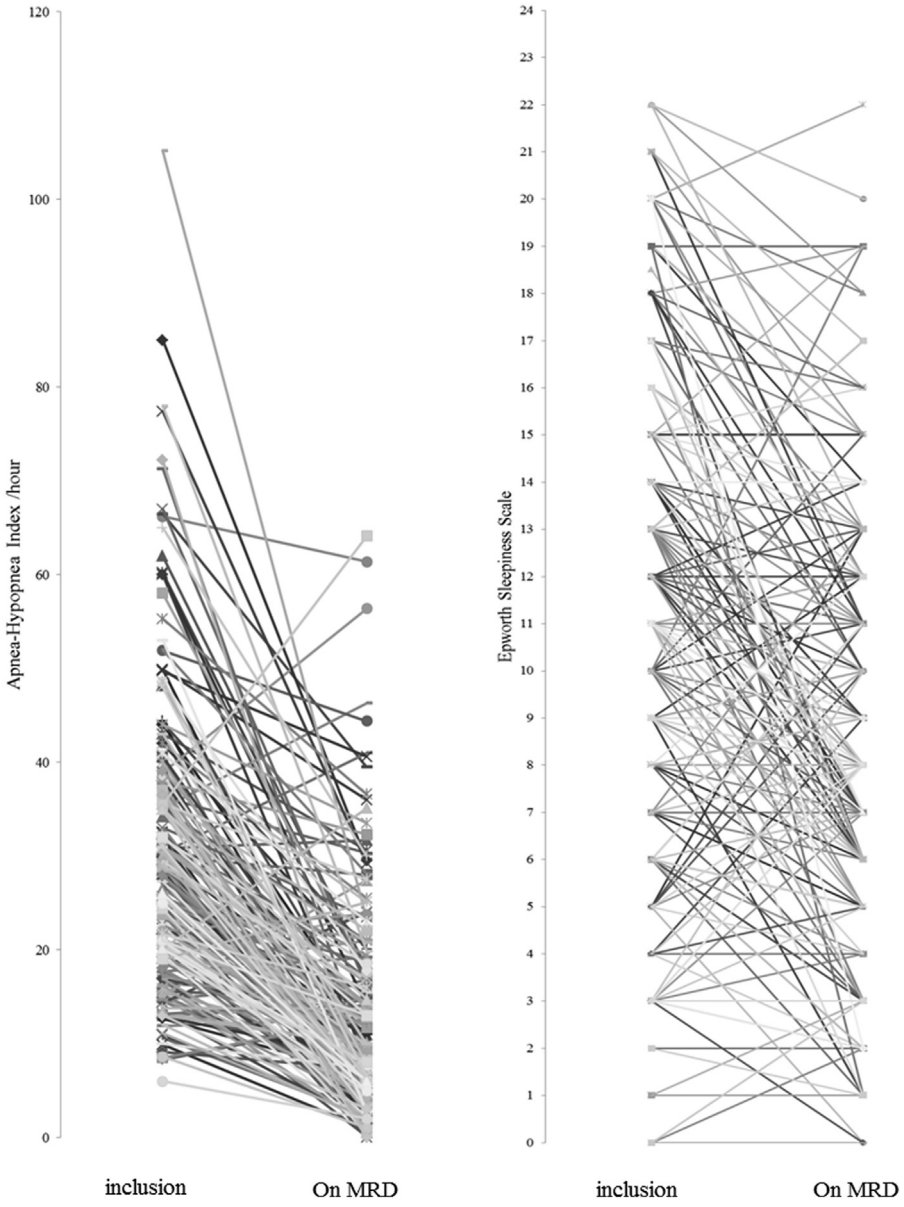

Fig. 2. Apnea-hypopnea index (left) and Epworth Sleepiness Scale score (right) at inclusion and at short-term evaluation on MRD, in the 213 patients having a short-term polysomnography.

years]). The Kaplan-Meier analysis (Fig. 4) shows that cessation of treatment may occur after long-term device use because 29/103 patients stopped after more than two years' use. The main reasons for stopping treatment were inefficacy (26.2%), discomfort (25.2%), side effects (21.4%) and no specific reason (27.2%). Stopping treatment for no specific reason was more common in those who stopped treatment after two years' use versus after less than two years' use (37% vs. 23%; $p = 0.004$), while stopping for discomfort was less common (14% vs. 30%; $p = 0.01$), and there were no differences between patient subgroups for discontinuation due to side effects (28% vs. 19%) and inefficacy (21% vs. 28%).

3.3. Multivariate analysis of predictive factors of long-term continuation of MRD

The univariate analysis identified significant predictors of long-term MRD use (Table 2). In the first adjusted multivariate model including all patients, two factors were predictors of continuation: MRD as first-line therapy (ie, no previous CPAP; odds ratio [OR] 1.77, 95% confidence interval [CI] 1.03–3.03; $p = 0.0375$) and complete symptom resolution at short-term evaluation (OR 1.78, 95% CI 1.03–3.08; $p = 0.0384$). In the second adjusted multivariate analysis including only patients with short-term PSG data, significant predictors of continuing MRD treatment included a $\geq$50% reduction in AHI at short-term evaluation (OR 2.73, 95% CI 1.466–5.10; $p = 0.0002$) and complete symptom resolution at short-term evaluation (OR 3.83, 95% CI 1.74–8.48; $p = 0.0014$).

3.4. Replacement of MRD

At the time of the long-term follow-up, MRD replacement had been done or was underway for 74 patients (27%). This replacement process was initiated after a median of 427 (350, 533) days. The MRD was not replaced in the majority of patients. The median treatment

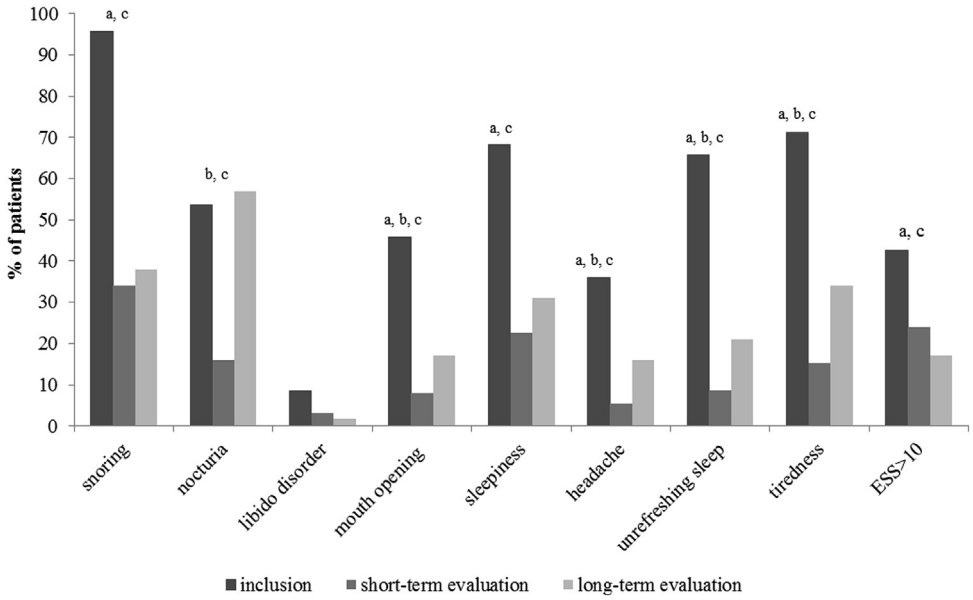

Fig. 3. Long-term efficacy of MRD in patients continuing to use the device (n = 164). [a]p<0.01 for long-term evaluation versus inclusion; [b]p < 0.01 for short-term versus long-term evaluation; [c]p < 0.01 for short-term evaluation versus inclusion.

time was 967 (561, 1325) days. Revaluation of AHI was available for 54 patients (35 with a replaced MRD) after a median time from treatment initiation of 846 (713, 1111) days. At this evaluation, the proportion of patients with a ≥50% reduction in AHI was 63%.

3.5. Evaluation of resources

Resource use data were extracted in a sample of 30 patients (ten who stopped after six months and 20 continuing patients). In this subgroup, the mean number of attended sleep visits, attended dental specialist visits, and polysomnographies was 4.2 ± 2.4, 5.9 ± 2.9 and 2.1 ± 1.2, respectively.

Table 2
Univariate predictors of long-term MRD use.

	MRD use		p-value
	Continued (n = 176)	Stopped (n = 103)	
Inclusion			
Diabetes, n (%)	14 (8)	17 (16)	0.0616
Dyslipidemia, n (%)	9 (5)	14 (14)	0.0223
Never smoker, n (%)	118 (67)	57 (55)	0.0268
MRD as first-line therapy, n (%)	86 (49)	36 (35)	0.0179
Overbite, mm	3.5 ± 1.6	2.4 ± 1.6	0.0079
Propulsion, mm	5.1 ± 1.4	5.6 ± 1.4	0.0103
First advancement, mm	6.0 ± 1.5	6.4 ± 1.8	0.0445
Final titration, mm	6.7 ± 1.7	7.1 ± 1.7	0.0451
Short-term evaluation			
Global clinical efficacy, n (%)	160 (91)	75 (73)	0.0007
Complete resolution of symptoms, n (%)	83 (47)	37 (36)	0.0673
ESS score (0–24)	8.3 ± 4.6	9.7 ± 5.2	0.0551
Somnolence, n (%)	49 (28)	44 (43)	0.0357
Snoring, n (%)	72 (41)	61 (59)	0.0559
Discomfort, n (%)	40 (23)	47 (46)	0.0006
Intolerance, n (%)	26 (15)	39 (38)	0.0002
No AEs, n (%)	84 (48)	34 (33)	0.0025
AHI reduction >50%[a], n (%)	132 (75)	53 (51)	0.0006

Values are mean ± standard deviation, or number of patients (%).
AE, adverse event; AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; MRD, mandibular repositioning device.
[a] In 213 patients with short-term PSG evaluation.

4. Discussion

This study showed that MRDs can be effective and safely used for long-term OSA therapy, with good compliance and patient satisfaction. Our study followed patients for up to 1000 days after initiation of MRD use and included a much larger population than previous similar analyses [12,14,16].

This study showed good long-term persistence with MRD use (63% at 2.5 years), accompanied by good clinical efficacy, good tolerability and excellent compliance. Although MRD treatment efficacy was effectively maintained with respect to the most specific symptoms of OSA (ie, snoring and sleepiness), treatment was less efficient for the long-term control of other symptoms, including nocturia, mouth opening, headache, unrefreshing sleep or tiredness. This may be due to natural progression in the severity of OSA [17], but is more likely the result of device wear after several years' use. Current guidelines recommend replacing an MRD after two to three years of use but do not provide specific guidance based on changes in clinical endpoints [18]. In our cohort, guidelines at the study center indicated that the MRD should have been replaced after two years in the 107 patients remaining on treatment at this time. However, only 74 patients had device replacement at the long-term follow-up. In practice, MRD replacement is not automatic after two years and a decision to replace the device with a new one is clinically driven and mainly based on the occurrence/rate of snoring and somnolence. Our results do highlight the importance of taking other OSA symptoms (eg, nocturia, headache, tiredness, mouth breathing during sleep or poor quality of sleep) into account as signals of loss of MRD efficacy that may occur earlier than relapses of snoring or somnolence. Prospective investigation into the predictive value of these symptoms for determining the timing of MRD replacement is an area for future research. It could be of importance to identify a loss of efficacy early on, because 26.2% of long-term stoppers in this study discontinued due to inefficacy. In addition, such clinical predictors would be useful because guidelines do not recommend repeating PSG over time after reaching the optimal titration.

Table 3
Baseline and short-term evaluation for all included patients, and long-term evaluation for continuing patients at the time of the study.

	Baseline n = 279	Short-term n = 279	Long-term evaluation in continuing patients by duration of MRD treatment n = 164			
			All	Subgroups by time interval		
			>6 months	>2 years	>3 years	>4 years
Number of patients	279	279	164	107	60	30
Snoring, n (%)	268 (96)	97 (35)	62 (38)	36 (34)	21 (35)	9 (30)
Nocturia, n (%)	135 (48)	36 (13)	93 (57)	61 (57)	36 (60)	19 (36)
Libido disorder, n (%)	21 (8)	7 (3)	3 (2)	2 (2)	1 (2)	0 (0)
Mouth opening, n (%)	113 (41)	19 (7)	28 (17)	19 (18)	12 (20)	6 (20)
Sleepiness, n (%)	189 (68)	66 (24)	50 (31)	26 (24)	14 (23)	7 (23)
Headache, n (%)	93 (33)	14 (5)	26 (16)	17 (16)	10 (17)	3 (10)
Unrefreshing sleep, n (%)	155 (56)	23 (8)	35 (21)	19 (18)	11 (18)	5 (17)
Tiredness, n (%)	186 (67)	37 (13)	55 (34)	32 (30)	15 (25)	7 (23)
ESS score >10, n (%)	145 (52)	68 (24)	28 (17)	18 (17)	9 (15)	3 (10)
No adverse events, n (%)	NA	142 (51)	115 (70)	78 (73)	44 (73)	21 (70)
Dental, periodontal or articular pain, n (%)	NA	40 (18)	45 (27)	27 (25)	14 (23)	8 (27)
Joint malfunction or occlusion, n (%)	NA	32 (12)	15 (9)	9 (8)	5 (8)	3 (10)
Bleeding or irritation, n (%)	NA	13 (5)	27 (17)	16 (15)	7 (12)	3 (10)
Dental mobility or migration, n (%)	NA	15 (5)	11 (7)	8 (8)	5 (8)	2 (7)
Compliance, days/week mean ± SD	NA	6.1 ± 1.8	6.1 ± 1.7	6.1 ± 1.7	6.1 ± 1.8	5.9 ± 2.0
Compliance, hour/night mean ± SD	NA	6.4 ± 1.9	6.9 ± 1.2	6.9 ± 1.2	6.8 ± 1.2	6.7 ± 0.9
AHI mean ± SD	29.8 ± 16.1	12.5 ± 11.2[a]	14.6 ± 10.2[b]	NA	NA	NA

For baseline and short-term evaluations, results were extracted from patient's medical record and are shown for all included patients (n = 279).
For long-term evaluation, results were assessed prospectively and based on one contact at the time of the study. As the duration of treatment was not the same for all patients at the time of this contact, results are shown for the whole group of continuing patients (n = 164, all patients were treated at least six months) and by subgroups (cumulative number by time intervals).
Values are number of patients (%), or mean ± standard deviation.
[a] Based on the 213 patients having a short-term polysomnography.
[b] Based on the 54 patients having a long-term polysomnography.

Overall tolerance of long-term MRD therapy was excellent in our cohort. However, there was a small, non-significant increase in dental migration or mobility between the short- and long-term evaluations. In addition, about 21.4% of the 103 patients who stopped MRD therapy during long-term follow did so because of side effects. Stopping therapy due to side effects was numerically more frequent in patients who had been using an MRD for >2 years, even not significant. Given that long-term occlusion changes may occur [19], our results support regular dental follow-up as an approach to avoid side effects and prevent treatment cessation in long-term MRD users.

Our conservative approach for assessing long-term stopping of MRD therapy showed that the proportion of patients who stopped long-term MRD therapy was very similar to those generally observed with CPAP, suggesting that MRDs are probably equivalent to CPAP with respect to long-term adherence, although reasons for non-adherence may be different.

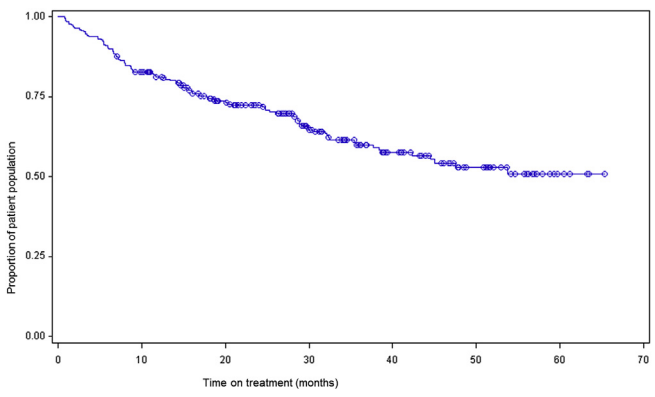

Fig. 4. Proportion of patients continuing MRD treatment over time.

Our findings support an important role for disease chronicity on compliance, which was similar to those reported for other chronic diseases [20]. Our univariate analysis identified three factors strongly associated with chronic diseases as predictors of continued MRD use. Patients who continued device use were less likely to have diabetes or dyslipidemia and were more likely to have never smoked. Short-term efficacy was also strongly predictive of continued MRD use, highlighting the importance of early follow-up in OSA patients, as in other chronic diseases. We also observed a lack of adherence to follow-up procedures, with 66 patients not undergoing the planned short-term PSG evaluation of MRD efficacy, which is again probably not uncommon for patients with a chronic disease. For these reasons we performed two different multivariate analyses. The first was based on clinical parameters for the whole population, irrespective of whatever a short-term PSG was done or not. This showed that MRD as first-line treatment was a strong predictor of continuation, reinforcing the link between chronicity of disease and long-term treatment persistence; this indicates that patients intolerant of, or non-compliant with CPAP are more likely to also stop MRD treatment. The second multivariate analysis model included patients who had undergone short-term PSG evaluation and showed that the AHI reduction and complete symptom resolution were strong predictors of long-term MRD continuation. These findings reinforce the importance of short-term follow-up and effective device titration, to ensure the long-term success of MRD therapy. Physicians should inform their patients of the importance of attending short-term follow-up visits, and need to undertake additional titration in patients whose PSG results and clinical examination indicate persistent symptoms, particularly in those using an MRD as a second-line treatment. Regular long-term follow-up visits are also probably important for maintaining long-term compliance because cessation after long-term device use is common (103 patients stopped after two years in this study). Patients appeared to do well in terms of

persisting with MRD therapy under the integrative care management approach. Nevertheless, the process of optimal device titration required that several steps were followed over a defined time period, including visits with two specialists, MRD manufacturing time, titration, and PSG evaluation. In our study, the median time between MRD prescription by the sleep specialist and initiation of treatment, and the median time between initiation and short-term PSG evaluation were respectively 162 days and 104 days. Titration may take longer in some patients to avoid side effects or discomfort. Time without treatment could be much longer in some centers and could be of importance in the most severe or sleepy patients. This is something that needs to be addressed when discussing different therapeutic options, particularly CPAP.

This study has numbers of strengths. Long-term assessment with at least one year of follow-up was done prospectively and included both symptomatic evaluation and patient satisfaction. One-year follow-up was chosen so that only patients with optimal MRD therapy after final titration of the device were included. All consecutive OSA patients meeting the inclusion criteria were systematically contacted and more than 90% agreed (279/309) to take part in the study. Based on previously published data on MRD efficacy, the number of patients was sufficient to detect a significant AHI reduction at the short-term assessment [21] and to analyze long-term compliance under real-life conditions in the patients continuing to use an MRD after a median of 1000 days. Although the trial design was not randomized or comparative, the aim of the study was to evaluate MRD treatment in a real-world setting without any influence of study-mandated procedures. However, baseline characteristics for our patients were comparable to those included in published randomized studies [6,13,22].

In conclusion, persistence with MRD therapy over the long term in patients treated under real-world conditions was good (approximately two-thirds of patients were still using the device after 1000 days of follow-up). In addition, MRD therapy was effective and well tolerated, and patients were satisfied with treatment. Short-term control of OSA by MAD was predictive of long-term efficiency. The major criteria were a $\geq$50% reduction in AHI and complete symptom resolution at short-term evaluation. These results also highlight the importance of integrated, multidisciplinary care with regular follow-up to ensure the long-term adherence to MRD treatment.

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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.2016.10.004.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.sleep.2016.10.004.

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