SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE



Effects of mandibular advancement devices on the evolution of obstructive sleep apnea

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Abstract

Purpose Mandibular advancement devices (MADs) are a treatment for obstructive sleep apnea (OSA). Titration is a necessary component of proper fitting of MADs, yet little is known about what happens at each step of the titration. The objectives of this study were to determine the clinical and paraclinical evolution of OSA at every mm of MAD advancement.

Methods Volunteers were fitted with MADs set to 50% of maximum advancement. MAD clinical and paraclinical results were recorded at every additional mm-titration, including apnea-hypopnea index (AHI), as well as symptoms of sleepiness and fatigue.

Results In 20 volunteers with OSA, the MAD had a significant effect on every polygraphic parameter at the onset of use. The mean AHI with MAD fell by 15.2/h (p < 0.001). The mean Epworth Sleepiness Score and Pichot Fatigue questionnaire with MAD fell by 2.0 (p = 0.0687) and 2.4 (p = 0.1073) respectively. There was no proportionality between clinical gains (drowsiness and fatigue) and AHI improvements.

Conclusions MADs led to a significant improvement in AHI and other polygraphic parameters from the onset of use. The decrease of clinical symptoms (drowsiness and fatigue) was more complex to interpret because of the small decreases observed. The absence of concordance between AHI improvement and clinical symptoms was nevertheless objectively quantified and symptoms were alleviated with advancements. The findings suggest that it may be appropriate to use clinical symptoms as a main aim of titration, since the improvement in AHI is reached at the onset of MAD use.

Keywords Obstructive sleep apnea · Mandibular advancement device · Apnea Hypopnea Index · Symptoms

Introduction

Obstructive sleep apnea (OSA) is defined by intermittent collapse of the upper airway during sleep, leading to oxygen desaturation and/or sleep disturbances. Mandibular advancement devices (MADs) present a viable therapeutic alternative to continuous positive airway pressure (CPAP) [1–6]. While the exact mechanisms through which MADs function remain somewhat ambiguous and multifactorial, research indicates that MADs enlarge the upper airway space [7–10] and enhance the reflex dilation of the pharynx, optimizing the performance of stretch receptors in the genioglossus muscle [9, 11].

In France, MADs are considered a second-line treatment for severe OSA when CPAP is declined or discontinued [12]. They are the first-line treatment for moderate OSA with three or more clinical symptoms, such as headaches, fatigue, daytime drowsiness, nycturia, nocturnal choking, vascular comorbidities, or traffic accidents due to sleepiness [12]. The fine tuning of MADs is flexible, allowing specialists like ear, nose, throat (ENT) doctors or dentists to adjust the appliance by progressively moving the mandible forward until symptoms show notable improvement [4, 5]. Our previous study [6] revealed that, on average, 2.0 ± 1.4 consultations are required for titration, ranging from 0 to 7. Subsequent to these adjustments, a sleep study is undertaken to ensure that the apnea hypopnea Iindex (AHI) has sufficiently decreased [12].

The following question remains unanswered: Does AHI or symptom severity change linearly with adjustments, or is there a certain point after which MAD efficacy plateaus or varies non-linearly?

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The main purpose of this study was to map the clinical and paraclinical progression of OSA for every millimeter of MAD advancement.

Methods

Study participants

Between September 21, 2021, and March 7, 2023, volunteer patients who were equipped with a MAD were prospectively included. Inclusion criteria for MAD were (1) severe OSA (AHI > 30/h) with clinical symptoms such as headaches, fatigue, drowsiness, nocturia, nocturnal suffocations, vascular comorbidities, road accidents from falling asleep, and refusal or intolerance to CPAP or (2) moderate OSA (AHI between 15/h and 30/h) with the above-mentioned clinical symptoms.

Patients were referred to the ENT doctor directly by general practitioners to perform a sleep study or by specialists such as pulmonologists, neurologists, or cardiologists after completion of a sleep study. Sleep studies were interpreted using the criteria established by the American Academy of Sleep Medicine [13].

MAD provision

Specifics on the prescription, contra-indications, and dental impressions have been detailed in a previous study [6]. The MAD utilized in this research was the Narval CC® titratable twin-block retention MAD, manufactured by ResMed (Saint-Priest, France). The same ENT doctor (author GB) dispensed the MAD to the patients. A multiparametric (subjective and objective) titration method [14] was performed as described: Initially, the MAD advancement was set at 50% of its maximum. Thereafter, at each 2-4-week-consultation, the MAD was advanced by increments of 1 mm until symptom improvement was observed. In parallel, patients underwent clinical symptom evaluations and polygraphy assessments by a specialized nurse, the day before titration consultations. The ENT specialist remained blinded to the polygraphy results during titration. After observing clinical improvement, patients underwent a concluding sleep study at the original location and under the same sleep expert as their initial assessment. The ENT relayed these findings to the patients and scheduled follow-up visits every 6 months in the first year and annually thereafter [6].

Research objectives

The primary objective was to explore AHI response to each millimeter of MAD advancement. Secondary objectives focused on the trajectories of other polygraphic metrics and the subjective experiences of sleepiness and fatigue corresponding to each millimeter of advancement.

Outcome metrics

Evaluations (polygraphy, questionnaires) were performed at every mm of titration. The clinical evaluator who was performing the titration (author GB) was not aware of the results of these evaluations. The necessity of an additional advancement was therefore judged according to subjective impressions of the patients of the efficacy of the MAD.

The principal outcome was the AHI for each millimeter of MAD advancement. Secondary outcome measures included:

- Polygraphic metrics: apnea index (AI), hypopnea index (HI), oxygen desaturation index (ODI), lowest oxygen saturation (LOS), and time below 90% saturation (T90)
- Patient-related outcome measures (PROMs): the Epworth Sleepiness Score (ESS) [15] and the Pichot Fatigue Questionnaire [16]

Data analysis

Means of polygraphic metrics were compared using Student's *t*-tests and PROMs with ANOVA. Comparisons were made at each point with the previous point.

All data analysis was performed using the R software.

Results

Patient population

Between September 21, 2021, and March 7, 2023, twenty patients were provided with a MAD. Their demographic and clinical details are tabulated in Table 1. Ultimately, comprehensive data from 18 patients was analyzed as one patient withdrew her consent and one did not tolerate the MAD and was given CPAP therapy.

MAD overall efficacy

On average, AHI was reduced by 15.2 event/h (p < 0.001), ESS was reduced by 2.0 points (p = 0.0687) and the Pichot Fatigue Score (PFS) was decreased by 2.4 points (p = 0.1073).

Granular efficacy of the mandibular advancement device (per millimeter)

Detailed outcomes for both the primary and secondary metrics are provided in Table 2.

Table 1 Population characteristics

Males/females n (%)	15 (75%)/5 (25%)
Mean age \pm SD [min; max] (yr)	60.8±12.8 [32, 79]
Body mass index \pm SD [min; max] (kg/m ²)	26.4±4.1 [20.5, 30.8]
Severe OSA/moderate OSA n (%)	5 (25%)/15 (75%)
Titration consultations <i>n</i> (%): 0 1 2 3	2 (10%) 18 (90%) 12 (60%) 2 (10%)
Mean absolute advancement \pm SD [min, max] (mm)	6.8 ± 1.3 [5, 9]
Mean relative advancement ± SD [min, max] (%)	72.4±9.1 [53.8, 83.3]
AHI: Mean AHI before mandibular advancement device ± SD [min, max] (/h) Mean AHI after mandibular advancement device ± SD [min, max] (/h) Mean AHI reduction ± SD [min, max] (%)	$26.9 \pm 8.6 [15.2, 51.4]$ $11.5 \pm 10 [4.0, 45.8]$ $-15.5 \pm 7.0 [-33.1, -5.6]$
Epworth Sleepiness Score Mean Epworth Sleepiness Score before mandibular advancement device \pm SD [min, max] Mean Epworth Sleepiness Score after mandibular advancement device \pm SD [min, max]	9.9±4.7 [2, 19] 7.9±4.5 [1, 19]
Pichot Fatigue Score Mean Pichot Fatigue Score before mandibular advancement device \pm SD [min, max] Mean Pichot Fatigue Score after mandibular advancement device \pm SD [min, max]	13.1±10.1 [2, 29] 10.7±8.9 [0, 27]

SD standard deviation, AHI Apnea Hypopnea Index, OSA obstructive sleep apnea

Relative advancement = advancement at the last consultation (mm)/maximal advancement (mm)

AHI evolution

Figures 1, 2, and 3 depict the trajectories of AHI, Epworth Sleepiness Score, and Pichot Fatigue Score in relation to titration increments, respectively. Individual patient trends for these parameters are shown in Figs. 4, 5, and 6. As illustrated in Fig. 4, the AHI reduction begins immediately upon MAD onset. Further analysis (Fig. 4 B and C) suggests a proportional relationship between MAD advancement and AHI reductions, with some minor fluctuations in AHI even noticed with advanced titrations, likely attributable to sampling variability and interpretative discrepancies.

Clinical symptom evolution

The clinical manifestations did not consistently align with the AHI trends. In Figs. 5B and 6B, the reductions in drowsiness and fatigue were not strictly proportional to AHI improvements. Figs. 5C, 5D, 6C, and 6D demonstrate an inconsistent correlation between MAD advancements and clinical signs of OSA, as determined by Patient Reported Outcome Measures. Notably, specific patient profiles (e.g., patients #5 and #1 in Figs. 5C and 5D respectively; patients #5 and 16 in Figs. 6C and 6D) revealed a tipping point in symptom progression. This

Table 2	Results of	clinical and	paraclinical	findings	according to	the titration	consultation	(T0 to T3)

	T0	T1	T2	T3
n	20	18	12	2
Mean AHI±SD [min, max] (/h)	26.9 ± 8.6 [15.2,51.4]	$11.1 \pm 10.1* [1.2,45.8]$	9.1±4.7* [3.2,15.8]	$6.3 \pm 1.8^*$ [5.0,7.6]
Mean ESS \pm SD [min, max]	9.9±4.7 [2, 19]	7.8±4.1 [3, 19]	9.1±4.6 [3, 17]	11.5±3.5 [9, 14]
Mean Pichot ± SD [min, max]	13.1±10.1 [0, 29]	12.4±9.6 [0, 31]	12.9±9.0 [1, 27]	13.0±9.9 [6, 20]
Mean AI \pm SD [min, max] (/h)	$10.4 \pm 8.2 \ [0.3, 23.8]$	2.4±4.2* [0, 18.1]	$2.5 \pm 3.1^{*} [0.1, 8.3]$	$1.0 \pm 1.2^* [0.1, 1.8]$
Mean HI \pm SD [min, max] (/h)	12.9 ± 4.8 [1.4, 24.8]	$6.0 \pm 3.8* [0.5, 11.4]$	6.1±3.9* [0.8, 14.4]	$5.3 \pm 3.0^{*}$ [3.2, 7.4]
Mean ODI ± SD [min,max] (/h)	23.7 ± 9.6 [14.1, 28.4]	$9.8 \pm 6.9* [0.8, 27.7]$	8.1±4.4* [2.9, 16.5]	8.3±4.7* [5.0, 11.6]
Mean SPO2 min \pm SD [min, max] (%)	81±4.8 [72, 88]	84.4±4.1* [76, 91]	$84.4 \pm 7.3^{*}$ [64, 90]	85±5.7* [81, 89]
Mean T90 \pm SD [min, max] (/h)	$39.4 \pm 53.4 \ [0.4, 230.6]$	$23.6 \pm 39.6 * [0, 140]$	$7.2 \pm 8.5^{*} [0, 30]$	$1 \pm 1.4* [0, 2]$

AHI Apnea Hypopnea Index, AI Apnea Index, HI Hypopnea Index, ESS Epworth Sleepiness Score, ODI Oxygen Desaturation Index, SPO2 min minimal oxygen saturation, T90 time below 90% saturation

p < 0.05 when compared to T0

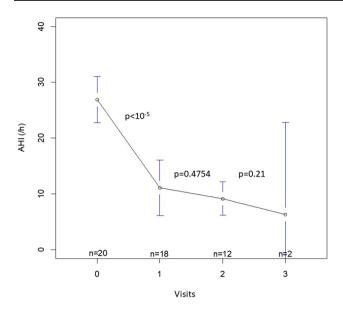


Fig. 1 Apnea hypopnea index (AHI) according to the timing of titration

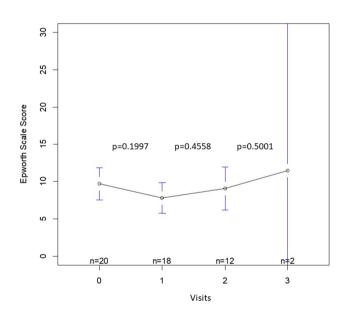


Fig. 2 Epworth Sleepiness Score according to the timing of titration

suggests that, up to a certain threshold, MAD effects were minimal, but beyond this point, their efficacy markedly increased.

Discussion

Regarding therapy efficacy, our results from sleep tests including AHI, oxygen desaturation index, lowest oxygen saturation, and time below 90% saturation—corroborated findings from previous studies [5, 6, 17]. Our study showed

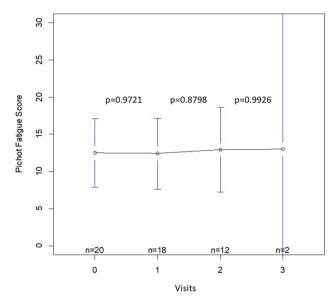


Fig. 3 Pichot Fatigue Score according to the timing of titration

that the introduction of MAD significantly influenced all polygraphic parameters (as depicted in Table 1 and 2). While MAD efficacy on AHI did rise with additional advancements, the increase was statistically insignificant (see Fig. 1). Furthermore, MAD's influence on the Epworth Scale Score, and the Pichot Fatigue Score was negligible (Table 1). Interestingly, there was no correlation between the paraclinical effects of MAD, which were significant, and the clinical effect, which was reduced and non-significant. For context, in the study of 369 patients by Vecchierini et al. [5], the Epworth Scale Score decreased from 11.2 ± 4.8 initially to 7.8 \pm 4.3 with MAD treatment ($p < 10^{-4}$). Similarly, the Pichot score decreased substantially from 14.1 ± 7.8 to 9.0 ± 7.2 ($p < 10^{-4}$). In our cohort of 20 patients, though the trends mirrored those of Vecchierini et al. [5], the results were non-significant during MAD therapy, (p=0.1073) possibly pointing to the limited power of our study. No proportionality-either absolute or relative-was observed between mandibular advancement and improvement in clinical symtoms. Profiles of drowsiness and fatigue evolution with breaks (patients #5, 1, and 16) were probably due to the dilation reflex of the mandibular advancement device as previously observed in studies [9, 11].

Overall adherence to MAD therapy was good. Patients demonstrated high tolerance towards MADs. Only a single participant found it intolerable, aligning with existing literature [5, 18]. Our observed adherence rates appeared to be better than those documented in CPAP follow-up studies [19, 20] or in studies comparing CPAP and MAD [21–23].

Although success metrics for MAD in OSA are still being debated, they predominantly revolve around AHI metrics. A partial response can be defined as a > 50%-AHI reduction

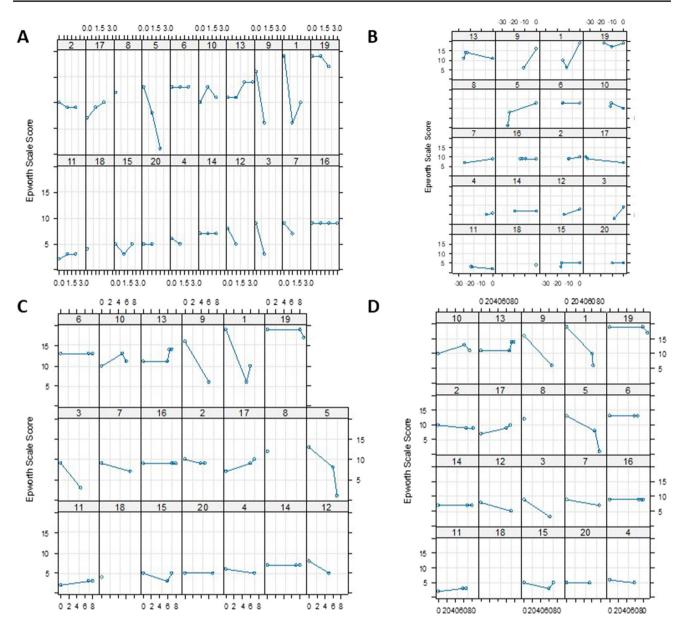


Fig.4 Individual results of apnea hypopnea index (AHI) according to: **A** the onset of titration, **B** the absolute protrusion (mm), and **C** the relative protrusion (%; i.e., absolute protrusion (mm)/maximal protrusion (mm)). Each patient is represented by an individual number

after MAD [24]. A complete response can be defined as a residual AHI \leq 5/h [25–28]. Success can be defined as a > 50% AHI reduction and/or a residual AHI < 10/h [4, 18, 25, 28–34]. Current research suggests the onset of MAD use brings about the most considerable effect on AHI, rendering subsequent titrations less important. This fact may call into question the utility of the current titration methods. On the contrary, if the primary objective of a mandibular advancement device treatment centers around clinical symptoms such as drowsiness and fatigue, our data imply that the significance of titration should be directed aimprt symptoms, even if our results were not statistically significant. One of the main limitation of our study was its limited patient sample size. However, monthly polygraphic recording present considerable challenges, making large-scale studies, like the ORCADES study [5], difficult to perform. The average age in our cohort (60.8 ± 12.8 years) was noticeably higher than in Vecchierini et al. [5] (52.6 ± 11.3). This may be explained by the added constraints on participants (1 or 2 additional sleep recordings), which favored retirees and explained the withdrawal of consent of one patient. For active patients, a 5-min teleconsultation can be remotely performed [35] to assess Epworth Sleepiness Score and Pichot Fatigue Score.

19

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16

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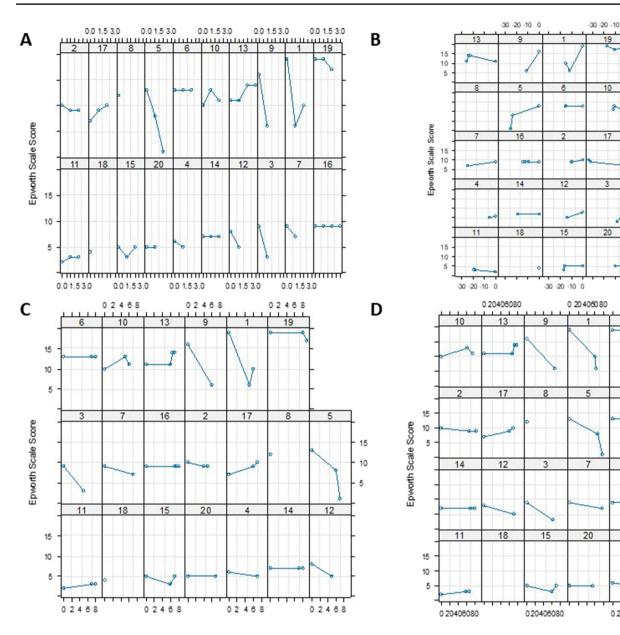


Fig. 5 Individual results of Epworth Sleepiness Score according to: A the timing of titration, B the AHI improvement (final AHI-initial AHI), C the absolute advancement (mm), and D the relative advance-

ment (%; i.e., absolute advancement (mm)/maximal advancement (mm)). Each patient is represented by an individual number

There is no consensus on the definition of success/failure of MAD. For Aarab et al. [34], a failure is defined by a residual AHI > 10/hr and less than 50% AHI improvement. For other authors [25, 26, 28, 30], a complete response is defined by a residual AHI < 5/hr; a partial response by symptomatic improvement and an AHI reduction > 50% but residual AHI > 5/hr; and a failure by the persistence of symptoms and/or reduction in AHI < 50%. For Dieltjens [14], Hoffstein [18], Doff [29], and Vanderveken [20], a response is defined by an AHI reduction > 50% and a success by the reduction > 50% and a residual AHI < 5 or 10/hr. The European Respiratory Society Task Force [24] defined success as a residual AHI < 10/hr and a partial response as a reduced AHI > 50% with a residual AHI > 10 or 20 with or without symptoms. Is it relevant to base the MAD success on AHI or on clinical parameters?

Conclusion

In this study, MAD therapy led to a significant improvement in AHI and other polygraphic parameters from the onset of use. While the symptom reduction (specifically, drowsiness and fatigue) was apparent, its interpretation was more

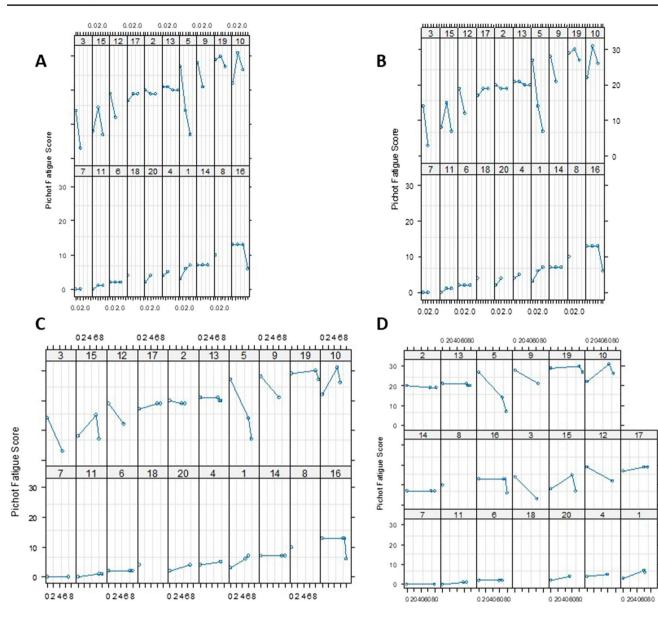


Fig. 6 Individual results of Pichot Fatigue Score according to: **A** the moment of titration, **B** the AHI gain (final AHI-initial AHI), **C** the absolute protrusion (mm), and **D** the relative protrusion (%; i.e., abso-

lute advancement (mm)/maximal advancement (mm)). Each patient is represented by an individual number

complex because of the small, non-significant decrease in PROMs, likely due to the study's limited sample size and a potential threshold of MAD's clinical efficacy. Nonetheless, the findings of the study suggest that the primary focus of titration should be clinical symptoms, given that the significant AHI improvements occurred at the onset of MAD use. The absence of concordance between AHI reduction and clinical symptoms was objectively quantified in this study, and symptoms such as sleepiness and fatigue may be improved with further mandibular advancement.

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Author contribution Study procedures and analyses were undertaken by GB principal investigator. The first draft of the manuscript was prepared by GB. The manuscript was reviewed and edited by all the authors. All authors made the decision to submit the manuscript for publication.

Data availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethical approval Our study adhered to ethical standards set by the institutional/national research committee and the 1964 Helsinki declaration (with later amendments). The research received approval from the French national review board (CPP IIe de France X #2021-A01466-35) on August 31, 2021, and is registered at clinicaltrials.gov (NCT05056766).

Informed consent Informed consent was signed by every patient.

Competing interests GB has received an unrestricted research funding from ResMed for this study.

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