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Drug-induced sleep endoscopy improves intervention efficacy among patients treated for obstructive sleep apnea with a mandibular advancement device

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Abstract

Purpose To compare the short-term treatment effect of a mandibular advancement device (MAD) with and without previous drug-induced sleep endoscopy (DISE) on polysomnography (PSG) and other sleep apnea–related treatment outcomes (Short Form Health Survey [SF-36] and Epworth Sleepiness Scale [ESS]) among adults with mild, moderate, and severe obstructive sleep apnea (OSA). We hypothesized that using DISE would improve the efficacy of MADs on the sleep apnea parameters.

Methods The study sample consisted of patients with OSA who were unable or unwilling to tolerate a CPAP device, divided into an experimental (with DISE) and a control (without DISE) group.

Results Of 50 patients with OSA, 40 men (80%), mean age was 48.8 ± 12,3 years. The mean apnea–hypopnea index (AHI) score of both groups decreased significantly between baseline and the 8-week follow-up titration PSG with MAD in situ, from 31.7 ± 17.3 (mean ± SD) apnea–hypopnea episodes/h to 7.0 ± 6.4/h ($p < 0.0001$) in the experimental group, and from 22.5 ± 16.6 episodes/h to 11.4 ± 8.0/h ($p < 0.024$) in the control group. Capillary oxygen saturation (SpO_2) levels did not change significantly between the two timepoints for either group. The SF-36 ($p < 0.023$) and ESS ($p < 0.036$) results of both groups improved significantly between baseline and the 8-week follow-up after starting MAD treatment; however, the improvement in quality of life was significantly more pronounced in the experimental group than in the control group ($p < 0.0001$).

Conclusion DISE provides a significant benefit to patients with OSA undergoing MAD treatment. It can be used as a valuable prediction tool in clinical practice for the management of patients with OSA, even those with moderate and severe disease.

Keywords Drug-induced sleep endoscopy · Mandibular advancement device · Obstructive sleep apnea · Dental sleep medicine

Background

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive episodes of upper-airway obstructions and disruptive snoring during sleep [1]. OSA affects 9% of women and 24% of men between the ages of 30 and 60 [2]. OSA has been associated with increased morbidity and mortality, mostly in the context of cardiovascular and cerebrovascular disease [3, 4]. Considering that a significant percentage of OSA cases remain undiagnosed and consequently untreated (82% of cases in men and 93% of those in women), the burden of OSA may be even greater [5].

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Polysomnography (PSG) conducted in a sleep laboratory is the gold-standard diagnostic test for diagnosing OSA, but it is time-consuming and expensive [6, 7]. Home respiratory polygraphy (HRP) with a technically adequate device is currently used as an alternative when laboratory PSG is not possible because of safety protocols, or patient immobility or critical illness [8].

Continuous positive airway pressure (CPAP) therapy delivered via a nasal or full-face mask is considered as the gold-standard treatment for patients with mild, moderate, and severe OSA [9]. Despite numerous technical improvements, long-term compliance with CPAP therapy remains suboptimal [10].

The American Academy of Dental Sleep Medicine recommends the use of MADs in patients with mild-to-moderate OSA and in patients with severe OSA who cannot tolerate CPAP therapy or would prefer an alternate therapy [11, 12]. MADs are thought to prevent obstruction of the upper airway during sleep by mechanically protruding the mandible and enhancing the patency of the patient's airway. This effect is probably achieved through activation of the stretch receptors in the upper-airway support muscles [13, 14]. MADs vary substantially in their design, e.g., in the number of pieces (one versus two), degree of customization to the patient's dentition, material, and occlusal coverage. These differences, as well as the mechanism that—in the case of two-piece appliances—attaches the two plates together, may affect important properties of the device, e.g., the permitted amount of vertical opening, degree of lateral jaw movement, and degree of advancement. Use of MADs is not free from side effects, most of which tend to be local, minor, and transient. Repetitive anterior positioning of the mandible may potentially hamper the harmony of the stomatognathic system, subsequently causing changes to the patient's temporomandibular joint (TMJ) and orofacial function. In turn, these changes may lead to the development of signs and symptoms of temporomandibular disorders (TMD) [15, 16] and promote lateral open bite [17].

Currently, the use of MADs as a suitable management option for patients with sleep-related breathing disorders is mainly based on the patient's AHI score [18]. However, the patient's individual response to a MAD may be clinically important: In some studies, MADs are reported to be effective (defined as reducing the AHI to fewer than 10 episodes per hour) in approximately 50% of patients, which means that a significant proportion of patients are left with suboptimal treatment [19, 20]. The ability to reliably predict which patients will benefit is therefore of paramount importance [21].

Several attempts have been made to develop prognostic indicators of MAD treatment success. Drug-induced sleep endoscopy (DISE) is considered as a valuable technique for identifying the location of upper-airway obstruction in patients with OSA [22] and may therefore be of prognostic value for successful MAD therapy [23, 24]. Huntley et al. found that patients whose airway space increased during the thrusting maneuver of the mandible during DISE were more likely to benefit from MAD treatment than a control group of patients who underwent MAD treatment without previous DISE. Unfortunately, because of the retrospective design of the study, the MAD provided by the oral surgery department in question was a custom-fit appliance adjusted to produce a symptomatic effect only, without any further description such as the amount of jaw thrust or measurements regarding the improvement in the upper-airway dimensions. Furthermore, only 50% of the experimental sample underwent a post-treatment sleep study [25].

The current study therefore aimed to compare the short-term effect of MAD treatment with and without previous DISE on PSG and other sleep apnea–related treatment outcomes among adult patients suffering from mild, moderate, and severe OSA. We hypothesized that DISE would improve the efficacy of treatment with a MAD on the studied parameters.

Material and methods

This clinical study was performed at the Orofacial Pain Clinic (Dental School) of the National and Kapodistrian University of Athens, Greece, and the Sleep Disorders Center of the University Department of Critical Care and Pulmonary Services at Evaggelismos General Hospital, Athens. The Ethics and Research Committee of the University's Dental School examined and approved the study protocol (approval number: 291/2016). This study was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all study participants before the study began.

Participants

The initial study population consisted of consecutive patients with OSA who had been referred to the Orofacial Pain Clinic of Athens University for treatment with a MAD between June 2012 and June 2017. All patients had been diagnosed as suffering from mild, moderate, or severe OSA by a doctor specialized in sleep medicine from the Sleep Disorders Center of the University Department of Critical Care and Pulmonary Services of Evaggelismos Hospital. All patients were unable or unwilling to tolerate a CPAP device. The inclusion criteria for the study participation were as follows: (1) reported sleep apnea episodes and an AHI score of more than five episodes/h in a recent PSG assessment, (2) reported loud snoring and subjective daytime symptoms

(daytime sleepiness, fatigue, impaired concentration), (3) enough teeth to support a MAD, and (4) formal written informed consent. Patients with sleep-related breathing disorders other than OSA and/or with a mandibular protrusive capacity of less than 5 mm were excluded from the study, as were patients with insufficient teeth or dental implants to support a MAD. A flowchart of the study design is represented in Fig. 1.

Interventions and study protocol

Before the study, DISE was offered as an option to all patients who met the inclusion criteria, as a useful method of assessing the location of upper-airway obstruction and thus possibly predicting the efficacy of a MAD for management of OSA. Patients were free to accept or decline the DISE examination. All DISE procedures were performed by the same specialized otorhinolaryngologist in an operating theater. Participants were prepared for the intraoperative recording, and an anesthesiologist administered intravenous sedation (propofol). Propofol was administered by the anesthesiologist as a hypnotic agent. The initial infusion rate of propofol was 50 to 75 µg/kg/min and the rate was adjusted to obtain a target level of anesthesia of arousal to loud verbal stimulation [26]. The observation window during DISE was determined as a period consisting of two or more respiratory cycles each of the including a stable sequence of snoring, obstructive apnea or hypopnea episode, oxygen desaturation, and restart of breathing [27]. Each patient was observed for 30 min. Observation was repeated at different levels of the upper airway according to the velum, oropharynx, tongue base, and epiglottis (VOTE) classification for DISE, which uses the following scoring system: 0 = no obstruction (no vibration); 1 = partial obstruction (vibration); and 2 = complete obstruction (collapse) [28]. A flexible nasopharyngoscope was inserted into the nasal and pharyngeal cavities to produce an image and record the pattern of the upper-airway obstruction. During this procedure, with the patient in the supine position, a head-tilt/chin lift (HT/CL) maneuver (tilting the head backward and lifting the chin vertically upwards) was used to gently advance the mandible anteriorly. The HT/CL maneuver was chosen in order to evaluate and record the effect of mandibular advancement on pharyngeal upper airway dimensions [29]. Patients were considered

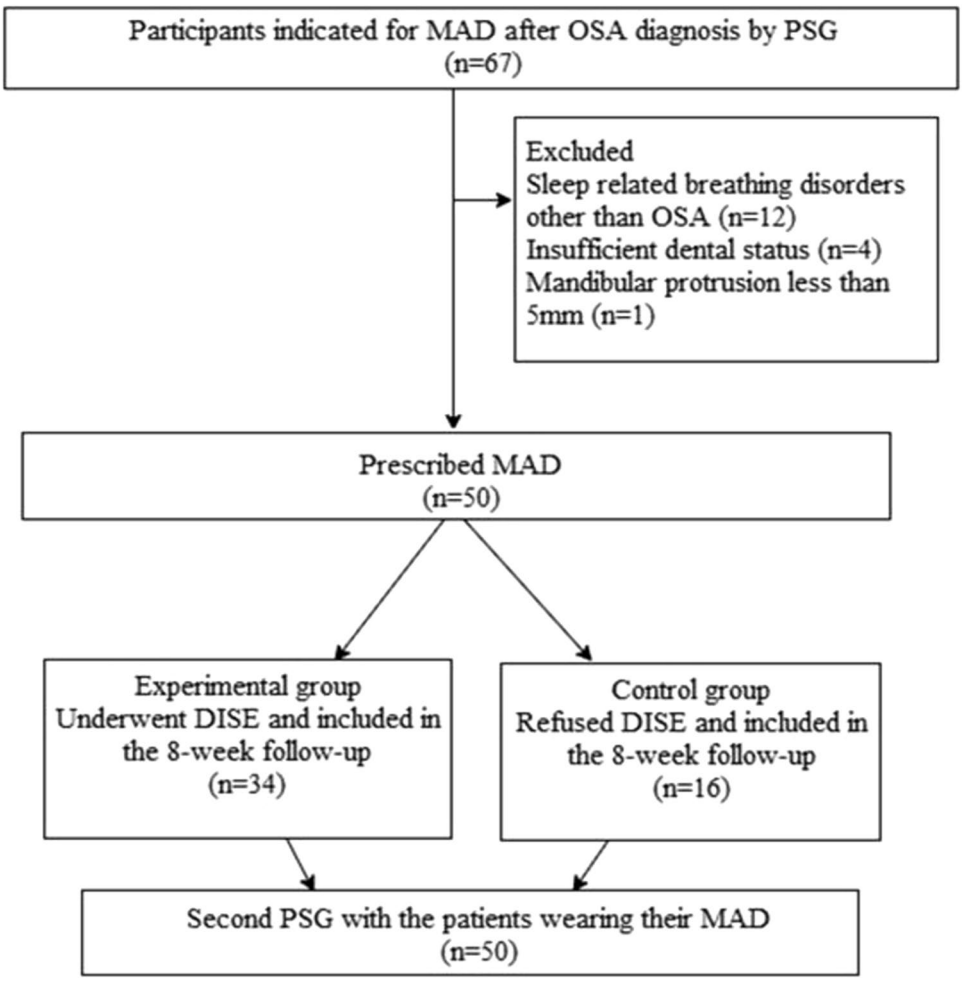

Fig. 1 Flowchart of the study design. DISE, drug-induced sleep endoscopy; MAD, mandibular advancement device; OSA, obstructive sleep apnea; PSG, polysomnography

eligible to enroll in the experimental group only if HT/CL maneuver resulted in the absence of obstructive episodes for at least 3 min, concurrently with endoscopic evidence of—at least—50% improvement in airway patency at one or more sites of obstruction, and/or a reduction in snoring. Only then, the mandibular advancement (the inter-incisal distance plus the overjet) was measured with a ruler and later used as the reference mandibular protrusion needed for the construction of MAD. Thus, DISE was used as a prognostic measure that would help maintain a tailored value for the protrusion of the patient's mandible. The total duration of the DISE procedure was approximately 40 min.

All OSA patients who participated in this study received a MAD because they were unable or unwilling to tolerate a CPAP device. They were divided into two therapy groups: an experimental group who underwent DISE, and a control group of patients who rejected DISE mainly due to financial or personal reasons.

A custom-made, two-piece adjustable MAD was individually fabricated for each patient. To increase patient comfort, the body of the MAD was constructed from 2-mm-thick full-coverage plates (maxillary and mandibular) made from soft thermoplastic film, and hard acrylic pads were added to the molar and premolar regions to provide additional support to the dentition (Fig. 2). The two plates were connected bilaterally by means of telescopic Herbst attachments (Scheu Dental GmbH; Iserlohn, Germany). These attachments consist of a piston that slides within a tube, thereby making it possible to vary the degree of mandibular protrusion. A George Gauge bite fork (Great Lakes Dental Technologies; Tonawanda, NY, USA) was used to measure and register each patient's maximum mandibular protrusion capacity, and to determine the appropriate antero-posterior and vertical mandibular positions needed for the construction of the oral appliance. For the experimental group, the patient's mandibular advancement was the one measured during the DISE and was kept stable during the study. For the control group, the range of initial mandibular advancement was set at 50–60% of the patient's maximum mandibular protrusion capacity. For both groups, the mandibular opening was kept to the minimum necessary in order to accommodate the dimensions of the acrylic plates resulting to an opening of 2–4 mm between the incisal edges of the upper and lower central incisors. The MADs of the control group were further titrated at the subsequent 1- and 3-week visits, based on the respective patient's subjective reporting of snoring and symptoms. All patients received detailed written information about the use of the oral appliances and their clinical implications, as well as the possible side effects.

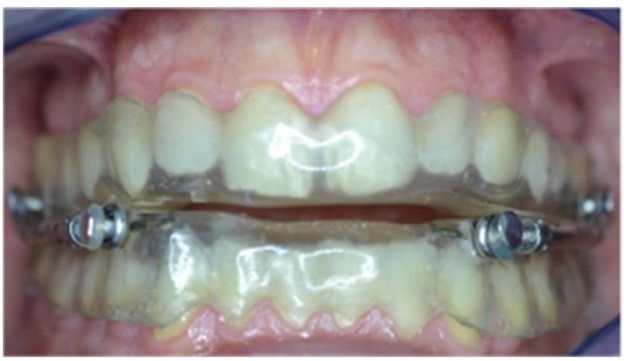

Fig. 2 Mandibular advancement device with Herbst telescopic attachments (Scheu Dental GmbH). The telescopic attachments, which connect the two pieces of the device, bilaterally, consist of a piston that slides within a tube, thereby making it possible to vary the degree of mandibular protrusion

Evaluation visits were scheduled for 1, 3, and 8 weeks after the beginning of treatment with the MAD. Patients were instructed to use the MAD every night during sleep hours. After an 8-week period of use, a second PSG with the patients wearing their oral devices was performed in a hospital-based sleep laboratory, in order to evaluate and determine the treatment efficacy.

Outcome measures and measurement instruments

All patients underwent an assessment at base line prior to treatment, and 8 weeks after MAD insertion. Assessment included (a) medical and sleep history, (b) a one-night in-laboratory diagnostic PSG, (c) assessment of daytime sleepiness with the Epworth Sleepiness Scale (ESS), and (d) assessment of quality of life with the Short Form Health Survey (SF-36) questionnaire. The therapeutic effect of the MAD in the titrated position was objectively assessed by comparing the two PSG assessments (at baseline and 8 weeks after MAD use), in terms of the patient's AHI score and capillary oxygen saturation (SpO_2) level. According to the American Academy of Sleep Medicine, OSA is categorized as mild when the apnea–hypopnea index (AHI, i.e., the average number of apnea and hypopnea episodes per hour of sleep) is ≥ 5 and < 15. Moderate OSA corresponds to an AHI of ≥ 15 and ≤ 30, and severe OSA to an AHI of > 30/h. An AHI score of fewer than five episodes/h has been considered normal for adults. The minimum duration to qualify as an episode is 10 s [30]. Treatment success was defined as a reduction in AHI score to fewer than five episodes/h with the use of the MAD. Patients whose AHI score had decreased by 50% or more from baseline according to the follow-up PSG results with the MAD in place were classified as responders. Non-responders were those with a decrease of less than 50% in their AHI score compared with baseline.

Subjective sleepiness was evaluated by use of the ESS, which is designed to measure a patient's general level of daytime sleepiness. The ESS consists of eight items representing

different hypothetical situations in daily life as a measure of the patient's probability of falling asleep. Dozing probability ratings are none (0), slight (1), moderate (2), and high (3). The patient's scores for each response are combined to give a total score ranging from 0 to 24 [31]. Excessive daytime sleepiness was defined as a total score of 10 or higher [32].

The Greek version of the 36-item Short Form Health Survey was used to evaluate health-related quality of life. The questionnaire measures limitations in eight domains of health: physical functioning (PF), physical role (PR), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role (ER), and mental health (MH) [33]. Because the SF-36 questionnaire uses different constructs to measure health-related quality of life, the use of an overall score is generally not recommended [34]. Based on the results of previous studies, three components were defined for the Greek version of the questionnaire: physical, mental, and well-being. The physical component (PC) is represented by the domains physical functioning, physical role, and bodily pain; the mental component (MC) by social functioning, emotional role, and mental health; and well-being (WB) by general health and vitality. Correct calculation of the SF-36 questionnaire requires the use of special algorithms, which are controlled by a private company. Scores represent the percentage of the total possible score achieved. Each item is scored from zero to 100, with high values considered to indicate good health [35].

Statistical analysis

Statistical analysis was carried out using a statistical package (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). The AHI and SpO_2 level were the main outcome variables of the study, whereas the ESS and SF-36 scores and maximum mandibular movement capacity were the secondary variables. Intervention (experimental vs. control group), sex, body mass index (BMI), and age (≤ 50 years old vs. > 50 years old) were the predictors under investigation. The analyses (i.e., comparisons of the baseline and 8-week follow-up measurements) were conducted at two levels: within each group, and between the two groups. While the raw data were approximately normally distributed, log transformation was applied to decrease their variability and to make them conform more closely to a normal distribution (Shapiro–Wilk's test $p > 0.05$ for all combinations of predictors and continuous outcomes); therefore, for continuous data, parametric tests were used [36]. More specifically, the paired samples *t*-test and McNemar's test were used to compare continuous and categorical data, respectively, between the baseline scores and follow-up scores of each group after 8 weeks of MAD use (within-groups design). In addition, the independent samples *t*-test and chi-square test were applied to identify differences between the experimental group and control group across continuous and categorical variables, respectively (between-groups design). Furthermore, regarding the AHI score after 8 weeks of MAD use, multiple regression analysis was applied, using the type of group (experimental vs. control group), sex, BMI, and age (≤ 50 years old vs. > 50 years old) as predictors. The level of statistical significance was $p < 0.05$ for all the tests.

Results

The study sample comprised 50 patients with OSA who were treated with a MAD because they were unable or unwilling to use CPAP device. The patients had a mean ($\pm$ SD) age of 48.8 ± 12.3 years (range: 21–80 years) and a mean ($\pm$ SD) BMI of 25.8 ± 3.0 K = kg/m^2 (range: 19–35 K = kg/m^2). The study sample was divided into an experimental group ($n = 34$, MAD after DISE) and a control group ($n = 16$, MAD without DISE). In the experimental group, the average ($\pm$ SD) protrusion of the mandible by the MAD, as determined based on the DISE results, was 4.7 ± 0.8 mm (corresponding to 46% of the patient's maximum mandibular protrusion capacity). In the control group, the MAD was initially adjusted to protrude the mandible by an average of 5.2 ± 0.9 mm (i.e., 53% of the patient's maximum mandibular protrusion capacity). The vertical interdental clearance between the incisal edges of the upper and lower central incisors was 2–4 mm for both groups. Patient characteristics are shown in Table 1.

DISE findings

Multilevel obstruction of the upper airway was observed in most of the patients who had the DISE examination, with 21 out of 34 patients (62%) presenting with complete antero-posterior obstruction at the base of the tongue and epiglottis and partial obstruction of the velum. Twelve patients (35%) had complete antero-posterior obstruction at the base of the tongue and partial obstruction of the velopharynx. Only one patient (3%) had complete antero-posterior obstruction at the base of the tongue and epiglottis. The improvement in the patients' AHI score after MAD treatment was not significantly related to DISE findings (McNemar test $p > 0.05$). Patients with complete antero-posterior obstruction at the base of the tongue and partial obstruction of the velopharynx had greater improvement in AHI score after MAD treatment compared with the patients with compete antero-posterior obstruction at the base of the tongue and epiglottis and partial obstruction of the velum as shown in Table 2. The site of obstruction in the experimental group was not a significant predictor for the improvement of the AHI score, according to the results of multiple linear regression analysis ($p > 0.05$) as shown in Table 3. All patients undergoing DISE showed

Table 1 Characteristics and sleep apnea parameters (mean ± SD) of patients (experimental group and control group) at baseline and 8 weeks after starting treatment with a mandibular advancement device (MAD)

Characteristics and sleep apnea parameters	Baseline		8 weeks after the start of MAD use	
	Experimental group ($n = 34$)	Control group ($n = 16$)	Experimental group ($n = 34$)	Control group ($n = 16$)
Age in years	46.4 ± 11.7	53.9 ± 12.2	=	=
Number of men/women	29/5	11/5	29/5	11/5
Apnea–hypopnea index (AHI), episodes/h	31.7 ± 17.3[*]	22.5 ± 16.6[⌐]	7.0 ± 6.4[*,‡]	11.4 ± 8.0[⌐,‡]
Body mass index (BMI), kg/m^2	25.8 ± 2.6	25.7 ± 3.8	=	=
Peripheral capillary oxygen saturation % (SpO_2)	94.6 ± 1.9	94.6 ± 1.2	94.1 ± 1.9	94.3 ± 1.6
Maximum mandibular protrusion, mm	10.3 ± 2.3	9.8 ± 2.5	10.3 ± 2.4	10.0 ± 2.5
Maximum mouth opening, mm	52.4 ± 5.1	51.6 ± 3.3	52.6 ± 5.0	52.3 ± 3.0
Maximum mandibular lateral movement, right, mm	9.7 ± 2.3	9.8 ± 2.3	9.7 ± 2.1	9.5 ± 2.0
Maximum mandibular lateral movement, left, mm	10.2 ± 2.0	9.7 ± 1.2	10.4 ± 1.7	10.1 ± 1.8

[*]Within group analysis; paired samples $t = 8.109$, $p < 0.0001$, $d = 2.27$

[⌐]Within group analysis; paired samples $t = 2.514$, $p < 0.05$, $d = 1.3$

[‡]Between group analysis; independent samples $t = 2.069$, $p < 0.05$, $d = 2.86$

d Cohen's effect size

increase of the pharyngeal upper airway dimensions and resolution of upper airway obstruction following the maneuver of the mandible.

Effect of MAD use on AHI and SpO_2

As shown in Table 1, MAD treatment significantly reduced the number of respiratory obstructive events in both the experimental and the control groups. More specifically, in the experimental group, the mean (± SD) AHI score decreased significantly from 31.7 ± 17.3 episodes/h at baseline to 7.0 ± 6.4 episodes/h, according to the follow-up titration PSG after 8 weeks with the MAD in situ ($t = 8.109$, $p < 0.0001$). In addition, the mean (± SD) AHI score in the control group decreased significantly from 22.5 ± 16.6 episodes/h at baseline to 11.4 ± 8.0 episodes/h at the 8-week follow-up PSG with the MAD in place ($t = 2.514$, $p < 0.05$). However, when calculating the effect size (Cohen's *d*), the decrease in AHI score of the experimental group was significantly larger than that of the control group ($d = 2.27$ and $d = 1.3$, respectively) (Table 1). Post hoc power analysis was conducted using the mean of effect sizes (Cohen's *d*); the achieved statistical power was sufficient (0.90) due to the large effect sizes (G*Power version 3.1). Overall, the experimental group of patients showed significantly greater improvement in AHI score as 62% of the patients with severe OSA presented normal AHI value after MAD treatment compared to the patients in the control group (33%) (between groups comparison, chi-square $p < 0.04$). Treatment success rates (defined as % of patients with AHI < 5 episodes/h) and MAD response rates in the experimental and control groups are shown in Table 4.

As demonstrated by the independent samples *t*-test conducted between the groups, no significant difference was found between the mean AHI scores of the two groups at baseline. However, at the follow-up 8 weeks after the start of treatment with the MAD, the two groups differed significantly (experimental group: mean AHI 7.0 ± 6.4 vs. control group: 11.4 ± 8.0, $p < 0.05$; Fig. 3).

In addition, the significant effect of the intervention (DISE) on the AHI score was confirmed by the results of the multiple linear regression analysis (Table 5). The type of group (i.e., experimental vs. control) was the only significant predictor of AHI score, and patients in the experimental group were more likely to have lower AHI scores than their control group counterparts ($B = 5.262$, $p < 0.05$).

Moreover, in the experimental group, no statistically significant ($p > 0.05$) difference in SpO_2 level was observed between the mean value at baseline (94.6 ± 1.9%) and the mean value 8 weeks after the start of the treatment with the MAD (94.1 ± 1.9%). In the control group, the mean SpO_2 also did not change significantly between baseline (94.6 ± 1.2%) and 8 weeks after the start of the treatment with the MAD (94.3 ± 1.6%), as shown in Table 1.

Effect of MAD use on maximum mouth-opening ability and maximum lateral and protrusive mandibular movements

Between baseline and 8 weeks after the start of treatment with the MAD, no significant changes were observed for either study group regarding mean values for maximum active mouth-opening, mandibular protrusion, and mandibular lateral movements as shown in Table 1.

Table 2 Treatment efficacy of MAD related to the site of upper airway obstruction recorded during DISE in the experimental group of patients

Sites of upper airway obstruction	Experimental group ($n=34$)							
	At baseline				8 weeks after the start of MAD use			
	Normal AHI < 5/h	Mild AHI ≥ 5 and < 15/h	Moderate AHI ≥ 15 and ≤ 30/h	Severe AHI > 30/h	Normal AHI < 5/h	Mild AHI ≥ 5 and < 15/h	Moderate AHI ≥ 15 and ≤ 30/h	Severe AHI > 30/h
Complete antero-posterior obstruction at the base of the tongue and epiglottis and partial obstruction of the velum $n=21$ (61.7%)	=	=	$n=8$ (38%)	$n=13$ (62%)	$n=9$ (43%)	$n=8$ (38%)	$n=4$ (19%)	=
Complete antero-posterior obstruction at the base of the tongue and partial obstruction of the velopharynx $n=12$ (35.2%)	=	$n=7$ (58%)	$n=5$ (42%)	=	$n=8$ (67%)	$n=3$ (25%)	$n=1$ (8%)	=
Complete antero-posterior obstruction at the base of the tongue and epiglottis $n=1$ (2.9%)	=	=	$n=1$ (100%)	=	$n=1$ (100%)	=	=	=

AHI, apnea–hypopnea index; *MAD*, mandibular advancement device; *DISE*, drug-induced sleep endoscopy

Table 3 Multiple linear regression analysis in the experimental group between site of obstruction, body mass index (BMI), peripheral capillary oxygen saturation (SpO_2), age, and apnea–hypopnea index (AHI) score (dependent variable) 8 weeks after the start of the intervention

Outcome	Predictor	*B*	*95% CI for B*	*Beta*	*t*	*p*
AHI score	Site of obstruction	−1.122	−5.324, 3.079	−.115	−.551	.586
	BMI	−.126	−.928, .677	−.071	−.323	.749
	SpO_2	−2.942	−136.9, 131	−.011	−.045	.964
	Age	0.64	−.167, .296	.137	.573	.572

Effect of MAD use on daytime sleepiness and quality of life outcomes

The results of the ESS and SF-36 are presented in Table 6. Daytime sleepiness (ESS) scores did not differ significantly between the two groups at baseline, but they were significantly ($p<0.05$) improved after 8 weeks of treatment, with the experimental group of patients experiencing significantly less daytime sleepiness than the control group.

Regarding quality of life, all within-group changes in the SF-36 domains (physical component, PC; mental health component, MC; well-being, WB) between baseline and the

Table 4 OSA severity and treatment efficacy of MAD for the experimental and control group of patients

Experimental group ($n=34$)			Control group ($n=16$)		
OSA	At baseline	8 weeks after the start of MAD use	At baseline		8 weeks after the start of MAD use
Normal AHI < 5/h	=	$n=17$ (50%)	=		$n=5$ (31%)
Mild AHI ≥ 5 and < 15/h	$n=7$ (21%)	Normal $n=7$ (21%)	$n=6$ (38%)		Normal $n=2$ (33%) Moderate $n=4$ (67%)
Moderate AHI ≥ 15 and ≤ 30/h	$n=14$ (41%)	Normal $n=2$ (14%) Mild $n=9$ (64.2%) Moderate $n=3$ (21.4%)	$n=7$ (44%)		Normal $n=2$ (29%) Mild $n=5$ (71%)
Severe AHI > 30/h	$n=13$ (38%)	Normal $n=8$ (62%) Mild $n=3$(23.0%) Moderate $n=2$(15.3%)	$n=3$ (19%)		Normal $n=1$ (33%) Mild $n=1$ (33%) Moderate $n=1$ (33%)
Responders	=	88% ($n=30$)		=	69% ($n=11$)
Non-responders	=	12% ($n=4$)		=	31% ($n=5$)

AHI, apnea–hypopnea index; *MAD*, mandibular advancement device; *OSA*, obstructive sleep apnea

Between groups comparison, chi-square $p<0.04$

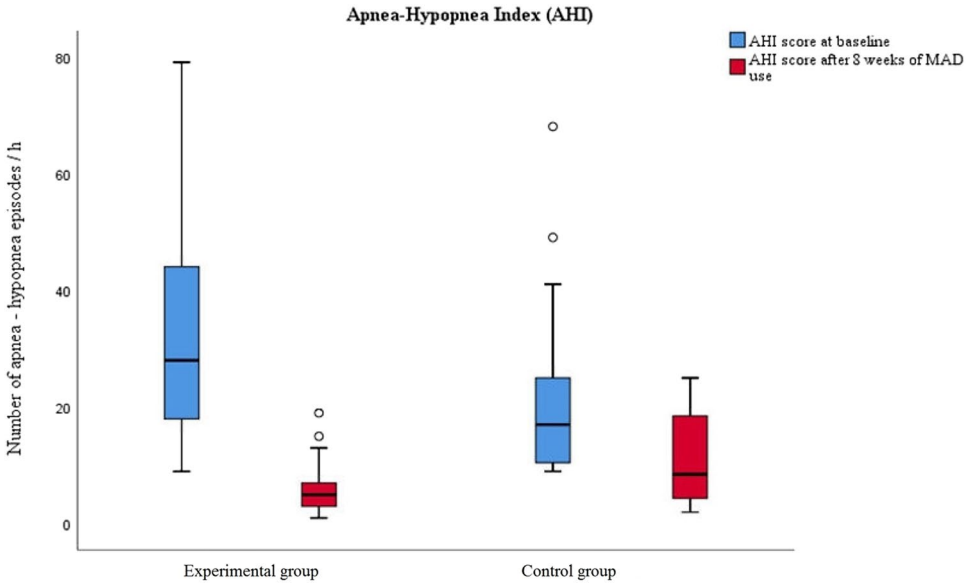

Fig. 3 Boxplots for apnea–hypopnea index (AHI) score according to the polysomnography results at baseline and 8 weeks after the start of treatment with the mandibular advancement device (MAD), for the experimental group and control group of patients. The AHI score at baseline did not differ significantly between the two groups. Eight weeks after the start of MAD use, the mean AHI score had improved significantly in both groups: from 31.7 ± 17.3 episodes/h to 7.0 ± 6.4 episodes/h (paired samples *t*-test, $p<0.0001$) in the experimental group, and from 22.5 ± 16.6 episodes/h to 11.4 ± 8.0 episodes/h (paired samples $t=2.514$, $p<0.05$) in the control group. At this timepoint, the mean AHI score differed significantly between the groups (experimental group: 7.0 ± 6.4 vs. control group: 11.4 ± 8.0, $p<0.05$)

8-week follow-up were statistically significant ($p<0.001$). The two groups did not differ significantly at baseline, but after 8 weeks the experimental (DISE) group showed significantly higher values ($p<0.05$) than the control group in two of the domains (PC and MC).

Discussion

The primary aim of this study was to evaluate the influence of DISE on the short-term efficacy of a MAD in the management of patients with OSA who were unable or unwilling to

Table 5 Multiple linear regression analysis between type of intervention group, body mass index (BMI), peripheral capillary oxygen saturation (SpO_2), age, and apnea–hypopnea index (AHI) score (dependent variable) 8 weeks after the start of the intervention

Outcome	Predictor	*B*	*95% CIfor B*	*Beta*	*t*	*p*
AHI score	Control group	5.262	.511, 10,013	376	2.240	031
	BMI	− .401	− .256, 1058	.187	1.234	.225
	SpO_2	− 32.302	− 157,886, 93,282	− .084	− .520	.606
	Age	1.698	-3.045, 6.442	.127	.724	.743

Table 6 Epworth Sleepiness Scale (ESS) and Short Form Health Survey (SF-36) outcomes of patients (experimental group and control group) at baseline and 8 weeks after the start of the treatment

		Baseline *n* (%)		8 weeks after start of treatment *n* (%)	
Variable	Range	Experimental group ($n=34$)	Control group ($n=16$)	Experimental group ($n=34$)	Control group ($n=16$)
Epworth Sleepiness Scale (ESS)	< 11	11 (32%)	4 (25%)	31 (91%)	10 (63%)
	11–14	9 (27%)	8 (50%)	3 (9%)	5 (31%)
	15–18	11 (32%)	3 (19%)	=	1 (6%)
	> 18	3 (9%)	1 (6%)	=	=
Between groups comparison		Not specified		$\chi^2=7.625$, (Fisher's exact) $p<0.05$	
Short Form (SF-36) Health Survey		Baseline (mean ± SD)		8 weeks after start of treatment (mean ± SD)	
SF-36 total score (%)	0–100	66.5 ± 11.6	60.8 ± 13.8	78.3 ± 10.5	70.0 ± 11.6
Physical component	0–100	74.8 ± 14.7 ǂ	68.7 ± 14.8 ⌐	84.8 ± 11.5 ǂ*	77.3 ± 11.8 ⌐*
Mental component	0–100	65.9 ± 11.4 ǂ	59.3 ± 14.1 ⌐	78.8 ± 10.7 ǂ*	67.7 ± 11.1 ⌐*
Well-being component	0–100	55.1 ± 13.7 ǂ	51.4 ± 16.7 ⌐	67.7 ± 13.1 ǂ	62.5 ± 15.2 ⌐

ǂ,⌐Significant difference of means ($p<0.001$) in the within groups comparison (*t*-test for paired samples)

*Significant difference of means ($p<0.05$) in the between groups comparison (*t*-test for independent samples)

be treated with CPAP. Our main finding is that the use of DISE before MAD resulted in a short-term benefit regarding improvement to PSG parameters (AHI), subjective sleepiness, and general health-related quality of life. Furthermore, this advantage was achieved with less mandibular protrusion than in the control group. After just 8 weeks, use of a MAD resulted in a significant positive effect on the objective (PSG) and subjective (ESS, SF-36) parameters of all patients in our study, with no adverse effects.

Identification of the sites of upper-airway obstruction may be an important means of determining which patients are suitable for treatment with a MAD, especially those with severe or moderate OSA. According to clinical studies, prediction of treatment efficacy is of utmost importance, especially in patients with moderate to severe OSA [37, 38]. To improve patient outcomes, it may be necessary to establish criteria for patient selection. DISE could be a valuable tool to distinguish responders to MAD treatment from non-responders before the initiation of therapy. It may also be used to evaluate the pattern of upper-airway collapse, so as to address further treatment options in cases of CPAP failure [39]. DISE may have clinical utility in predicting the outcome of treating OSA with a MAD, thereby improving the selection of patients for this treatment modality and their adherence to the treatment. According to Johal et al., patient's response to the mandibular maneuver used during DISE to mimic the effect of a MAD may be a valuable prognostic indicator of a successful MAD therapy [40]. In other studies, authors suggest that the chin-lift maneuver into maximum protrusion may be clinically less relevant for therapeutic decision-making because each oral appliance causes a certain amount of vertical mouth-opening, and the maneuver is not reproducible in terms of the degree of mandibular advancement [41]. The findings of the present clinical study suggest that an increase of upper-airway dimensions during mandibular advancement during DISE may have predictive value regarding the likelihood of successful treatment with a MAD. At the 8-week follow-up PSG with MAD in place, the experimental group of patients who underwent a DISE examination had lower AHI scores than the control group of patients who did not undergo DISE. We therefore believe that DISE can be used as a valuable prediction tool in clinical practice. Furthermore, by using DISE, the full short-term efficacy of MAD treatment was achieved

with less initial mandibular protrusion than in the control group. This is an additional benefit in terms of patient comfort and initial treatment adherence.

The AHI score of both groups (experimental [with DISE] and control [without DISE]), as recorded at the diagnostic PSG at baseline and after 8 weeks with the MAD in place, significantly improved after the therapy with the MAD. The two groups of patients did not differ from each other at baseline regarding age, BMI, AHI, SpO_2, and other parameters, and all used the MAD for a similar number of hours during sleep. Accordingly, the results are consistent with those of other studies and show that the MAD is an effective treatment modality for patients with OSA, at least in the short term [11, 42]. In our study, the induced effect was objectively verified in a PSG with the oral device in situ, because it is important to protect the patient from potentially suboptimal treatment. Hoekema et al. reported that MAD treatment was effective for 76.5% of patients using an oral appliance, compared with 82.7% of those using CPAP, and that oral appliance therapy was not inferior to CPAP therapy. The treatment results of the present study were similarly impressive, with a treatment response achieved in 88% and 69% of patients in the experimental and the control groups, respectively. However, our results do not confirm the second finding of Hoekema et al., namely that oral appliance therapy is less effective in individuals with severe OSA (AHI > 30/h) [43]. The absence of a significant change in the SpO_2 level might be attributable to the short observation time. In their study, Ezmek et al. only observed significant differences in the SpO_2 level of patients with OSA at the end of the twelfth or twenty-fourth week of treatment with a MAD [44].

Regarding subjective sleepiness, in our clinical study, the experimental group of patients showed a greater improvement in ESS score than the control group. Health-related quality of life improved significantly in both groups after 8 weeks, and the experimental group achieved significantly better scores than the control group at recall for the physical and mental components of the SF-36. These results corroborate those of Gagnadoux et al. who observed that MAD treatment resulted in significantly better emotional and subjective sleep quality outcomes [45].

Numerous randomized controlled trials have studied the efficacy of both CPAP and MAD therapy in the treatment of OSA [46, 47]. However, in most of these studies, only patients who used a CPAP device were titrated objectively (i.e., based on their PSG results). When both treatment modalities were titrated objectively, no clinically relevant difference was found between MAD and CPAP in the treatment of mild and moderate OSA [48, 49]. CPAP treatment incorporates a well-established objective measurement of CPAP use. By contrast, objective measurement of compliance during MAD therapy for patients with OSA remains limited. Vanderveken et al. used an embedded microsensor thermometer to assess the safety and feasibility of the objective measurement of compliance during MAD therapy for sleep-disordered breathing. The results of the study suggest that although CPAP is more therapeutically effective at reducing the AHI score than a MAD, inferior CPAP compliance may result in similar overall effectiveness [50]. The smaller initial amount of mandibular protrusion achieved with DISE in our study may help to improve patient compliance with MAD treatment.

All patients in this study were referred by the Sleep Disorders Center of the University Department of Critical Care and Pulmonary Services of the Medical School of Athens University and were unable or unwilling to tolerate and use a CPAP device. Having considered the condition of the patients, the use of a placebo device was not acceptable for ethical reasons. Furthermore, blinding was also not possible. There are many models of MADs, and various types of adjustment mechanisms. Custom-made, adjustable devices make it easier to change the mandibular positioning in order to achieve the desired effects and are considered the standard MADs for treating OSA. In the present study, a two-piece, adjustable oral appliance (i.e., a MAD) with Herbst telescopic tube connectors was individually constructed for each patient and was adjusted to protrude the patient's mandible into the most effective position based on the DISE results. This titration of the mandibular protrusion resulted in a substantial decrease in AHI value.

It is reported that patients need a period of acclimatization when using a MAD because of the occurrence of various side effects, e.g., jaw discomfort, tooth tenderness, and excessive salivation [51]. In this study, no adverse effects were reported or observed for the MADs. The short duration of the present study, the strict inclusion criteria, the limited sample size of the control group of patients, the repeated checking and adjustment of the device by a TMD specialist, and the design of the MAD used (which permitted limited opening, protrusion, and side-to-side movements of a patient's jaws) should be taken into account when interpreting our results.

Conclusions

This clinical study suggests that DISE may have a significant treatment benefit for patients with OSA using custom-made MADs with Herbst tube connectors, in terms of AHI score, and SpO_2 level, ESS score, and the physical and mental components of the SF-36. The results indicate that DISE enables significantly greater treatment efficacy with less mandibular protrusion in patients with mild, moderate, and even severe OSA who may be effectively treated with oral appliances when a CPAP device cannot be used. DISE may improve the acceptance of and adherence to oral appliances for the treatment of OSA. Furthermore, DISE may be a valuable tool for the prediction of treatment outcome of MADs. Larger samples and

long-term prospective cohort studies are required to assess the long-term efficacy and possible adverse effects of MADs.

Author contribution Evgenia Gogou was involved in the study design and was responsible for the clinical work and data collection and interpretation; Vasilios Psarras was involved in the study design and manuscript preparation; Ioannis Koutsourelakis was involved in the drug-induced sleep endoscopy procedure and interpretation; Demetrios Halazonetis contributed to data acquisition and interpretation; Nikolaos Nikitas Giannakopoulos was involved in data analysis, interpretation of the results, and manuscript preparation; Michail Tzakis was involved in the supervision of the project, the study design, the fabrication details of the mandibular advancement device, data analysis, and manuscript preparation. All authors critically revised the manuscript and gave final approval.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethical approval This study was conducted in accordance with the tenets of the 1964 Declaration of Helsinki and its later amendments, and all procedures involving human participants were approved by the Ethics Committee of the Dental School of Athens University (approval number: 291). Written informed consent was obtained from all study participants.

Conflict of interest The authors declare no competing interests.

References

1. Punjabi NM (2008) The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 5(2):136–143
2. Garvey JF, Pengo MF, Drakatos P, Kent BD (2015) Epidemiological aspects of obstructive sleep apnea. J Thorac Dis 7(5):920–929
3. Tietjens JR, Claman D, Kezirian EJ, De Marco T, Mirzayan A, Sadroonri B, Goldberg AN, Long C, Gerstenfeld EP, Yeghiazarians Y (2019) Obstructive sleep apnea in cardiovascular disease: a review of the literature and proposed multidisciplinary clinical management strategy. J Am Heart Assoc 8(1):e010440
4. Xie W, Zheng F, Song X (2014) Obstructive sleep apnea and serious adverse outcomes in patients with cardiovascular or cerebrovascular disease: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore) 93(29):e336
5. Ho ML, Brass SD (2011) Obstructive sleep apnea. Neurol Int 3(3):e15
6. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, Harrod CG (2017) Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 13(3):479–504
7. Rundo JV, Downey R 3rd (2019) Polysomnography. Handb Clin Neurol 160:381–392
8. Masa JF, Corral J, Pereira R, Duran-Cantolla J, Cabello M, Hernández-Blasco L, Monasterio C, Alonso A, Chiner E, Rubio M, Garcia-Ledesma E, Cacelo L, Carpizo R, Sacristan L, Salord N, Carrera M, Sancho-Chust JN, Embid C, Vázquez-Polo FJ, Negrín MA, Montserrat JM (2011) Effectiveness of home respiratory polygraphy for the diagnosis of sleep apnoea and hypopnoea syndrome. Thorax 66(7):567–573
9. Cao MT, Sternbach JM, Guilleminault C (2017) Continuous positive airway pressure therapy in obstuctive sleep apnea: benefits and alternatives. Expert Rev Respir Med 11(4):259–272
10. Rotenberg BW, Murariu D, Pang KP (2016) Trends in CPAP adherence over twenty years of data collection: a flattened curve. J Otolaryngol Head Neck Surg 45(1):43
11. Park P, Jeon HW, Han DH, Won TB, Kim DY, Rhee CS, Kim HJ (2016) Therapeutic outcomes of mandibular advancement devices as an initial treatment modality for obstructive sleep apnea. Medicine (Baltimore) 95(46):e5265
12. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD (2015) Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. J Clin Sleep Med 11(7):773–827
13. Basyuni S, Barabas M, Quinnell T (2018) An update on mandibular advancement devices for the treatment of obstructive sleep apnoea hypopnoea syndrome. J Thorac Dis 10(1):S48–S56
14. Chan AS, Sutherland K, Schwab RJ, Zeng B, Petocz P, Lee RW, Darendeliler MA, Cistulli PA (2010) The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax 65(8):726–732
15. Doff MH, Veldhuis SK, Hoekema A, Slater JJ, Wijkstra PJ, de Bont LG, Stegenga B (2012) Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on temporomandibular side effects. Clin Oral Investig 16(3):689–697
16. Pliska BT, Nam H, Chen H, Lowe AA, Almeida FR (2014) Obstructive sleep apnea and mandibular advancement splints: occlusal effects and progression of changes associated with a decade of treatment. J Clin Sleep Med 10(12):1285–1291
17. Fransson AM, Tegelberg A, Johansson A, Wenneberg B (2004) Influence on the masticatory system in treatment of obstructive sleep apnea and snoring with a mandibular protruding device: a 2-year follow-up. Am J Orthod Dentofacial Orthop 126(6):687–693
18. Lim J, Lasserson TJ, Fleetham J, Wright J (2004) Oral appliances for obstructive sleep apnoea. Cochrane Database Syst Rev 4:CD004435
19. Dieltjens M, Vanderveken OM, Hamans E, Verbraecken JA, Wouters K, Willemen M, De Backer WA, Van de Heyning PH, Braem MJ (2013) Treatment of obstructive sleep apnea using a custom-made titratable duobloc oral appliance: a prospective clinical study. Sleep Breath 17(2):565–572
20. Burlon G, Tepedino M, Laurenziello M, Troiano G, Cassano M, Romano L, Rinaldi R, Ciavarella D (2020) Evaluation of factors that influence the success rate of OSA treatment with a customised adjustable MAD device - a retrospective study. Acta Otorhinolaryngol Ital 40(4):297–303
21. Vanderveken O, Vroegop A, de Heyning van, Braem M (2011) Drug-induced sleep endoscopy completed with a simulation bite approach for the prediction of the outcome of treatment of obstructive sleep apnea with mandibular repositioning appliances. Oper Tech Otolayngol Head Neck Surg 22(2):175–182
22. Gillespie MB, Reddy RP, White DR, Discolo CM, Overdyk FJ, Nguyen SA (2013) A trial of drug-induced sleep endoscopy in the surgical management of sleep-disordered breathing. Laryngoscope 123(1):277–282
23. De Corso E, Bastanza G, Della Marca G, Grippaudo C, Rizzotto G, Marchese MR, Fiorita A, Sergi B, Meucci D, Di Nardo W, Paludetti G, Scarano E (2015) Drug-induced sleep endoscopy as a selection tool for mandibular advancement therapy by oral device in patients with mild to moderate obstructive sleep apnoea. Acta Otorhinolaryngol Ital 35(6):426–432
24. Johal A, Hector MP, Battagel JM, Kotecha BT (2007) Impact of sleep nasendoscopy on the outcome of mandibular advancement

splint therapy in subjects with sleep-related breathing disorders. J Laryngol Otol 121(7):668–675
25. Huntley C, Cooper J, Stiles M, Grewal R, Boon M (2018) Predicting success of oral appliance therapy in treating obstructive sleep apnea using drug-induced sleep endoscopy. J Clin Sleep Med 14(8):1333–1337
26. Koutsourelakis I, Safiruddin F, Ravesloot M, Zakynthinos S, de Vries N (2012) Surgery for obstructive sleep apnea: sleep endoscopy determinants of outcome. Laryngoscope 122(11):2587–2591
27. Gobbi R, Baiardi S, Mondini S, Cerritelli L, Piccin O, Scaramuzzino G, Milano F, Melotti MR, Mordini F, Pirodda A, Cirignotta F, Sorrenti G (2017) Technique and preliminary analysis of drug-induced sleep endoscopy with online polygraphic cardiorespiratory monitoring in patients with obstructive sleep apnea syndrome. JAMA Otolaryngol Head Neck Surg 143(5):459–465
28. Kezirian EJ, Hohenhorst W, de Vries N (2011) Drug-induced sleep endoscopy: the VOTE classification. Eur Arch Otorhinolaryngol 268(8):1233–1236
29. Jo S, Lee JB, Jin Y, Jeong T, Yoon J, Park B (2019) Change in peak expiratory flow rate after the head-tilt/chin-lift maneuver among young, healthy, and conscious volunteers. Clin Exp Emerg Med 6(1):36–42
30. Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD (2009) Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine 2009. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 5(3):263–76
31. Tsara V, Serasli E, Amfilochiou A, Constantinidis T, Christaki P (2004) Greek version of the Epworth Sleepiness Scale. Sleep Breath 8(2):91–95
32. Thorarinsdottir EH, Bjornsdottir E, Benediktsdottir B, Janson C, Gislason T, Aspelund T, Arnardottir ES (2019) Definition of excessive daytime sleepiness in the general population: feeling sleepy relates better to sleep-related symptoms and quality of life than the Epworth Sleepiness Scale score. Results from an epidemiological study. J Sleep Res 28(6):e12852
33. Anagnostopoulos F, Niakas D, Pappa E (2005) Construct validation of the Greek SF-36 Health Survey. Qual Life Res 14(8):1959–1965
34. Silva GE, Goodwin JL, Vana KD, Quan SF (2016) Obstructive sleep apnea and quality of life: comparison of the SAQLI, FOSQ, and SF-36 questionnaires. Southwest J Pulm Crit Care 13(3):137–149
35. Lins L, Carvalho FM (2016) SF-36 total score as a single measure of health-related quality of life: scoping review. SAGE Open Med 4:2050312116671725
36. Mishra P, Pandey CM, Singh U, Gupta A, Sahu C, Keshri A (2019) Descriptive statistics and normality tests for statistical data. Ann Card Anaesth 22(1):67–72
37. Okuno K, Sasao Y, Nohara K, Sakai T, Pliska BT, Lowe AA, Ryan CF, Almeida FR (2016) Endoscopy evaluation to predict oral appliance outcomes in obstructive sleep apnoea. Eur Respir J 47(5):1410–1419
38. Koutsourelakis I, Kontovazainitis G, Lamprou K, Gogou E, Samartzi E, Tzakis M (2021) The role of sleep endoscopy in oral appliance therapy for obstructive sleep apnea. Auris Nasus Larynx 48(2):255–260
39. Dieleman E, Veugen CCAFM, Hardeman JA, Copper MP (2021) Drug-induced sleep endoscopy while administering CPAP therapy in patients with CPAP failure. Sleep Breath 25(1):391–398
40. Johal A, Battagel JM, Kotecha BT (2005) Sleep nasendoscopy: a diagnostic tool for predicting treatment success with mandibular advancement splints in obstructive sleep apnoea. Eur J Orthod 27(6):607–614
41. Vroegop AV, Vanderveken OM, Dieltjens M, Wouters K, Saldien V, Braem MJ, Van de Heyning PH (2013) Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome. J Sleep Res 22(3):348–355
42. Aarab G, Lobbezoo F, Wicks DJ, Hamburger HL, Naeije M (2005) Short-term effects of a mandibular advancement device on obstructive sleep apnoea: an open-label pilot trial. J Oral Rehabil 32(8):564–570
43. Hoekema A, Stegenga B, Wijkstra PJ, van der Hoeven JH, Meinesz AF, de Bont LG (2008) Obstructive sleep apnea therapy. J Dent Res 87(9):882–887
44. Ezmek B, Piskin B, Sipahi C (2021) Therapeutic efficiency analyses of mandibular advancement devices using polysomnography, smartphone sleep applications, and simple pulse oximetry. Gulhane Med J 63:52–58
45. Gagnadoux F, Fleury B, Vielle B, Petelle B, Meslier N, N'Guyen XL, Racineux JL (2009) Titrated mandibular advancement versus positive airway pressure for sleep apnoea. Eur Respir J 34(4):914–920
46. Sharples LD, Clutterbuck-James AL, Glover MJ, Bennett MS, Chadwick R, Pittman MA, Quinnell TG (2016) Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. Sleep Med Rev 27:108–124
47. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, Marks GB, Cistulli PA (2013) Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 187(8):879–887
48. Francis CE, Quinnell T (2021) Mandibular advancement devices for OSA: an alternative to CPAP? Pulm Ther 7(1):25–36
49. Aarab G, Lobbezoo F, Heymans MW, Hamburger HL, Naeije M (2011) Long-term follow-up of a randomized controlled trial of oral appliance therapy in obstructive sleep apnea. Respiration 82(2):162–168
50. Vanderveken OM, Dieltjens M, Wouters K, De Backer WA, Van de Heyning PH, Braem MJ (2013) Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. Thorax 68(1):91–96
51. Sutherland K, Vanderveken OM, Tsuda H, Marklund M, Gagnadoux F, Kushida CA, Cistulli PA (2014) Oral appliance treatment for obstructive sleep apnea: an update. J Clin Sleep Med 10(2):215–227