Developments in diagnosis and treatment of obstructive sleep apnea

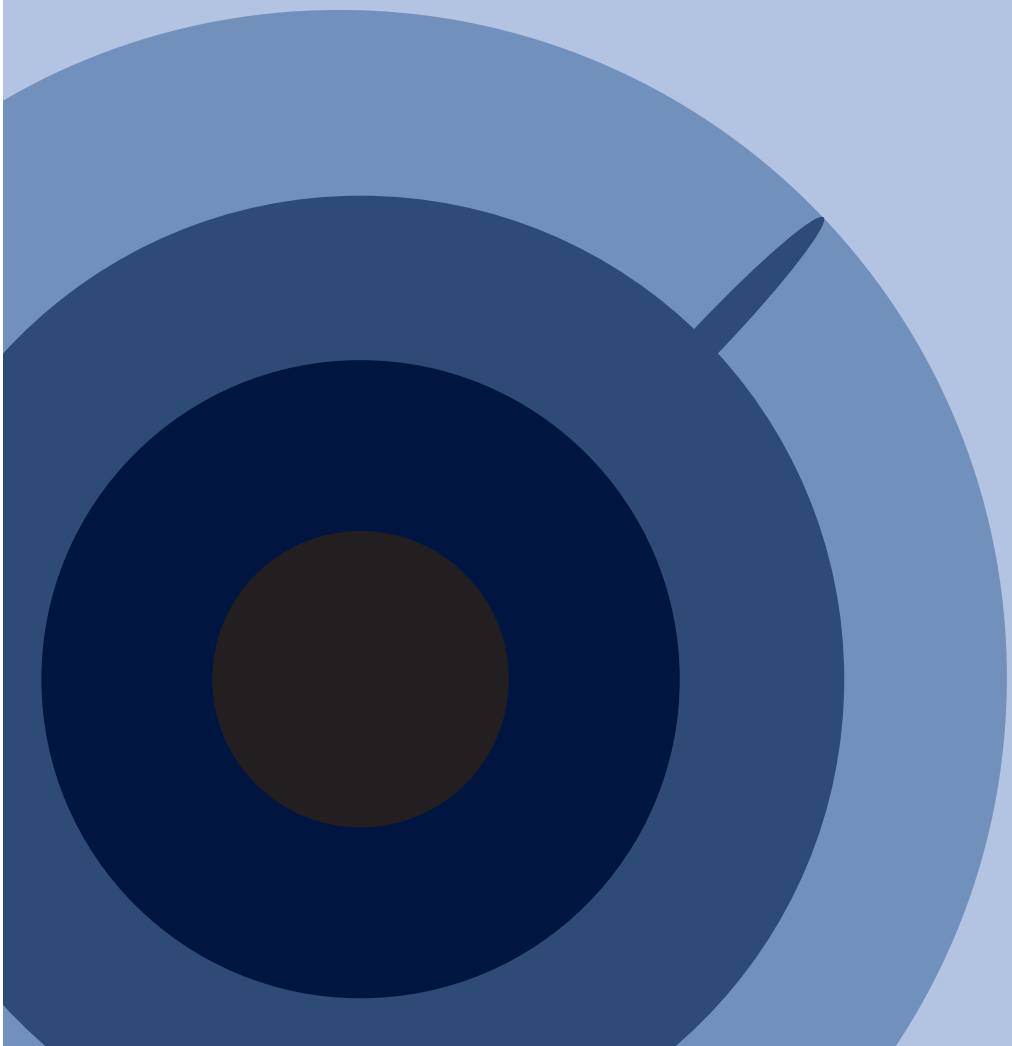
Bosschieter, P.F.N.

Publication date
2022

7 Equal effect of a non-custom versus a custom mandibular advancement device in treatment of obstructive sleep apnea

Bosschieter PFN, Uniken Venema JAM, Vonk PE, Plooij J, Ravesloot MJL, Lobbezoo F, Hoekema A, de Vries N.

Accepted by J Clin Sleep Med.



ABSTRACT

Purpose Numerous types of mandibular advancement devices (MADs) are available to treat patients with obstructive sleep apnea (OSA), varying from non-custom to custom devices. Only a limited number of studies have been performed to determine whether a non-custom MAD could be used to predict treatment success of a custom MAD. In this study, we investigated the potential of a new generation non-custom MAD, by comparing its effectiveness with a custom MAD. We hypothesize that the effectiveness of the devices is similar with regard to both objective (polysomnography; PSG) and self-reported (questionnaires, adherence, and patient satisfaction) outcomes.

Methods Single-center prospective randomized cross-over study including a consecutive series of patients with OSA. Patients were randomized to start either with the non-custom or custom MAD. Both MADs were applied for 12 weeks, followed by a PSG with MAD *in situ* and questionnaires. After the first 12 weeks of follow-up, a wash out period of one week was applied. Equal effectiveness was defined as no significant differences in both objective and self-reported outcomes between both devices.

Results Fifty-eight patients were included; forty completed the full follow-up. The median apnea-hypopnea index significantly reduced from 16.3 [7.7; 24.8] events/hr to 10.7 [5.6; 16.6] events/hr with the custom MAD ($p=0.010$) and to 7.8 [2.9; 16.1] events/hr with the non-custom MAD ($p<0.001$). Self-reported outcomes significantly improved in both groups. No significant differences were found between both devices.

Conclusion The effectiveness of a non-custom and custom MAD is comparable, which suggest that a non-custom MAD can be used as a selection tool for MAD treatment eligibility to improve MAD treatment outcome.

Keywords: obstructive sleep apnea, sleep-disordered breathing, mandibular advancement device, treatment success, drug-induced sleep endoscopy

INTRODUCTION

A mandibular advancement device (MAD) is one of the treatment options for patients with obstructive sleep apnea (OSA),1, 2 especially in patients with mild to moderate OSA. Other OSA treatments include continuous positive airway pressure (CPAP), upper airway surgery, upper airway stimulation, maxillomandibular advancement surgery and positional therapy.3 MADs are designed to advance the mandible preventing upper airway collapse. Advancement of the tongue base, epiglottis and soft palate improves upper airway patency.4 Depending on OSA severity and the criteria used to define treatment success, the efficacy of MADs ranges from 40% to 92%.5

Numerous types of MADs are available, varying from non-custom (thermoplastic ‘’boil-and-bite’’ or new generation devices) to custom MADs, each consisting of a single part (monobloc) or two separate parts (bibloc).4, 6

Some studies have been performed to determine whether a non-custom (‘’boil-and-bite’’) MAD could be used to predict the treatment success of a subsequently produced custom MAD.7, 8 Vanderveken et al.8 compared the efficacy of a non-custom thermoplastic monobloc MAD (hereafter; non-custom MAD) with that of a custom MAD. They concluded that a custom MAD was more effective than a non-custom one and, in addition, that the effect of a non-custom MAD does not predict the effect of the subsequently produced custom MAD.8 In 69% of the patients, treatment failed (no treatment success or not compliant) with the non-custom MAD compared to 40% with the custom MAD.8 In addition, the poor adherence with the non-custom MAD mainly resulted from poor retention of the device, suggesting the need for a non-custom device with better retention.

The oral device industry has improved MAD designs significantly over the last few decades. Historically, most thermoplastic “boil-and-bite” devices are monoblocs, which are set to a predetermined, arbitrary position. A new generation of non-custom thermoplastic MADs are titratable, utilizing trays for both the upper and lower dentition, joined by a mechanism that moves the mandible forward in relationship to the maxilla. All oral appliances are classified as custom and non-custom based on whether an impression is used to construct the trays. This new generation of non-custom MADs is more comfortable and has better retentive features. They can be fitted chairside within 15 minutes, so therapy can be initiated immediately. In addition, non-custom MADs are potentially cheaper than a custom MAD. These features allow the patients to experience the benefits and possible disadvantages of

MAD therapy before a more expensive custom MAD is applied, providing an efficient and cost-effective way of screening MAD treatment eligibility.

So far, the effectiveness of this new generation of non-custom MADs has not been compared to custom MADs. Bearing this in mind, we tested the potential of a non-custom (new generation) MAD to its antecedent device that is of similar design mechanically but differs in terms of the material. We hypothesized that the devices are similar with regard to objective and self-reported outcomes in treating patients with OSA and therefore a non-custom MAD might be used as a screening tool for MAD treatment eligibility.

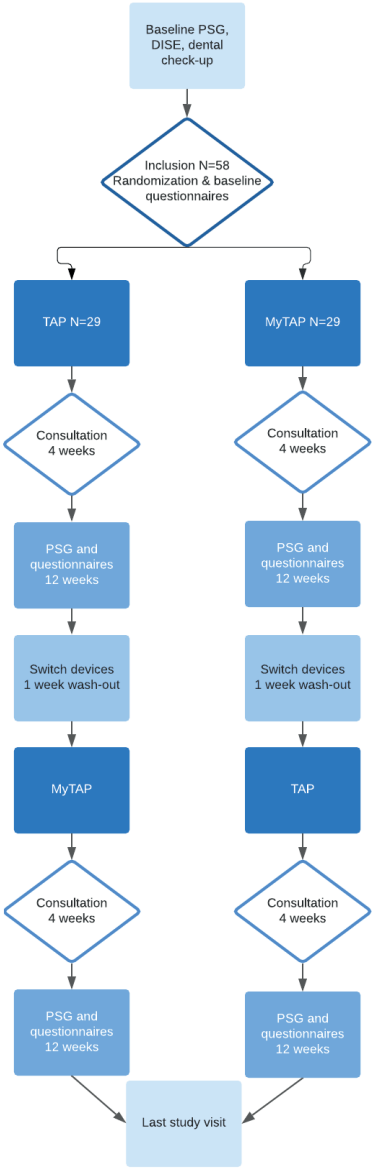
METHODS

Study participants

We performed a single-center prospective randomized cross-over study with a follow-up of 12 weeks in each allocation group in a consecutive series of patients with OSA. Patients were diagnosed through an overnight polysomnography (PSG). Patients were included if they were 18 years or older and had an AHI≥5 events/hr. Written informed consent was obtained for all patients prior to inclusion. Patients were excluded if they had reversible morphological upper airway abnormalities (e.g. enlarged tonsils), clear failure or non-acceptance of previous MAD therapy, Central Sleep Apnea syndrome (> 50% of central apneas confirmed by PSG), (extensive) periodontal disease or tooth decay (confirmed by orthopantomagram X-ray), active temporomandibular joint disease (including severe bruxism), restrictions in maximal mouth opening (<25 mm) or in protrusion of the mandible (<5 mm), or partial or complete edentulous (less than 8 teeth in upper or lower jaw). Patients were subsequently randomized to start with either the non-custom MAD or the custom MAD. We used a validated variable block randomization model, which was constructed in such a way that randomized inclusions are divided across groups (without stratification) in variable block sizes (4, 6, 8) to ensure true randomness during the allocation. Allocation was automatically reported in the online case report forms prior to informing the clinical staff. During all baseline measurements, MAD allocation was not determined yet. Thereafter, both the participants and the practitioners were informed about which MAD was applied. Scoring of the PSG's by the somnotechnicians was performed blinded. Both MADs were applied during a follow-up of 12 weeks with a consultation after four weeks. After 12 weeks of follow-up, treatment effect was measured by a PSG and self-reported outcomes were obtained. Therapy was discontinued during a wash-out period of one week. Subsequently, patients used the

non-custom or custom MAD for 12 weeks, depending on randomization, with the same clinical analyses and self-reported outcomes after 12 weeks (Figure 1).

Figure 1. Study procedures flow-diagram



PSG = polysomnography, DISE = drug-induced sleep endoscopy
TAP=custom MAD, myTAP=non-custom MAD

Outcome measures

Primary outcome measures were respiratory PSG outcomes, including total apnea-hypopnea index (AHI), apnea-index (AI), supine AHI, non-supine AHI, percentage of total sleeping time (TST) in supine position, oxygen desaturation index (ODI, 3%), mean saturation and lowest saturation.

Secondary outcome measures included self-reported outcomes using three different questionnaires: the Epworth Sleepiness Scale (ESS),9 the Functional Outcomes of Sleep Questionnaire (FOSQ),10 and the Research and Development-36 Survey (RAND-36).11 Data on adherence was based on self-reported therapy usage. Patient satisfaction and complaints were evaluated by collecting side-effects mentioned during follow-up visits. Secondary outcome measures were collected at baseline, and after 12 weeks of follow-up for both devices.

Both primary and secondary outcome measures were analyzed comparing baseline and results after 12 weeks of follow-up for both devices and comparing the results between the non-custom and custom MAD.

Definitions

We defined equal effectiveness of the custom and non-custom MAD as no significant differences between in the two devices regarding the primary outcome variables, which were the PSG outcomes.

Complete MAD treatment success was achieved when the post-treatment AHI was less than 5 events/hr. Partial success was defined as a reduction in the AHI of more than 50% and an AHI> 5 events/hr. Patients were considered non-responders when not meeting the criteria for complete or partial treatment success.

TAP™ (Figure 2)

As a custom MAD we used the TAP1 (Thornton Adjustable Positioner™ type-1, Airway Management Inc., Dallas, TX, USA), consisting of two separate trays covering the upper and lower dental arches. Custom MAD fabrication requires either a digital or physical impression, and a cast or milled technology. Thin, resilient trays are made from an impression, which has two main features: retention and protrusion. Retention prevents the tray from dislodging from the teeth, and protrusion by a mechanism

moves the mandible forward in increments of 1mm or less. The protrusive mechanism used in custom TAP appliances is single point mid-line traction. The TAP™ moves the mandible in a forward position by a screw mechanism incorporated in the frontal area of the appliance and has a protrusive range of over 20 mm. The TAP1 has an AccuTherm™ (Airway Management Inc., Dallas, TX, USA) thermoplastic lining to achieve maximum retention and comfort.

Figure 2. TAPTM Custom mandibular advancement device

Thornton Adjustable Positioner™ type-1, Airway Management Inc., Dallas, TX, USA

myTAP™ (Figure 3)

As a new generation non-custom MAD we used the myTAP™ (My Thornton Adjustable Positioner™, Airway Management Inc., Dallas, TX, USA), which utilizes all the features of a custom oral appliance. This novel thermoplastic MAD consists of two separate trays of hard plastic framework overmolded with ThermAcryl™ (Airway Management Inc., Dallas, TX, USA) material, which fully covers the upper and lower dental arches. This combination of materials provides accurate molding capabilities, using a thin, durable tray system that can be reheated and remolded as many times as necessary to achieve maximum retention and comfort. The thermoplastic material virtually takes an impression of the teeth, similar to a custom thermoplastic impression material. Upon cooling, the material retains its shape and is as resilient as a custom appliance. The protrusive mechanism used in myTAP™ is single point

mid-line traction. The myTAP™ moves the mandible forward by a single screw (covered in plastic) with a protrusive range of over 20 mm. Titration, both protrusive and vertical (up to 12mm with adjustment stops), can be easily adjusted by the clinician or patient. After fitting both trays chairside, the patients can immediately start wearing the device.

Figure 3. myTAPTM Non-custom mandibular advancement device

My Thornton Adjustable Positioner™, Airway Management Inc., Dallas, TX, USA

Titration of the devices

Before initiation of the trial, maximum voluntary mandibular protrusion was determined. The maximum voluntary mandibular protrusion was achieved by twisting the screw in the frontal area of the myTAP™until patients started to experience pain or discomfort in their teeth, jaw, or muscles. From that point, the device was set to retrude the mandible for one millimeter. When initiating, both the custom and non-custom MAD were positioned at 50% of the maximum protrusion, as determined by a George Gauge bite registration.12. Patients were instructed to advance the devices during the first 4 weeks of follow-up until the maximum voluntary protrusion was reached. This procedure was the same for both devices. In both study arms,

at the first follow-up visit (4 weeks), the amount of protrusion was determined. At the 3-months follow-up visit, it was verified whether the amount of protrusion had changed since the 4-weeks follow-up visit.

Polysomnography

A standard PSG (SomnoscreenTM, SOMNOmedics GmbH, Randersacker, Germany) was performed in all patients. To determine the stages of sleep, an electroencephalogram (F3, F4, C3, C4, M1, M2, O1, O2), electro-oculogram and electromyogram of the submental muscle were obtained. Nasal airflow was measured by a nasal cannula/ pressure transducer inserted in the opening of the nostrils. An oronasal thermal flow sensor was used to determine the difference between the temperature of exhaled and ambient air to estimate airflow and detect mouth breathing. Arterial blood oxyhemoglobin was recorded with the use of a finger pulse oximeter. Thoracoabdominal excursions were measured qualitatively by respiratory effort belts placed over the rib cage and abdomen. Body position was determined by a position sensor, which differentiates between the upright, left side, right side, prone and supine position. Limb movements were detected with an anterior tibial electromyogram with surface electrodes. Electrocardiography was performed to score cardiac events and snore sensor was applied for occurrence of snoring.

Statistical analysis

Statistical analysis was performed using SPSS (version 26, SPSS Inc, Chicago, IL, USA).

Quantitative data were reported as mean and standard deviation (SD) or as median and (Q1, Q3) when not normally distributed. To determine whether continuous variables were normally distributed, the Shapiro-Wilk Test was used. A p-value of < 0.05 was considered to indicate statistical significance. Primary outcomes, adherence, and ESS are reported with both per-protocol and intention-to-treat (ITT) analysis.. For the latter, missing follow-up data were replaced by baseline data. In the assessment of therapy effect, the follow-up AHI values were used as primary outcome measure.

To compare the outcomes of the baseline PSG and follow-up PSG (both custom and non-custom) a paired t-test was used in the case of normally distributed data, and

the Wilcoxon signed rank test in the case of not normally distributed data. The same analysis was used for the evaluation of differences in PSG outcomes comparing the two devices. To evaluate differences in self-reported outcomes between baseline and follow-up visit at 12 weeks (both devices), the Wilcoxon signed rank test was used. The Wilcoxon signed rank test was also used for the evaluation of the self-reported outcomes and treatment outcomes between the two devices. A paired samples t-test was used to analyze differences in titration of the devices. To investigate the role of potential predictors for treatment success, such as age, BMI, AHI, and adherence, a Mann-Whitney-U test was performed comparing responders and non-responders for each device.

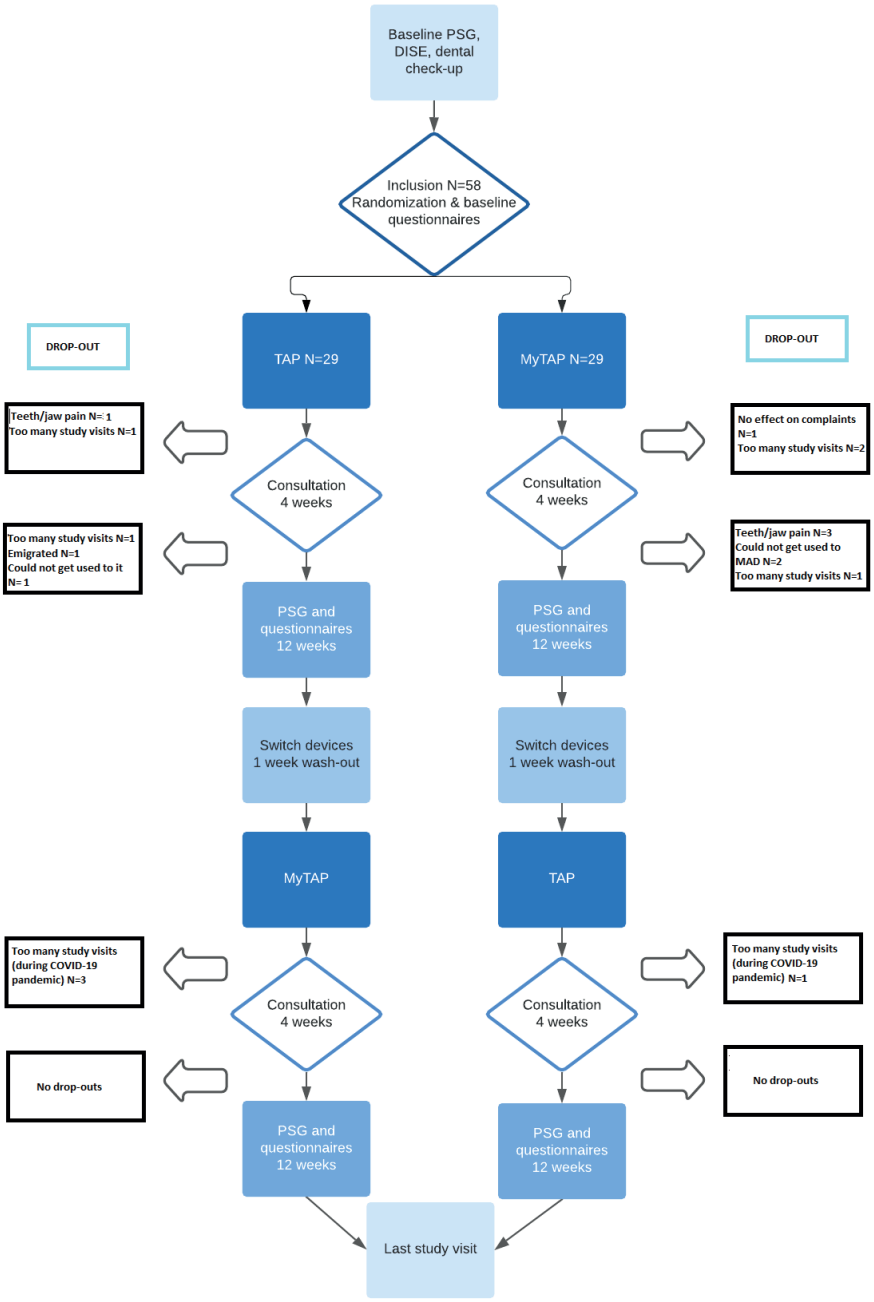
Sample size

Sample size calculation was performed with the statistical program G*Power-3.1. The sample size estimation was based on the primary outcome measure, the AHI. For the calculation, we used results of the study performed by Vanderveken et al.8 Based on an estimated AHI reduction of 9 events with a standard deviation of 9 events with the custom MAD and 5 events ± 8 events with the non-custom MAD an alpha of 0.05 and power of 0.85, 43 patients were required per treatment group. It was expected that 25% of patients would drop out.8 Therefore, the estimated number for this randomized controlled trial was 58 patients in a total.

RESULTS

In total, 58 patients were included, of whom 18 did not complete follow-up. Figure 4 shows the specific time points and reasons for dropping out. The majority of the patients (n=58) were male (n=45, 78%), median age was 51 [38; 56] years, and median BMI 26.2 [24.2; 29.2]kg/m2. The median AHI at baseline was 16.2 [7.4; 21.9] events/hr (Table 1). The maximum voluntary protrusion at baseline was 70.9% ± 33.7% of maximum protrusion. At 4-weeks follow-up, the percentage of maximal protrusion was for the custom MAD and non-custom MAD was 71.1 ± 27.9% and 97.4 ± 43.4% respectively. The amount of protrusion did not significantly differ between baseline and follow-up values or between the two MADs.

Figure 4. Dropouts



PSG = polysomnography, DISE = drug-induced sleependoscopy
TAP=custom MAD, myTAP=non-custom MAD

Table 1. Patient characteristics

	Total
Number of patients (N)	58
Sex (male: female)	45: 13
Age (years)	51 [38; 56]
BMI (kg/m^2)	26.2 [24.2; 29.2]
Pre-treatment AHI (events/hr)	16.2 [7.4; 21.9]
Set protrusion (% of maximum protrusion)	70.9 ± 33.7

Data presented as mean ± SD or median [Q1; Q3]
BMI body mass index, AHI apnea-hypopnea index

Primary outcome measures

Comparison of a custom MAD and a non-custom MAD regarding respiratory PSG outcomes

The median AHI at baseline of the 40 patients who completed follow-up was 16.3 [7.7; 24.8] events/hr (Table 2A). The AHI was significantly reduced to 10.7 [5.6; 16.6] events/hr with the custom MAD (p=0.010) and to 7.8 [2.9; 16.1] events/hr with the non-custom MAD (p<0.001). The small difference between both devices in follow-up AHI was not statistically significant (p=0.346). The median ODI 3% at baseline was 17.1 [8.4; 28.1]events/hr. The ODI was significantly reduced to 9.6 [4.6; 15.5] events/hr with the custom MAD (p=0.011) and to 6.9 [2.4; 13.3] events/hr with the non-custom MAD (p=0.003). In addition, the AI and the AHI in supine and non-supine position significantly decreased using both devices, without significant differences between both. The percentage of TST in supine position did not significantly change. The mean lowest measured saturation at baseline was 85.5% [82.0; 90.0], which increased to 88% with both devices; this improvement was not significant. ITT analysis of the data, showed significant improvement of the AHI, AI, supine AHI, ODI, and mean saturation for both devices, without significant differences between the two devices (Table 2B). Complete treatment success with the custom MAD was achieved in 20% (Table 2A). With the non-custom MAD, this outcome was 35%, demonstrating a significant difference (p<0.001). With the custom MAD, the AHI did not decrease sufficiently in 60% of the patients. With the non-custom MAD the AHI was significantly (p=0.003) less, viz., 47.5%. Additional analysis showed now impact of potential predictors (age, BMI, baseline AHI and adherence) on treatment outcome. No significant carry-over and period effects were found.

Table 2A. PSG outcomes, custom versus non-custom MAD (per-protocol analysis)

N=40	PSG baseline	TAP PSG 12 weeks	myTAP PSG 12 weeks	Baseline vs. TAP p-value	Baseline vs. myTAP p-value	TAP vs. myTAP p-value
Total AHI (events/hr)	16.3 [7.7; 24.8]	10.7 [5.6; 16.6]	7.8 [2.9; 16.1]	0.010*	<0.001*	0.346
Total AI (events/hr)	5.2 [2.2; 11.2]	1.9 [0.4; 4.4]	1.2 [0.5; 5.7]	0.010*	0.002*	0.821
Supine AHI (events/hr)	25.2 [11.0; 39.8]	14.3 [7.3; 27.7]	10.7 [3.9; 24.2]	0.004*	<0.001*	0.179
Non-supine AHI (events/hr)	6.6 [2.3; 15.8]	5.4 [1.2; 9.2]	4.4 [1.4; 10.8]	0.245	0.197	0.896
% of TST in supine position	38.9 [24.5; 51.2]	42.4 [21.6; 61.3]	43.6 [27.5; 53.7]	0.308	0.398	0.676
ODI (3%, events/hr)	17.1 [8.4; 28.1]	9.6 [4.6; 15.5]	6.9 [2.4; 13.3]	0.011*	0.003*	0.637
Mean saturation (%)	95.0 [94.0; 96.0]	95.0 [93.0; 96.0]	95.0 [93.3; 96.0]	0.105	0.030*	0.652
Lowest saturation (%)	85.5 [82.0; 90.0]	88.0 [82.0; 91.0]	88.0 [84.3; 90.8]	0.367	0.192	0.908
Treatment outcome						
Complete success	NA	8 (20%)	14 (35%)	NA	NA	0.001*
Partial success	NA	8 (20%)	7 (17.5%)	NA	NA	0.030*
Non-responder	NA	24 (60%)	19 (47,5%)	NA	NA	0.003*

Data presented as median [Q1, Q3], PSG=polysomnography, TAP=custom MAD, myTAP=non-custom MAD, AHI=apnea-hypopnea index, AI=apnea index, TST=total sleeping time, NA=not applicable
*p-value <0.05

Table 2B. PSG outcomes, custom versus non-custom MAD (intention to treat analysis)

N=58	PSG baseline	TAP PSG 12 weeks	myTAP PSG 12 weeks	Baseline vs. TAP p-value	Baseline vs. myTAP p-value	TAP vs. myTAP p-value
Total AHI (events/hr)	16.2 [7.4; 20.9[]	11.0 [5.7; 16.8]	10.6 [4.9; 16.9]	0.002*	0.001*	0.950
Total AI (events/hr)	4.7 [2.8; 11.5]	2.5 [0.6; 6.1]	2.5 [0.6; 7.9]	0.003*	0.002*	0.302
Supine AHI (events/hr)	25.2 [10.6; 40.4]	14.3 [7.8; 31.8]	13.3 [6.8; 34.4]	0.002*	<0.001*	0.476
Non-supine AHI (events/hr)	6.3 [2.4; 14.5]	5.3 [1.6; 9.5]	4.4 [1.8; 10.6]	0.123	0.162	0.638
% of TST in supine position	39.3 [24.1; 59.4]	42.3 [20.1; 65.7]	41.3 [27.1; 54.7]	0.372	0.401	0.614
ODI (3%, events/hr)	16.4 [10.3; 26.6]	10.9 [4.9; 16.0]	10.6 [3.8; 16.6]	<0.001*	<0.001*	0.669
Mean saturation (%)	95.0 [94.0; 96.0]	95.0 [94.0; 96.0]	95.0 [94.0; 96.0]	0.013*	0.002*	0.557
Lowest saturation (%)	87.0 [82.0; 90.0]	88.0 [82.0; 90.5]	88.0 [85.0; 90.0]	0.740	0.461	0.951

Data presented as mean ± SD median [Q1, Q3], PSG=polysomnography, TAP=custom MAD, myTAP=non-custom MAD, AHI=apnea-hypopnea index, AI=apnea index, TST=total sleeping time
*p-value <0.05

Secondary outcome measures

Adherence

The mean self-reported therapy usage was seven hours per night, seven nights per week, which equals 49 hours per week for both devices without significant differences between the two MADs (Table 3A).

Questionnaires

Daytime sleepiness using the ESS was significantly reduced with both devices (p=0.005), without significant differences between the two groups (p=0.890). Self-reported outcomes from questionnaires are displayed in table 3A. As part of the FOSQ questionnaires, activity and general productivity level significantly improved with both devices. However, the latter significantly differed between the two devices. General productivity increased significantly more with the non-custom MAD than with custom MAD (p=0.038). Vigilance increased with both devices. This increase was only significant with the non-custom MAD (p=0.044). Regarding the RAND-36 questionnaire, no significant differences between the two MADs were found.

Table 3A. self-reported outcomes (questionnaires), custom versus non-custom MAD (per-protocol analysis)

	Baseline N=36	TAP 12 weeks N=39	myTAP 12 weeks N=39	Baseline vs. TAP p-value	Baseline vs. myTAP p-value	TAP vs. myTAP p-value
Adherence (h/wk)	N.A.	49	49	N.A.	N.A.	0.519
ESS	5 [0-20]	5.0 [0-17]	5 [0-16]	0.005*	0.005*	0.890
FOSQ						
General productivity	2.6 [1.1-3.0]	2.9 [0.9-3.0]	2.9 [1.0-3.0]	0.035*	0.001*	0.038*
Social outcome	4.0 [1.0-4.0]	4.0 [0.0-4.0]	4.0 [.0.-4.0]	0.088	0.058	0.204
Activity level	3.4 [1.3-4.0]	3.8 [0.3-4.0]	3.7 [0.3-4.0]	0.016*	0.006*	0.977
Vigilance	3.5 [1.1-4]	3.7 [0.6-4.0]	3.7 [0.6-4.0]	0.101	0.044*	0.831
Intimate relationships and sexual activity	4.0 [0.0-4.0]	4.0 [0.0-4.0]	4.0 [0.3-4.0]	0.097	0.198	0.335
RAND-36						
Physical functioning	100 [45.0-100]	100 [40.0-100]	100 [40-100]	0.301	0.482	0.208
Social functioning	100 [12.5-100]	88.0 [0.0-100]	88.0 [37.5-100]	0.190	0.183	0.742
Role limitations due to physical health	100 [0.0-100]	100 [0.0-100]	100 [0.0-100]	0.080	0.061	0.566
Role limitations due to emotional problems	100 [0.0-100]	100 [0.0-100]	100 [0.0-100]	0.592	0.784	0.502
Emotional well-being	78.0 [28.0-100]	76.0 [44.0-96.0]	76.0 [28.0-100]	0.437	0.779	0.992
Energy, fatigue	60.0 [20.0-100]	65.0 [8.00-100]	65.0 [30.0-100]	0.104	0.156	0.531
General health	77.0 [40.0-92.0]	72.0 [35-97]	72.0 [30.0-100]	0.619	0.569	0.634
Change in Health	50 [0.0-100]	50 [25-100]	50.0 [25.0-100]	0.013*	0.045*	0.868
Pain	*100 [10.0-100]*	*100 [41-100]*	*100 [30.0-100]*	*0.022**	*0.256*	0.133

Data presented as median [Q1, Q3], TAP=custom MAD, myTAP=non-custom MAD, mm=millimeters, 4 patients did not complete the questionnaires at baseline
*p-value <0.05

Table 3B. self-reported outcomes, custom versus non-custom MAD (intention to treat analysis)

	Baseline	TAP 12 weeks	myTAP 12 weeks	Baseline vs. TAP	Baseline vs. myTAP	TAP vs. myTAP
Adherence (h/wk) N=58	N.A.	49	49	N.A.	N.A.	0.776
ESS N=49	6 [2; 11]	5 [2; 8]	5 [2; 8]	0.017	0.005*	0.893

Data presented as median [Q1, Q3], TAP=custom MAD, myTAP=non-custom MAD
*p-value <0.05*Side effects*

After four and 12 weeks of follow-up, patients were interviewed with respect to side effects while wearing the devices (Figure 5). Overall, more complaints were reported for the non-custom device; n=28 patients had complaints after four weeks and n=22 after 12 weeks follow-up. For the custom MAD, n=23 patients had complaints at four weeks and n=8 after 12 weeks follow-up. The most reported issue concerned the fit of the device, which was described as uncomfortable, painful, too tight, or too loose. Two patients reported changes in teeth position at 12 weeks wearing the custom MAD; for the non-custom MAD, this phenomenon was not reported. The majority of complaints decreased over time; at 12 weeks follow-up, most reported complaints were less than at the consultation after one month. Only complaints of a dry mouth increased over time, for both devices. At the end of the study, n=19 patients preferred the custom MAD, n=16 patients preferred the non-custom MAD and n=5 patients had no preference, this difference was not significant.

Figure 5. Reported side effects, custom versus non-custom MAD

TMD=temporomandibular disorders, TAP=custom MAD, myTAP=non-custom MAD

''Patients reported complaints'' is the total number of patients who had at least one of the complaints as described in de table.

DISCUSSION

This prospective randomized controlled cross-over trial evaluated the effectiveness of a non-custom (e.g. myTAPTM) and custom MAD (e.g. TAPTM) and the potential of a non-custom MAD in providing an efficient and cost-effective way of screening MAD treatment eligibility for patients with OSA. Intuitively one would expect that the more precise a design (i.e., custom), the better the results. This does not apply to the

devices evaluated in the present study. Our findings suggest that the effect of a non-custom MAD is comparable to that of a custom MAD, in terms of respiratory PSG outcomes and self-reported outcomes. AHI, AI and ODI significantly improved for both devices, with no significant differences between the two MADs. In addition, the ESS, general productivity, activity level, and changes in health significantly improved with both devices. General productivity, as measured by FOSQ, did significantly differ between the two subgroups. Since the mean outcome was the same for both subgroups and significantly improved, we do not regard this as a clinically important difference.

To prevent from a reporting bias, given the relatively high drop-out rate, an intention to treat analysis was performed. The outcomes at 3-months follow-up were slightly less favorable, but AHI, AI, and ODI significantly improved for both devices, with no significant differences between them.

The fact that we did not find significant differences between the effectiveness of both devices, suggests the possibility of using the myTAPTM as a temporary MAD in screening patients with OSA for treatment eligibility for custom MAD. Advantages of using a non-custom device prior to a custom one, include that it is cheaper, directly ready for use, and patients can experience potential benefits and complaints of (sleeping with) the device before making a custom MAD, which is overall more expensive.

The results of this study are not in line with the previously published studies of Johal et al7 and Vanderveken et al.8 Their results showed that a custom MAD was more efficacious than a non-custom one. This might be explained by the fact that different non-custom devices were used than in our study.13, 14 The study by Vanderveken et al.8 and of Johal et al.7 were performed with a non-custom thermoplastic monobloc MAD for which the amount of protrusion was not adjustable. In the study by Vanderveken et al.8 the protrusion of the custom MAD was set at 65%, against 50% for the non-custom MAD. Therefore, the treatment effect of the custom MAD might have been stronger. Johal et al.7 also reported a significant difference in amount of protrusion in favor of the custom MAD. These differences in amount of protrusion and differences in patient comfort and retention (and therefore adherence) could have caused a better outcome of the custom MAD, found in these studies. The oral device industry has improved MAD designs significantly by adding the possibility for titration, which could result in more comparable effectiveness

using either a non-custom or custom MAD. In our study, the titration and therefore amount of protrusion of the non-custom and the custom MAD was instructed to the same amount of protrusion. In both study arms the amount of protrusion did not significantly differ from maximum voluntary protrusion at baseline, which means the devices were optimally titrated. In addition, the amount of protrusion during PSG did not significantly differ between the two MADs. Therefore, in our study this variable could not affect outcome differences between the devices.

Overall, treatment success was not as high as expected for both devices. A potential explanation for this outcome could come from the included population. We have also included eight patients with an AHI above 30 events/hr and five patients with a BMI above 30 kg/m2. For such patients, standard of care is CPAP. If CPAP is not tolerated, other treatment options, such as a MAD, are considered. These inclusions might have contributed to less favorable MAD treatment outcomes, since BMI>32 and baseline AHI >30 negatively influence treatment outcome.15-17 To determine the influence of these inclusions, we performed additional analysis. We did not find a relation between these parameters and treatment outcome. This could be explained by the small sample size of patients with a high BMI or high baseline AHI. A higher baseline AHI and BMI are often related to a larger degree of mandibular advancement but also induce a greater degree of short-term muscle and dental discomfort.14, 18, 19 This could explain the lower adherence of the non-custom MAD compared to the custom MAD in the study of Johal et al.7

Another interesting finding, is that adherence in our study was relatively high, which in the end can lead to better therapeutic efficacy. During the past 15 years, thermoplastic MADs have also been improved regarding comfort and retention. In the study of Vanderveken et al.8 adherence with the thermoplastic MAD was lower than with the custom MAD which had a negative influence on treatment outcome of the non-custom device. In our study, however, the adherence of both MADs was similar and therefore had no influence on treatment outcomes.

A recent systematic review by Uniken Venema et al.5 compared several types of MADs. They found that a custom MAD is more comfortable, yields better objective and self-reported treatment outcomes, and is associated with a more favorable adherence when compared with a thermoplastic MAD. However, quality of thermoplastic devices can vary. In their systematic review, different thermoplastic devices were evaluated; none of them being the myTAPTM. In our study, patients

had also more complaints wearing the non-custom MAD than the custom MAD: six patients ended their participation prematurely because of complaints with the device compared to two dropouts wearing the custom MAD. Interestingly, these complaints did not influence adherence, which was similar for both conditions. In contrast to the results of this systematic review, treatment success was even higher with the non-custom MAD in our study, while objective and self-reported outcomes were similar.

Limitations

This study has some limitations. Due to the impact of the COVID-19 pandemic, the outcomes of the questionnaires are less reliable. At baseline, the pandemic was not present yet, but at 12 weeks at least half of the patients completed the questionnaires in the middle of the pandemic. This obviously had impact on their daytime routine, social activities, stress level, and maybe health. Therefore, the pandemic probably influenced the outcomes of the quality of life and sleep questionnaires. In addition, all non-urgent consultations were converted into telephone consultations. This has influenced our titration protocol. We aimed to have a consultation at four and 12 weeks after starting therapy. The consultation at 12 weeks included a dental check-up, completion of questionnaires, evaluating (side) effects of the MAD, and checking the amount of protrusion of the device before the final PSG. Due to the reduction of consultations, we postponed this consultation until after the PSG to be able to directly discuss the PSG results and provide the second MAD. This protocol deviation influenced the titration process. Instead of checking the amount of protrusion prior to the PSG, we checked the used setting afterwards by asking the patient if changes were made and by checking the set protrusion on the used MAD. Since this was done after performing the PSG, we are not certain about the exact amount of protrusion in 10% of the PSGs with the non-custom MAD and in 15% of the PSGs with the custom MAD.. Having fewer consultations to titrate patients, could explain the low treatment success rates for both MADs, since we know that titration is crucial for a positive MAD treatment outcome. Our dropout rate was 31%, which is quite high; 50% of the dropouts was related to the amount of study visits. This could partially be explained by the fact that during the pandemic, patients were less willing to come to the hospital for non-urgent care. Two comparable studies of Johal et al.7 and Vanderveken et al.8 reported similar dropout rates of 29% and 34% respectively. Due to the high drop-out rate, the sample size for this trial was too small to really declare equivalence for all patients at randomization, especially for those who have stopped using the MAD for whatever reason.

Clinical relevance and future perspectives

The clinical consequences of this study can be substantial. The durability of a custom MAD is at least five years, which is in line with the guarantee period of TAPTM. For this type of non-custom MAD (the myTAPTM), the durability is one year, and the guarantee period is 90 days. This means patients have a year to explore if a MAD works for their complaints (objectively and subjectively) and if they tolerate wearing the device. When satisfied with the non-custom MAD, the custom MAD can be provided. If not satisfied or when patients are not compliant, other therapy options can be considered. While prices of MADs differ greatly per country, in general, custom MADs are more expensive than thermoplastic designs. With an overall success rate of roughly 65%, one out of three of these expensive MADs will not be effective or tolerated, representing a considerable waste of time and money, since these products cannot be returned or used by other patients.

CONCLUSION

In the present study, the effectiveness of a non-custom MAD is similar to that of a custom MAD in treatment of patients with mild to severe OSA, The PSG outcomes did not differ significantly between the two devices, nor did the self-reported outcomes. These outcomes open the avenue to the possibility of using a non-custom MAD as a selection tool for MAD treatment eligibility to improve MAD treatment outcome. An advantage of using a non-custom MAD prior to a custom MAD is that therapy can be initiated directly. This allows the patient to experience the benefits and possible disadvantages of MAD therapy before a more expensive custom MAD is applied, thus providing an efficient and potentially cost-effective way of screening MAD treatment eligibility.

ACKNOWLEDGEMENTS

The authors would like to thank Anja van de Velde and Karlijn Beers for their help in preparing the study materials, organizing the inclusion of patients and their study consultations.

REFERENCES

1. Ramar K, Dort LC, Katz SG, et al. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2015;11(7):773-827.
2. Rotenberg BW, Vicini C, Pang EB, Pang KP. Reconsidering first-line treatment for obstructive sleep apnea: a systematic review of the literature. *Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale*. 2016;45:23.
3. Epstein LJ, Kristo D, Strollo PJ, Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2009;5(3):263-76.
4. Dieltjens M, Vanderveken O. Oral Appliances in Obstructive Sleep Apnea. *Healthcare (Basel, Switzerland)*. 2019;7(4).
5. Venema J, Rosenmöller B, de Vries N, et al. Mandibular advancement device design: A systematic review on outcomes in obstructive sleep apnea treatment. *Sleep medicine reviews*. 2021;60:101557.
6. Almeida FR, Lowe AA. Principles of oral appliance therapy for the management of snoring and sleep disordered breathing. *Oral and maxillofacial surgery clinics of North America*. 2009;21(4):413-20.
7. Johal A, Haria P, Manek S, Joury E, Riha R. Ready-Made Versus Custom-Made Mandibular Repositioning Devices in Sleep Apnea: A Randomized Clinical Trial. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2017;13(2):175-82.
8. Vanderveken OM, Devolder A, Marklund M, et al. Comparison of a custom-made and a thermoplastic oral appliance for the treatment of mild sleep apnea. *American journal of respiratory and critical care medicine*. 2008;178(2):197-202.
9. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-5.
10. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997;20(10):835-43.
11. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. *Health economics*. 1993;2(3):217-27.
12. George PT. A new instrument for functional appliance bite registration. *Journal of clinical orthodontics : JCO*. 1992;26(11):721-3.
13. Quinnell TG, Bennett M, Jordan J, et al. A crossover randomised controlled trial of oral mandibular advancement devices for obstructive sleep apnoea-hypopnoea (TOMADO). *Thorax*. 2014;69(10):938-45.
14. Johnston CD, Gleadhill IC, Cinnamond MJ, Gabbey J, Burden DJ. Mandibular advancement appliances and obstructive sleep apnoea: a randomized clinical trial. *European journal of orthodontics*. 2002;24(3):251-62.
15. Petri N, Christensen IJ, Svanholt P, Sonnesen L, Wildschiødtz G, Berg S. Mandibular advancement device therapy for obstructive sleep apnea: a prospective study on predictors of treatment success. *Sleep medicine*. 2019;54:187-94.

16. Marklund M, Stenlund H, Franklin KA. Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. *Chest*. 2004;125(4):1270-8.
17. Cunha TCA, Guimaraes TM, Schultz TCB, et al. Predictors of success for mandibular repositioning appliance in obstructive sleep apnea syndrome. *Brazilian oral research*. 2017;31:e37.
18. Dieltjens M, Braem MJ, Vroegop A, et al. Objectively measured vs self-reported compliance during oral appliance therapy for sleep-disordered breathing. *Chest*. 2013;144(5):1495-502.
19. Gao X, Otsuka R, Ono T, Honda E, Sasaki T, Kuroda T. Effect of titrated mandibular advancement and jaw opening on the upper airway in nonapneic men: a magnetic resonance imaging and cephalometric study. *American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics*. 2004;125(2):191-9.