Non-CPAP Therapies in Obstructive Sleep Apnoea

Mandibular advancement device therapy

M. Marklund1, J. Verbraecken2, W. Randerath3

1 Department of Orthodontics, Faculty of Medicine, Umeå University, Umeå, Sweden; 2 Dept of Pulmonary Medicine and Multidisciplinary sleep Disorders Centre Antwerp University Hospital and University of Antwerp, Belgium; 3 Bethanien Hospital, Institute of Pneumology, University Witten/Herdecke, Solingen, Germany

Address for correspondence:

Marie Marklund, Department of Orthodontics, Umeå University, SE-901 87 Umeå, Sweden
Telephone: +46907856195
Mobile: +46706360729
Fax: +4690132578
e-mail: Marie.Marklund@odont.umu.se

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**ABSTRACT:** Mandibular advancement devices (MADs) represent the main non-CPAP therapy for patients with obstructive sleep apnoea (OSA). The aim of the European Respiratory Society task force was to review the evidence in favour of MAD therapy. Effects of tongue retaining devices are not included in this report.

Custom-made MADs reduce AHI and daytime sleepiness compared with placebo devices. CPAP more effectively diminishes AHI, while increasing data suggest fairly similar outcomes in relation to symptoms and cardiovascular health from these treatments. Patients often prefer MADs to CPAP. Milder cases and patients with a proven increase in upper airway size as a result of mandibular advancement are most likely to experience treatment success with MADs. A custom-made device titrated from an initial 50% of maximum mandibular advancement has been recommended. More research is needed to define the patients who will benefit from MAD treatment, in terms of the effects on sleep-disordered breathing and on other diseases related to OSA compared with CPAP.

In conclusion, MADs are recommended for patients with mild to moderate OSA (Recommendation Level A) and for those who do not tolerate CPAP. The treatment must be followed up and the device adjusted or exchanged in relation to the outcome.
INTRODUCTION

Mandibular advancement devices (MADs) represent the main non-CPAP alternative for patients with obstructive sleep apnoea (OSA). These devices aim to increase the upper airway size and reduce the risk of sleep apnoeas and snoring in patients with OSA. The upper airway is widened particularly in its lateral dimension [1, 2]. The pharyngeal fat pads relocate laterally from the airway and the tongue base muscles move anteriorly [1]. This leads to a reduction in pharyngeal collapsibility [3]. There are indications that MADs cause a change in muscle activity during sleep, with the relaxation of the genioglossus muscle during incremental mandibular advancement [4] and the activation of the masseter and submental muscles [5].

Tongue retaining devices (TRDs) are another type of intra-oral device that has been suggested for the treatment of patients with OSA. This device is designed to produce suction of the tongue into an anterior bulb, move the tongue forwards and widen the upper airway dimensions during sleep. There is insufficient evidence for TRDs and the effects from these devices will therefore not be discussed any further in this report [6].

MADs have been recommended for patients with mild to moderate OSA who prefer an MAD to continuous positive airway pressure (CPAP), provided that the MAD has a sufficient objective effect [7, 8]. MADs may also be used in patients with more severe disease who do not respond to or who fail treatment attempts with CPAP. Some studies have suggested that the efficacy of MADs in modifying the health risks associated with OSA is somewhat similar to that of CPAP [9]. The treatment effect of MADs has to be verified in a renewed sleep apnoea recording with the device in all patients with OSA [7], since patients may have a suboptimal treatment response. One major limitation of MAD treatment is its dependence on
oral health and the fact that it takes some time to become accustomed to the device. Side-effects from the treatment, such as pain from the teeth and jaws, are generally mild and transient [8, 9]. In the longer term, bite changes become more common, but these are usually minor and do not disturb patients who are satisfied with the treatment outcome in terms of snoring and daytime symptoms [9]. The patients may continue with their devices for many years, although the treatment needs to be followed up in terms of side-effects and effectiveness.

The European Respiratory Society funded a task force with the aim of screening the scientific literature on non-positive-pressure therapies, to evaluate the studies according to the criteria for evidence-based medicine and to make recommendations for use in OSA patients. The results produced by the task force are presented in a summary report [6] and in more detail in the current paper.

**Search criteria**

A literature search ending on 1 January 2009 was performed, with additional controls in May 2010 and July 2011 for more recently published papers containing information that was of importance for the results of this report. The search used PubMed with the Mesh terms: sleep apnoea syndromes AND orthodontic appliances; functional or removable, activator appliances or mandibular advancement. In addition, a search in PubMed using the terms: sleep apnoea AND oral appliances, mandibular advancement devices, mandibular advancement splints, mandibular repositioning appliances or mandibular repositioning splints was used. Limit: Clinical Trial. The Cochran Library and the reference lists from the included studies were searched for articles about MADs in the treatment of patients with OSA. No reviews,
guidelines or studies that aimed specifically to determine the type and degree of side-effects, such as bite changes and influence on craniofacial morphology from MAD treatment, were included. Of a total of 84 articles, 29 were excluded because the topic was covered in the RCTs or the aims were not directly related to the efficacy of the device.

Twenty-nine randomised studies of the treatment effects of MADs [10-38] and 5 RCTs investigating other outcomes of MAD treatment [39-43] were found. In addition, 21 further clinical trials that highlighted particular aspects of MAD treatment such as the mechanisms of action and prediction of treatment outcome were identified [1-3, 44-61]. A table is available in the online supplementary material.

**Description of the included studies**

RCTs evaluated the effects of MADs compared with placebo treatment [11, 13, 14, 22, 23, 25, 28-30], CPAP [11, 13, 16-19, 24, 26, 32, 34] or between appliance designs [15, 20, 27, 31, 33, 35, 36, 38]. Three studies reported longer term results from MAD treatment after 1-4 years, compared with CPAP [12], surgery [37] or between two types of MAD [21]. The sample sizes ranged between 19 and 114 patients, with between 15 and 103 patients completing the trials. Eight of the 17 RCTs comparing MADs with placebo or CPAP evaluated 25 or fewer patients, while six studies included more than 70 completing participants. The patients were overweight or obese; their BMI ranged between means of 27 and 33 kg/m². The age of the included patients was between means of 44 and 57 years. The ESS values ranged between means of 8 and 14. The completing samples comprised between 69% and 100% men.
The majority of the RCTs used polysomnography (PSG) (74%), while the other researchers utilised limited sleep recordings or combinations of these methods to analyse sleep-disordered breathing. The apnoea-hypopnoea index (AHI) was used for diagnosis in 86% of the studies, while the remaining studies used the respiratory disturbance index (RDI).

Adjustable custom-made MADs were used in most of the RCTs comparing MADs with placebo and/or CPAP [11, 13, 18, 19, 22, 24, 28, 29, 32]. The remaining studies utilised monoblock devices, either custom-made [14, 16, 25, 26, 30, 34] or prefabricated ones [17, 23]. Some studies used more than one type of device [16, 34]. In all the studies that compared the effect of MADs with positive airway pressure, CPAP with fixed pressure was used [11, 13, 16-19, 24, 26, 32, 34].

**Effects on obstructive sleep apnoea**

MADs reduced AHI or RDI compared with placebo devices in all studies [11, 22, 23, 25, 28-30]. CPAP was more effective in reducing obstructive sleep apnoea, as MADs may be partially effective or ineffective in some patients [11, 13, 16-19, 24, 26, 32, 34].

Patients included in the RCTs had mild to severe OSA [13, 14, 17, 18, 20, 24-27, 29-38], with AHI or RDI varying between means of 10 and 50. With MADs, AHI or RDI decreased to mean values of between 4.5 and 34, which corresponded to reductions in the frequency of respiratory disturbances of means of between 28% and 80% (mean reduction from all studies = 55%). CPAP reduced the indices from means of between 18 and 40 to treated values of between 2.4 and 8.0 [13, 16-18, 24, 26, 32, 34]. This corresponded to reductions of between 74% and 94% (mean reduction from all studies = 83%). There was no change in AHI or RDI.
with placebo treatment or conservative treatment [13, 22, 23, 25, 26, 28-30], although borderline significant reductions have been observed [11, 14].

**Effects on symptoms and quality of life**

Subjective daytime sleepiness evaluated by the ESS score was reduced by MADs compared with placebo devices in three studies [22, 29, 30] and there were positive effects on sleepiness with active treatment in four other smaller studies [14, 23, 25, 28]. Control interventions reduced daytime sleepiness in some studies, despite no influence on sleep apnoea [22, 26]. CPAP and MADs usually had a similar effect on daytime sleepiness [11, 13, 18, 19, 24, 32, 34]. CPAP may produce a better outcome than MADs when it comes to sleepiness [16, 17, 26], even in milder cases [16].

Objective evaluations of daytime sleepiness revealed an improvement in the MSLT by MAD compared with a placebo device in one study [22]. A similar outcome in terms of daytime sleepiness from both MADs and CPAP was reported in two studies using the MWT [16] or the Osler test [19]. Another study revealed no effect by either MADs or CPAP, according to the results of the MWT [13]. About half the patients who were objectively sleepy during MAD treatment had poor apnoea control [22]. Simulated driving performance has been shown to improve to a similar degree as that produced by CPAP, according to one study [40].

Snoring was more effectively controlled with CPAP than with MADs [11, 18], but MADs had a better effect than placebo [11, 22, 28]. Persistent snoring during MAD treatment may be a sign of poor apnoea control [17].
More self-reported sexual dysfunction was identified in OSA patients compared with control subjects, but there was no significant improvement after 2-3 months treatment with either MAD or CPAP in that study [41].

Quality of life was improved by MADs compared with control treatments [13, 26, 29, 30]. The effect of MADs and CPAP was similar [13, 19, 24] or better with CPAP treatment [16]. Factors that have been discussed as being as important as daytime sleepiness, such as vigour, fatigue and reaction times, were improved by an active device compared with a control device [29]. Some effects on neurobehavioral function were no better than the placebo effect [13].

**Effects on cardiovascular health**

A significant reduction in blood pressure has been reported from MAD treatment [13, 20, 26, 39]. A 2 mmHg decrease in 24-hour diastolic blood pressure was found, together with a halving of the mean AHI, as a result of MAD compared with a control splint after 4 weeks’ treatment [39]. Blood pressure during wakefulness decreased significantly by 3 mmHg, but there was no difference in blood pressure measured while asleep in that study. Another study reported a significant improvement in night-time diastolic blood pressure, together with a reduction in mean AHI of one third, as a result of MAD treatment compared with the effects of a placebo tablet or CPAP after 3 months’ intervention [13]. The 24-hour blood pressure was unchanged by both MADs and CPAP. MADs normalised the nocturnal dips in blood pressure in a significant proportion of non-dipper subjects compared with CPAP or a placebo tablet that produced no effects [13]. Another two studies evaluated blood pressure on single occasions during wakefulness and found significant reductions compared with baseline [20, 26].
Improved endothelial reactivity has been found in conjunction with MAD therapy. One small RCT revealed a similar improvement in microvascular reactivity as a result of MAD or CPAP [43]. There was a smaller reduction in AHI but a higher compliance with MAD than with CPAP during two months of treatment in that study. Furthermore, the increase in vasodilation during treatment correlated with the decrease in nocturnal oxygen desaturation. Another small study reported an improvement in endothelial function to levels similar to those seen in a healthy control group after one year of treatment with MADs [51]. In addition, markers of oxidative stress improved. There was a partial treatment response, with a halving of the AHI after 3 months and a decrease of about one third after one year of MAD treatment in that study.

Improved cardiac autonomic modulation was found after 3 months’ treatment with MADs in a small sample of otherwise healthy patients with mild OSA [47]. Further support for improved cardiac function was reported from an RCT including patients with moderate to severe OSA. Significant changes in NT-pro-BNP values were found with effective MAD therapy but not with CPAP [42].

**Definition of treatment success**

Treatment success with MADs defined as an AHI of < 5 was found in 19-75% of the patients and an index of < 10 was reported in 30-94% of the patients in all the included studies [10, 13, 15-20, 22, 25, 28-32, 34-36, 38, 50, 55]. A partial treatment success is often defined as a reduction in AHI of > 50%, sometimes with the requirement of a treated AHI below a specific level of 20, for example. Definitions of success for MAD therapy were based on the
frequency of sleep-disordered breathing, sometimes with an additional requirement of a symptomatic improvement. A more detailed definition of MAD treatment response based on sleep disordered breathing and symptoms and extended to include other health outcomes may be of interest when defining treatment success in the future.

**Prediction of treatment success**

Patient selection is important in order to improve the more variable outcome in terms of sleep-disordered breathing as a result of MADs compared with CPAP. An improved effect in milder cases has been found in some studies [24, 28, 30]. Complete treatment success, defined as an AHI of below 5 with MADs, was reported in 8 of 26 patients with severe OSA and in 21 of 25 patients with mild to moderate OSA [24]. The success rate was similar for MAD and CPAP in patients with mild to moderate OSA, as 20 of a further 25 patients who had been randomised to CPAP treatment had a successful outcome [24]. Younger or leaner patients, women or patients with supine-dependent sleep apnoea have been reported to experience particular success with the device [28, 32, 36, 53, 55], although the result for obesity was favourable in one study [32].

Promising prediction methods based on the mechanism of MADs and their influence on upper airway structures have been proposed. Various imaging techniques have been used to visualise the individual increase in upper airway size during mandibular advancement. The velopharyngeal area is central to this modification process [2, 45], which leads to reduced pharyngeal collapsibility and sleep apnoea [3]. Good responders had a larger increase in velopharyngeal airway size compared with poor responders [1, 45]. The airway was still open during a Muller manoeuvre and mandibular advancement in good responders compared with a
A previous small study produced similar results on MRI [57]. A model of the upper airway using combined upper airway imaging and computational fluid dynamics has been used to evaluate the influence of MADs on upper airway volume and resistance and this method has future potential for the prediction of treatment success [48].

A remotely controlled device represents another promising prediction method for MAD therapy, since the use of this device during an initial night at the sleep laboratory showed high sensitivity and specificity for the assessment of treatment success or failure in a small sample of OSA patients [49].

The localisation of the upper airway obstruction contains predictive information. A collapse in the oropharyngeal area has been related to a successful outcome with MADs compared with the occurrence of a velopharyngeal collapse in two studies [44, 56]. In one of these studies, the upper airway collapse was mimicked by phrenic nerve stimulation [44]. The use of morphological predictors, measured on cephalograms, has produced inconsistent results [28, 53, 58]. A high position of the hyoid bone and smaller upper airways have been related to treatment success [53, 58].

The measurement of flow volume curves [46, 60] or nasal resistance [61] has been suggested as other ways of predicting success with MADs. Validations of prediction methods are few in number and they have only been performed on small samples [44, 46]. Combined functional and morphological assessments have been suggested for future prediction models [46].
For patients who have already tried CPAP, an optimal pressure of 10 mmHg or below was related to a higher chance of success with MADs than higher CPAP pressures [59].

**Mandibular positioning**

The degree of mandibular advancement is an important modulator of the treatment outcome, since there is a dose-dependent effect on nocturnal oxygenation and pharyngeal collapsibility [52]. Mandibular titration is therefore a key procedure when it comes to obtaining optimal effects on obstructive sleep apnoea with the device. A small advancement produces a suboptimal treatment effect, while too large an advancement produces more side-effects [10]. A non-advanced device is ineffective in reducing sleep apnoea [23, 25, 30] and may even increase the apnoea frequency. One study revealed an impaired effect by MADs during the first 6 weeks without titration [32]. A titration procedure millimetre by millimetre has therefore been recommended to achieve optimal results [50]. To optimise the mandibular positioning, a remotely controlled MAD can be used during the concomitant measurement of respiratory events during sleep [49]. The combined evaluation of the symptomatic improvement and oximetry, which has been recommended to find the most effective mandibular positioning, is probably easier in the clinic [50]. It is possible that the exact degree of mandibular advancement is of less importance for patients with mild to moderate disease compared with patients with more severe sleep apnoea [35, 36]. A mouth opening of between 4 and 14 mm has not been found to influence the treatment outcome in terms of sleep apnoea, although patients preferred the device with a smaller opening [31]. There is currently no agreement regarding the method to measure and define the degree of mandibular repositioning in the individual patient, which causes uncertainty regarding comparisons between studies.
Device design

Mandibular advancement devices exist in many designs and with various types of adjustment mechanism. With adjustable devices, it is easy for the patient or the dentist to change the mandibular positioning in order to achieve the desired effects. The monoblock devices have to be adjusted at a dental laboratory. The variety of device designs may explain some of the variability in outcome between patients and studies. Comparison studies between the many custom-made device designs are few in number. These studies have indicated that there may be some differences in treatment effects, albeit minor [15, 20, 27, 33]. The stability of the device is probably a limiting factor for its effectiveness [38]. Poor retention and a high compliance failure rate have been reported for a thermoplastic non-custom-made device compared with a custom-made device [38]. This thermoplastic device was not recommended as a screening tool for a custom-made device [38]. A comparison after two years’ treatment showed that two different types of adjustable custom-made MAD were equally effective in patients who chose to continue treatment [21].

In the studies comparing adjustable MADs with placebo and/or with CPAP, the mandibular positioning was titrated to the maximum comfortable position [13, 22, 29] and/or until the relief of symptoms [18, 24, 28]. In another study, four different positions were tested and the most effective one was finally thereafter used to evaluate the effect of MADs [10, 11]. A larger advancement of 50% or 75% of maximum mandibular advancement was most effective in all but one of 17 patients in that study. The authors recommended starting the titration at 50% of maximum advancement in order to reduce the initial side-effects. In another study, both CPAP and MADs were titrated during the nights before the trial in order to find the most
effective mandibular position [19]. The majority of the studies using monoblock devices reported no change in mandibular positioning [14, 16, 17, 23, 25, 26], while some studies described reconstruction of the device in order to optimize the lower jaw position in relation to the outcome on sleep disordered breathing [30, 34]. More standardisation of these methodologies of advancing the mandible is required for reliable comparison of results between studies.

An MAD is usually adjusted using a screw located in the midline, anteriorly or in the palate or laterally with arms of different lengths or screws on both sides of the appliance. Some designs permit the opening of the mandible and/or some lateral movement, while others fixate the jaws more rigidly. The use of rigid intermaxillary elastics makes these two types approach each other. The stability of these designs in the longer term is unknown. More research is needed about the influence of various MAD designs on the efficacy of the treatment in order to further improve the quality of this treatment modality.

**Side-effects, preference and compliance**

Side-effects, such as jaw discomfort, tooth tenderness and excessive salivation, occur more frequently as a result of MADs than a control plate [11, 22]. The patients therefore need an adaptation period that may sometimes last for months before they become accustomed to the device [22, 28, 29]. Side-effects of similar severity have been reported from MADs and CPAP [16].

Patients generally prefer MADs to CPAP or a control plate [17, 18, 22, 32, 34]. Similar preferences for MADs and CPAP have been reported [13, 16]. There is probably a difference
between patient groups, since overweight patients and those with more severe symptoms favoured CPAP in one study of sleepy OSA patients [16]. Self-reported short-term compliance with MAD treatment ranged from 76% to 95% of the patients [17, 18, 34, 38]. Some studies observed a higher nightly compliance with MADs than with CPAP [19, 32], while other studies described a similar nightly compliance [11, 16-18, 24]. Compliance monitors have been introduced into the market and are being evaluated [54]. Objective compliance monitoring of MAD use is currently not widely available and generally only subjective compliance reporting has been relied upon in the studies. This is a shortcoming in truly being able to compare compliance between MAD and CPAP treatments.

**Long term efficacy**
In the longer term, patients usually continue to use their MADs, although compliance appears to decrease slightly with time. After one year, 76% of the patients were still on treatment [55] and, after 2-4 years, about half the patients were still using their devices [21, 37]. The treatment effect by MADs on AHI was usually stable or decreased slightly in patients who had a good initial treatment outcome. After two years, MADs effectively reduced the apnoea-hypopnoea index in those who continued with the device, which constituted about half the study sample [21]. Daytime sleepiness was reported to increase, despite the good effect on sleep apnoea [21]. After 4 years, the AHI was still significantly reduced by MADs, although the treated index was higher than after one year [37]. The only longer term comparison between MADs and CPAP revealed a larger reduction in AHI as a result of using CPAP compared with MAD after one year of treatment [12]. About a quarter of the patients discontinued treatment in each group, because of either side-effects or ineffective treatment.
Conclusions from the studies

In patients with mild to moderate sleep apnoea, MADs reduce sleep apnoea and subjective daytime sleepiness and improve quality of life compared with placebo devices. The apnoea reduction produced by MADs is smaller and more variable than that achieved by CPAP. An increasing number of studies report similar results from MADs and CPAP in terms of other health outcomes, such as blood pressure, microvascular reactivity, cardiac function, symptoms, quality of life and driving performance. These results suggest that MADs have complex effects on OSA and its consequences. Patients often prefer and comply better with MADs than with CPAP, which may influence the final outcome in comparisons between these treatments.

The variable response to MAD treatment, with some patients experiencing no improvement in OSA, highlights the necessity of objective assessment of treatment outcome and also the need for better understanding predictors of treatment success. Some studies show that MADs more effectively reduce sleep apnoea in milder cases than in more severe ones, although patients with severe OSA may have a successful outcome. These predictions are usually based on the results of PSG and the use of other methods of sleep monitoring might influence the results. Promising results for prediction of treatment outcome are reported from various techniques that visualise an improvement in pharyngeal size during mandibular advancement. The identification of the airway collapse in the oropharyngeal region might be another useful predictor of success. For patients who have already tried CPAP, low therapeutic pressure has been related to success with MADs.

There is insufficient evidence to indicate the type of custom-made device that is most effective and how these devices should be adjusted to produce the optimal effects on OSA. A
titration procedure, starting at 50% of maximum mandibular advancement, is recommended, together with the use of the combined improvement in symptoms and oxygenation or sleep-disordered breathing.

The longer term treatment effect of MADs on sleep apnoea is stable or may slightly diminish in patients who have an initially successful outcome and choose to continue with the device in the long term. There is a need for more knowledge about the long-term outcome of MAD treatment. Mild oral side-effects such as tender teeth and bite changes are consistently found.

More knowledge about symptomatic effects, cardiovascular effects and other health-related effects of MADs is desirable. Studies that identify patients who will benefit from MAD as an alternative treatment to CPAP, also in a long-term perspective, are needed. This will form the basis of more precise indications and longer term follow-up guidelines for MAD treatment in teamwork between various specialists.

**Summary**

MADs are indicated in the treatment of patients with mild to moderate OSA (Recommendation Level A) and in patients who do not tolerate CPAP. MADs reduce sleep apnoea and daytime sleepiness and improve quality of life compared with placebo devices. CPAP more effectively reduces sleep apnoea, while an increasing number of studies suggest fairly similar outcomes in terms of symptoms and cardiovascular health as a result of these treatments. Patients generally prefer MADs to CPAP. A custom-made MAD titrated from an initial 50% of maximum mandibular advancement has been recommended. The follow-up of treatment effects is necessary, even in the longer term, because of the larger variability in
treatment effects from MADs compared with CPAP. More research is needed to define the patients who will benefit from MAD treatment for OSA and its consequences compared with positive airway pressure, in order to provide patients with the most optimal treatment for OSA.
REFERENCES


