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Use of Mandibular Advancement Devices for Obstructive Sleep Apnoea Treatment in Adults

REVIEW

Cauby Maia Chaves Jr[1], Cibele Dal Fabbro[2], Marco Antonio Cardoso Machado[3], Veralice Meireles Sales de Bruin[4], Pedro Felipe Carvalhedo de Bruin[4], Marcela Lima Gurgel[5], Sonia Maria Guimarães Pereira Torgeiro[2], Lucia Cevidanes[6], Fernanda Louise Martinho Haddad[7], Lia Bittencourt[8]

1 Full Professor, Clinical Dentistry Department-Federal University of Ceara, Brazil.
2 Department of Psychobiology-Federal University of Sao Paulo, Brazil.
3 Department of Neurology-Federal University of Sao Paulo, Brazil.
4 Associate Professor, School of Medicine-Federal University of Ceara, Brazil.
5 Clinical Dentistry Department- Federal University of Ceara, Brazil.
6 Assistant Professor, Department of Orthodontics-University of Michigan, United States.
7 Department of Otolaryngology and Head and Neck Surgery-Federal University of Sao Paulo, Brazil.
8 Associate Professor, Department of Psychobiology-Federal University of Sao Paulo, Brazil.

Contact information:

Cauby Maia Chaves Jr.

cmcjr@uol.com.br

Abstract

Introduction: This article is based on Clinical Guidelines for obstructive sleep apnoea (OSA) established by a taskforce coordinated by the Brazilian Sleep Association.

Objective: The aim of this article is to evaluate the available scientific evidence regarding the efficacy, adherence and safety of using mandibular advancement devices (MAD) as a therapeutic course for treating obstructive sleep apnoea in adult patients.

Method: Active searches were performed in the PubMed/MEDLINE, EMBASE, Scielo/LILACS and Cochrane Library databases. Methodological aspects were used to rank the levels of evidence according to the criteria of the Centre for Evidence-Based Medicine at Oxford.

Results: Mandibular advancement devices offer the best results for patients with primary snoring, upper airway resistance syndrome and mild or moderate OSA (Levels of Evidence I and II). Continuous positive airway pressure (CPAP) is more effective in controlling OSA (Level of Evidence I). However, patients seem to exhibit greater adherence to oral appliances (MAD) than (CPAP) devices. The long-term side effects most observed after the use of MADs are related to changes in the mandibular and dental positions (Levels of Evidence I and II).

Conclusion: MAD constitute a therapeutic alternative for OSA and promote favourable results with good efficacy and adherence to

treatment. Side effects can arise in the short, medium or long term. Patients must be informed about the possible occurrence of these adverse effects, and the orthodontist must be able to manage any side effects that occur due to the use of these devices.

Keywords
Oral Appliances, Mandibular Advancement Devices, Obstructive Sleep Apnea, Side Effects.

Introduction

Obstructive Sleep Apnoea (OSA) is characterized by upper airway obstruction events during sleep in the presence of respiratory movements. This obstruction is manifested as recurrent, involving an awakening due to increased respiratory effort, limitation, reduction (hypopnea), or complete cessation (apnea) of airflow. It is the most prevalent disorder among respiratory sleep disorders, being more prevalent in males and increased with increasing age. OSA prevalence is also greater in obese men and women [1].

Patients with untreated OSA have more cardiovascular events when compared to treated patients. OSA is now recognized as an independent risk factor for developing comorbidities and increased mortality [2]. It has even been suggested that OSA should be considered a systemic disorder and not just a disorder of the upper airways (UAW). The systemic impact may involve cardiovascular and metabolic consequences [3].

OSA is one of many obstructive respiratory disorders during sleep; however, these disorders are not limited only to patients who suffer typical OSA; instead, they are included on a continuum that ranges from snoring until OSA. Upper Airway Resistance Syndrome (UARS) was initially described by Guilleminault et al. in 1993 [4]. This syndrome was described based on the assumption that the repetitive increase in respiratory effort during sleep, in the absence of apneic and hypopneic events, will induce arousals that can lead to excessive daytime sleepiness and functional symptoms and is associated with cognitive and cardiovascular morbidity [5]. Definitions of sleep-related respiratory disorders, published by the taskforce of the American Academy of Sleep Medicine (AASM) in 1999 did not include UARS but described respiratory effort-related arousals (RERA). Thus, the International Classification of Sleep Disorders (ICSD-III) recommends that UARS still be included as part of OSA rather than as a separate entity [6].

OSA is considered mild when daytime sleepiness or involuntary sleep episodes occur during activities that require little attention, such as watching TV, reading or riding in a vehicle as a passenger. At this degree of the disorder, the symptoms produce discreet changes in social or occupational functions. On a polysomnogram, the apnea and hypopnea index (AHI) is greater than or equal to 5 and less than or equal to 15 per hour of sleep.

When OSA is moderate, drowsiness or involuntary sleep episodes occur during activities that require some attention, such as attending social events. The symptoms produce changes in social or occupational functions. The AHI is greater than 15 and less than or equal to 30 per hour sleep.

In severe OSA, daytime sleepiness or involuntary sleep episodes occur during activities that require greater attention, such as eating, talking, walking or driving. The symptoms cause marked changes in social or occupational functions. The AHI is usually greater than 30 per hour of sleep [6-8].

OSA treatment includes clinical and surgical modalities. Surgery is nowadays not often indicated, and among clinical managements CPAP and Mandibular advancement devices (MAD) are the

most used modalities due to their research results in literature. CPAP is the gold standart treatment, but its acceptance and compliance is low, and Oral Appliance (OA) treatment has a better compliance than CPAP.

Mandibular advancement devices (MAD) prevent collapse of the oropharynx tissues and represents a potentially important therapy for OSA patients. However, the clinical applicability regarding effectiveness, adherence and side effects still need to be elucidated [9].

The text of the present article is based on Clinical Guidelines for OSA established by a taskforce coordinated by the Brazilian Sleep Association. The goal of this article is to evaluate the scientific evidence on the efficacy, adherence and safety (i.e., possible damage caused by therapy and/or side effects) of using MAD as a therapeutic course for OSA.

Methods

Active searches were performed in the PubMed/MEDLINE, EMBASE, Scielo/LILACS and Cochrane Library databases using the following search terms: *(Oral OR Orally OR Intraoral OR dental OR Tooth) AND (Appliance OR Appliances OR Devices OR Device) AND ("sleep apnea, obstructive"[MeSH Terms]) OR (Apnea Obstructive Sleep) OR (Apneas Obstructive Sleep) OR (Obstructive Sleep Apneas) OR (Sleep Apneas Obstructive) OR (Syndrome Sleep Apnea Obstructive) OR (Sleep Apnea Syndrome Obstructive) OR (Syndrome Obstructive Sleep Apnea) OR (Obstructive Sleep Apnea) OR (Obstructive Sleep Apnea Syndrome) OR (Upper Airway Resistance Sleep Apnea Syndrome) OR (Syndrome Upper Airway Resistance Sleep) AND (randomized controlled trial [pt]) OR (controlled clinical trial [pt]) OR (randomized [tiab]) OR (placebo [tiab]) OR (drug therapy [sh]) OR (randomly [tiab]) OR (trial [tiab]) OR (groups [tiab]) AND (humans[mh]).*

Table 1. Research question.

Does the intervention work?	
Benefits of a treatment	
Level I[1]	Systematic review of randomized controlled clinical trials or *n-of-1* trials.[3]
Level II[1]	Randomized controlled clinical trial or observational study with significant magnitude of the estimate
Level III[1]	Non-randomized controlled studies (cohort)/follow-up studies[2]
Level IV[1]	Case series, case-control studies or controlled studies with historical comparisons[2]
Level V[1]	Mechanism-based reasoning (biological plausibility)

Table 2. Possible damages associated with the therapy used.

What are the most common damages?	
Damages associated with treatment	
Level I[1]	Systematic review of randomized controlled clinical trials, systematic review of nested case-control studies, n- of-1 trials, with a patient suffering a clinical situation in question, or an observational study with significant magnitude of effects
Level II[1]	Individual randomized controlled studies or, exceptionally, observational studies with significant magnitude of the estimate
Level III[1]	Non-randomized controlled studies (cohort)/follow-up studies (post-marketing surveys) with sufficient sampling power to rule out common damages (for long-term damages, the follow-up period should be sufficiently long)[2]
Level IV[1]	Case series, case-control studies or studies with a historical control[2]
Level V[1]	Mechanism-based reasoning (biological plausibility)

[1]: The level of evidence can vary depending on the quality of the study, the accuracy, the agreement among the available studies, the magnitude of the estimate, and the directness of the evidence [indirect evidence is that where one or more elements of the research question do not fully match the desired items of the research question].

[2]: A systematic review is generally more reliable than an individual study.

[3]: n-of-1 trials: randomized and blinded (using masking) trials in which a single patient suffers a series of treatment pairs composed of an active treatment and a placebo (or alternative) per pair, with the other pair determined by random allocation. Appropriate treatment goals (i.e., signs, symptoms, laboratory indicators) are used as measures of efficacy. The trial continues until the efficacy is established or disproven.

Source: OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

Specific methodology was used in an attempt to identify data on the efficacy and safety of intervention (therapy with Oral Appliance-OA), ranking the levels of evidence according to the criteria of the Centre for Evidence-Based Medicine at Oxford. The following instrument was used to classify the evidence **(Table 1 and 2)**.

Oral Appliances (OA)

OA are used in the oral cavity during sleep to prevent collapse of the oropharynx tissues, thereby reducing obstructive events in the upper airways (UAW).

Currently there are numerous devices with different designs and materials, which fit into two main categories: tongue-retaining devices (TRD) **(Figure 1)** and mandibular advancement devices (MAD) or mandibular repositioners **(Figure 2)**. Mandibular repositioning appliances have the largest number of publications because tongue retainers are less commonly used and, for this reason, little studied. Therefore, only MADs will be addressed in terms of their efficacy, adherence and safety.

Figure 1: Tongue-retaining device (TRD).

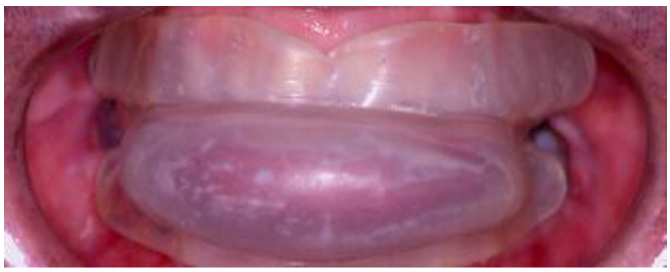
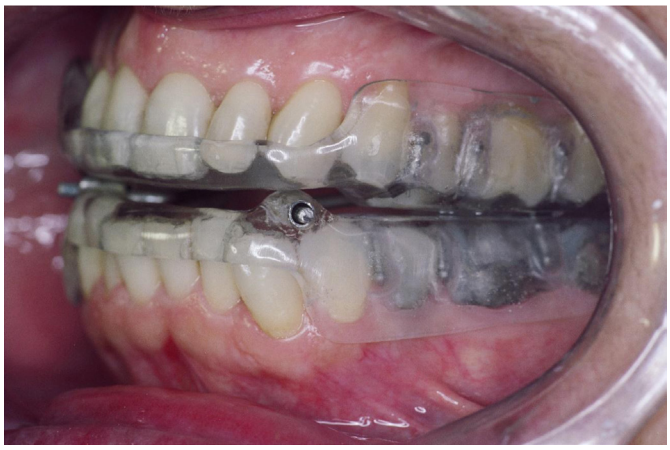


Figure 2: Mandibular advancement device (mandibular repositioner) (MAD).



Efficacy of MAD in sleep parameters and excessive sleepiness

A Cochrane systematic review, published in 2006 [10], and another published in 2011 [11] demonstrate that there is growing scientific evidence suggesting that treatment with MADs improves the subjective symptoms of drowsiness and significantly reduces the respiratory abnormal events during sleep (AHI and minimum oxyhemoglobin saturation) in patients with OSA compared with a placebo device. According to these studies, treatment with MADs is indicated for patients with snoring, upper airway resistance syndrome (which most researchers consider an initial stage of OSA) and mild OSA (Level of Evidence I).

When treatment with MADs is compared to CPAP (Continuous Positive Airway Pressure – devices that use positive-pressure ventilation in the airways), the literature shows that CPAP is more effective for improving respiratory parameters of sleep (AHI and oxyhemoglobin saturation), although improvement in excessive daytime sleepiness (SDE) is similar between the two treatments (Level of Evidence I) [10, 12]. The authors also warn that the number of randomized trials with appropriate duration and sample size is still insufficient and suggested future studies on the efficacy against excessive drowsiness (Level of Evidence I) [10]. It has been suggested that the absence of difference in improved drowsiness over the long-term between MAD and CPAP groups may indicate that the greater reduction in the AHI values for the CPAP group may not be clinically relevant (Level Evidence II) [13].

A single trial comparing MAD with a surgical procedure suggests that the OA was more effective

than uvulopalatopharyngoplasty (UPPP) for improving rates of sleep respiratory events (Level of Evidence II) [14].

We must remember that there are many aspects that interfere with the efficacy of treatment with OA. One of the most important factors is the design of the device, as demonstrated in the systematic review published in 2011 with mandibular repositioning (or mandibular advancement) devices. According to that review, there does not seem to be one MAD model that is better than another for improving sleep parameters. However, it was demonstrated that the efficacy of devices that advance the jaw depends on a number of factors, such as the OA fabrication material and manufacturing method (non-customized or customized), if the OA is of the monobloc or gradual mandibular advancement type, with or without mandibular freedom of movement, and the degree of protrusion (sagittal and vertical), among other factors (Level of Evidence I) [11].

Customized oral appliance are more effective in the treatment of OSA than non-customized devices. However, it seems that among personalized devices, there is no significant difference in efficacy between different models (Level of Evidence II) [15, 16].

Predicting the success of treatment with MAD has been the aim of many studies. Some cephalometric measurements have been described as predictors, such as smaller soft palate, greater upper airway space in the retropalatal region, less distance between the mandibular plane and the hyoid bone, proper SNA angle and smaller SNB angle (Level of Evidence IV) [17-19].

However, some studies contradict those findings, showing that the cephalometric measurements do not differ between patients with success or failure in treatment with MADs (Level of Evidence IV) [20]. The efficacy of treatment with MADs seems to be influenced by the body position, with the best results achieved in patients who suffer most events in supine position (Level of Evidence IV) [21, 22]. Women have demonstrated a greater success rate when using MADs versus men (Level of Evidence III) [23]. Cephalometric measurements are used in many studies due to easy access, fast analysis and low cost. Nevertheless, it has the limitation of being a two-dimensional exam.

Efficacy of MAD in cognition and quality of life

A randomized clinical trial showed improvements in fatigue/energy levels and vigilance/psychomotor speed when MADs were compared to placebo (Level of Evidence II) [24]. A systematic review and meta-analysis published in 2013 showed that the effects on health related to aspects of quality of life and cognitive performance were similar between MADs and CPAP (Level of Evidence I) [12].

A study showed that the improvement in the quality of life (Nottingham Health Profile) was greater for MADs compared to CPAP in various aspects, such as physical mobility, social isolation, pain, emotional function and sleep [25]. Thus, while treatments with oral appliances may not reduce AHI as much as CPAP, consistently and over several studies, they significantly improve the quality of life of individuals with OSA (Level of Evidence II).

Efficacy of MAD in cardiovascular parameters

It has been demonstrated that treatment with MADs can improve cardiovascular complications of OSA. A systematic review and meta-analysis published in 2013 showed that the effects of MADs and CPAP were similar regarding the decrease in systemic blood pressure (Level of Evidence I) [12].

It has also been demonstrated that the improvement in blood pressure persisted over 3 years of treatment with MADs (Level of Evidence IV) [26]. Additionally, there was a positive correlation between the decline in AHI and the reduction of systemic blood pressure after treatment with MADs (Level of Evidence IV) [21].

Other cardiovascular outcomes have been evaluated, but only in a few studies. One study showed that blood biomarkers of oxidative stress and endothelial function were improved in a group of OSA patients treated with MADs compared to a reference group of patients without OSA (Level of Evidence IV) [27]. Interestingly, these changes were observed after 12 months of treatment, despite the persistence of residual sleep respiratory events. The effects of treatment with MADs were also found in the autonomic nervous system, with improvements in heart rate variability, showing a modulation in autonomic nervous system (Level of Evidence IV) [28].

Adherence to MAD

A Cochrane Review published in 2006 assessed treatment with CPAP compared to control and MAD treatment. This review included 36 studies involving 1,718 patients and showed that although CPAP is better than MADs in reducing respiratory events on a polysomnogram, those who responded to both treatments had a strong preference for the MAD, which directly influences adherence to therapy, especially in the long term (Level of Evidence I) [29].

However, a systematic review and meta-analysis, published in 2013, showed that adherence, preference and the abandonment rate were similar between the two treatments (MADs and CPAP) (Level of Evidence I) [12].

Adherence to MADs is typically measured subjectively for daily use. The adherence to MADs, monitored subjectively at the beginning of the treatment, seems to occur in approximately 90% of patients, reducing to 77% at the end of one year (Level of Evidence V) [30]. Another study showed that 64% of patients continued to use MADs 5.7 years after installation, where the main reasons for abandoning treatment were: discomfort caused by MADs (44.4%), the absence of the desired effect (33.6%) and switching to CPAP treatment (23.3%). [31] That study found that 40% of non-adherence occurred in the first 6 months of using the device (Level of Evidence III) [31].

In 2000, a study used a thermosensitive battery placed inside the resin device to detect the use of the MADs through body temperature (Level of Evidence IV) [32]. A similar methodology was only reassessed recently and is now available. That study showed that a thermal microsensor embedded in the resin of the device is a valid measure of adherence. The average usage was 6.6±1.3h per night in 82% of the 51 patients who regularly used the MADs (Level of Evidence III) [33]. Some predictors of adherence have been attributed to the material and equipment type, the presence of mandibular mobility and the adjustment in terms of the protrusion.

MADs personalized to the individual seem to promote greater adherence than non-customized devices (Level of Evidence II) [34]. Some surveys compared several device models with different results. Some authors suggest that the patient's preference in terms of the device model is important for adherence to treatment (Level of Evidence II) [35, 36].

Safety of using MAD

Possible side effects of treating OSA with MADs can occur with short-, medium- or long-term use. The most common and observed side effects are short- and medium-term effects, such as complaints of excessive salivation or dry mouth, followed by pain and/or discomfort in the support teeth, pain due to temporomandibular dysfunction (TMD), and pain and/or discomfort in intraoral soft tissue.

In general, the side effects when MAD is well indicated seem to be minimal, according to most of the assessments found in the literature (Levels of Evidence I-III) [12].

In studies with long-term evaluations, the most observed side effects are related to changes in mandibular position and dental positions (Levels of

Evidence I and II) [31, 37]. Therefore, when proposing this modality of treatment, patients must be informed about the possible occurrence of these adverse effects, and the orthodontist must be able to manage any side effects that may arise due to the use of OA.

Complications from TMD can also occur, but there is little evidence. A randomized study assessed pain intensity and impairments in mandibular function with MAD and CPAP usage after 2 months, 1 year and 2 years. Treatment with MADs resulted in more pain from TMD than CPAP in the initial period of use, although this pain was transient and generally not severe. However, there were no limitations in mandibular function during the 2 years with both treatments. According to that study, in general, pain is not a reason to contraindicate MADs, and it appears that TMD and the risk of developing pain and changes in the function of the TM complex are limited with long-term MAD usage (Level of Evidence II) [38].

Results

Growing scientific evidence suggests that treatment with MADs improves the subjective symptoms of drowsiness and significantly reduces the respiratory abnormal events during sleep in patients with OSA, significantly improving the quality of life of these individuals (Level of Evidence I).

MADs yield the best results in patients with snoring, UARS and mild or moderate OSA (Levels of Evidence I and II). Although not as effective in controlling OSA as CPAP, patients seem to exhibit greater adherence to MADs (Level of Evidence I).

When MAD usage is well indicated, the side effects seem to be minimal. In the long term, the most observed side effects are related to changes in mandibular position and dental positions (Levels of Evidence I and II).

Future studies are needed to evaluate the best device design, the predictive factors for success with OA and the clinical efficacy and adverse effects in the long term.

Discussion

According to this study, a lot of papers related an improvement of sleep parameters and excessive sleepiness with MADs treatment. A recent paper revealed similar data with significant changes in Snore index, Apnea-hypopnea index, oxygen saturation and sleepiness (Epworth Sleepiness Scale) [39]. Improvements in cognitive performace and quality of life, as well as a reduction in risk of cardiovascular events, were also observed in the present study. Likewise, this result was evidenced by Galic et al (2016) and Anandam et al (2013) [40, 41].

Some reviews reported in this study showed substantial limitations due to the use of two-dimentional (2D) cephalometry as methodology. Conventional 2D lateral cephalographs provides changes in magnification, geometric distortion, superimposed structures and inconsistent head position. One of the key advantages of three-dimentional (3D) computed tomography over 2D radiography is its ability to provide 3D volumetric, surface and sectional information about the craniofacial structures with great accuracy [42].

Three-dimentional upper airway changes with mandibular advancement device in patients with obstructive sleep apnea has been observed. According to Shete and Bhad (2017), MAD´s use increases the mean upper pharyngeal airway volume in this cohort. This increase in volume appeared to be related to increased oxygen saturation. Thus, the MAD's efficacy are also observed in 3D studies [43].

Tison et al (2011), showed a satisfactory adherence and satisfaction in a population of 113 patients treated with MAD. The present study reported a similar result, with considerable adherence to the MAD's use [44].

It was observed with this study that personalized devices with gradual mandibular advancement

are more effective in OSA treatment than non-customized devices. The maximum level of advancement should be assessed for each case. Weekly adjustments are usually made until the maximum confortable protrusion established for each patient. One month after MAD collocation, patients were asked about the event of side effects for the use of MAD. Three months after MAD collocation, once the patient and his bed partner reported an evident clinical improvement, the next step is the polysomnography evaluation with MAD at the adequate advancement level [39].

When compared with CPAP, MAD is clinically effective and cost-effective in mild to moderate OSA. It is the appropriate first choice in most patients in the short term. Nevertheless, more studies should explore more additional clinical and cost benefits of MADs [45].

Conclusions

MADs are a therapeutic alternative for OSA and promote favourable results with good efficacy and adherence to treatment. Possible side effects can occur in the short-, medium- or long-term. Patients must be informed about the possible occurrence of these adverse effects, and the orthodontist must be able to manage any side effects that may arise due to the use of these devices.

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