Update on oral appliance therapy

Marie Marklund[1], Marc J.A. Braem[2,3] and Johan Verbraecken[4,5]

Affiliations: [1]Dept of Odontology, Medical Faculty, Umeå University, Umeå, Sweden. [2]Translational Neurosciences, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium. [3]Dept of Special Dentistry Care, Antwerp University Hospital, Antwerp, Belgium. [4]LEMP, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium. [5]Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital, Antwerp, Belgium.

Correspondence: Marie Marklund, Dept of Odontology, Medical Faculty, Umeå University, 906 87 Umeå, Sweden. E-mail: marie.marklund@umu.se

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Oral appliances are increasingly used in the treatment of patients with obstructive sleep apnoea. This update highlights the most recent knowledge about this therapy. http://bit.ly/2Za1IGl

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ABSTRACT Oral appliances are increasingly recommended for selected patients with obstructive sleep apnoea (OSA) and those who do not tolerate nor prefer continuous positive airway pressure. The most commonly used oral appliance advances the lower jaw during sleep, the so-called mandibular advancement device (MAD). Patients seek treatment because of disturbing snoring, daytime symptoms, apnoeas that disturb sleep and the longer term consequences with regard to cardiovascular risks. MADs reduce the apnoea–hypopnoea index, although to various degrees among patients. Effects on daytime sleepiness have been observed mainly among the more severe OSA patients. Blood pressure may be reduced in MAD-treated OSA patients. There is, however, uncertainty about which patients will respond to this therapy in terms of apnoea reductions, decreased sleepiness and other symptoms, and reduced risk for future impaired health. The occurrence of side-effects also remains difficult to predict at present. The majority of sleep apnoea patients suffer from various comorbidities in terms of cardiovascular diseases, type 2 diabetes and depression. The most recent findings indicate that phenotyping of patients, considering various aspects of this multifaceted disease, will shed more light on the indications for MADs in patients with nightly sleep breathing disturbances. This review summarises the most recent knowledge about MAD treatment.

Introduction

Mandibular advancement devices (MADs) represent a well-tolerated treatment for selected patients with obstructive sleep apnoea (OSA) or those who do not tolerate nor want to use continuous positive airway pressure (CPAP) [1–6]. MADs reduce upper airway collapsibility, often in a dose-dependent manner, by increasing the pharyngeal dimensions upon protrusion of the lower jaw [7]. There are no effects on other OSA-related pathophysiological traits such as sensitivity of the respiratory control system [8]. Many randomised studies have confirmed that the apnoea–hypopnoea index (AHI) is reduced, although to different degrees among patients [1–6]. The effects on symptoms and longer term cardiovascular consequences are more variable and less studied [3, 6, 9–12]. More knowledge about phenotyping of patients will therefore become an important tool in improving the selection process for this non-CPAP therapy. In addition, there is a need for more standardisation of MAD therapy in terms of appliance selection and follow-up of the odontological consequences of treatment [13].

Patient selection

Patients with a moderate pharyngeal collapsibility and low loop gain are likely to respond to MAD therapy, *i.e.* characteristics that have been identified as beneficial with respect to the mechanism of action

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of MAD treatment [8, 14]. Milder OSA patients have also been recognised as responders. The common use of the AHI to identify this complex disease and make recommendations for treatment has, however, been questioned [15]. The AHI has been found to be a weaker predictor to identify MAD treatment responders than previously believed and severe patients might also have a good outcome [16–18]. Instead, more advanced ways to interpret sleep apnoea recordings are under development [19, 20]. This will allow the identification of various phenotypes of sleep apnoea patients and provide a more promising way forward to find patients who respond to OSA treatment in different ways.

Non-responders to MAD therapy are more likely among severe OSA patients with non-positional OSA [21–23]. Evaluation of the upper airways during drug-induced sleep endoscopy (DISE), showing a complete circular collapse or lack of widening of the upper airway during a mandibular advancement test, has been successful in order to identify poor responders [24, 25]. Also, when using a remotely controlled mandibular positioner, one is able to determine the most effective target protrusion during a single-night titration of the lower jaw [26]. Although major efforts are now being directed towards more accurate prediction of the required mandibular protrusion, at present there is unfortunately still no clinical routine protocol allowing this [27]. Obesity, older age and male sex relate to a poorer outcome, although with some variability in results [21, 28, 29]. However, early treatment might be beneficial in order to reduce the risk for systemic hypertension as a consequence of untreated OSA [30].

It will be important to define clusters of characteristics that represent phenotypes that respond to MAD therapy. Table 1 summarises the current knowledge about possible phenotypes of interest for identifying good and poor responders to MAD therapy and the efficacy of the device on comorbidities. New studies can, for instance, use the clusters that have been identified in the Icelandic Sleep Apnoea Cohort and include patients who are minimally symptomatic, sleepy or suffer from disturbed sleep, or those with cardiovascular or other identified OSA comorbidities [31, 32].

Symptoms

Symptomatic patients diagnosed with OSA complain about a combination of daytime sleepiness and fatigue.

The effect of OSA on daytime sleepiness, evaluated by the Epworth Sleepiness Scale, is uncertain and has mainly been found among severe OSA patients [3, 6, 12]. Milder OSA patients may become less sleepy during treatment, but the effect is probably more diluted by sleepiness from other causes [12, 33, 34]. A good approach in patients with mild symptomatic OSA is to test whether treatment with CPAP reduces daytime symptoms before treatment with an oral appliance is initiated [35].

The effect of OSA on fatigue is less well studied; furthermore, hypersomnolence and fatigue are often mixed up, although they are two distinct symptoms. Fatigue is defined as the subjective feeling of tiredness

TABLE 1 Phenotypes of obstructive sleep apnoea (OSA) patients of interest for mandibular advancement device therapy

	Phenotypes that have been related to treatment success	Phenotypes of interest to study
Anthropometric	Females; younger age; less overweight/obesity	
Polysomnographic	Positional OSA	More sophisticated ways to interpret polysomnographic sleep recordings; simpler methods to evaluate treatment effects
Functional	DISE defining type of collapse and increase in airway size during advancement	
Symptomatic		Sleepiness and fatigue; headaches; restless legs; nasal symptoms; insomnia; disturbed sleep; minimally symptomatic
Cardiovascular		Systemic hypertension; other cardiovascular diseases
Metabolic/endocrine		Type 2 diabetes
Other comorbidities		More overall knowledge on relationships between OSA and comorbidities

DISE: drug-induced sleep endoscopy.

or exhaustion and is a commonly reported symptom among patients with chronic conditions such as OSA [36, 37]. Recent results indicated that the Checklist Individual Strength (a 20-item self-report questionnaire) was a reliable tool to demonstrate MAD treatment efficacy as well as improvement in health outcome characteristics such as fatigue upon MAD treatment; after 3 months of MAD treatment, fatigue was significantly reduced under the level of increased risk for prolonged absence at work [38, 39].

OSA patients may suffer from symptoms other than sleepiness, such as headaches, insomnia, restless legs, disturbed sleep and sleep bruxism. Few studies have evaluated the effects of MADs on such symptoms. Positive effects on symptoms of restless legs have been found in two studies [12, 40]. Some findings indicated that headaches, nasal congestion and insomnia were reduced with MAD treatment [12]. Short-term positive effects of MADs on sleep bruxism have been detected in small samples, although the longer term benefits are unclear [41]. Identification of various symptomatic phenotypes of OSA patients would be of interest in order to better understand the effects of MADs on various symptoms as well as comorbidities.

Blood pressure and cardiovascular health

Blood pressure is reduced from MAD treatment compared with placebo and mostly to a similar degree as with CPAP in the relatively small samples studied [5, 9, 11]. The blood pressure effects are particularly evident at night-time, in hypertensive patients and probably among females [18, 42–47]. Sex differences in effects from OSA treatments are mainly unknown, since mixed samples have included a majority of males (80% on average). In light of two recent studies, where untreated females with OSA were found to be particularly at risk to develop cardiovascular disease [48] or cancer [49], there is a risk of females being undertreated.

The effect of treatment of sleep apnoea in order to reduce future long-term consequences, in terms of cardiovascular risks, also needs to be studied in relation to OSA phenotype. For instance, other concomitant conditions to sleep apnoea such as periodic leg movements or disturbed sleep have been found to be more related to longer term risks for cardiovascular disease than the presence of apnoeas and hypopnoeas [50]. Another example would be to test whether sleepy OSA patients have a larger chance than non-sleepy OSA patients to reduce the risk for cardiovascular disease in terms of systemic hypertension during MAD treatment. This difference has been found for CPAP, possibly related to some degree to adherence to treatment [51], although it has now become clear that this must be studied in more detail given the heterogeneity in the types of MADs. Since adherence has been found to be better with MADs than with CPAP [18], such findings might be of help to find the best treatment for patients with comorbidities who need treatment for several diseases. The development of compliance monitors for MADs, in accordance with what is available for CPAP, will facilitate such comparisons [52].

No effect on inflammatory and metabolic markers has, however, been found during MAD treatment of severe OSA patients in a recent study, which suggests that earlier interventions are needed [53].

Device design and advancement

It is generally unknown if various brands of custom-made MADs produce significantly different effects on sleep apnoeas, although some design details have been found to be of importance. Custom-made devices have been found to be more effective and better tolerated than prefabricated devices [54–56]. A larger advancement of the mandible will generally produce a better effect of the MAD [7, 57, 58], but there is no precise linear relationship between mandibular advancement and treatment success [59, 60]. It is, however, important to secure the degree of mandibular advancement by the MAD in order to produce the intended outcome on sleep apnoeas. This can be achieved either by an adjustment mechanism that stabilises the lower jaw firmly to the upper jaw or attaches the lower part to the upper part by, for example, elastic bands [61, 62]. A stable position of the lower jaw will also be important when it comes to the prediction of responders, since otherwise efficacy in the supine position might be suboptimal [61, 62]. Indeed, during DISE it was found that increased mouth opening will counteract the stability of the upper airway in the large majority of patients [63].

Bite changes

Oral appliances are attached to the teeth and therefore this therapy is highly dependent on a healthy dentition. Forces will arise on the teeth during appliance use and there is a risk for bite changes [64, 65]. The overjet, *i.e.* the horizontal distance between the upper and lower front teeth (figure 1), will decrease and patients may lose antagonistic contacts between the molar teeth, although to various degrees between patients. The bite changes are noticed early during the first years of treatment and will thereafter gradually continue (figure 2) [65–85]. The initial type of bite is associated with the degree of bite changes from MAD treatment: patients with a deep bite, *i.e.* a large vertical overlap between the front teeth, are to some

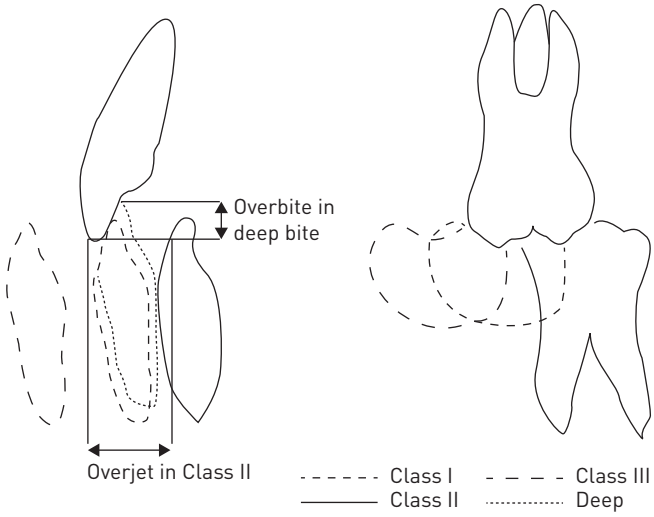

FIGURE 1 Various types of dental occlusion of interest for mandibular advancement device therapy.

degree protected from overjet changes (figure 1) [69, 72]. Those with normal bites or Angle Class III, *i.e.* lower front teeth located anterior to the upper front teeth, seem to be more at risk for negative bite changes. Patients with Angle Class II, *i.e.* lower front teeth much posteriorly located from the upper front, might receive positive orthodontic effects of oral appliance treatment. Consequently, bite changes do not necessarily need to be considered as disadvantageous to a particular dentition and, indeed, some patients could benefit.

Device design will also influence the risk of bite changes. One study describes that a device that is attached mainly to the front teeth will produce a faster and larger change in dental occlusion compared with a device that is attached to the whole dentition [83].

Although most patients are unaware of bite changes [86], the changed dental occlusion might influence the efficacy of the device. The advancement of the mandible by the device might diminish if the device is left unadjusted in patients with larger bite changes.

Treatment years	First author, year [ref.]	Device(s)	Patients n
17	Marklund, 2016 [66]	Monobloc	9
11	Pliska, 2014 [67]	Klearway	77
10	Fransson, 2017 [68]	Monobloc	60
7	de Almeida, 2006 [69]	Klearway	70
5	Gong, 2013 [70]	Monobloc	25
	Martinez-Gomis, 2010 [71]	Herbst	15
	Marklund, 2006 [72]	Monobloc	156
4	Wang, 2015 [73]	Silensor	42
	Ringqvist, 2003 [74]	Monobloc	30
3	Battagel, 2005 [75]	Herbst	30
	Hou, 2006 [76]	Monobloc	67
	Ghazal, 2008 [77]	TAP	24
2	Robertson, 2003 [78]	Monobloc	20
	Rose, 2002 [79]	Adjustable activator	34
	Hammond, 2007 [80]	SomnoMed	45
	Fritsch, 2001 [81]	Herbst, monobloc	22
	Fransson, 2004 [82]	Monobloc	65
	Uniken Venema, 2018 [83]	SomnoDent	31
	Doff, 2013 [84]	TAP	29
	Bondemark, 1999 [85]	Monobloc	30

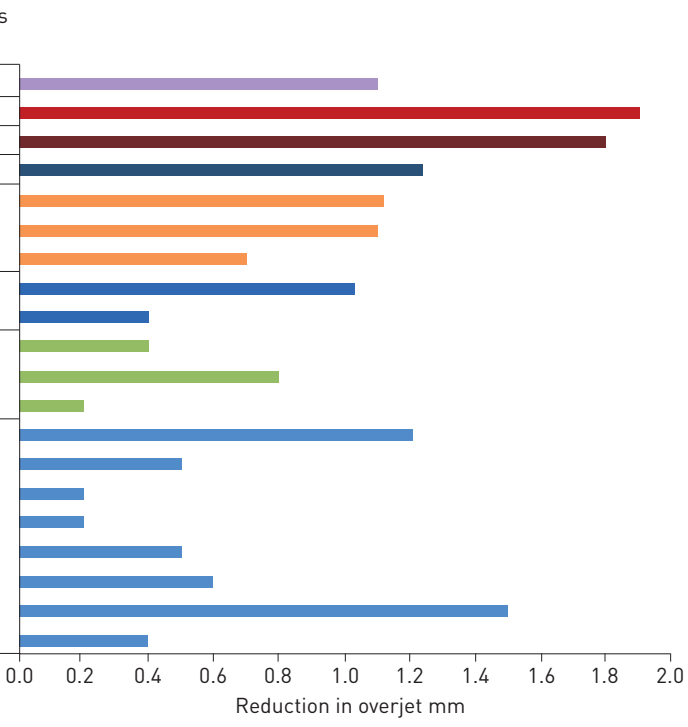

FIGURE 2 Reduction in overjet in various studies. TAP: Thornton Anterior Positioner.

Conclusions

MADs represent an appealing treatment for selected patients with OSA. The variability in efficacy of MADs means, however, that identification of OSA phenotypes that respond to this treatment is urgently needed. Females and younger individuals may be currently undertreated. Standardisation of the methodology is required and the longer term health outcomes have to be explored further.

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