Eur Respir J 2012; 39: 1241–1247
DOI: 10.1183/09031936.00144711

REVIEW

Non-CPAP therapies in obstructive sleep apnoea: mandibular advancement device therapy

Marie Marklund*, Johan Verbraecken# and Winfried Randerath¶

ABSTRACT: Mandibular advancement devices (MADs) represent the main non-continuous positive airway pressure (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 apnoea/hypopnoea index (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 compared with CPAP, in terms of the effects on sleep-disordered breathing and on other diseases related to OSA.

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.

KEYWORDS: Mandibular advancement device, mandibular advancement splint, mandibular repositioning appliance, oral appliance, sleep apnoea

AFFILIATIONS
*Dept of Orthodontics, Faculty of Medicine, Umeå University, Umeå, Sweden.
#Dept of Pulmonary Medicine and Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium.
¶Bethanien Hospital, Institute of Pneumology, University Witten/Herdecke, Solingen, Germany.

CORRESPONDENCE
M. Marklund
Dept of Orthodontics
Umeå University
SE-901 87 Umeå
Sweden
E-mail: Marie.Marklund@odont.umu.se

Received:
Aug 22 2011
Accepted after revision:
Nov 01 2011
First published online:
Nov 10 2011

Mandibular advancement devices (MADs) represent the main non-continuous positive airway pressure (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 a MAD to 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

This article has supplementary material available from www.erj.ersjournals.com

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

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 review.

SEARCH CRITERIA

A literature search ending on January 1, 2009 was performed, with additional searches 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 for clinical trials and randomised controlled trials used PubMed with the following Mesh terms: sleep apnoea syndromes AND orthodontic appliances; functional or removable activator appliances or mandibular advancement. In addition, a search in PubMed was performed using the following terms: sleep apnoea AND oral appliances; mandibular advancement devices; mandibular advancement splints; mandibular repositioning appliances; or mandibular repositioning splints. The Cochrane 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 randomised controlled trials (RCTs) or the aims were not directly related to the efficacy of the device.

29 randomised studies of the treatment effects of MADs [10–38] and five 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

The 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 yrs, compared with CPAP [12], surgery [37] or between two types of MAD [21]. The sample sizes ranged between 19 and 114 patients, with 15–103 patients completing the trials. Eight out of the 17 RCTs comparing MADs with placebo or CPAP evaluated $\leqslant$25 patients, while six studies included >70 completing participants. The patients were overweight or obese; their range of mean body mass index was 27–33 $kg \cdot m^{-2}$. The range of mean age of the included patients was 44–57 yrs. The mean Epworth Sleepiness Scale (ESS) values ranged 8–14. The completing samples comprised 69–100% males.

The majority (74%) of the RCTs used polysomnography (PSG), 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 OSA

MADs reduced AHI or RDI compared with placebo devices in all studies [11, 22, 23, 25, 28–30]. CPAP was more effective in reducing OSA, 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 mean AHI or RDI of 10–50. With MADs, AHI or RDI decreased to mean values of 4.5–34, which corresponded to reductions in the frequency of respiratory disturbances of means of 28–80% (mean reduction from all studies of 55%). CPAP reduced the indices from means of 18–40 to treated values of 2.4–8.0 [13, 16–18, 24, 26, 32, 34]. This corresponded to reductions of 74–94% (mean reduction from all studies of 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 having 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 multiple sleep latency test by a 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 maintenance of wakefulness test (MWT) [16] or the Osler test [19]. Another study revealed no effect of 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 with a MAD as with 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 the 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 neurobehavioural 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-h diastolic blood pressure was found, together with a halving of the mean AHI, as a result of a 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 of intervention [13]. The 24-h 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 a MAD or CPAP [43]. There was a smaller reduction in AHI but a higher compliance with the MAD than with CPAP during 2 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 1 yr 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 1 yr 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 N-terminal pro-brain natriuretic peptide 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 <5 with MADs, was reported in eight out of 26 patients with severe OSA and in 21 out of 25 patients with mild to moderate OSA [24]. The success rate was similar for MADs and CPAP in patients with mild to moderate OSA, as 20 out of a further 25 patients who had been randomised to CPAP treatment had a successful outcome [24]. Younger or leaner patients, females 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 clear collapse in poor responders visualised by nasendoscopy [45]. A previous small study produced similar results by magnetic resonance imaging [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] have 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 $\leqslant$10 mmHg 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 OSA 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 in order 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 4–14 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 for measuring and defining the degree of mandibular repositioning in the individual patient, which causes uncertainty regarding comparisons between studies.

DEVICE DESIGN

MADs 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 2 yrs of 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 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 out 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 optimise 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.

A 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]. Therefore, the patients 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 1 yr, 76% of the patients were still on treatment [55] and, after 2–4 yrs, 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 2 yrs, MADs effectively reduced the AHI 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 yrs, the AHI was still significantly reduced by MADs, although the treated index was higher than after 1 yr [37]. The only longer-term comparison between MADs and CPAP revealed a larger reduction in AHI as a result of using CPAP compared with MADs after 1 yr 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 a 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.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Chan AS, Sutherland K, Schwab RJ, *et al.* The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. *Thorax* 2010; 65: 726–732.
2 Kyung SH, Park YC, Pae EK. Obstructive sleep apnea patients with the oral appliance experience pharyngeal size and shape changes in three dimensions. *Angle Orthod* 2005; 75: 15–22.
3 Ng AT, Gotsopoulos H, Qian J, *et al.* Effect of oral appliance therapy on upper airway collapsibility in obstructive sleep apnea. *Am J Respir Crit Care Med* 2003; 168: 238–241.
4 Almeida FR, Tsuiki S, Hattori Y, *et al.* Dose-dependent effects of mandibular protrusion on genioglossus activity in sleep apnoea. *Eur Respir J* 2011; 37: 209–212.
5 Kurtulmus H, Cotert S, Bilgen C, *et al.* The effect of a mandibular advancement splint on electromyographic activity of the submental and masseter muscles in patients with obstructive sleep apnea. *Int J Prosthodont* 2009; 22: 586–593.
6 Randerath WJ, Verbraecken J, Andreas S, *et al.* Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J* 2011; 37: 1000–1028.
7 Kushida CA, Morgenthaler TI, Littner MR, *et al.* Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. *Sleep* 2006; 29: 240–243.
8 Lim J, Lasserson TJ, Fleetham J, *et al.* Oral appliances for obstructive sleep apnoea. *Cochrane Database Syst Rev* 2006; 1: CD004435.
9 Chan AS, Cistulli PA. Oral appliance treatment of obstructive sleep apnea: an update. *Curr Opin Pulm Med* 2009; 15: 591–596.

10 Aarab G, Lobbezoo F, Hamburger HL, *et al.* Effects of an oral appliance with different mandibular protrusion positions at a constant vertical dimension on obstructive sleep apnea. *Clin Oral Investig* 2010; 14: 339–345.

11 Aarab G, Lobbezoo F, Hamburger HL, *et al.* Oral appliance therapy *versus* nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial. *Respiration* 2011; 81: 411–419.

12 Aarab G, Lobbezoo F, Heymans MW, *et al.* Long-term follow-up of a randomized controlled trial of oral appliance therapy in obstructive sleep apnea. *Respiration* 2011; 82: 162–168.

13 Barnes M, McEvoy RD, Banks S, *et al.* Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. *Am J Respir Crit Care Med* 2004; 170: 656–664.

14 Blanco J, Zamarron C, Abeleira Pazos MT, *et al.* Prospective evaluation of an oral appliance in the treatment of obstructive sleep apnea syndrome. *Sleep Breath* 2005; 9: 20–25.

15 Bloch KE, Iseli A, Zhang JN, *et al.* A randomized, controlled crossover trial of two oral appliances for sleep apnea treatment. *Am J Respir Crit Care Med* 2000; 162: 246–251.

16 Engleman HM, McDonald JP, Graham D, *et al.* Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. *Am J Respir Crit Care Med* 2002; 166: 855–859.

17 Ferguson KA, Ono T, Lowe AA, *et al.* A randomized crossover study of an oral appliance *vs* nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. *Chest* 1996; 109: 1269–1275.

18 Ferguson KA, Ono T, Lowe AA, *et al.* A short-term controlled trial of an adjustable oral appliance for the treatment of mild to moderate obstructive sleep apnoea. *Thorax* 1997; 52: 362–368.

19 Gagnadoux F, Fleury B, Vielle B, *et al.* Titrated mandibular advancement *versus* positive airway pressure for sleep apnoea. *Eur Respir J* 2009; 34: 914–920.

20 Gauthier L, Laberge L, Beaudry M, *et al.* Efficacy of two mandibular advancement appliances in the management of snoring and mild-moderate sleep apnea: a cross-over randomized study. *Sleep Med* 2008; 10: 329–336.

21 Ghazal A, Sorichter S, Jonas I, *et al.* A randomized prospective long-term study of two oral appliances for sleep apnoea treatment. *J Sleep Res* 2009; 18: 321–328.

22 Gotsopoulos H, Chen C, Qian J, *et al.* Oral appliance therapy improves symptoms in obstructive sleep apnea: a randomized, controlled trial. *Am J Respir Crit Care Med* 2002; 166: 743–748.

23 Hans MG, Nelson S, Luks VG, *et al.* Comparison of two dental devices for treatment of obstructive sleep apnea syndrome (OSAS). *Am J Orthod Dentofacial Orthop* 1997; 111: 562–570.

24 Hoekema A, Stegenga B, Wijkstra PJ, *et al.* Obstructive sleep apnea therapy. *J Dent Res* 2008; 87: 882–887.

25 Johnston CD, Gleadhill IC, Cinnamond MJ, *et al.* Mandibular advancement appliances and obstructive sleep apnoea: a randomized clinical trial. *Eur J Orthod* 2002; 24: 251–262.

26 Lam B, Sam K, Mok WY, *et al.* Randomised study of three non-surgical treatments in mild to moderate obstructive sleep apnoea. *Thorax* 2007; 62: 354–359.

27 Lawton HM, Battagel JM, Kotecha B. A comparison of the Twin Block and Herbst mandibular advancement splints in the treatment of patients with obstructive sleep apnoea: a prospective study. *Eur J Orthod* 2005; 27: 82–90.

28 Mehta A, Qian J, Petocz P, *et al.* A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. *Am J Respir Crit Care Med* 2001; 163: 1457–1461.

29 Naismith SL, Winter VR, Hickie IB, *et al.* Effect of oral appliance therapy on neurobehavioral functioning in obstructive sleep apnea: a randomized controlled trial. *J Clin Sleep Med* 2005; 1: 374–380.

30 Petri N, Svanholt P, Solow B, *et al.* Mandibular advancement appliance for obstructive sleep apnoea: results of a randomised placebo controlled trial using parallel group design. *J Sleep Res* 2008; 17: 221–229.

31 Pitsis AJ, Darendeliler MA, Gotsopoulos H, *et al.* Effect of vertical dimension on efficacy of oral appliance therapy in obstructive sleep apnea. *Am J Respir Crit Care Med* 2002; 166: 860–864.

32 Randerath WJ, Heise M, Hinz R, *et al.* An individually adjustable oral appliance *vs* continuous positive airway pressure in mild-to-moderate obstructive sleep apnea syndrome. *Chest* 2002; 122: 569–575.

33 Rose E, Staats R, Virchow C, *et al.* A comparative study of two mandibular advancement appliances for the treatment of obstructive sleep apnoea. *Eur J Orthod* 2002; 24: 191–198.

34 Tan YK, L'Estrange PR, Luo YM, *et al.* Mandibular advancement splints and continuous positive airway pressure in patients with obstructive sleep apnoea: a randomized cross-over trial. *Eur J Orthod* 2002; 24: 239–249.

35 Tegelberg A, Walker-Engstrom ML, Vestling O, *et al.* Two different degrees of mandibular advancement with a dental appliance in treatment of patients with mild to moderate obstructive sleep apnea. *Acta Odontol Scand* 2003; 61: 356–362.

36 Walker-Engstrom ML, Ringqvist I, Vestling O, *et al.* A prospective randomized study comparing two different degrees of mandibular advancement with a dental appliance in treatment of severe obstructive sleep apnea. *Sleep Breath* 2003; 7: 119–130.

37 Walker-Engstrom ML, Tegelberg A, Wilhelmsson B, *et al.* 4-year follow-up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea: a randomized study. *Chest* 2002; 121: 739–746.

38 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. *Am J Respir Crit Care Med* 2008; 178: 197–202.

39 Gotsopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized, controlled trial. *Sleep* 2004; 27: 934–941.

40 Hoekema A, Stegenga B, Bakker M, *et al.* Simulated driving in obstructive sleep apnoea-hypopnoea; effects of oral appliances and continuous positive airway pressure. *Sleep Breath* 2007; 11: 129–138.

41 Hoekema A, Stel AL, Stegenga B, *et al.* Sexual function and obstructive sleep apnea-hypopnea: a randomized clinical trial evaluating the effects of oral-appliance and continuous positive airway pressure therapy. *J Sex Med* 2007; 4: 1153–1162.

42 Hoekema A, Voors AA, Wijkstra PJ, *et al.* Effects of oral appliances and CPAP on the left ventricle and natriuretic peptides. *Int J Cardiol* 2008; 128: 232–239.

43 Trzepizur W, Gagnadoux F, Abraham P, *et al.* Microvascular endothelial function in obstructive sleep apnea: impact of continuous positive airway pressure and mandibular advancement. *Sleep Med* 2009; 10: 746–752.

44 Bosshard V, Masse JF, Series F. Prediction of oral appliance efficiency in patients with apnoea using phrenic nerve stimulation while awake. *Thorax* 2011; 66: 220–225.

45 Chan ASL, Lee RWW, Srinivasan VK, *et al.* Nasopharyngoscopic evaluation of oral appliance therapy for obstructive sleep apnoea. *Eur Respir J* 2010; 35: 836–842.

46 Chan AS, Lee RW, Srinivasan VK, *et al.* Use of flow–volume curves to predict oral appliance treatment outcome in obstructive sleep apnea: a prospective validation study. *Sleep Breath* 2011; 15: 157–162.

47 Coruzzi P, Gualerzi M, Bernkopf E, *et al.* Autonomic cardiac modulation in obstructive sleep apnea: effect of an oral jaw-positioning appliance. *Chest* 2006; 130: 1362–1368.

48 De Backer JW, Vanderveken OM, Vos WG, *et al.* Functional imaging using computational fluid dynamics to predict treatment success of mandibular advancement devices in sleep-disordered breathing. *J Biomech* 2007; 40: 3708–3714.

49 Dort LC, Hadjuk E, Remmers JE. Mandibular advancement and obstructive sleep apnoea: a method for determining effective mandibular protrusion. *Eur Respir J* 2006; 27: 1003–1009.

50 Fleury B, Rakotonanahary D, Petelle B, *et al.* Mandibular advancement titration for obstructive sleep apnea: optimization of the procedure by combining clinical and oximetric parameters. *Chest* 2004; 125: 1761–1767.

51 Itzhaki S, Dorchin H, Clark G, *et al.* The effects of 1-year treatment with a Herbst mandibular advancement splint on obstructive sleep apnea, oxidative stress, and endothelial function. *Chest* 2007; 131: 740–749.

52 Kato J, Isono S, Tanaka A, *et al.* Dose-dependent effects of mandibular advancement on pharyngeal mechanics and nocturnal oxygenation in patients with sleep-disordered breathing. *Chest* 2000; 117: 1065–1072.

53 Liu Y, Lowe AA, Fleetham JA, *et al.* Cephalometric and physiologic predictors of the efficacy of an adjustable oral appliance for treating obstructive sleep apnea. *Am J Orthod Dentofacial Orthop* 2001; 120: 639–647.

54 Lowe AA, Sjoholm TT, Ryan CF, *et al.* Treatment, airway and compliance effects of a titratable oral appliance. *Sleep* 2000; 23: Suppl. 4, S172–S178.

55 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: 1270–1278.

56 Ng AT, Qian J, Cistulli PA. Oropharyngeal collapse predicts treatment response with oral appliance therapy in obstructive sleep apnea. *Sleep* 2006; 29: 666–671.

57 Sanner BM, Heise M, Knoben B, *et al.* MRI of the pharynx and treatment efficacy of a mandibular advancement device in obstructive sleep apnoea syndrome. *Eur Respir J* 2002; 20: 143–150.

58 Skinner MA, Robertson CJ, Kingshott RN, *et al.* The efficacy of a mandibular advancement splint in relation to cephalometric variables. *Sleep Breath* 2002; 6: 115–124.

59 Tsuiki S, Kobayashi M, Namba K, *et al.* Optimal positive airway pressure predicts oral appliance response to sleep apnoea. *Eur Respir J* 2010; 35: 1098–1105.

60 Zeng B, Ng AT, Darendeliler MA, *et al.* Use of flow–volume curves to predict oral appliance treatment outcome in obstructive sleep apnea. *Am J Respir Crit Care Med* 2007; 175: 726–730.

61 Zeng B, Ng AT, Qian J, *et al.* Influence of nasal resistance on oral appliance treatment outcome in obstructive sleep apnea. *Sleep* 2008; 31: 543–547.