



**TITLE: Oral Appliances for Treatment of Snoring and Obstructive Sleep Apnea: A Review of Clinical-Effectiveness**

**DATE:** 20 April 2009

**CONTEXT AND POLICY ISSUES:**

Obstructive sleep apnea (OSA) syndrome is a disorder characterized by repetitive or partial closure of the upper airway during sleep, resulting in sleep fragmentation and oxygen desaturation.<sup>1</sup> OSA is defined as more than five apneas and/or hypopneas per hour of sleep [i.e., the apnea hypopnea index (AHI) being greater than five per hour].<sup>2</sup> The symptoms are snoring, excessive daytime sleepiness, and deficits in neuropsychological function.<sup>1</sup> Long-term untreated OSA is associated with cardiovascular morbidity, including hypertension, myocardial infarction, and stroke.<sup>2</sup>

Continuous positive airway pressure (CPAP) is the most effective treatment to control respiratory abnormalities during sleep.<sup>3</sup> CPAP applies to the upper airway through a nose mask during sleep and requires sealed tubing and a device connected to a power source. Many patients refuse or discontinue CPAP therapy due to its cumbersome nature.<sup>3</sup>

Oral appliances (OA) are a simpler alternative to CPAP for the treatment of OSA.<sup>4-6</sup> Two types of OA are mandibular advancement devices (MAD) and tongue-retaining devices (TRD).<sup>4</sup> MAD generally attach to the dental arches and mechanically protrude the mandible, while TRD uses suction pressure to maintain the tongue in a protruded position during sleep.<sup>4</sup> Hence, MAD requires patients to have sufficient teeth, whereas TRD can be used by edentulous patients.<sup>4</sup> MAD is the most common type of OA being tested in many studies.<sup>4</sup>

This report reviews the clinical-effectiveness, compliance, and side effects of OA for the treatment of snoring and OSA.

**RESEARCH QUESTION:**

What are the clinical-effectiveness, compliance, and side effects of oral appliances for the treatment of snoring and obstructive sleep apnea?

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**METHODS:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 1, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. Results include articles published between 2004 and March, 2009, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, and observational studies. Internet links are provided, where available.

**SUMMARY OF FINDINGS:**

Three systematic reviews/meta-analyses,<sup>7-9</sup> nine randomized controlled trials,<sup>10-18</sup> and 26 observational studies<sup>19-44</sup> were identified on the effects of oral appliances for OSA. No health technology assessments or controlled clinical trials were identified.

**Systematic reviews and meta-analyses**

Lim et al. (2009)<sup>7</sup> reviewed the effects of oral appliance (OA) in the treatment of obstructive sleep apnea-hypopnea (OSAH) in adults. The selection criteria were randomized controlled trials (RCT) comparing OA with control or other treatment. Seventeen trials (831 participants) were included for analysis. Six trials reported data comparing mandibular advancement devices (MAD) or active OA to devices that did not protrude the mandible. Ten trials compared data on OA to CPAP. One study reported data for OA versus upper airway surgery. Shortcomings of the trials included small sample size, under reporting of methods and data, and lack of blinding. Appendix 1 shows comparative data of active OA versus control OA, active OA versus CPAP, and active OA versus surgery.

*Active OA versus control OA*

Active OA significantly reduced Epworth Sleepiness Scores (ESS, a measurement of daytime sleepiness), apnea hypopnea index (AHI), and arousal index. Active OA significantly improved minimum arterial oxygen saturation (MinSaO<sub>2</sub>) in the crossover studies, but not from the parallel studies. There was no significant difference between active and control OA for numbers of patients who stopped using the device (withdrawals). One trial reported blood pressure outcomes, where active OA therapy led to lower blood pressure compared to control, particularly blood pressure taken for 24 hours and during the day (diurnal). Three crossover trials reported side effects and tolerability. Participants given the active OA suffered side effects more frequently than those given the control device. Most frequent side effects reported were jaw discomfort, tooth tenderness, excessive salivation, mouth dryness, and gum irritation. Compliance was 68% for OA (wearing device almost every night).

*Active OA versus CPAP*

There was no statistically significant difference in term of ESS between treatments. OA was significantly less effective in reducing apnea/hypopnea, MinSaO<sub>2</sub>, and arousal index scores than CPAP as shown in both parallel and crossover trials. Patients treated with OA were more likely to withdraw than those treated with CPAP. Noticeable adverse effects such as jaw and oral pain occurred more frequently with OA. There were higher rates of excessive salivation and appliance removal during sleep with OA, while there were higher rates of leak, dry upper airway, stuffy nose, and inconvenience with CPAP. No statistically significant differences on blood pressure were observed. There were conflicting results in terms of quality of life and preference.

Some studies showed that there was no statistically significant difference between treatment groups, while the others showed a significant effect in favor of CPAP versus OA.

### *Active OA versus upper airway surgery*

Symptoms of daytime sleepiness were initially lower with surgery, but the difference disappeared at 12 months. Mean AHI was not different between OA and surgery at six months, but was statistically different at 12 months and four years in favor of OA. Oxygen desaturation indices were not significantly different at six months and 12 months, but were significantly different at four years follow-up. For quality of life, there were improvements in both groups compared with baseline in terms of vitality and sleep. At 12 months, there was a significant difference detected in favor of surgery on the contentment component (27.4 in OA versus 33.7 in surgery,  $p < 0.05$ ). No difference was detected between groups on vitality and sleep components.

The authors concluded that OA improves subjective sleepiness and sleep disordered breathing compared with a control. CPAP appears to be more effective in improving sleep disordered breathing than OA. OA therapy should be recommended to patients with mild OSA, and those patients who are unwilling and are unable to tolerate CPAP therapy.

Hoekema et al. (2004)<sup>8</sup> reviewed the efficacy and co-morbidity of OA therapy in OSAH syndrome. Sixteen controlled trials related to efficacy were included. Fourteen trials used crossover design and two applied a parallel study design. The overall quality of the 16 trials was adequate (ranged from 38 to 86 points, maximum 100 points). Shortcomings of the trials included lack of blinding to the assessors and lack of details of randomization. Fourteen studies related to co-morbidity were included. The majority of included studies were patient series and they are rated as adequate, despite the non-controlled design of most studies.

### *Active OA versus control devices*

Control devices were designed to increase vertical opening minimally without advancing the mandible. Compared with the control devices, all four trials reported that active OA therapy was more effective in improving AHI, mean arousal index, MinSaO<sub>2</sub>, and snoring frequency and intensity. Active OA therapy improved both subjective and objective daytime sleepiness. Although patients generally experienced more side effects with OA therapy, poorer patient satisfaction, and compliance were reported with control devices.

### *Active OA versus upper airway surgery*

One trial compared the effect of OA treatment with surgery. At one year treatment, OA was more effective in improving AHI compared with surgery. Other physiological parameters such as oxygen desaturation, registered snoring time, and daytime sleepiness did not differ between treatments. The surgery group showed a greater level of contentment than the OA-treated patients after one year treatment.

### *Active OA versus CPAP*

Compared with OA treatment, CPAP resulted in a significant improvement in the AHI in five out of six trials and MinSaO<sub>2</sub> in three trials. There was no difference in arousal index and ESS between interventions. CPAP was more effective in reducing the frequency of snoring compared with OA. The included studies showed conflicting results on quality of life between interventions.

### *Co-morbidity*

Eight of included articles studied co-morbidity of active OA on the craniomandibular complex, and six articles assessed orthodontic side effects (dental and skeletal changes) of active OA by

means of upright cephalometry. Some changes in the craniomandibular complex were observed with OA therapy. The degree of significance varied between studies. For cranial facial complex, significant decreases in dental overbite and overjet were observed with OA therapy.

The authors concluded that OA therapy is a viable treatment for mild-to-moderate OSA, despite the higher effectiveness of CPAP and adverse effects of OA.

Carvalho (2009)<sup>9</sup> reviewed the efficacy of oral appliances or functional orthopaedic appliances for OSA in children. One study was included. The study was a quasi-randomized controlled trial comparing personalized oral appliance versus no treatment. Participants were 32 patients of four years to 10 years of age, with AHI >1. Follow-up was 6 months.

Compared to baseline, the treated group had a significant reduction in night-time symptoms including habitual snoring ( $p < 0.001$ ) and restless sleep ( $p < 0.001$ ) at six months. For daytime symptoms, OA therapy significantly improved sleepiness ( $p = 0.002$ ), irritability ( $p < 0.001$ ), tiredness ( $p = 0.002$ ), thirst in the morning ( $p = 0.002$ ), oral breathing ( $p < 0.002$ ), and nasal stuffiness ( $p < 0.001$ ). There was no significant change in school problems or morning headache. The control group had no significant differences in either night-time symptoms or daytime symptoms compared with the baseline at six months. OA therapy reduced AHI by at least 50% from  $7.1 \pm 4.6$  to  $2.6 \pm 2.2$  ( $p < 0.001$ ). Compliance was 73.7%, while 26.3% discontinued therapy.

The authors concluded that there is no sufficient evidence to state that OA or functional orthopaedic appliances are effective in the treatment of OSA in children.

### Randomized controlled trials

Appendix 2 summarizes the characteristics, outcomes, compliance, and side effects of oral appliances (OA) in nine trials. Of the included RCTs, four used parallel design,<sup>12-15</sup> while the remaining five were cross-over trials.<sup>10,11,16-18</sup> One trial<sup>10</sup> evaluated the efficacy of tongue retaining device and the rest assessed the efficacy of mandibular advancement device (MAD) as OA therapy for the treatment of snoring and OSA.

#### *Tongue retaining device (active suction versus non-suction)*

One RCT by Dort et al. (2008)<sup>10</sup> with a two-period crossover design of 1 week per period with a 1-week washout period. The participants were 38 patients of mild-to-moderate OSA or severe OSA who failed CPAP therapy. The active suction device significantly reduced AHI and snoring index compared with the non-suction device. Compliance was 54% for the active suction device and 12% for the non-suction device. Thus, the RCT showed that the tongue retaining suction device showed better outcomes than the non-suction device.

#### *Custom-made MAD (MAD<sub>CM</sub>) versus pre-fabricated MAD (MAD<sub>PF</sub>)*

One RCT by Vandervaken et al. (2008)<sup>11</sup> with a two-period crossover design of 4 months per period and 1 month washout was identified. The MAD<sub>CM</sub> was tailored-made to the patient's dentition with a laboratory-controlled protrusion. The fitting of MAD<sub>PF</sub> started from a pre-fabricated mold out of polymeric material, allowing for adjustment and advancement. Thirty-eight OSA patients participated in the study (AHI: 20-40). AHI was significantly reduced with MAD<sub>CM</sub> ( $p = 0.005$ ); no difference in AHI was seen with MAD<sub>PF</sub>. Treatment success was higher with MAD<sub>CM</sub> compared with MAD<sub>PF</sub> (60% versus 31%). Compliance failure was lower with MAD<sub>CM</sub> compared with MAD<sub>PF</sub> (6% versus 31%) and 82% preferred MAD<sub>CM</sub> while 9% had no preference. The authors concluded that custom-made MAD was more effective than a thermoplastic device in the treatment of sleep-disordered breathing.

*MAD versus mandibular non-advancement device (MND)*

Four RCTs<sup>12,15,16,18</sup> comparing the efficacy of MAD versus MND, which had no mandibular advancement function, were identified. The MND is also referred to as inactive oral device or control oral appliance. Total participants were 251 OSA patients (ranged from 24 to 93 patients). Details of outcomes, compliance, and side effects of each trial are summarized in Appendix 2. Overall, MAD was better than MND in the improvement of AHI, daytime sleepiness, snoring, and quality of life. One trial<sup>18</sup> showed a significant reduction in blood pressure in the MAD treatment group. Limited information on compliance and side effects were reported in those trials. All trials concluded that MAD offers a better treatment of OSA than MND.

*Non-adjustable OA versus CPAP*

One RCT by Lam et al. (2007)<sup>13</sup> using parallel design was identified. Among the 101 OSA patients (AHI: 21.4 ± 1.1), CPAP was significantly better than non-adjustable OA in improving AHI, overall quality of life, and morning diastolic blood pressure. Side effects of OA included excessive salivation, temporomandibular joint discomfort, dry throat, and tooth discomfort. The authors concluded that CPAP produced the best improvement in terms of physiological, symptomatic, and health-related quality of life measures, while the OA was slightly less effective.

*MAD versus CPAP*

Two trials (one parallel<sup>14</sup> and one crossover<sup>17</sup> design) having 48 and 114 OSA patients, respectively, were identified. The study period was 8 weeks for the parallel RCT and three months per period with two weeks washout for the crossover trial. Hoekema et al. (2007)<sup>14</sup> evaluated the effects of MAD and CPAP on sexual functioning. It was found that no significant changes in the sexual satisfaction or testosterone levels were observed in the patients who underwent MAD and CPAP therapy. Barnes et al. (2004)<sup>17</sup> evaluated the efficacy of CPAP and MAD therapy of mild-to-moderate OSA. It was found that CPAP and MAD both improved sleep outcomes (AHI), but CPAP had a greater effect. Both active treatments improved quality of life, symptoms, and subjective sleepiness in a similar fashion. Thus, the RCTs indicated that CPAP was more effective than MAD in treating obstructive breathing events, whereas both therapies had no significant changes in sexual functioning.

**Observational studies**

Appendix 3 summarizes the characteristics, outcomes, compliance, and side effects of MAD from 26 included articles, which studied the effects of MAD therapy on various clinical aspects of snoring and OSA. The numbers of participants ranged from 10 to 544, including mild, moderate and severe OSA, as well as non-OSA patients with severe snoring. Most were case series with pre-post treatment comparison. Of the included studies, all reported effectiveness except six studies.<sup>20,21,23,31,32,36</sup> Fourteen studies<sup>19,21,22,25,28,32-34,37,40-44</sup> also reported compliance and 17 studies<sup>19-24,27,28,32,36,37,39-44</sup> also reported side effects.

*Effectiveness*

Compared to baseline, MAD therapy significantly improved AHI, oxygen desaturation, snoring, daytime sleepiness, and blood pressure. Treatment effectiveness, including complete and partial responses in improving AHI and snoring, ranged from 52% to 97%. One study<sup>33</sup> showed that OA altered upper airway morphometry towards a profile consistent with decreased propensity to collapse, which may have contributed to improvement of OSA. Most studies showed that AHI was reduced more than 50% compared to baseline. One study correlated a modest decrease in blood pressure with the reduction in AHI.<sup>34</sup> Snoring was satisfactorily

controlled in 75% users in two studies,<sup>39,40</sup> and 86% of subjects' partners had better quality of sleep as reported in one study.<sup>39</sup> In predicting the treatment success for an individually adjusted, one piece MAD in patients with snoring and OSA, one study<sup>42</sup> found that women with sleep apnea (both supine and lateral position) and men with supine dependent sleep apneas, as well as snorers without sleep apnea had a high likelihood of success.

### *Compliance*

In the 14 studies reporting compliance, the compliance ranged from 88% to 51% (median 65%).<sup>19,21,22,25,28,32-34,37,40-44</sup> A survey<sup>21</sup> of 180 OSA patients who had been using MAD for 10 years reported a 65% compliance, of which 47% wore the device every night and 18% wore the device up to 6 nights per week. A second survey<sup>28</sup> of 260 snoring and OSA patients who were treated with OA for over 5 years showed that, of the respondents, 51.9% were frequent users, 17.8% were infrequent users, 14% were discontinued, and 16% had modified treatment. Mild cases of OSA were likely to continue treatment than more severe cases. A third survey<sup>40</sup> of 544 patients who used OA for treatment of snoring or OSA for over five years concluded that subjects who were compliant with OA therapy reported long periods of use and adequate control of snoring.

### *Side effects*

No serious side effects of causes of pathology of aggravation occurred in the 17 studies that reported side effects.<sup>19-24,27,28,32,36,37,39-44</sup> Common side effects included jaw discomfort, tooth tenderness, excessive salivation, difficulty sleeping, difficulty breathing, dental damage, and dry mouth. These side effects often prevented the use of MAD.<sup>37</sup> Orthodontic side effects were occlusal changes including significant reductions in overbite and overjet. Two studies<sup>20,36</sup> showed that after long-term use (>5 years), OA appeared to cause changes in tooth positions that also might affect mandibular posture.

### **Limitations**

Since OSA is associated with cardiovascular mortality, long-term data on cardiovascular health with OA use in OSA patients are lacking. Evidence on the effectiveness of OA in children and patients with more severe symptoms of OSA is inadequate. Evidence on the effectiveness of a tongue-retaining device, another form of OA, was also insufficient. The assessment on the effect of variations in OA design on clinical outcomes is currently lacking.

### **CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:**

The literature showed that compared with inactive devices or compared to pre-treatment, MAD therapy is effective in improving sleep disordered breathing and quality of life in snoring and OSA patients. The compliance for MAD therapy was high in the included studies, and patients who were compliant tended to be long-term users. There were no serious adverse events associated with MAD therapy in the literature, but occlusal changes were noted over long period of use. Some common side effects, which occurred during acclimatization period in the studies, were usually minor and self-limiting, but they could discourage some patients to continue the therapy. The literature indicated that both MAD and CPAP treatments improved sleep outcomes, but CPAP was found to be more effective. Compared with upper airway surgery, MAD therapy appeared to be more effective over long-term use. Thus, MAD may be a simpler alternative to CPAP and surgery. Recent systematic reviews/meta-analyses recommended the prescription of MAD therapy to patients with mild-to-moderate OSA, and those patients who are unwilling and are unable to tolerate CPAP therapy. There is evidence that patients with mild cases of OSA were likely to continue treatment than patients with more severe cases. One

study recommended MAD for all women with sleep apnea, for men with supine dependent sleep apnea, and for non-OSA snorers.

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## REFERENCES:

1. Flemons WW. Obstructive sleep apnea. *N Engl J Med* 2002;347(7):498-504 (accessed 2009 Apr 16).
2. Scottish Intercollegiate Guidelines Network. *Management of obstructive sleep apnoea/hypopnoea syndrome in adults: a national clinical guideline*. Edinburgh: The Network; 2003 Jun. Clinical guideline no 73. Available: <http://www.sign.ac.uk/pdf/sign73.pdf> (accessed 2009 Apr 16).
3. LifeShirt: non-invasive sleep diagnostics for the clinic or for the home. In: *VivoMetrics* [Internet site]. Ventura (CA): VivaMetrics; 2008. Available: <http://www.vivometrics.com/lifeshirt/lifeshirt-technology> (accessed 2009 Apr 20).
4. Chan AS, Lee RW, Cistulli PA. Dental appliance treatment for obstructive sleep apnea. *Chest* 2007;132(2):693-9. Available: <http://www.chestjournal.org/content/132/2/693.full.pdf+html> (accessed 2009 Apr 20).
5. Ng A, Gotsopoulos H, Darendeliler AM, Cistulli PA. Oral appliance therapy for obstructive sleep apnea. *Treat Respir Med* 2005;4(6):409-22.
6. Cuccia AM, Caradonna C. Mandibular advancement devices: indications and predictors of treatment outcome. A review. *Minerva Stomatol* 2007;56(9):427-43.
7. Lim J, Lasserson TJ, Fleetham J, Wright J. Oral appliances for obstructive sleep apnoea [Cochrane review]. *Cochrane Database Syst Rev* 2006;(1):CD004435.
8. Hoekema A, Stegenga B, de Bont LG. Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. *Crit Rev Oral Biol Med* 2004;15(3):137-55.
9. Carvalho FR, Lentini-Oliveira D, Machado MA, Prado GF, Prado LB, Saconato H. Oral appliances and functional orthopaedic appliances for obstructive sleep apnoea in children [Cochrane review]. *Cochrane Database Syst Rev* 2007;(2):CD005520.
10. Dort L, Brant R. A randomized, controlled, crossover study of a noncustomized tongue retaining device for sleep disordered breathing. *Sleep Breath* 2008;12(4):369-73.
11. Vanderveken OM, Devolder A, Marklund M, Boudewyns AN, Braem MJ, Okkerse W, 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(2):197-202.
12. Petri N, Svanholt P, Solow B, Wildschjødzt G, Winkel P. Mandibular advancement appliance for obstructive sleep apnoea: results of a randomised placebo controlled trial using parallel group design. *J Sleep Res* 2008;17(2):221-9.
13. Lam B, Sam K, Mok WY, Cheung MT, Fong DY, Lam JC, et al. Randomised study of three non-surgical treatments in mild to moderate obstructive sleep apnoea. *Thorax* 2007;62(4):354-9.

14. Hoekema A, Stel AL, Stegenga B, van der Hoeven JH, Wijkstra PJ, van Driel MF, 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(4 Pt 2):1153-62.
15. Blanco J, Zamarrón C, Abeleira Pazos MT, Lamela C, Suarez Quintanilla D. Prospective evaluation of an oral appliance in the treatment of obstructive sleep apnea syndrome. *Sleep Breath* 2005;9(1):20-5.
16. Naismith SL, Winter VR, Hickie IB, Cistulli PA. Effect of oral appliance therapy on neurobehavioral functioning in obstructive sleep apnea: a randomized controlled trial. *J Clin Sleep Med* 2005;1(4):374-80.
17. Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, 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(6):656-64.
18. Gotsopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized, controlled trial. *Sleep* 2004;27(5):934-41.
19. Vecchierini MF, Léger D, Laaban JP, Putterman G, Figueredo M, Levy J, et al. Efficacy and compliance of mandibular repositioning device in obstructive sleep apnea syndrome under a patient-driven protocol of care. *Sleep Med* 2008;9(7):762-9.
20. Ueda H, Almeida FR, Lowe AA, Ruse ND. Changes in occlusal contact area during oral appliance therapy assessed on study models. *Angle Orthod* 2008;78(5):866-72.
21. Jauhar S, Lyons MF, Banham SW, Cameron DA, Orchardson R. Ten-year follow-up of mandibular advancement devices for the management of snoring and sleep apnea. *J Prosthet Dent* 2008;99(4):314-21.
22. Gindre L, Gagnadoux F, Meslier N, Gustin JM, Racineux JL. Mandibular advancement for obstructive sleep apnea: dose effect on apnea, long-term use and tolerance. *Respiration* 2008;76(4):386-92.
23. Otsuka R, Almeida FR, Lowe AA. The effects of oral appliance therapy on occlusal function in patients with obstructive sleep apnea: a short-term prospective study. *Am J Orthod Dentofacial Orthop* 2007;131(2):176-83.
24. Maurer JT, Huber K, Verse T, Hörmann K, Stuck B. A mandibular advancement device for the ENT office to treat obstructive sleep apnea. *Otolaryngol Head Neck Surg* 2007;136(2):231-5.
25. Levendowski DJ, Morgan TD, Patrickus JE, Westbrook PR, Berka C, Zavora T, et al. In-home evaluation of efficacy and titration of a mandibular advancement device for obstructive sleep apnea. *Sleep Breath* 2007;11(3):139-47.
26. Machado MA, Juliano L, Taga M, de Carvalho LB, do Prado LB, do Prado GF. Titratable mandibular repositioner appliances for obstructive sleep apnea syndrome: are they an option? *Sleep Breath* 2007;11(4):225-31.

27. Hammond RJ, Gotsopoulos H, Shen G, Petocz P, Cistulli PA, Darendeliler MA. A follow-up study of dental and skeletal changes associated with mandibular advancement splint use in obstructive sleep apnea. *Am J Orthod Dentofacial Orthop* 2007;132(6):806-14.
28. Marklund M, Franklin KA. Long-term effects of mandibular repositioning appliances on symptoms of sleep apnoea. *J Sleep Res* 2007;16(4):414-20.
29. Itzhaki S, Dorchin H, Clark G, Lavie L, Lavie P, Pillar G. The effects of 1-year treatment with a Herbst mandibular advancement splint on obstructive sleep apnea, oxidative stress, and endothelial function. *Chest* 2007;131(3):740-9. Available: <http://www.chestjournal.org/content/131/3/740.full.pdf+html> (accessed 2009 Mar 30).
30. Otsuka R, Ribeiro de Almeida F, Lowe AA, Linden W, Ryan F. The effect of oral appliance therapy on blood pressure in patients with obstructive sleep apnea. *Sleep Breath* 2006;10(1):29-36.
31. Hou HM, Sam K, Hägg U, Rabie AB, Bendeus M, Yam LY, et al. Long-term dentofacial changes in Chinese obstructive sleep apnea patients after treatment with a mandibular advancement device. *Angle Orthod* 2006;76(3):432-40.
32. Marklund M. Predictors of long-term orthodontic side effects from mandibular advancement devices in patients with snoring and obstructive sleep apnea. *Am J Orthod Dentofacial Orthop* 2006;129(2):214-21.
33. Sam K, Lam B, Ooi CG, Cooke M, Ip MS. Effect of a non-adjustable oral appliance on upper airway morphology in obstructive sleep apnoea. *Respir Med* 2006;100(5):897-902.
34. Yoshida K. Effect on blood pressure of oral appliance therapy for sleep apnea syndrome. *Int J Prosthodont* 2006;19(1):61-6.
35. Kuna ST, Giarraputo PC, Stanton DC, Levin LM, Frantz D. Evaluation of an oral mandibular advancement titration appliance. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;101(5):593-603.
36. Almeida FR, Lowe AA, Sung JO, Tsuiki S, Otsuka R. Long-term sequelae of oral appliance therapy in obstructive sleep apnea patients: Part 1. Cephalometric analysis. *Am J Orthod Dentofacial Orthop* 2006;129(2):195-204.
37. Izci B, McDonald JP, Coleman EL, Mackay TW, Douglas NJ, Engleman HM. Clinical audit of subjects with snoring & sleep apnoea/hypopnoea syndrome fitted with mandibular repositioning splint. *Respir Med* 2005;99(3):337-46.
38. Aarab G, Lobbezoo F, Wicks DJ, Hamburger HL, Naeije M. Short-term effects of a mandibular advancement device on obstructive sleep apnoea: an open-label pilot trial. *J Oral Rehabil* 2005;32(8):564-70.
39. Johal A, Arya D, Winchester LJ, Venn PJ, Brooks H. The effect of a mandibular advancement splint in subjects with sleep-related breathing disorders. *Br Dent J* 2005;199(9):591-6.

40. de Almeida FR, Lowe AA, Tsuiki S, Otsuka R, Wong M, Fastlicht S, et al. Long-term compliance and side effects of oral appliances used for the treatment of snoring and obstructive sleep apnea syndrome. *J Clin Sleep Med* 2005;1(2):143-52.
41. Eskafi M, Ekberg E, Cline C, Israelsson B, Nilner M. Use of a mandibular advancement device in patients with congestive heart failure and sleep apnoea. *Gerodontology* 2004;21(2):100-7.
42. Marklund M, Stenlund H, Franklin KA. Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. *Chest* 2004;125(4):1270-8. Available: <http://www.chestjournal.org/content/125/4/1270.full.pdf+html> (accessed 2009 Mar 30).
43. Vanderveken OM, Boudewyns AN, Braem MJ, Okkerse W, Verbraecken JA, Willems M, et al. Pilot study of a novel mandibular advancement device for the control of snoring. *Acta Otolaryngol* 2004;124(5):628-33.
44. Tsai WH, Vazquez JC, Oshima T, Dort L, Roycroft B, Lowe AA, et al. Remotely controlled mandibular positioner predicts efficacy of oral appliances in sleep apnea. *Am J Respir Crit Care Med* 2004;170(4):366-70.

**Appendix 1: Effects of Interventions from the Lim et al. Systematic Review (2009)<sup>7</sup>**

Interventions	Outcome measures
<b>Active OA versus control OA</b>	
<ul style="list-style-type: none"> <li>• Epworth Sleepiness Scores               <ol style="list-style-type: none"> <li>1. Four parallel (n=130)</li> <li>2. Two crossover (n=91)</li> </ol> </li> </ul>	Mean difference (95% CI) -2.09 (-3.80, -0.37), p=0.02 -1.81 (-2.72, -0.90), p<0.0001
<ul style="list-style-type: none"> <li>• Apnea hypopnea index               <ol style="list-style-type: none"> <li>1. Five parallel (n=156)</li> <li>2. Four crossover (n=155)</li> </ol> </li> </ul>	Mean difference (95% CI) -10.78 (-15.53, -6.03), p<0.00001 -15.15 (-19.40, -10.89), p<0.00001
<ul style="list-style-type: none"> <li>• Minimum arterial oxygen saturation               <ol style="list-style-type: none"> <li>1. Three parallel (n=117)</li> <li>2. Two crossover (n=97)</li> </ol> </li> </ul>	Mean difference (95% CI) 1.79 (-0.29, 3.87), p=0.092 3.39 (2.25, 4.54), p<0.0001
<ul style="list-style-type: none"> <li>• Arousal index               <ol style="list-style-type: none"> <li>1. Three parallel (n=112)</li> <li>2. Two crossover (n=97)</li> </ol> </li> </ul>	Mean difference (95% CI) -10.66 (-16.03, -5.29), p=0.0001 -10.72 (-15.05, -6.39), p<0.00001
<ul style="list-style-type: none"> <li>• Withdrawals (4 trials)               <ol style="list-style-type: none"> <li>1. Three parallel (n=65)</li> </ol> </li> </ul>	Odds ratio (95% CI) 0.83 (0.24, 2.86), p=0.77
<ul style="list-style-type: none"> <li>• Blood pressure (1 trial, n=67)               <ul style="list-style-type: none"> <li>- Systolic BP (24h)</li> <li>- Systolic BP (diurnal)</li> <li>- Systolic BP (nocturnal)</li> <li>- Diastolic BP (24h)</li> <li>- Diastolic BP (diurnal)</li> <li>- Diastolic BP (nocturnal)</li> <li>- Mean BP (24h)</li> <li>- Mean BP (diurnal)</li> <li>- Mean BP (nocturnal)</li> </ul> </li> </ul>	Mean difference (95% CI) -1.50 (-2.87, -0.13) -3.00 (-4.96, -1.04) 0.10 (-2.45, 2.65) -1.60 (-2.58, -0.62) -3.10 (-4.67, -1.53) -0.40 (-2.16, 1.36) -1.50 (-2.48, -0.52) -3.20 (-4.77, -1.63) -0.30 (-2.26, 1.66)
<b>OA versus CPAP</b>	
<ul style="list-style-type: none"> <li>• Epworth Sleepiness Scores               <ol style="list-style-type: none"> <li>1. 3 parallel (n=268)</li> <li>2. 4 crossover (n=168)</li> </ol> </li> </ul>	Mean difference (95% CI) 0.64 (-0.57, 1.86), p=0.30 0.54 (-0.29, 1.38), p=0.20
<ul style="list-style-type: none"> <li>• Apnea hypopnea index               <ol style="list-style-type: none"> <li>1. 4 parallel (n=283)</li> <li>2. 7 crossover (n=192)</li> </ol> </li> </ul>	Mean difference (95% CI) 9.08 (4.78, 13.38), p=0.000034 7.97 (6.38, 9.56), p<0.00001
<ul style="list-style-type: none"> <li>• Minimum arterial oxygen saturation               <ol style="list-style-type: none"> <li>1. 3 parallel (n=189)</li> <li>2. 4 crossover (n=139)</li> </ol> </li> </ul>	Mean difference (95% CI) 4.59 (2.55, 6.64), p=0.00001 5.16 (3.25, 7.06), p<0.00001
<ul style="list-style-type: none"> <li>• Arousal index               <ol style="list-style-type: none"> <li>1. 3 parallel (n=189)</li> <li>2. 6 crossover (n=184)</li> </ol> </li> </ul>	Mean difference (95% CI) 5.21 (2.48, 7.94), p=0.00018 2.24 (0.43, 4.05), p=0.015
<ul style="list-style-type: none"> <li>• Withdrawals               <ol style="list-style-type: none"> <li>1. 6 parallel (n=411)</li> </ol> </li> </ul>	Odds ratio (95% CI) 2.05 (1.15, 3.67), p=0.015
<b>OA versus surgery</b>	
<ul style="list-style-type: none"> <li>• Apnea hypopnea index               <ol style="list-style-type: none"> <li>1. 6 months</li> <li>2. 12 months</li> <li>3. 4 years</li> </ol> </li> </ul>	6.6 ± 8.8 vs 8.6 ± 7.2 5.9 ± 9 vs 10.4 ± 9.3, p<0.05 6.7 ± 6.8 vs 13.1 ± 10.7, p<0.05
<ul style="list-style-type: none"> <li>• Oxygen desaturation index               <ol style="list-style-type: none"> <li>1. 6 months</li> <li>2. 12 months</li> <li>3. 4 years</li> </ol> </li> </ul>	6.4 ± 8.5 vs 8.0 ± 8.0 6.1 ± 6.8 vs 9.3 ± 9.9 6.7 ± 6.8 vs 13.1 ± 10.7, p<0.01

AHI: apnea hypopnea index; BP: blood pressure; CI: confidence interval; CPAP: continuous positive airway pressure

## Appendix 2: Characteristics, Effectiveness, Compliance, and Side Effects in the Randomized Controlled Trials

Study / Objectives	Interventions, comparators / Duration	Patients	Effectiveness	Compliance	Side effects	Conclusion
<p>Dort (2008)<sup>10</sup></p> <p>RCT- Two-period randomized crossover</p> <p>To evaluate a non-customized tongue retaining device (suction) compared to a control device (non-suction)</p>	<p>Active suction device (S) versus non-suction device (NS)</p> <p>1 week per period and 1-week washout</p>	<p>n=38</p> <p>19 patients in each arm</p> <p>Two-period crossover</p> <p>16 patients in each arm completed the study</p> <p>Mild-to-moderate OSA or severe OSA failed CPAP</p>	<p>The S device significantly reduced the AHI by 4.9 events (95% CI 0.85-8.9) more than the NS device</p> <p>S device significantly reduced snoring index (p=0.027)</p>	<p>54% of patients would continue using S device</p> <p>12% of patients would continue using the NS device</p> <p>19% would use either device</p>	<p>Minor side effects included excessive saliva, and tender oral mucosa and tongue for both devices</p>	<p>The tongue retaining suction device showed better objective and subjective outcomes compared with the non-suction device</p>
<p>Vandervaken (2008)<sup>11</sup></p> <p>RCT- Two-period randomized crossover</p> <p>To compare the efficacy of prefabricated MAD and custom made MAD for treatment of sleep-disordered breathing</p>	<p>Pre-fabricated MAD thermoplastic (MAD<sub>TP</sub>) versus custom-made MAD (MAD<sub>CM</sub>)</p> <p>4 months per period and 1 month washout</p>	<p>38 OSA patients [20≤AHI≤40]</p>	<p>35 patients completed the study</p> <p>AHI was significantly reduced with MAD<sub>CM</sub> (6 ± 8 vs 14 ± 12, p=0.005); MAD<sub>TP</sub> no effect on AHI (11 ± 9 vs 14 ± 12)</p> <p>Treatment success</p> <ul style="list-style-type: none"> <li>• MAD<sub>TP</sub>: 31%</li> <li>• MAD<sub>CM</sub>: 60%</li> </ul> <p>Treatment failure</p> <ul style="list-style-type: none"> <li>• MAD<sub>TP</sub>: 37%</li> <li>• MAD<sub>CM</sub>: 34%</li> </ul>	<p>Compliance failure</p> <ul style="list-style-type: none"> <li>• MAD<sub>TP</sub>: 31%</li> <li>• MAD<sub>CM</sub>: 6%</li> </ul> <p>19 out of 23 subjects (82%) who completed both arms preferred MAD<sub>CM</sub>, whereas two patients (9%) had no preference</p>	<p>No serious side effects with either MAD during the study</p>	<p>Custom-made MAD was more effective than a thermoplastic device in the treatment of sleep-disordered breathing.</p> <p>Thermoplastic device cannot be recommended as therapeutic option nor can it be used as screening tool to find candidates for MAD therapy.</p>

Study / Objectives	Interventions, comparators / Duration	Patients	Effectiveness	Compliance	Side effects	Conclusion
			Total failure <ul style="list-style-type: none"> <li>• MAD<sub>TP</sub>: 69%</li> <li>• MAD<sub>CM</sub>: 40%</li> </ul>			
Petri (2008) <sup>12</sup> RCT – parallel To evaluate the efficacy of MAD for OSA	MAD versus mandibular non-advancement device (MND) versus no intervention (NI) 4 weeks	93 OSA patients MAD (n=33) MND (n=30) NI (n=30) AHI 34.7 (95%CI: 29.7 – 39.6)	87% of patients completed the trial MAD (n=27) MND (n=25) NI (n=29) MAD significantly reduced AHI (p<0.001) and the Epworth Sleepiness Score (p<0.001) MAD significantly improved quality of life (p<0.05)	Discontinued due to side effects: MAD (n=4) MND (n=2) NI (n=0)	Could not tolerate, suffered from loosening teeth (n=2 in MAD group), and suffered pain of the temporomandibular joint (n=1 in MAD group).	MAD has significant beneficial effects on OSA, including cure in some cases of severe OSA. MND has no placebo effect.
Lam (2007) <sup>13</sup> RCT – parallel To compare the effectiveness of three commonly used non-surgical treatment modalities for OSA	CPAP versus non-adjustable OA (NOA) versus conservative measures (CM) 10 weeks	101 OSA patients [AHI 21.4 ± 1.1]	91 patients completed the study At 10 weeks, AHI reported as: CPAP: 2.8 ± 1.1 (p<0.001) NOA: 10.6 ± 1.7 (p<0.05) CM: 20.5 ± 2.5 (NS) CPAP was significantly better than NOA or CM in improving overall quality of life	NR	Side effects of oral appliance <ul style="list-style-type: none"> <li>• Excessive salivation (56%)</li> <li>• Temporomandibular joint discomfort (38%)</li> <li>• Dry throat (33%)</li> <li>• Tooth discomfort (33%)</li> </ul>	CPAP produced the best improvement in terms of physiological, symptomatic, and health-related quality of life measures, while the OA was slightly less effective

Study / Objectives	Interventions, comparators / Duration	Patients	Effectiveness	Compliance	Side effects	Conclusion
			CPAP and NOA significantly lowered the morning DBP			
Hoekema (2007) <sup>14</sup> RCT – parallel  To evaluate the effects of OA (MAD) and CPAP on sexual functioning	CPAP versus MAD  8 weeks	OSA patients (N=48)  AHI ≥ 5  Erectile dysfunction (OSA 8.7 ± 3.8 vs. controls 6.8 ± 2.6)  Sexual dissatisfaction (OSA 9.7 ± 4.2 vs. controls 8.1 ± 2.6)  MAD (n=21) CPAP (n=27)	Completed study MAD (n=20) CPAP (n=27)  No significant changes in the sexual satisfaction or testosterone levels were observed in the patients underwent MAD and CPAP therapy	NR	NR	No significant improvements in sexual functioning in MAD or CPAP treated group
Blanco (2005) <sup>15</sup> RCT – parallel  To investigate the effects of OA, with or without mandible advance, in the treatment of OSA	MAD versus MND  3 months	OSA patients (N=24)  AHI ≥ 10  MAD (n=12) MND (n=12)	Completed study MAD (n=8) MND (n=7)  No treatment failure in either group  MAD decreased AHI from 33.8 ± 14.7 to 9.6 ± 12.1 (p<0.01)  MND decreased AHI from 24.0 ±	Average time patients used the device per night MAD: 7.7 ± 0.5 h versus MND: 6.5 ± 1.4 h	Excessive salivation (n=2 in MAD group)	Oral appliances, especially those that advance the mandible, offer an effective treatment for OSA

## HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Study / Objectives	Interventions, comparators / Duration	Patients	Effectiveness	Compliance	Side effects	Conclusion
			12.2 to 11.7 ± 7.9 (p=0.05) MAD, but not MND, significantly (p<0.05) decreased the scores of Epworth Sleepiness Scale, snoring, and Functional Outcomes of Sleep Questionnaire			
Naismith (2005) <sup>16</sup> RCT – Two-period crossover  To assess the efficacy of a custom-made MAD for the treatment of OSA with respect to neuropsychological and mood state	MAD versus inactive oral device  4 weeks per period and 1 week washout	73 OSA patients (AHI≥10)	55% reduction in AHI with MAD relative to baseline  Compared with control, MAD significantly improved AHI, AHI-REM, AHI-NREM, MinSaO <sub>2</sub> , and arousal index (p<0.01) MAD treatment significantly improved Epworth Sleepiness Scale scores, Vigor-Activity and Fatigue-Inertia scales, and somatic items of Beck Depression Inventory (p<0.01)	NR	NR	Treatment with MAD resulted in improvements in self-reported sleepiness, fatigue/energy levels, and vigilance/psychomotor speeds in OSA patients
Barnes (2004) <sup>17</sup>	MAD versus	114 OSA	CPAP and MAD	NR	NR	Both CPAP and MAD

Study / Objectives	Interventions, comparators / Duration	Patients	Effectiveness	Compliance	Side effects	Conclusion
<p>RCT – Three-way crossover</p> <p>To evaluate the efficacy of CPAP and oral appliance therapy of mild-to-moderate OSA</p>	<p>CPAP versus placebo tablet</p> <p>3 months per period and 2 weeks washout</p>	<p>patients (AHI: 5-30)</p> <p>Baseline AHI: <math>21.3 \pm 1.3</math></p>	<p>both improved sleep outcomes (AHI), but CPAP had a greater effect</p> <p>Both active treatments improved quality of life, symptoms, and subjective sleepiness in a similar fashion</p>			<p>were more effective than placebo in treating obstructive breathing events, sleep fragmentation and hypoxia, but CPAP was superior to MAD in this regard. Both treatments were more effective than placebo in improving quality of life, symptoms, and subjective sleepiness, with neither treatment being better than the other</p>
<p>Gotsopoulos (2004)<sup>18</sup></p> <p>RCT – Two-period crossover</p> <p>To investigate the short-term (4 weeks) effect of oral appliance therapy for OSA on blood pressure</p>	<p>MAD versus control oral appliance</p> <p>4 weeks per period and 1 week washout</p>	<p>61 OSA patients (AHI<math>\geq</math>10)</p>	<p>MAD therapy resulted in 50% reduction in mean AHI and significant improvement in both MinSaO<sub>2</sub> and arousal index (p&lt;0.05) compared with the control</p> <p>MAD significantly (p=0.001) reduced 24-h DBP, but not 24-h SBP compared with control</p> <p>MAD significantly reduced awake blood pressure [both DBP</p>	NR	NR	<p>Oral appliance therapy for OSA over 4 weeks results in a reduction in blood pressure</p>

## HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Study / Objectives	Interventions, comparators / Duration	Patients	Effectiveness	Compliance	Side effects	Conclusion
			(p<0.0001) and SBP (p=0.003)]			

AHI: apnea-hypopnea index; CM: conventional measures (sleep hygiene); CPAP: continuous positive airway pressure; DBP: diastolic blood pressure; OSA: obstructive sleep apnea; MAD: mandibular advancement device; MinSaO<sub>2</sub>: minimum arterial oxygen saturation; MND: mandibular non-advancement device; NI: no intervention; NOA: non-adjustable oral appliance; NR: not reported; NREM: non-rapid eye movement; NS: not significant; REM: rapid eye movement;

## Appendix 3: Characteristics, Effectiveness, Compliance, and Side Effects of the Observational Studies

Study / Objectives	Patients	Interventions / Duration	Effectiveness	Compliance	Side effects	Conclusion
<p>Vecchierini (2008)<sup>19</sup></p> <p>Cohort, pre-post treatment</p> <p>To assess the efficacy and compliance of a traction-based mandibular repositioning device (MRD) for the treatment of OSA patients</p>	<p>40 OSA patients</p> <p>10 severe, [AHI] &gt;30; 30 moderate, 15&lt;[AHI]&lt;30</p>	<p>Traction-based MDR</p> <p>45 days</p>	<p>35 completed the study</p> <p>Response rate: 46%</p> <p>Success rate: 52%</p> <p>Moderate OSA: AHI decreased 57±35% (p&lt;0.001)</p> <p>Severe OSA: AHI decreased 33±36% (p&lt;0.05)</p> <p>Significant improvement in nocturnal ODI, frequency of respiratory events, daytime sleepiness, snoring, sleep quality, health-related quality of life (p&lt;0.05)</p>	<p>80% patient were wearing the MRD every night</p>	<p>No serious side effects of cases of pathology of aggravation</p>	<p>MRD significantly improved AHI and nocturnal ODI, quality of life, and quality of sleep parameters</p>
<p>Ueda (2008)<sup>20</sup></p> <p>Follow-up</p> <p>To study the effect of long-term use of an oral appliance (OA) in the changes in the occlusal contact area (OCA) (biting surface of a molar or premolar tooth)</p>	<p>45 OSA patients had been using an OA for 4 or more days/week</p>	<p>Advancement OA with full occlusive coverage of the teeth</p> <p>&gt;5 years</p>	<p>NR</p>	<p>NR</p>	<p>86.7% of patients had total OCA change; 66.7% had a decrease, 33.3% had an increase in OCA</p> <p>&gt;90% of patients had &gt;5% regional changes (molar, pre-molar and anterior regions)</p>	<p>Long-term OA therapy resulted in dramatic changes of occlusion</p>
<p>Jauhar (2008)<sup>21</sup></p> <p>Survey</p>	<p>Records of 180 OSA patients had been using MAD</p>	<p>MAD</p> <p>10 years</p>	<p>NR</p>	<p>65% compliance [47% wearing the device every</p>	<p>Few side effects reported</p>	<p>MAD appears to be an effective long-term solution</p>

## HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Study / Objectives	Patients	Interventions / Duration	Effectiveness	Compliance	Side effects	Conclusion
To investigate the long-term compliance of patients who were provided with a mandibular advancement device (MAD)	52 mild OSA (AHI 5-14); 34 moderate (AHI 15-30); 21 severe (AHI>30)  Response rate: 40% (72 replies)			night; 18% wearing up to 6 nights per week]	Side effects included pain/discomfort (9), excessive salivation (2), dry mouth/difficulty breathing if nose blocked (2), loose (2), teeth more stained (1), mandible displace (1), repositioned jaw (1), excessive flatulence (1)	for a significant number of OSA patients
Gindre (2008) <sup>22</sup>  Cohort, follow-up  To describe the course of the AHI and snoring index (SI) during progressive mandibular advancement (MA), and to evaluate the long-term efficacy, tolerance and usage of MA therapy	66 OSA patients (50 had been treated with CPAP; 16 had not)  Mean AHI: 38.6 ± 20.3	MAD MA titration: initial advancement of 80% of maximum MA; advancement of 1 mm every 2 weeks  16.6 ± 7.7 months	70% of patients had one increment in MA [AHI decreased from 36 ± 19 to 10.1 ± 11.2 (p<0.001)]  24% of patients had two increments in MA [AHI decreased from 24 ± 13 to 15 ± 8 (p=0.02)]  6% of patients had three increments in MA (AHI: no significant different to baseline)  54% complete responses; 29% partial responses; 17% no response	82% of patients were still using OA after 17 months	Subjective occlusal changes (frequent but mild)	Improvement in AHI during OA is dependent on the amount of MA. Long term MA therapy is effective and well tolerated.
Otsukal (2007) <sup>23</sup>	12 OSA patients	MAD	NR	NR	Post-treatment	Attention should

Study / Objectives	Patients	Interventions / Duration	Effectiveness	Compliance	Side effects	Conclusion
<p>Cohort; pre-post treatment</p> <p>To assess whether oral appliances (OA) alter occlusal function in patients treated for snoring and OSA</p>		<p>2 to 8 months</p> <p>Post-treatment occlusal contact area (OCA) and bite force (Bf) were compared with pre-treatment measurements</p>			OCA and Bf measurements were significantly smaller than those of the pre-treatment	be given to the possible side effects of OA on the dentition when treating patients with snoring or OSA.
<p>Maurer (2007)<sup>24</sup></p> <p>Case series; pre-post treatment</p> <p>To evaluate the efficacy of the MAD in the treatment of OSA patients</p>	<p>44 OSA patients, including non-compliant to CPAP</p> <p>AHI: 32 ± 17.6</p>	<p>MAD</p> <p>Follow-up: 19 to 543 days</p>	<p>41% of patients were cured, 27% were improved, 18% were unchanged and 14% worsened.</p> <p>Mean AHI decreased from 32 ± 17.6 to 18.2 ± 17.0 (p&lt;0.05)</p> <p>Minimal oxygen saturation increased from 78 ± 13 to 82 ± 13% (p&lt;0.05)</p> <p>Snoring time decreased from 223 ± 132 to 183 ± 134 min (p&lt;0.05)</p>	NR	<p>Excessive saliva production (n=44), uncomfortable (n=4), tooth pain (n=1), weary teeth (n=10), aching masseter (n=5), losing device during sleep (n=8)</p>	With the MDA, 68% of OSA patients could be cured or substantially improved.
<p>Levendowski (2007)<sup>25</sup></p> <p>Case series, pre-post treatment</p> <p>To assess the effectiveness of MAD therapy</p>	30 OSA patients	<p>MAD</p> <p>3-4 weeks</p>	<p>Significant reductions in the AHI, hypoxemia measures, and snoring level in post-treatment</p> <p>90% of patients had AHI below cut-off</p>	The mean time usage per night was 7.34 ± 1.3 h	NR	A treatment efficacy rate was 90% using an AHI-4% clinical cut-off of 10, and 97% when 50% reduction in AHI was included in

Study / Objectives	Patients	Interventions / Duration	Effectiveness	Compliance	Side effects	Conclusion
using a limited channel recorder			point 97% of patients exhibited at least 50% decrease in AHI			determining a successful outcome.
Machado (2007) <sup>26</sup> Cohort, pre-post treatment To evaluate the efficacy of MAD in the treatment of OSA on the criteria of AHI<5	83 OSA patients  23 severe, 40 moderate, and 20 mild OSA patients	MAD  4 months	62.6% of patients were treated successfully (AHI<5)  Successful treatment in 75% mild, 65% moderate, and 52% severe OSA patients  AHI decreased from 26 ± 17.7 to 4.8 ± 5.3	NR	NR	Intra-oral appliances are efficacious in treating OSA.
Hammond (2007) <sup>27</sup> Cohort, survey To investigate side effects and possible changes in the dentofacial complex associated with long-term use of MAD	64 OSA patients who had been using MAD	MAD  25.1 ± 11.8 months	88% of patients improved in snoring  Epworth Sleepiness Scale decreased from 11.4 to 7.1, p<0.001	NR	Common side effects: jaw discomfort, tooth tenderness, excessive salivation, and dry mouth.  12.5% of patients experienced occlusal changes.  Significant reductions in overbite (p<0.01) and overjet (p<0.05)	Side effects over long term periods are common but mild and well tolerated by most patients, and dental facial changes are negligible
Marklund (2007) <sup>28</sup> Cohort, survey To evaluate the long-term	260 snoring and OSA patients who were treated with appliances	MAD  Patients using appliances on an average of 5.4 years	71% responded the questionnaires  Frequent users had significant reduction	Of the respondents, 51.9% were frequent users, 17.8% were	Increased salivation, dry mouth, bad taste in the mouth, dry lips, and occlusal	Custom-made MAD reduced sleep apnea symptoms in long-term.

Study / Objectives	Patients	Interventions / Duration	Effectiveness	Compliance	Side effects	Conclusion
symptomatic effects of custom-made MAD and to identify the patients who will experience subjective benefits from treatment			in apnea, fewer night-time awakening, fewer complaints of sleepiness, headache and daytime naps.	infrequent users, 14% were discontinued, and 16.3% had modified treatment.  Mild cases of OSA were more likely to continue treatment than more severe cases.	changes. Frequent users had more occlusal changes than infrequent users  Side effects occurred in all users	Mild cases are likely to continue treatment and experience greatest long-term benefit
Itshaki (2007) <sup>29</sup> Cohort, pre-post treatment, and untreated controlled  To assess the effect of long-term MAD treatment on OSA, oxidative stress markers, and on endothelial function (EF)	16 OSA patients 12 completed 1-year evaluation  Comparators: 6 untreated patients and 10 non-OSA subjects	MAD 1 year	AHI decreased from $29.7 \pm 18.5$ (pre-treatment) to $19.6 \pm 11.5$ (post-treatment) ( $p < 0.005$ )  Epworth Sleepiness Scale score decreased from $12.4 \pm 6$ to $7.8 \pm 3.8$ ( $p < 0.001$ )  The measurements of oxidative stress and EF were significantly improved ( $p < 0.05$ ) after treatment.	NR	NR	MAD may be a moderately effective long-term treatment for patients with OSA
Otsuka (2006) <sup>30</sup> Case series, pre-post treatment  To investigate the effects of OA therapy on	11 OSA patients	MAD 2-8 months titration	AHI decreased from $24.7 \pm 20.1$ (pre-treatment) to $6.1 \pm 4.5$ (post-titration)  Over 20-h period, SBP: $118.4 \pm 10$ to	NR	NR	MAD may be beneficial in lowering blood pressure in OSA patients

Study / Objectives	Patients	Interventions / Duration	Effectiveness	Compliance	Side effects	Conclusion
ambulatory blood pressure in patients with OSA			113.7 ± 9.1 DBP: 79.5 ± 5.5 to 74.6 ± 6.0 MAP: 95.9 ± 5.4 to 91.2 ± 5.9			
Hou (2006) <sup>31</sup> Prospective, pre-post treatment To evaluate long-term dentofacial changes in Chinese OSA patients	67 OSA patients	MAD 1 year	NR	NR	Changes in some dentofacial variables were small, but significant (p<0.05) [increase in the mandibular plane angle and reductions in the overjet and overbite]	Dentofacial changes occurred at the initial stage of the treatment and were statistically significant. However, the changes were small in magnitude
Marklund (2006) <sup>32</sup> Prospective, follow-up To find predictors of dental side effects from monoblock MAD	450 snoring and OSA patients 423 patients completed study (27 patients had moved or died)	MAD Follow-up 5.4 ± 0.8 years	NR	56% continued treatment [of those, 79% reported compliance rates of ≥50%]	A small, but significant reduction in the overjet and overbite	Orthodontic side effects might be predictable on the basis of initial characteristics in dental occlusion and the design of MAD
Sam (2006) <sup>33</sup> Cohort, pre-post treatment To evaluate the effect of OA on upper airway morphology and its relationship with treatment response in subjects with OSA	40 moderate OSA patients 23 completed study	Custom-made, non-adjustable OA 2 months	Median AHI decreased from 26.4 (14.1-36) to 8.4 (2.4-12.5)  OA decreased the cross-sectional area of the hypopharynx (p<0.05), and increased overall upper airway volume (p=0.006)  No relationship	Compliance: 88% (6 nights per week, 6-8 h per night)	NR	OA altered upper airway morphometry towards a profile consistent with decreased propensity to collapse, which may have contributed to improvement of OSA.

Study / Objectives	Patients	Interventions / Duration	Effectiveness	Compliance	Side effects	Conclusion
			between upper airway parameters and treatment outcome			
<p>Yoshida (2006)<sup>34</sup></p> <p>Cohort, pre-post treatment</p> <p>To evaluate the effect of individually prescribed OA for the treatment of OSA on blood pressure, as well as factors influencing the efficacy</p>	161 mild-to-moderate OSA patients	MAD 60 days	<p>43% responders, 29% partial responders, and 28% non-responders</p> <p>Significant decrease in blood pressure (<math>p &lt; 0.05</math>)</p> <p>SBP decreased from <math>132 \pm 16</math> to <math>128 \pm 15</math></p> <p>DBP decreased from <math>82 \pm 11</math> to <math>79 \pm 10</math></p> <p>MAP decreased from <math>107 \pm 13</math> to <math>103 \pm 12</math></p> <p>The decrease in blood pressure in the responders and partial responders correlated with the reduction in AHI</p>	Mean usage $6.9 \pm 1.3$ h each night	NR	The effective OA therapy for OSA patients with hypertension can lead to a substantial reduction in daytime blood pressure
<p>Kuna (2006)<sup>35</sup></p> <p>Cohort, pre-post treatment</p> <p>To determine whether a manually adjustable MAD predicts successful long-term treatment</p>	21 OSA patients AHI: $33.5 \pm 18.3$	MAD Polysomnogram titration: $44 \pm 40.1$ days (range 12 to 153 days)	43% of patients achieved AHI < 10	NR	NR	MAD lowered the AHI to efficacious levels in 43% of patients, but this acute response did not predict the efficacy of long-term MAD treatment
Almeida (2006) <sup>36</sup>	71 snoring and	MAD	NR	NR	Significant	After long-term

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<p>Cohort, pre-post treatment</p> <p>To evaluate the long-term effects of OA therapy on cranial facial structures in snoring and OSA patients</p>	OSA patients	7.3 ± 2.1 years of MAD wearing			<p>(p&lt;0.01) changes in many variables:</p> <ul style="list-style-type: none"> <li>• Increase in mandibular plane and ANB angle</li> <li>• Decrease in overbite and overjet</li> </ul>	use, OA appeared to cause changes in tooth positions that also might affect mandibular posture
<p>Izci (2005)<sup>37</sup></p> <p>Retrospective, survey</p> <p>To evaluate patient compliance, perceived efficacy, satisfaction, and side effects of MAD in the treatment of patients with snoring and OSA</p>	<p>177 snoring and OSA patients</p> <p>Response rate: 81% (144 patients)</p> <p>AHI: 24 ± 21</p>	<p>MAD</p> <p>Median 7 months (5-11)</p>	<p>Epworth Sleepiness Score fell slightly [2.4 ± 3.5, (p=0.005)]</p> <p>7 daytime and 2 nocturnal symptoms in MAD users improved (p&lt;0.05)</p> <p>Marital status did not change</p>	<p>51% of patients continued using MAD at median 7 months after fitting</p> <p>12% still using MAD at 12 months</p>	<p>Side effects that preventing the use of MAD</p> <p>Non-retention (12)</p> <p>Sore mouth (13)</p> <p>Sore jaw (7)</p> <p>Difficult sleeping (10)</p> <p>Difficult breathing (7)</p> <p>Excessive salivation (4)</p> <p>Dental damage (4)</p> <p>Other problems (3)</p>	<p>MAD may offer a simple and effective treatment of snoring to severe OSA in selected patients who are unwilling or unable to use nasal CPAP. However, the authors concluded that patients' use of MAD and their therapeutic response to this treatment was disappointing</p>
<p>Aarab (2005)<sup>38</sup></p> <p>Case studies, pre-post treatment</p> <p>To study the initial efficacy of MAD in OSA patients</p>	10 OSA patients (6 mild, 4 moderate)	MAD 2-14 weeks	<p>Mean AHI reduced with MAD <i>in situ</i> (p=0.017)</p> <p>Larger decrease in AHI in the moderate cases than in the mild cases</p>	NR	NR	MAD might be an effective tool in the treatment of moderate OSA
<p>Johal (2005)<sup>39</sup></p>	20 OSA and 6 non-apnoeic	MAD	Overall reduction in the numbers of	NR	Side effects were transient (jaw	MAD improved AHI in OSA

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Retrospective, survey  To assess the effectiveness of MAD in patients with sleep-related breathing disorders	snoring patients	3 years	subjects with OSA, from 20 to 13  No significant changes in the Epworth Sleepiness Scale score  AHI of OSA patients reduced from 18 to 7 (p<0.05)  15 patients improved in snoring  86% of subjects' partners had better quality of sleep		ache, dry mouth, and mouth ulceration)	patients
de Almeida (2005) <sup>40</sup>  Retrospective, survey  To quantify the compliance with and side effects of the use of an OA for more than five years in patients with snoring or OSA	544 patients who used OA for treatment of snoring or OSA	OA  5.7 ± 3.5 years	46.1% returned the questionnaire  64.1% users and 35.9% non-users  Snoring was satisfactorily controlled in 75.6% users and 43.2% non-users	Of the returned sample, 64.1% still wearing OA (users)	Reasons for discontinued wearing: <ul style="list-style-type: none"> <li>• Uncomfortable (44.4%)</li> <li>• Little or no effect (33.6%)</li> <li>• Switch to CPAP (23.3%)</li> </ul> Side effects: dry mouth, tooth and/or jaw discomfort, temporomandibular joint symptoms	Subjects who were compliant with OA therapy reported long periods of use and adequate control of snoring
Eskafi (2004) <sup>41</sup>  Cohort, pre-post treatment  To evaluate the practical use of	25 congestive heart failure patients with OSA	MAD  4-6 weeks  6 months  1 year	AHI fell from 19.3 ± 12.1 to 11.8 ± 9.5 (P=0.004)	64% of patients still using MAD at 1 year follow-up	Most patients had no severe effects on the signs and symptoms of temporomandibular disorders	Oral health in congestive heart failure patients with OSA had an impact on their ability to benefit

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MAD for treatment of OSA in patients with congestive heart failure					10 patients reported pain in temporomandibular joints, soreness in the teeth, and tiredness in the jaws.  Two patients had dental complications	from MAD therapy. The MAD therapy had no severe effect on the masticatory system and patients with complete dentures could also be treated
Marklund (2004) <sup>42</sup> Prospective, follow-up  To evaluate the tolerability and to find predictors of treatment success for an individually adjusted, one piece MAD in patients with snoring and OSA	630 patients received treatment for snoring and OSA  AHI≥10	MAD  from February 1989 to August 2000	Predicted treatment success  <ul style="list-style-type: none"> <li>• Women: Odds ratio 2.4 (p=0.01) for both supine and lateral position; 12 (p=0.04) for mild sleep apnea; and 0.1 (p=0.03) for complaints of nasal obstruction</li> <li>• Men: Odds ratio 6.0 (p&lt;0.001) for supine dependent sleep apnea; 2.5 (p=0.04) for mild sleep apnea; 1.3 (p=0.03) for each mm mandibular advancement; and 0.8 (p=0.001) for each kg weight</li> </ul>	76% continued treatment  24% discontinued treatment	Causes of the discontinuation of treatment <ul style="list-style-type: none"> <li>• Discomfort (58.1%)</li> <li>• Poor effect on snoring (14.9%)</li> <li>• Odontologic problems (8.7%)</li> <li>• Another treatment demanded (6.8%)</li> <li>• Other causes (2.0%)</li> <li>• Unknown (9.5%)</li> </ul>	MAD is recommended for women with sleep apnea, for men with supine dependent sleep apneas, and for snorers without sleep apnea. Men with weight increase during treatment reduce their chance of treatment success

Study / Objectives	Patients	Interventions / Duration	Effectiveness	Compliance	Side effects	Conclusion
			increase			
<p>Vanderveken (2004)<sup>43</sup></p> <p>Cohort, pre-post treatment</p> <p>To evaluate the efficacy, feasibility, acceptance, and patient compliance of a low-cost fabricated MAD made from a thermoplastic material, which can be directly adapted intraorally</p>	<p>25 heavy snorers</p> <p>AHI&lt;20</p>	<p>“one-size-only” MAD</p> <p>1 and 6 months</p>	<p>60% of patients had an important reduction in snoring</p> <p>AHI decreased from <math>8.4 \pm 2.9</math> to <math>3.9 \pm 1.8</math> (<math>p&lt;0.001</math>)</p> <p>Significant reductions in snoring index (<math>p&lt;0.001</math>) and the Epworth Sleepiness Scale score (<math>p=0.036</math>)</p>	<p>60% of patients using MAD every night at 1 month</p> <p>35% of patients still using the device every night at 6 months</p>	<p>Side effects: hyper salivation, discomfort, breathing problems, nausea, suffocation, device too big</p>	<p>Immediate intraoral adaptation of a low-cost fabricated “one-size-only” MAD is a feasible treatment for snoring and OSA.</p>
<p>Tsai (2004)<sup>44</sup></p> <p>Cohort, pre-post treatment</p> <p>To evaluate the efficacy of remotely controlled MAD in the treatment of OSA</p>	<p>23 OSA patients</p> <p>AHI<math>\geq</math>15</p> <p>19 completed the study</p>	<p>Remotely controlled MAD that can advance or retract the mandible</p> <p>4 <math>\pm</math> 3 months</p>	<p>Efficacy: 53%</p> <p>AHI reduced from 34 <math>\pm</math> 4.9 to 17 <math>\pm</math> 4.7 (<math>p&lt;0.0001</math>)</p>	<p>82% compliance</p>	<p>Jaw discomfort (4), repetitive breakage of OA (1), initial difficulty with gagging (1)</p>	<p>The remotely controlled MAD is promising for predicting treatment outcome</p>

AHI: apnea-hypopnea index; ANB angle: relationship between molar height and basal bone; BF: bite force; CPAP: continuous positive airway pressure; DBP: diastolic blood pressure; EF: endothelial function; MA: mandibular advancement; MAD: mandibular advancement device; MAP: mean arterial pressure; MDR: mandibular repositioning device; MRD: mandibular repositioning device; NR: not reported; OA: oral appliance; OCA: occlusal contact area; OSA: obstructive sleep apnea; ODI: oxygen desaturation index; s: second; SBP: systolic blood pressure