

## Chapter 2.2

# Efficacy and co-morbidity of oral-appliance therapy in obstructive sleep apnea-hypopnea: a systematic review

This chapter is based on the following publications:

\* Hoekema A, Stegenga B, de Bont LGM. Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. *Critical Reviews in Oral Biology & Medicine* 2004;15:137-155.

\* Hoekema A, Marklund M. Oral Appliance Treatment of SRBD. In: Kushida C. *Handbook of sleep disorders*. 2<sup>nd</sup> ed. New York, USA: Taylor & Francis (in press).

## Summary

**Background** The obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common sleep-related breathing disorder characterized by repetitive obstructions of the upper airway during sleep. Modification of pharyngeal patency by oral-appliance therapy has been suggested as an alternative to various treatment modalities for OSAHS. To determine the evidence base with respect to the efficacy and co-morbidity of oral-appliance therapy in OSAHS, a systematic review of the available literature was conducted.

**Methods** In order to identify studies related to the efficacy and co-morbidity of oral-appliance therapy for OSAHS, a highly sensitive search was performed in several medical databases. Primary outcome measures were the reduction in number of upper airway obstructions and co-morbidity related to the craniomandibular or craniofacial complex, respectively. Eligible studies regarding efficacy were independently assessed by two assessors with a quality assessment scale. Effect sizes of methodologically sound studies were calculated. In identical interventions, effect sizes were pooled using a random effects model. Given the scarceness of controlled studies related to co-morbidity, appraisal was confined to a description of eligible studies.

**Results** Sixteen controlled trials related to efficacy were identified. With respect to the primary outcome measure, oral-appliance therapy was clearly more effective than an “inactive” control device (pooled effect size -0.96 [95% confidence interval -1.49 to -0.42]) and possibly more effective than uvulopalatopharyngoplasty. Although patients generally preferred oral-appliance therapy, improvement of respiratory variables, such as the number of upper airway obstructions, was usually better in continuous positive airway pressure (CPAP) therapy (pooled effect size 0.83 [95% confidence interval 0.59 to 1.06]). Moreover, specific aspects related to oral-appliance design may influence patient perceived efficacy and preference. Twelve patient-series and one controlled trial related to co-morbidity were identified. Data suggest that oral-appliance therapy may have adverse effects to the craniomandibular and craniofacial complex.

**Conclusions** Although CPAP is apparently more effective and adverse effects of oral-appliance therapy have been described, it can be concluded that oral appliances are a viable treatment modality for OSAHS. Controlled studies addressing the specific indication and co-morbidity of oral-appliance therapy are warranted.

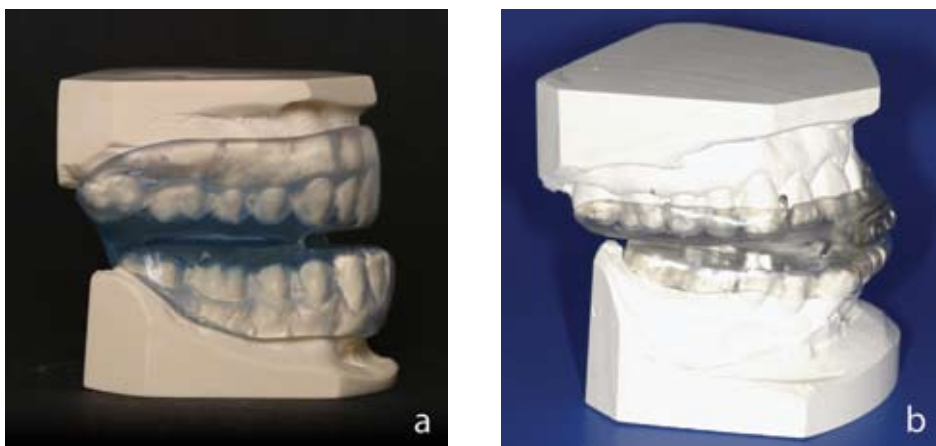
## Introduction

Dental devices represent a common alternative for patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) who are unsuitable candidates for treatment with continuous positive airway pressure (CPAP).<sup>1</sup> These intraoral devices, commonly known as oral appliances, aim at relieving upper airway obstruction and snoring by modifying the position of the mandible, tongue and other oropharyngeal structures. Oral-appliance therapy for OSAHS has gained considerable popularity because of its simplicity and supposed reversibility. In 1902 the French physician Pierre Robin laid the foundation for oral-appliance therapy. With a “monobloc” appliance Robin treated children that suffered from breathing difficulties and glossoptosis due to hypoplasia of the mandible.<sup>2</sup> The first case of an oral appliance that repositioned the mandible in an adult patient with OSAHS was not reported until 1980.<sup>3</sup> The first patient-series of oral-appliance therapy for OSAHS was reported in 1982 and described the effects of an appliance that repositioned the tongue.<sup>4</sup> Currently, well over 89 different oral appliances are marketed for the treatment of snoring and OSAHS.<sup>5</sup>

### Types of oral appliances

Based on their mode of action, oral appliances may be roughly divided into tongue retaining appliances and mandibular repositioning appliances. Tongue retaining appliances reposition the tongue in an anterior position by securing it with negative pressure in a soft plastic bulb or with a plastic depressor that directly contacts the base of the tongue. The latter device, known as SnorEx<sup>®</sup> (Depita, Nienhagen, Germany), is limited for large-scale use because of poor results and non-compliance.<sup>6</sup> The Tongue-Retaining Device, which incorporates a plastic bulb in a custom-made dental retained soft acrylic appliance, has been demonstrated to effectively reduce the number of upper airway obstructions in OSAHS patients.<sup>4</sup> However, a compromised nasal passage or discomfort and loss of negative pressure in the bulb may hamper full-night application of this appliance. The Tongue-Stabilizing Device, an “off-the-shelf” appliance somewhat similar to the Tongue-Retaining Device, shows comparable results.<sup>7</sup> Although rarely used because of poor results and patient intolerance, palatal lifting devices, tongue posture trainers and labial shields are also oral appliances that claim to improve snoring and OSAHS.<sup>8-10</sup> Mandibular repositioning appliances (MRA's) are used most commonly in clinical practice, and the quantity and quality of scientific literature supporting their use is far greater than for the other types of oral appliances.<sup>1</sup> This systematic review is limited to the application of the MRA as oral appliance for the treatment of OSAHS.

Mandibular repositioning appliances are either of a one-piece (“monobloc”) or a two-piece (“bibloc”) design (Figure 1), and may be custom-made or prefabricated.<sup>11</sup>



**FIGURE 1.** Lateral view of a one-piece and two-piece mandibular repositioning appliance.

(a) one-piece appliance placed on plaster casts; (b) upper- and lower-part of two-piece appliance placed on plaster casts (Figure 1b adopted from; Hoekema A, Wijkstra PJ, Buijter CT, van der Hoeven JH, Meinesz AF, de Bont LGM. Treatment of the obstructive sleep-apnoea syndrome in adults. *Ned Tijdschr Geneesk* 2003;147:2407-2412).

A prefabricated MRA only requires individual molding of a thermolabile material, while custom made appliances necessitate dental impressions, bite registration and construction by a dental laboratory. Retention for an MRA in upper and lower dentition is provided by clasps, acrylic, or thermoplastic polymer embedded in the appliance.<sup>12</sup> A one-piece MRA rigidly fixes the mandible in an anterior position, whereas a two-piece MRA usually allows for some freedom of mandibular movement (*i.e.*, lateral, vertical or anterior). It has been suggested that this latter feature decreases the chance of temporomandibular disorders and improves comfort.<sup>13</sup> Two-piece MRA's are sagittally adjustable, thereby allowing for individual titration of the appliance and a more optimal degree of mandibular advancement.<sup>14</sup> Conversely, fixation of the mandible with a one-piece appliance is suggested to prevent suppression of tongue protruding muscles, resulting in a less collapsible upper airway during sleep.<sup>15</sup> Another feature in MRA design is the degree of bite-opening imposed by the appliance. Fluoroscopic recordings suggest that bite-opening should be kept to a minimum since in awake OSAHS patients it results in posterior movement of both tongue and soft palate.<sup>16</sup> However, increased baseline genioglossus muscle activity is implicated in downward rotation of the mandible.<sup>17</sup> Moreover, bite-opening may improve upper airway patency by stretching the palatoglossus and superior pharyngeal constrictor muscle.<sup>15</sup>

## Mechanism of action

Forward displacement of the mandible in oral-appliance therapy appears to prevent snoring and airway obstruction by indirectly moving the suprahyoid and genioglossal muscles anteriorly.<sup>18</sup> It has also been suggested that forward and inferior displacement of the mandible decreases the gravitational effect of the tongue on upper airway patency and preserves the velopharyngeal airway by stretching the palatoglossal and palatopharyngeal arch.<sup>18-20</sup> Moreover, stabilization of the mandible and hyoid bone prevents posterior rotation of the mandible and retrolapse of the tongue during sleep.<sup>9</sup> Three dimensional imaging and (supine-) cephalometric studies have demonstrated that mandibular repositioning increases hypo-, oro- and velopharyngeal airway dimensions (Figure 2).<sup>20-27</sup> Endoscopic and computerized tomography studies have shown that mandibular advancement results in, particularly, an increased cross-section of the lateral dimensions in the oro- and velopharynx.<sup>19,28,29</sup> It has also been demonstrated that mandibular advancement has a positive effect on airflow dynamics in the upper airway during sleep by diminishing airway curvature in the velopharynx.<sup>30</sup> Beside anatomical changes, the effect of MRA therapy has also been attributed to changes in neuromuscular properties of the upper airway.<sup>31</sup> For example, both mandibular rotation and advancement have been implicated in an increased muscle activity in the upper airway.<sup>17,31</sup> Conflicting results and the fact that most imaging studies have been performed in the wake state, requisite further elucidation of the precise biomechanical mechanism of MRA therapy.

## Titration procedures

Most studies suggest that an MRA derives its therapeutic effect mainly from the amount of mandibular advancement imposed by the appliance.<sup>1,32</sup> However, in some OSAHS patients the number of upper airway obstructions may increase when the mandible is protruded towards its maximum.<sup>9</sup> Determination of the amount of mandibular advancement required to prevent snoring or OSAHS in a given patient is therefore generally a matter of trial and error. Treatment usually commences with an adaptation period (generally four weeks) that is followed by a titration period (generally two to three months).<sup>1</sup> Titration of the appliance should be aimed at accomplishing the amount of mandibular advancement that yields a resolution of symptoms with minimum discomfort and side effects. Because a two-piece MRA is in most cases sagittally adjustable, titration is usually more straightforward when compared with a one-piece MRA. However, details of the titration process, including the initial and target degree of mandibular advancement, are highly variable between different types of appliances and practitioners.<sup>1</sup> The need for an acclimatization period is considered a drawback of oral-appliance therapy, particularly in situations where rapid initiation of treatment is required (e.g., severe OSAHS). Recent studies have reported on the feasibility



**FIGURE 2.** Effects of an oral appliance on upper airway patency and dentition.

Illustration of the increase in upper airway dimensions following repositioning of the mandible with oral-appliance therapy. The arrows on the teeth indicate the reciprocal forces that are generated by holding the mandible in a forward and vertically opened position. These forces transmit in a labial direction against the lower incisors and in a palatal direction against the upper incisors. On the long-term, this may change the inclination and position of teeth, affect the position of the mandible and increase the loading of the craniomandibular complex.

of a single-night titration of an MRA by using remotely controlled appliances.<sup>33,34</sup> This technique may offer the advantage of directly ascertaining the likelihood of treatment success as well as the amount of mandibular advancement required in an individual patient. However, the difficulty of achieving the required mandibular advancement without discomfort on the first night and the laborious character may limit wide scale application of this technique.

### Effectiveness

Based on reports of patients and their bed-partners, oral-appliance therapy generally results in a reduction of snoring in a high proportion of patients.<sup>12,35</sup> Other reported benefits of therapy include substantial improvements in daytime sleepiness, work performance and sleep quality of both patient and bed partner.<sup>36-39</sup> Sleep registration generally confirms the patient-perceived benefits by demonstrating improvements in snoring frequency and intensity, apnea-hypopnea index (AHI), oxygen desaturation frequency and intensity, and the number of arousals during sleep.<sup>38-41</sup> Therapy is also associated with significant increases in slow-wave and rapid-eye-movement (REM) sleep.<sup>40,42</sup> Despite an inadequate improvement in the AHI, OSAHS patients may report fewer symptoms when initiating oral-appliance therapy.<sup>43</sup> In fact, an increase in the AHI has been

reported in approximately 13% of OSAHS patients following therapy.<sup>35</sup> Because of this risk of an increased or suboptimal AHI, a follow-up sleep registration should always be conducted in MRA therapy.

### *Long-term effects*

Studies on the long-term effects of oral appliances in the treatment of OSAHS suggest high success rates after follow-up periods ranging from two to five years.<sup>45-48</sup> Approximately 80% of patients that were initially successfully treated also experienced long-term control of their OSAHS. A slightly lesser percentage of patients also experience a satisfactory effect on snoring with long-term oral-appliance therapy. On the long-term a gradual decline in treatment effect should therefore be anticipated. These numbers, however, also reflect bias because not all patients originally treated were included in these analyses. Long-term effectiveness of oral-appliance therapy in unselected OSAHS patients is therefore probably lower.<sup>1</sup> The main reasons for an attenuation of the treatment effect following an initially successful treatment relate to a failure of maintaining advancement of the mandible in the prescribed position and an increase in body weight during the follow-up period.<sup>47,49</sup>

### *Oral appliances as adjuvant treatment*

Although oral appliances have been shown effective as sole treatment for OSAHS, they may also be used as an adjuvant to other therapies. In situations where there is a desire to reduce the CPAP pressure to control OSAHS, the combined use of CPAP and oral-appliance therapy may be an option.<sup>1</sup> Oral-appliance therapy has also been shown highly successful for the treatment of OSAHS following an unsuccessful uvulopalatopharyngoplasty (UPPP).<sup>50</sup> In addition to oral appliances being used in combination with another treatment, they may also be used as a predictor for the outcome of other interventions. Oral-appliance therapy has been suggested to be a good predictor for the outcome of maxillomandibular advancement surgery in OSAHS patients.<sup>51</sup> An MRA may be used to simulate the effects and allow patients to accustom to the idea of surgical advancement of their mandibular complex. Although there is little evidence that supports the routine use of oral appliances as an adjuvant treatment for OSAHS,<sup>52</sup> it may offer some potential advantages in selected cases.

### *Treatment compliance*

Patient-reported compliance with oral-appliance therapy is generally high with studies reporting regular use in 75 to 100% of patients initiating therapy.<sup>12</sup> Long-term compliance has been reported to decrease over time. After a four year period one study reported appliance use as prescribed in only 32% of patients.<sup>52</sup> Others have observed higher therapeutic adherence ranging from 48 to 76% after a two- to five-year follow-up period.<sup>14,45,47,53</sup> Discontinuation of oral-appliance therapy is generally

related to side effects, complications or the lack of perceived benefits.<sup>54</sup> Data on the impact of side effects on long-term compliance are however conflicting. Some studies observe similar frequencies of side-effects in compliant and non-compliant patients, whereas others report a higher number of side-effects in patients who discontinued treatment.<sup>53,54</sup> Although patient-reported compliance may be an overestimate of actual use, covert compliance monitoring has shown excellent agreement between objective and patient-reported compliance.<sup>44</sup> Compliance rates of oral-appliance compared with CPAP therapy have been reported variably. Some studies did not find any differences between treatments<sup>55,56</sup> whereas others suggest superior compliance with oral-appliance therapy.<sup>57,58</sup>

### **Adverse effects & complications**

Most oral appliances are anchored to the patient's dentition, but may also extend over the oral mucosa in order to increase the area of retention. Consequently, teeth and surrounding tissues are continuously loaded when the appliance is worn. By holding the mandible in a forward and vertically opened position, reciprocal forces are generated that transmit in a labial direction against the lower incisors and in a palatal direction against the upper incisors (Figure 2). This may change the inclination and position of teeth, affect the position of the mandible and increase the loading of the craniomandibular complex.<sup>59-66</sup> Almost 90% of patients who continue treatment on a regular basis consider that the benefits of treatment outweigh any adverse effects.<sup>1</sup>

#### *Short-term*

In the initial period of use patients commonly report tenderness of the teeth and jaws, gum irritation, excessive salivation or xerostomia.<sup>38,56,67</sup> Mild complaints of pain and strain of the masticatory muscles and the temporomandibular joint also frequently occur when initiating oral-appliance therapy.<sup>18,67</sup> A temporary bite change in the morning after removal of the appliance occurs in almost all patients.<sup>12</sup> This phenomenon has been attributed to a partially contracted lateral pterygoid muscle and accumulation of retrodiskal blood in the temporomandibular joint area after full-night mandibular protrusion.<sup>15</sup> However, to date this hypothesis has never been scientifically supported. In more exceptional cases, treatment may be complicated by involuntary removal of the device, an exaggerated gag reflex, periodontal damage or fractured teeth and fillings.<sup>67,68,69</sup> Problems of discomfort and salivation are usually mild and acceptable with most symptoms subsiding when treatment is continued.<sup>12,70</sup> Small adjustments of treatment may, however, enhance the tolerability to the appliance and increase the chance of success.

#### *Long-term*

On the long-term oral-appliance therapy has been suggested to initiate or aggravate temporomandibular joint disease in individual patients.<sup>45</sup> Although

some studies have observed an increase in bruxism in response to MRA therapy,<sup>38</sup> in the clinical situation signs or symptoms of temporomandibular joint disorders that result from oral-appliance therapy are not commonly reported.<sup>59</sup> In contrast to the temporomandibular joints, orthodontic effects on teeth and dentofacial skeleton are observed more frequently with long-term oral-appliance therapy.<sup>59</sup> In most cases these orthodontic effects amount to (permanent) alterations in the dental occlusion.<sup>71</sup>

Several features in MRA design have been implicated in the occurrence of side-effects. It has been suggested that an MRA with full dental coverage, a minimum degree of bite-opening, and both soft elastomeric and rigid acrylic appliances minimize the chance of occlusal changes.<sup>60,66</sup> Others suggest that occlusal side-effects in MRA therapy are not related to the specific design of the oral appliance.<sup>67,72</sup> It should, however, be noted that other factors including periodontal health, patient compliance and the amount of mandibular advancement may affect the frequency and severity of side-effects with oral-appliance therapy.<sup>59</sup> Provided there is a good patient follow-up, it is thought reasonable to persist with oral-appliance therapy in the presence of acceptable and non-progressive adverse effects.<sup>67,72</sup> However, the likelihood of adverse effects or complications should always be discussed and include the patient's written informed consent before oral-appliance therapy is initiated.

## Patient selection

### *Contraindications*

When considering oral-appliance therapy several dental exclusion criteria should be taken into account. In up to 34% of cases an MRA cannot be inserted because of dental contraindications.<sup>73</sup> Factors of consideration include (extensive) periodontal disease and dental decay, active temporomandibular joint disorders, and restrictions in mouth opening (*i.e.*, <25 mm) or advancement of the mandible (*i.e.*, <5 mm). In the majority of cases, however, there are an insufficient number of teeth to support and retain the appliance.<sup>73</sup> This is especially the case in edentulous patients. Several types of oral appliances have been described for the treatment of OSAHS in edentulous patients (*e.g.*, tongue retaining appliances).<sup>74</sup> Full-night application of these appliances is generally compromised by discomfort or poor retention. Although some consider a minimum of ten sound teeth in each of the maxillary and mandibular arches a requisite in MRA therapy, the location rather than the number of teeth may be more important (*i.e.*, posterior teeth provide more adequate retention).<sup>73</sup> In order to stabilize and retain an MRA in edentulous patients, osseointegrated dental implants may be used.<sup>74</sup> Because this technique requires a longer period before therapy may be initiated, it is generally only worth considering in selected patients. The dental limitations must be considered in overall evaluations of oral-appliance therapy.

### *Predictors of treatment outcome*

Although oral-appliance therapy usually reduces snoring, it is not always effective in OSAHS patients.<sup>59,75,76</sup> Predictors of treatment outcome are therefore of importance for selecting suitable patients that may benefit from therapy. Several clinical and polysomnographic variables have been reported to correlate with increased effectiveness of oral-appliance therapy. For example, the outcome of therapy is generally more favorable in patients who have a lower AHI.<sup>20,77</sup> Treatment may also be more successful in patients who are younger, have a lower body-mass index (*i.e.*,  $\frac{\text{patient's weight (kg)}}{\text{square of patient's height (m)}}$ ) or smaller neck circumference,<sup>38,78</sup> and in patients with a more extended maximum mandibular advancement.<sup>77</sup> Others suggest that, possibly due to lower pharyngeal collapsibility, oral-appliance therapy is particularly effective in women, and in men with supine-dependent OSAHS (defined by an AHI <10 in the lateral position).<sup>49,77,79</sup> In addition to clinical and polysomnographic predictors, a variety of variables in craniofacial and upper airway morphology have been implicated in a favorable outcome of oral-appliance therapy.<sup>20,22,78,80-83</sup> Variables obtained from these cephalometric and magnetic resonance imaging studies include a cranial position of the hyoid bone, a smaller mandibular plane angle, a reduced anterior face height, a longer anterior cranial base, an increased maxillary length, a larger intermaxillary discrepancy or mandibular deficiency, a more pronounced overjet and overbite, a shorter soft palate, and a relatively “normal” airway diameter or soft-palate and tongue proportion.

A significant shortcoming in literature is that most clinical, polysomnographic and morphological predictors for treatment outcome of oral-appliance therapy are not reported uniformly.<sup>49</sup> In addition, predictors have not been systematically validated to test their accuracy in a separate population of patients.<sup>76</sup> Recent studies suggest an important role for more sophisticated techniques to predict the outcome of oral-appliance therapy in OSAHS patients. It has, for instance, been shown that a remotely controlled mandibular positioner during an overnight sleep study<sup>34</sup> or mimicking the action of an MRA during sleep nasendoscopy<sup>84</sup> is highly predictive for the response to oral-appliance therapy. Although these techniques may be of additional value in selecting suitable candidates, they are generally costly, laborious or sensitive to a specific operator. Therefore, the ability to predict treatment outcome and preselect suitable OSAHS patients for oral-appliance therapy is still limited in clinical practice.

### *Treatment guidelines*

Since oral appliances generate orthodontic forces they should generally not be contemplated when treating children or adolescents. However, oral-appliance therapy has been described effective for the treatment of OSAHS in children with malocclusions.<sup>85</sup> According to recommendations of the American Sleep Disorders Association from 1995, oral-appliance therapy should be considered in patients

with simple snoring or mild OSAHS who do not respond to or are not appropriate candidates for conservative measures (e.g., weight loss or regulation of sleeping position).<sup>86</sup> In moderate to severe OSAHS, the recommendation is to consider oral-appliance therapy when patients do not tolerate or refuse CPAP, and when patients are not candidates for or refuse surgical intervention. Recent reports demonstrating the effectiveness of oral appliances in moderate and severe OSAHS probably necessitate redefinition of these recommendations.<sup>87</sup>

It is advised that oral appliances should be fitted by dental specialists who are trained and experienced in this field. Following the final adjustments of treatment in OSAHS patients, effectiveness of therapy should always be evaluated by poly(somno)graphy with the appliance in place. Once optimal fit is obtained and efficacy shown, it is recommended that patients have follow-up visits by a dental specialist every six months for the first year and at least annually thereafter. During these consultations patient adherence, the condition of the appliance, health and integrity of the dentition should be evaluated and the patient can be questioned for worsening of symptomatology and increases in weight. Besides these regular dental follow-up visits patients should also return for periodic follow-up visits with the referring physician. Should oral-appliance therapy cause discomfort or fail during the follow-up period, treatment should be adjusted or patients may discontinue therapy and start with an alternative treatment.

### **Objective systematic review**

Since their introduction in the 1980's, treatment of OSAHS with oral appliances has gained considerable popularity as an alternative to current modalities because of their simplicity and supposed reversibility. Since patients generally prefer oral-appliance to CPAP therapy,<sup>88</sup> some patients are preferably treated with this treatment modality. Despite a possible favorable outcome of oral appliances in the treatment of OSAHS, comparative studies regarding efficacy and co-morbidity of this dental treatment modality are scarce. In this chapter, the available literature regarding the efficacy and co-morbidity of oral appliances as a treatment modality for OSAHS is systematically reviewed.

## **Methods**

### **Study selection**

In order to identify studies related to the efficacy and co-morbidity of oral-appliance therapy for OSAHS, a highly sensitive search was performed in the databases of Medline (1966-2002), Embase (1989-2002) and Cinahl (1982-2002). The search was supplemented with a systematic search in the "Cochrane central register of controlled trials" (CENTRAL) (1800-2002). The search strategy regarding

**TABLE 1.** Literature search strategy.

#1: sleep and (apnea or apnoea or hypopnea or hypopnoea)
#2: sleep and (respiratory disorder* or breathing disorder* or disordered breathing)
#3: explode "Sleep-Apnea-Syndromes"/ MeSH all subheadings
#4: #1 or #2 or #3
#5: #4 and (oral near [device* or appliance*])
#6: #4 and (intraoral near [device* or appliance*])
#7: #4 and (dental near [device* or ortho* or appliance*])
#8: #4 and (ortho* near [device* or appliance*])
#9: #4 and (splint* or denture*)
#10: #4 and (tongue or mandib* or prosth*)
#11: #4 and (explode "orthodontics"/ MeSH all subheadings)
search Medline/ Embase/ Cinahl: #5 or #6 or #7 or #8 or #9 or #10 or #11
search CENTRAL: #1 or #2

Abbreviations: CENTRAL = Cochrane central register of controlled trials, MeSH = thesaurus word,  
\* = truncation of a text word.

the applied thesaurus (*i.e.*, medical subject headings; MeSH) and text words in these databases is summarized in Table 1. To preclude that eligible studies were overlooked, several experts in the field of oral-appliance therapy were contacted for unpublished or ongoing studies. Checking references of relevant review articles and eligible studies for missing publications complemented the search. No language restrictions were used throughout the study selection procedure.

On the basis of title and abstract it was decided whether an identified article was relevant to the topic under study (*i.e.*, oral-appliance therapy for OSAHS). A full-text document of each "relevant" article was retrieved in order to decide whether the study was eligible for methodological appraisal. Studies regarding the efficacy of oral-appliance therapy in OSAHS treatment were eligible for further appraisal when they met with the following criteria: (1) studied patients diagnosed with OSAHS (*i.e.*, AHI >5); (2) studied patients aged 21 or older; (3) intervention group treated with an MRA; (4) control group treated with any conservative, surgical or non-invasive treatment modality for OSAHS (including none or a placebo intervention); (5) main outcome measure of treatment being the AHI assessed during a full-night sleep registration (*i.e.*, no split-night studies). In common with studies related to efficacy, studies related to co-morbidity of oral-appliance therapy had to meet with the first three of these criteria. However, contrary to studies related to efficacy, studies related to co-morbidity were still eligible for further appraisal if the studied patients represented a non-homogenous group (*i.e.*, OSAHS and primary snoring patients). Studies related to co-morbidity were eligible for further methodological

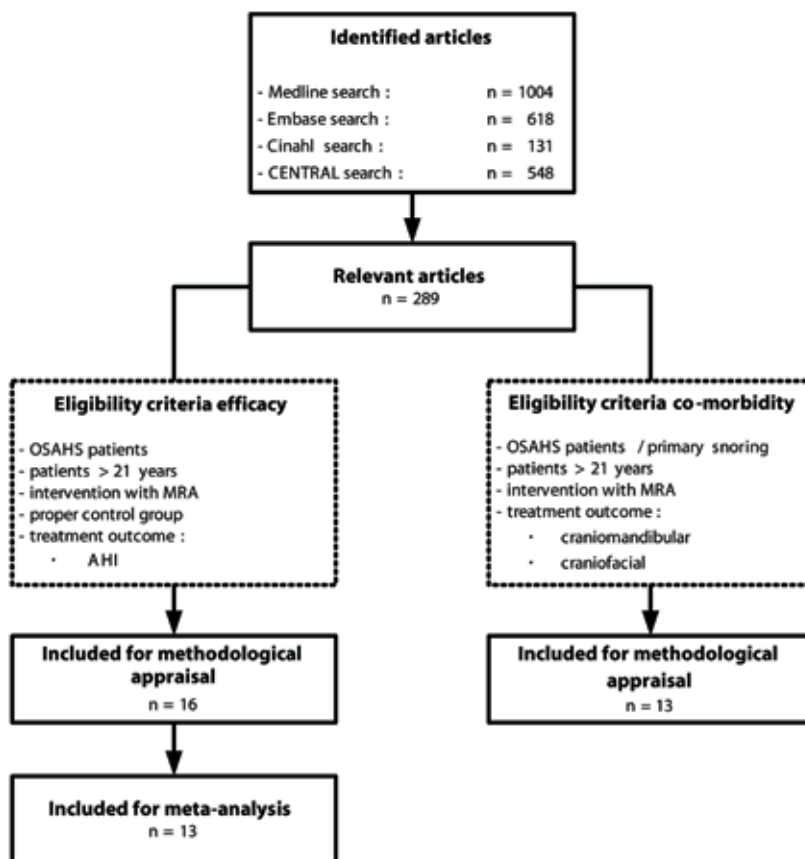
appraisal when the main outcome measure objectively identified side effects of oral-appliance therapy related to the craniomandibular or craniofacial complex. Studies regarding patient-perceived co-morbidity of oral-appliance therapy were, therefore, excluded from further analysis. Moreover, articles in Hebrew or Asian, case-reports, abstracts or letters with respect to the subjects under study were not considered for further analysis. Figure 3 outlines the algorithm of the study selection procedure.

### Methodological appraisal

Eligible studies included for methodological appraisal were independently assessed by two observers (A. Hoekema, B. Stegenga). In order to minimize observer bias, all included papers were blinded with respect to title, authors, and journal name. Prior to the appraisal the two observers discussed all relevant methodological items in order to reach consensus about their content. When they could not agree on a subject during the methodological appraisal, consensus was reached by consulting a third party (L.G.M. de Bont).

#### Efficacy

The methodological quality of all eligible papers related to efficacy was evaluated with the “quality of study tool” developed by Sindhu *et al.*<sup>89</sup> Using a Delphi technique, this quality tool was especially developed to rate the methodological quality of randomized clinical trials to be included in a meta-analysis. The “quality of study tool” consists of 53 items in 15 different dimensions, with each dimension having a specific weight. The 15 dimensions evaluate the following variables of a study: control group (maximum weight = 15), randomization (maximum weight = 10), measurement outcomes (maximum weight = 10), study design (maximum weight = 8), conclusions (maximum weight = 8), “intention-to-treat” analysis (maximum weight = 8), statistical analysis (maximum weight = 6), adherence to study protocol (maximum weight = 6), blinding (maximum weight = 5), research question (maximum weight = 5), loss to follow-up (maximum weight = 4), outcomes (maximum weight = 4), reporting of findings (maximum weight = 4), patient compliance (maximum weight = 4) and remaining variables (maximum weight = 3). The observers scored each of the included trials according to the 15 dimensions. The two observers reached agreement on the weight of each dimension in a consensus meeting. In sum of the 15 dimensions a study can theoretically score a maximum of 100 points. On the basis of this total score it was decided whether a study should be considered for inclusion in a meta-analysis. For this purpose a threshold value was set. The two observers independently determined the minimum number of items required in each dimension for considering a study “methodologically sound”. In a consensus meeting agreement was reached on the required weights in each dimension. The sum of the required weights in the 15 dimensions resulted in a threshold value of 47 points.



**FIGURE 3.** Algorithm of study selection procedure.

Abbreviations: AHI = apnea-hypopnea index, CENTRAL = Cochrane central register of controlled trials, MRA = mandibular repositioning appliance, OSAHS = obstructive sleep apnea-hypopnea syndrome.

### Co-morbidity

Based on the eligibility criteria related to co-morbidity, studies without a concurrent control group could also be included. Thereby, the methodological quality of included studies did (possibly) not meet with the most important parameter in design of observational studies.<sup>90</sup> The methodological appraisal of studies related to co-morbidity was limited to an overall impression of the study (*i.e.*, poor, adequate or good). Again the two observers reached agreement on the overall impression of each study in a consensus meeting.

## Presentation of data

The two observers independently performed the data extraction. Consensus was reached in cases of disagreement.

### *Efficacy*

The methodological quality of each included paper is presented according to the total score. If possible, we report data on the study design, type of MRA (including mean amount of mandibular advancement), type of control, number of patients included in the study, number of patients completing the study, and the reported success percentage of both MRA and control treatment. With respect to the main outcome measure (*i.e.*, AHI) and the Epworth sleepiness scale (ESS; a self-administered questionnaire in which patients rate their propensity to fall asleep), effect sizes and approximate 95% confidence intervals (CI) of “methodologically sound” trials were calculated. Furthermore, relevant outcomes related to other physiological parameters, quality of life indicators, sleepiness scores and behavioral- or cognitive function indices are reported. A meta-analysis was carried out on the effect sizes of “methodologically sound” trials with comparable (control) interventions.

### *Co-morbidity*

The methodological quality of each included paper is presented according to the overall impression of the study. The following data are presented: study design, type of MRA (including mean amount of mandibular advancement), type of patients studied, number of patients completing the study, mean duration of treatment and patient-reported compliance. Of each included study the co-morbidity of MRA therapy related to the craniomandibular and craniofacial complex is reported.

## Analysis

Statistical analyses were performed with the StatsDirect software package (version 2.2.3, StatsDirect Ltd, Cheshire, UK). The degree of agreement with respect to the methodological appraisal of eligible studies before the consensus meeting is expressed as percentage of agreement and weighted Cohen’s kappa. Because we expected clinical heterogeneity between the included trials related to efficacy of oral-appliance therapy, effect sizes of trials with comparable control interventions were pooled using a random-effects model (DerSimonian-Liard random effects analysis), in which smaller studies (with larger variances) contribute less than larger studies to the pooled effect.

## Results

The Medline search yielded 1004 publications, the Embase search 618, the Cinahl search 131, and the CENTRAL search 548. Systematic assessment of this output

revealed 289 relevant publications (Figure 3). Although reference checking of included studies and relevant review papers did not reveal additional articles, contact with experts in the field yielded one eligible article *in press* related to co-morbidity.<sup>60</sup>

## Efficacy

Using the specified criteria, 17 trials related to efficacy were considered eligible for further appraisal. Because one trial reported on the four-year follow-up of another eligible study,<sup>45</sup> 16 studies were included for methodological appraisal (Figure 3, Table 2). Four trials compared MRA therapy with an “inactive” control device.<sup>38,39,41,91</sup> Two trials studied the effect of anterior and vertical mandibular-displacement in MRA therapy, respectively,<sup>92,93</sup> whereas three trials compared several different oral appliances.<sup>10,40,68</sup> In one trial, MRA therapy was compared with UPPP<sup>94</sup> and six trials compared MRA therapy with CPAP.<sup>42,55-58,95</sup> Patient baseline characteristics of the included trials were generally comparable with respect to male to female ratio, age (means ranging from 44.0 to 57.6) and body-mass index (means ranging from 26.9 to 32.0).

The majority of the 16 included trials used a crossover design with only two studies applying a parallel study design.<sup>91,94</sup> In three studies subjects were not randomly allocated to the treatment groups.<sup>10,42,92</sup> Methodological quality of the included trials, according to the total score on the quality tool, ranged from 38 to 86 points (Table 2). The overall quality of the 16 trials was adequate with three studies not meeting the predetermined threshold value of 47 points.<sup>10,91,92</sup> Two of the three studies that did not meet the threshold lacked randomization for treatment allocation. However, studies meeting the threshold value also had methodological deficits. Although most of these studies were described as randomized, the method of randomization was generally not detailed nor reported as secure and “blind” to the assessors. Moreover, only one study reported blinding of patients to active and control treatment.<sup>39</sup> Because of the lack of a comparable placebo or control intervention, blinding of patients and therapists was usually not possible in these trials. However, reasons as to why assessment was not blinded were generally not provided nor was there a discussion of possible bias resulting from non-blind assessment. Conversely, in six trials the assessor of sleep variables was blinded to treatment.<sup>38,39,42,55,94,95</sup> Finally, in several “methodologically sound” trials the results could have been biased due to selective dropouts (*i.e.*, no “intention to treat” analysis).<sup>42,56,57,68,95</sup> Inter-rater agreement on the methodological quality of each trial, according to the assigned weights, was very good (agreement 97%, Cohen’s kappa 0.91 [95% CI 0.82 to 0.99]). Disagreements were generally caused by slight differences in interpretation and were easily resolved in the consensus meeting.

### *MRA versus control device*

Control devices were designed to minimally increase vertical opening without advancing the mandible. They consisted either of a modified MRA or the lower or upper piece of a two-piece MRA. Compared with the control device, MRA therapy was reported significantly more effective in improving the AHI in all four trials. This positive effect on physiological parameters was confirmed by studies demonstrating significant improvements with MRA therapy in the mean number of arousals per hour sleep (arousal-index), lowest oxyhemoglobin saturation during sleep (minSaO<sub>2</sub>), and snoring frequency and intensity when compared with control devices.<sup>38,39</sup> In one study the hourly rate of oxyhemoglobin desaturations ( $\geq 4\%$  fall in SaO<sub>2</sub>) decreased significantly following MRA therapy when compared with the control device.<sup>41</sup> Although two trials could not demonstrate significant differences in the Epworth sleepiness scale,<sup>41,91</sup> one trial reported a small but significant reduction in the Epworth sleepiness scale with MRA therapy when compared with the control device.<sup>39</sup> Moreover, objective daytime sleepiness according to the multiple sleep latency test improved significantly with MRA therapy when compared with the control device.<sup>39</sup> In one study, a significant increase in rapid-eye-movement sleep was observed when comparing MRA therapy with the control group.<sup>38</sup> In another study this phenomenon could not be demonstrated.<sup>39</sup> When compared with the control device, the patient-reported frequency and intensity of snoring significantly improved with MRA therapy in one trial but did not in another.<sup>39,41</sup> Although patients generally experienced more side-effects with MRA therapy, poorer patient satisfaction and compliance were reported with the control devices.<sup>39,91</sup>

In one trial the effect sizes were not calculated.<sup>91</sup> This was due to the inadequate methodological quality of this study. Moreover, the effect size of the Epworth sleepiness scale of a second trial could not be calculated because the scale was not administered when treating with the control device.<sup>38</sup> When pooling the remaining effect sizes, the AHI significantly improved (effect size -0.96 [95% CI -1.49 to -0.42]), while there was no significant change in the Epworth sleepiness scale (effect size -0.22 [95% CI -0.51 to 0.08]) in the comparison of MRA therapy with control devices (Figure 4).

### *Variability in mandibular advancement and bite-opening*

In one study the effect of progressive mandibular advancement on AHI was studied in seven OSAHS patients.<sup>92</sup> By progressively increasing the amount of mandibular protrusion and evaluating the effect in a sleep study, the amount of advancement could be identified as one factor that decreased the AHI with MRA therapy. In another study, the effect of bite-opening in MRA therapy was evaluated on efficacy and side-effects in 24 OSAHS patients.<sup>93</sup> Except for an interincisal opening of 4 and 14 mm, patients were treated with two identical appliances. Although with

**TABLE 2.** Characteristics of included trials related to efficacy.

Study*	Design trial	(1) MRA		(2) Control
		Type	Advancement†	
Hans <i>et al.</i> , 1997 <sup>91</sup>	randomized parallel	one-piece: SnoreGuard	6-8 mm	control device: modified MRA
Mehta <i>et al.</i> , 2001 <sup>38</sup>	randomized crossover	two-piece	78%	control device: lower piece MRA
Gotsopoulos <i>et al.</i> , 2002 <sup>39</sup>	randomized crossover	two-piece	80%	control device: upper piece MRA
Johnston <i>et al.</i> , 2002 <sup>41</sup>	randomized crossover	one-piece	75%	control device: modified MRA
de Almeida <i>et al.</i> , 2002 <sup>92</sup>	crossover	two-piece: Klearway™	60%	identical MRA with more protrusion
Pitsis <i>et al.</i> , 2002 <sup>93</sup>	randomized crossover	two-piece	87%	identical MRA with more bite-opening
Barthlen <i>et al.</i> , 2000 <sup>10</sup>	crossover	one-piece: SnoreGuard	NR	Tongue Retaining Device and palatal lifting device
Bloch <i>et al.</i> , 2000 <sup>40</sup>	randomized crossover	one-piece: OSA-Monobloc	(1) 75% <sup>  </sup> (2) 75% <sup>  </sup>	two-piece: OSA-Herbst
Rose <i>et al.</i> , 2002 <sup>68</sup>	randomized crossover	two-piece: Karwetzky	(1) 75% (2) 75%	two-piece: Silensor®
Wilhelmsson <i>et al.</i> , 1999 <sup>94</sup>	randomized parallel	one-piece	50%	UPPP
Clark <i>et al.</i> , 1996 <sup>42</sup>	crossover	two-piece	66.7%	CPAP
Ferguson <i>et al.</i> , 1996 <sup>56</sup>	randomized crossover	one-piece: SnoreGuard	3mm < max. protrusion	CPAP
Ferguson <i>et al.</i> , 1997 <sup>57</sup>	randomized crossover	two-piece: AMP	>70%	CPAP
Engleman <i>et al.</i> , 2002 <sup>55</sup>	randomized crossover	one-piece: 2 different designs	80%	CPAP
Randerath <i>et al.</i> , 2002 <sup>68</sup>	randomized crossover	two-piece: ISAD	66%	CPAP
Tan <i>et al.</i> , 2002 <sup>95</sup>	randomized crossover	one-piece & two-piece (Silensor®)	≥75%	CPAP

Included	Patients		Quality score	AHI <sup>‡</sup>	ESS <sup>‡</sup>	Treatment success <sup>§</sup>
	Included	Completing				
(1) 12 (2) 12	(1) 10 (2) 8	43.5	NC	NC	(1) NR (2) NR	
28	24	77	-1.61 (-2.26 to -0.96)	NR	(1) 62.5% <sup>o+¶</sup> (2) NR	
85	73	86	-0.76 (-1.09 to -0.42)	-0.23 (-0.56 to 0.09)	(1) 63% <sup>c</sup> (2) NR	
21	20	68	-0.61 (-1.24 to 0.03)	-0.14 (-0.80 to 0.51)	(1) 33% <sup>b</sup> (2) NR	
7	6	44	NC	NR	(1) 4 of 6 <sup>c</sup> (2) 5 of 6 <sup>c</sup>	
24	23	79	-0.26 (-0.84 to 0.32)	0.00 (-0.58 to 0.58)	(1) 74% <sup>o+¶</sup> (2) 61% <sup>o+¶</sup>	
8	(1) 8 (2) 5 and 2	38	NC	NR	(1) 5 of 8 <sup>d</sup> (2) 2 of 5 <sup>d</sup> / 0 of 2 <sup>d</sup>	
24	24	68.5	-0.10 (-0.67 to 0.46)	NC	(1) 75% <sup>b+¶</sup> (2) 67% <sup>b+¶</sup>	
26	(1) 20 (2) 18	52	-0.43 (-1.07 to 0.22)	NR	(1) NR (2) NR	
(1) 49 (2) 46	(1) 37 (2) 43	76	-0.47 (-0.91 to -0.02)	NR	(1) 81% <sup>e</sup> (2) 60% <sup>e</sup>	
23	21	52	0.91 (0.28 to 1.55)	NR	(1) NR (2) NR	
27	(1) 19 (2) 20	68.5	1.14 (0.46 to 1.82)	NR	(1) 48% <sup>b+¶</sup> (2) 62% <sup>b+¶</sup>	
24	(1) 19 (2) 19	72.5	0.95 (0.28 to 1.62)	-0.13 (-0.77 to 0.50)	(1) 55% <sup>b+¶</sup> (2) 70% <sup>b+¶</sup>	
51	48	78	0.57 (0.16 to 0.98)	0.79 (0.38 to 1.21)	(1) 47% <sup>b</sup> (2) 66% <sup>b</sup>	
20	20	75	1.28 (0.60 to 1.96)	NR	(1) 30% <sup>b</sup> (2) NR	
24	(1) 23 (2) 22	59	0.60 (0.00 to 1.20)	0.19 (-0.40 to 0.78)	(1) 70% <sup>b</sup> (2) 100% <sup>b</sup>	

**APPENDIX TABLE 2.**

\* Arranged according to appearance in the results section.

† Reported as mean percentage of maximum mandibular advancement or as range in mandibular advancement.

‡ Reported as effect size and approximate 95% confidence interval in parenthesis.

§ Number or percentage of patients completing the study that meet with the pre-defined criterion for success.

|| Initial amount of mandibular advancement.

¶ Improvement or resolution of OSAHS symptoms.

# Patient satisfied with effect of treatment.

Criterion for treatment success: a = AHI <5 or reduction AHI >50%, b = AHI <10, c = AHI <10 and reduction AHI >50%, d = AHI <15, e = reduction AHI >50%.

Abbreviations: (1) = mandibular repositioning appliance therapy, (2) = control therapy, AHI = apnea-hypopnea index, CPAP = continuous positive airway pressure, ESS = Epworth sleepiness scale, MRA = mandibular repositioning appliance, NC = not calculated, NR = not reported, UPPP = uvulopalatopharyngoplasty.

both appliances the AHI and arousal-index decreased significantly, no significant differences could be demonstrated between the devices. Moreover, subjective outcomes like the Epworth sleepiness scale, sleep quality and improvements in snoring did not differ between the two appliances. Although side-effects and reported compliance did not differ, a significantly higher proportion of patients preferred using the MRA with lower vertical dimension.

The effect size of the AHI in one trial was not calculated due to inadequate overall methodological quality.<sup>92</sup> Although there was a trend toward greater efficacy with the MRA with lower vertical dimension, no significant differences in effect sizes with respect to the AHI (effect size -0.26 [95% CI -0.84 to 0.32]) and Epworth sleepiness scale (effect size 0.00 [95% CI -0.58 to 0.58]) could be demonstrated (Figure 4).<sup>93</sup>

### *Variability in appliance design*

In one trial, the effect of an MRA was compared with a Tongue-Retaining Device and a soft palatal lifting device in eight patients with severe OSAHS.<sup>10</sup> Compared to baseline values the AHI significantly decreased with MRA therapy whereas it did not with the Tongue-Retaining Device or the soft palatal lifting device. Moreover, the success of the latter two appliances was compromised by poor patient tolerance. Two other trials compared a one-piece MRA (OSA-Monobloc) with a two-piece MRA (OSA-Herbst) and two two-piece MRA's (Karwetzky-activator vs. Silensor®), respectively.<sup>40,68</sup> In both studies the amount of mandibular advancement was identical with either appliance. Although no significant difference in the AHI could be demonstrated when comparing a one-piece with a two-piece MRA,<sup>40</sup> the Karwetzky-activator was reported significantly more effective with respect to the AHI.<sup>68</sup> Both studies could not demonstrate a significant difference between the appliances with respect to improvements in oxyhemoglobin saturation parameters. Moreover, no significant

differences in the arousal-index, snoring frequency, percentage of slow-wave sleep or Epworth sleepiness scale were demonstrated between the Monobloc- and Herbst-appliance.<sup>40</sup> Patient-perceived relieve of symptoms and snoring was slightly better with the Monobloc-appliance,<sup>40</sup> whereas, in this respect, no difference was observed between the Karwetzky-activator and the Silensor®.<sup>68</sup> Although the prevalence of side-effects was equal with the Herbst- and Monobloc-appliance, the majority of patients preferred Monobloc-therapy.<sup>40</sup> Side-effects were more frequent with the Karwetzky-appliance but the majority of patients preferred it to the Silensor®.<sup>68</sup>

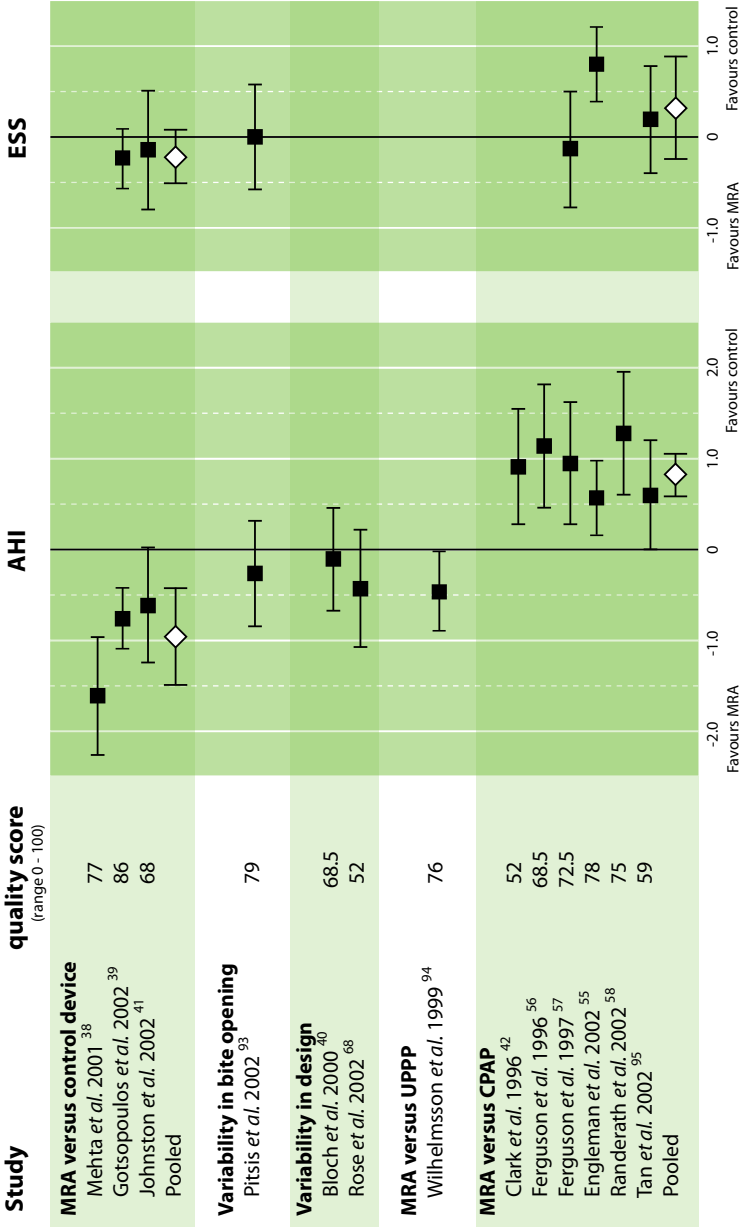
The effect size of the AHI of one trial was not calculated due to inadequate overall methodological quality.<sup>10</sup> Furthermore, effect size of the Epworth sleepiness scale could not be calculated in a second trial because only median and quartile range were reported.<sup>40</sup> The remaining effect sizes were not pooled due to the disparities between the (control) interventions (Figure 4). Although there was a trend toward greater success with the one-piece MRA with identical protrusion, no significant difference in effect size with respect to the AHI (effect size -0.10 [95% CI -0.67 to 0.46]) was observed.<sup>40</sup> Contrary to the reported significant difference in AHI, the calculated effect size (-0.43 [95% CI -1.07 to 0.22]) did not demonstrate a significant difference between the two-piece MRA's.<sup>68</sup>

#### *MRA versus UPPP*

The effect of MRA therapy was compared with UPPP in one trial.<sup>94</sup> After a one-year treatment period, a significant difference in the AHI in favor of MRA therapy was observed. However, other physiological parameters including the hourly rate of oxyhemoglobin desaturations ( $\geq 4\%$ ) and registered snoring time did not differ between the two interventions. Although after six months of treatment subjective daytime sleepiness was less in the UPPP group, no significant difference in sleepiness was observed after a one-year treatment period. In a separate publication reporting on changes in quality of life, the UPPP group showed a greater level of contentment than the MRA treated patients after a one-year treatment period.<sup>96</sup> Since no other trials compared MRA therapy with UPPP, a pooled estimate could not be calculated. The effect size of the AHI demonstrated that MRA therapy was more effective than UPPP (effect size -0.47 [95% CI -0.91 to -0.02]) (Figure 4).

#### *MRA versus CPAP*

Three of the included trials compared a one-piece MRA with CPAP<sup>55,56,95</sup> whereas the other three trials employed a two-piece appliance.<sup>42,57,58</sup> However, in one trial, patients were randomized to a one-piece MRA with a flexible or rigid construction.<sup>55</sup> Moreover, due to nocturnal breathing difficulties one trial replaced their one-piece appliance halfway the study with a two-piece MRA.<sup>95</sup> Since both studies did not observe differences in efficacy as a result of appliance design, data on the different appliances were pooled.



**FIGURE 4.** Effect sizes with approximate 95% confidence intervals of methodologically sound trials related to efficacy.

Abbreviations: AHI = apnea-hypopnea index, ESS = Epworth sleepiness scale, MRA = mandibular repositioning appliance, UPPP = uvulopalatopharyngoplasty, CPAP = continuous positive airway pressure.

Compared with MRA therapy, CPAP resulted in a significant improvement in the AHI in five out of six trials.<sup>42,55-58</sup> Although there were no significant differences in the arousal-index between the interventions, snoring frequency did significantly differ in favor of CPAP.<sup>58,95</sup> With CPAP, the minSaO<sub>2</sub> improved more when compared with MRA therapy in three trials<sup>56-58</sup> whereas it did not in another trial.<sup>42</sup> Variability in the changes of other parameters of oxyhemoglobin saturation during sleep was also reported. Two trials demonstrated significant improvements in the hourly rate of oxyhemoglobin desaturations (oxyhemoglobin saturation <90%) with CPAP but not with MRA therapy,<sup>56,57</sup> whereas another trial did not observe significant differences in oxyhemoglobin desaturation intensity and duration between CPAP and MRA therapy.<sup>95</sup>

Although in two trials the Epworth sleepiness scale improved with both CPAP and MRA therapy, no significant difference could be demonstrated between the interventions.<sup>57,95</sup> In one trial, CPAP resulted in a more significant improvement in the Epworth sleepiness scale and the functional outcomes of sleepiness questionnaire.<sup>55</sup> However, the same trial could not demonstrate a significant difference between CPAP and MRA therapy in objective sleepiness according to the maintenance of wakefulness test and home portable sleep time registration. Moreover, none of the other trials found a significant difference between CPAP and MRA therapy in sleep quality related variables like the amount of rapid-eye-movement or slow-wave sleep. Although “mental well-being” and “health transition” according to the short-form 36 health survey were significantly better with CPAP, no significant differences between the treatments were observed using the hospital anxiety and depression scale or cognitive performance tests.<sup>55</sup> Three trials demonstrated more pronounced improvements in patient-reported symptomatology like snoring and sleepiness with CPAP therapy<sup>55-57</sup> whereas the remaining trials could not. Although the severity of adverse events was generally not different between the two interventions, one trial reported more side-effects with CPAP therapy.<sup>56</sup> Patient-reported use generally did not differ between CPAP and MRA therapy.<sup>55-57</sup> In one study patient-reported compliance was greater with MRA therapy.<sup>58</sup> Moreover, patients were generally less satisfied with CPAP and found MRA therapy easier to use.<sup>42,56-58,95</sup>

When pooling the available effect sizes, a significant improvement in the AHI (effect size 0.83 [95% CI 0.59 to 1.06]) was observed with CPAP compared with MRA therapy. Conversely, no significant difference in the pooled effect size of the Epworth sleepiness scale (effect size 0.32 [95% CI -0.24 to 0.89]) could be demonstrated when comparing MRA therapy with CPAP (Figure 4).

## Co-morbidity

Using the specified criteria, 14 articles related to co-morbidity were considered eligible. Because the journal's permission to use the article *in press* was not granted,<sup>60</sup> 13 articles were included for methodological appraisal (Figure 3, Table 3). Eight of the included articles studied co-morbidity of MRA therapy with respect to the craniomandibular complex.<sup>18,45,67,92,97-100</sup> Orthodontic side-effects of MRA therapy were assessed in six studies.<sup>18,67,70,72,99,100</sup> Finally, in six studies dental and skeletal changes resulting from MRA therapy were assessed by means of upright cephalometry.<sup>70,72,98,101-103</sup> In six studies, overlap with respect to baseline characteristics was noted. Two studies reported on the one- and four-year follow-up of adverse effects of MRA therapy on the stomatognathic system.<sup>18,45</sup> Two similar studies reported on the effect of MRA therapy on the craniofacial and craniomandibular complex.<sup>98,99</sup> Finally, dental and skeletal changes associated with MRA therapy were studied in one study and further explored with respect to the upper facial skeleton in a second study.<sup>101-103</sup>

In two studies, more than one appliance design was used.<sup>70,100</sup> The amount of mandibular advancement with MRA therapy was comparable between the 13 included studies (Table 3). However, the duration of the follow-up period was different between some studies (means ranging from six months to four years). Moreover, by taking the review cephalogram at six month intervals (six to 30 months), two studies tried to establish whether changes in craniofacial characteristics were progressive with continuing treatment.<sup>101,103</sup> Although compliance was not reported in all studies, patients generally used their MRA more than five nights per week for five hours or more per night. Except for the male to female ratio in two studies,<sup>98,99</sup> patient baseline characteristics of the 13 included studies were generally comparable with respect to male to female ratio, age (means ranging from 46.7 to 55.3) and body-mass index (means ranging from 26.3 to 29.2).

The majority of the included studies were patient-series with only one study using a concurrent control group.<sup>100</sup> Despite the non-controlled design of most studies, methodological quality was generally rated as "adequate". The single study that used a control group was rated as "good" whereas one study was rated as "poor".<sup>67</sup> This was mainly due to the unclear description of the material and methods in the latter study. Inter-rater agreement on the methodological quality of each study, according to the overall impression, was good (agreement 97%, Cohen's kappa 0.65 [95% CI 0.32 to 0.98]).

### *Craniomandibular complex*

MRA therapy did not result in significant changes in maximum mouth opening, laterotrusion or protrusion in the short- or long-term in three studies.<sup>18,45,99</sup> However, in one study an increased mouth opening was observed in 28% of

patients following a mean treatment period of 31 months.<sup>67</sup> Except for individual patients, no significant changes in pain on movement or palpation of the temporomandibular joints and masticatory muscles were detected.<sup>18,99</sup> Moreover, changes in joint function as a result of treatment were generally minor.<sup>45,67,99</sup> When quantifying changes in these clinical parameters according to the Helkimo clinical dysfunction index or score, minor and insignificant changes in craniomandibular status were observed.<sup>18,97,99</sup> Moreover, no changes could be demonstrated in the relation between centric occlusion and centric relation (*i.e.*, no “dual bite”).<sup>98,100</sup> Finally, in six out of seven patients magnetic resonance imaging studies of the temporomandibular joint and masticatory muscles did not reveal any changes in function and morphology as a result of MRA therapy after a mean treatment period of one year.<sup>92</sup>

### *Craniofacial complex*

In five studies, plaster cast measurements demonstrated significant decreases in dental overbite and overjet as a result of MRA therapy.<sup>67,70,72,98,100</sup> Although patient follow-up was shorter, in one study clinical examination could not demonstrate significant changes in dental occlusion.<sup>18</sup> In four studies, long-term MRA therapy resulted in a mesial shift of the mandibular first molars relative to the maxillary first molars (mesial shift intermolar relationship).<sup>70,72,99,100</sup> In one of these four studies, the changes were accompanied by a posterior open bite in 26% of patients and a significant reduction in anterior mandibular crowding.<sup>72</sup> Although transverse measurements demonstrated a significant decrease in maxillary inter-canine width in MRA users compared to controls,<sup>100</sup> no significant inter-arch changes could be demonstrated in another study.<sup>72</sup> The proportion of patients with occlusal changes tended to increase with length of MRA use in up to two years of treatment.<sup>67</sup> More than half of the patients with occlusal changes in this latter study were not aware of the changes. No correlation could be demonstrated between orthodontic side-effects and the amount of advancement, treatment duration, age, gender or (skeletal) dentofacial pattern.<sup>67,70,72</sup> A correlation was demonstrated between patient's impression of tooth movements and a mesial shift in intermolar relationship.<sup>70</sup>

Three cephalometric studies confirmed the results from plaster cast measurements by demonstrating a decreased dental overbite and overjet.<sup>72,98,101</sup> Whereas some studies did not observe changes in upper incisor inclination,<sup>98,102</sup> others demonstrated a more lingual inclination of the maxillary incisors following MRA therapy.<sup>70,72,101</sup> In addition, some studies did not observe any changes in lower incisor inclination,<sup>70,98</sup> whereas others demonstrated a more labial inclination of the mandibular incisors following MRA therapy.<sup>72,101,102</sup> Variable results were also reported with respect to changes in mandibular position. As a result of treatment, two studies observed a posterior rotation of the mandible in relation to the skull

**TABLE 3.** Characteristics of included studies related to co-morbidity.

Study	Design study	(1) MRA		Patients	
		Type	Advancement*	Type	No.
Bernhold <i>et al.</i> , 1998 <sup>97</sup>	patient-series	two-piece	50-70% <sup>§</sup>	OSAHS/ primary snoring	25
Bondemark, 1999 <sup>98</sup>	patient-series	one-piece	70%	OSAHS/ primary snoring	30
Pantin <i>et al.</i> , 1999 <sup>67</sup>	patient-series	one-piece	75% <sup>§</sup>	OSAHS/ primary snoring	106
Tegelberg <i>et al.</i> , 1999 <sup>18</sup>	patient-series	one-piece	50%	OSAHS	37
Bondemark <i>et al.</i> , 2000 <sup>99</sup>	patient-series	one-piece	50-70%	OSAHS/ primary snoring	32
Fritsch <i>et al.</i> , 2001 <sup>70</sup>	patient-series	one-piece & two-piece	75% <sup>§</sup>	OSAHS	22
Marklund <i>et al.</i> , 2001 <sup>100</sup>	patient-control	one-piece: 2 different designs	5.7±1.6 mm <sup>  </sup>	OSAHS/ primary snoring	75 & 17 <sup>†</sup>
Robertson, 2001 <sup>101</sup>	patient-series	one-piece	75%	OSAHS/ primary snoring	100
de Almeida <i>et al.</i> , 2002 <sup>92</sup>	patient-series	two-piece: Klearway™	60% + 2.4-5.3 mm	OSAHS	7
Fransson <i>et al.</i> , 2002 <sup>102</sup>	patient-series	one-piece	75% & ≥5 mm	OSAHS/ primary snoring	65
Robertson, 2002 <sup>103</sup>	patient-series	one-piece	75%	OSAHS/ primary snoring	100
Rose <i>et al.</i> , 2002 <sup>72</sup>	patient-series	two-piece: Karwetzky	4-6 mm <sup>§</sup>	OSAHS	34
Walker-Engström <i>et al.</i> , 2002 <sup>45</sup>	patient-series	one-piece	50%	OSAHS	27

Follow-up period <sup>†</sup>	Therapeutic compliance <sup>‡</sup>	Study quality	Co-morbidity of MRA therapy
6 months	nightly use in all patients	adequate	no adverse effects on craniomandibular complex
2 years	6-8 hours/night 5-7 nights/week	adequate	no "dual bite", forward/downward movement of mandible, increased mandibular length, decreased overjet/overbite
31 ± 18 months	regular use in 76% of patients	poor	increased mouth opening in 28% of patients, joint noises and occlusal changes (decreased overjet) in a few patients
12 months	6 nights/week	adequate	few adverse effects on craniomandibular complex, no changes in dental occlusion
2 years	6-8 hours/night 5-7 nights/week	adequate	few adverse effects on craniomandibular complex, decreased overjet/overbite, mesial shift intermolar relationship
median 14 months (range 12-30)	median 7 nights/week	adequate	decreased overjet/overbite, mesial shift intermolar relationship, posterior rotation of mandible, lingual inclination of maxillary incisors
2.5 ± 0.5 years	>50% nights/week	good	no "dual bite", decreased overjet/overbite/ maxillary intercanine width, mesial shift intermolar relationship
6, 12, 18, 24 or 30 months	>5-6 hours/night 7 nights/week	adequate	decreased overjet/overbite, lingual inclination of maxillary incisors, labial inclination of mandibular incisors, increased anterior/posterior face height, change in vertical condylar position
11.5 ± 5.3 months	NR	adequate	according to MRI no morphologic changes in craniomandibular complex
2 years	nightly use in 83% of patients	adequate	posterior rotation mandible, labial inclination mandibular incisors, increased anterior face height
6, 12, 18, 24 or 30 months	>5-6 hours/night 7 nights/week	adequate	change in vertical condylar position
29.6 ± 5.1 months	6-8 hours/night >5 nights/week	adequate	decreased overjet/overbite, mesial shift intermolar relationship, reduced anterior mandibular crowding, 26% of patients with posterior open bite, lingual inclination maxillary incisors, labial inclination mandibular incisors
mean 4.1 years (range 3.8-5.4)	6.1 nights/week	adequate	few adverse effects on craniomandibular complex

**APPENDIX TABLE 3.**

\* Reported as mean percentage of maximum mandibular advancement or as range in mandibular advancement.

† Reported as mean  $\pm$  standard deviation or as mean/median and range.

‡ Reported as mean, range or percentage of MRA use.

§ Initial amount of mandibular advancement.

|| Mean amount of mandibular advancement  $\pm$  standard deviation.

¶ Number of patients included in control group.

Abbreviations: MRA = mandibular repositioning appliance, NR = not reported, OSAHS = obstructive sleep apnea-hypopnea syndrome.

base,<sup>70,102</sup> whereas others did not observe a change in mandibular position.<sup>72</sup> In a third study, a relatively forward and downward change in mandibular position, accomplished by an increased mandibular length, was observed following MRA therapy.<sup>98</sup> Although changes in mandibular posture in the latter study were suggested to result from condylar or glenoid fossa remodeling, more recent studies demonstrating changes in condylar vertical position following MRA therapy suggest that alterations in mandibular position are causal for changes in mandibular posture.<sup>101,103</sup> Changes in anterior face height, mainly resulting from an increased lower anterior face height, were demonstrated in two studies.<sup>101,102</sup> Although similar changes in posterior face height were demonstrated,<sup>101</sup> these were not reported uniformly.<sup>102</sup> No correlation could be demonstrated between dental side-effects and the amount of mandibular advancement, treatment duration, patient perceived side-effects, age, gender or (skeletal) dentofacial pattern.<sup>70,72,98</sup> A correlation was demonstrated between treatment duration and changes in mandibular posture relative to the skull base.<sup>70</sup>

## Discussion

Systematic review of the available literature regarding efficacy and co-morbidity of oral appliances in the treatment of OSAHS indicates that oral-appliance therapy is a viable treatment modality in the adult patient with OSAHS, although CPAP is apparently more effective and adverse effects of oral-appliance therapy have been described. However, definite conclusions with respect to the precise indications of oral appliances in the management of OSAHS cannot be drawn. Moreover, the evidence base regarding the co-morbidity of oral-appliance therapy is generally obscured by methodological limitations of the available literature. Therefore, a discussion of our findings seems appropriate.

### Efficacy

When compared with a control device, MRA therapy was clearly more effective in improving the AHI and other physiological indicators. Superior results of MRA

therapy with respect to objective daytime sleepiness, patient compliance and patient satisfaction are supportive of the efficacy of MRA therapy in OSAHS. In contrast to these favorable results, the effect of MRA therapy on sleep architecture varied among different reports. However, with CPAP therapy also non-significant differences in sleep quality have been observed when compared with a placebo intervention.<sup>104</sup> Variable results in improvements of subjective parameters like the Epworth sleepiness scale and reported snoring are suggestive of a placebo effect of oral appliances. However, these findings may also be attributed to factors other than mandibular advancement, such as stimulation of neuromuscular reflexes and changes in the bite relationship, in both MRA and control therapy.<sup>38</sup> Future studies using a “true placebo” rather than an intra-oral control device may further elucidate the possible placebo effect of oral-appliance therapy.

Outcomes of variability in mandibular advancement and bite-opening suggest that MRA therapy derives its therapeutic effect mainly from the amount of mandibular advancement imposed by the appliance. Studies observing higher success rates of MRA therapy in patients with a greater mandibular advancement capacity support this suggestion.<sup>77</sup> Moreover, other studies on progressive mandibular advancement observed a similar “protrusion-dependent” effect in MRA therapy.<sup>105,106</sup> However, in some patients in these studies bite-opening also had a favorable effect on the treatment outcome. Moreover, in some OSAHS patients, the number of upper airway obstructions may even increase when the mandible is protruded towards its maximum.<sup>9,107</sup> These findings suggest that the optimum in mandibular advancement in MRA therapy is not always equal to the maximum mandibular protrusion. Although a relationship between the degree of mandibular advancement and the therapeutic efficacy of an MRA seems evident, shortcomings in the available literature and conflicting findings do not allow for definite conclusions. Variability in MRA bite-opening appears to be of no consequence in both physiological and subjective parameters. Therefore, the controversy persists regarding the amount of bite-opening indicated with MRA therapy.<sup>15</sup> However, patient preference may be an argument to keep the bite-opening in MRA therapy to a minimum.

With respect to both physiological parameters and patient acceptance, MRA therapy proved superior to other types of oral appliances in the management of OSAHS. These findings correspond to results of a similar study in primary snoring patients in which MRA therapy was compared with a palatal lifting device and a mouth shield.<sup>8</sup> When compared with an MRA, employability of tongue retaining appliances is probably poorer due to clinical limitations and patient acceptance.<sup>10,108</sup> However, it has been reported that unlike most MRA's, tongue retaining appliances are suitable for the edentulous patient as well.<sup>7</sup> Similar to variability in bite-opening, MRA design (*i.e.*, one-piece or two-piece) had no serious consequences

on the physiological outcomes. Moreover, MRA design generally did not affect patient-perceived symptomatology. These observations correspond to the findings of a review of 21 publications on oral-appliance therapy, which was published in 1995.<sup>35</sup> In their review, Schmidt-Nowara *et al.* concluded that despite considerable variations in appliance design, reported clinical effects of oral appliances that reposition the mandible are remarkably consistent. However, it should be noted that appliance design may influence therapeutic efficacy by affecting patient preference or patient-perceived symptomatology. The precise benefits of specific features in MRA design, such as adjustable mandibular advancement and freedom of mandibular movement, need to be further elucidated.

The one-year follow-up of patients treated with an MRA or UPPP suggests that the former should be preferred in the treatment of mild to moderate OSAHS. Although success rates of both interventions showed a tendency to decrease over a four-year period, MRA therapy remained more successful than UPPP.<sup>45</sup> However, it should be noted that after a one-year treatment period, UPPP treated patients generally showed a greater level of contentment than MRA treated patients.<sup>96</sup> Moreover, the number of drop-outs in the MRA group at the four-year follow-up limits definitive conclusions with respect to the long-term results of these interventions in OSAHS.

Results of crossover trials comparing MRA therapy with CPAP indicate that, when considering physiological outcomes like the AHI, CPAP should be preferred over MRA therapy. This is confirmed in another study that showed poor patient tolerance to MRA therapy in patients already on CPAP.<sup>109</sup> However, patient acceptance of the MRA in the latter study could have been affected by negative expectations and the specific design of the appliance. It is suggested that MRA therapy is generally more successful in patients with mild to moderate OSAHS.<sup>41,77</sup> In their crossover study, Engleman *et al.* performed a subgroup analysis on effectiveness of MRA therapy in patients with mild OSAHS.<sup>55</sup> Although in this subgroup changes in AHI did not significantly differ between CPAP and MRA therapy, efficacy and subjective parameters like patient satisfaction and sleepiness were better with CPAP. Contrary to these findings, other included trials did not demonstrate a significant difference in most subjective parameters between CPAP and MRA therapy. Moreover, changes in sleep quality like the amount of rapid-eye-movement or slow-wave sleep did not differ between the interventions. Because some suggest MRA therapy as first-line alternative in mild to moderate OSAHS,<sup>57,95</sup> and others obtain superior results with CPAP in this respect,<sup>55,58</sup> the precise indication for MRA therapy in OSAHS management requires further study. Although the non-significant changes in subjective sleepiness according to the Epworth sleepiness scale may be related to a placebo effect of oral-appliance therapy, a clear patient preference for MRA therapy indicates that CPAP should not be considered ideal in the management of OSAHS.

While the included trials related to efficacy were generally of adequate quality, some general aspects should be taken into consideration. In the included trials the reported success percentage of MRA therapy ranged from 30 to 81% (Table 2). However, among other factors such as the amount of mandibular advancement, these figures probably reflect bias due to the various definitions of treatment success. A recent literature review identified at least seven different definitions of treatment success in oral-appliance therapy.<sup>43</sup> In order to compare different studies of MRA therapy in OSAHS, a uniform definition of treatment success is clearly indicated. We suggest defining complete response to treatment as a correction of the AHI to normal levels (*i.e.*, AHI <5). A partial “laboratory response” to treatment may be defined as a satisfactory improvement of symptoms combined with a 50% or greater reduction in the AHI. In addition, since this is associated with an increased mortality, the post-treatment AHI in partial responders should not exceed 20.<sup>110</sup> Patients not meeting these criteria after follow-up poly(somno)graphy should be considered “nonresponsive” to treatment. Patients who discontinue treatment for any reason should be considered “nonadherent” to treatment.

In some trials, external validity may have been compromised due to the inclusion of patients of generally mild to moderate severity.<sup>40,56-58,68,92-95</sup> Moreover, in three trials, bias may have been incorporated due to the inclusion of patients that failed or refused CPAP therapy.<sup>10,40,68</sup> Most of the included studies used a crossover design. Although this offers the advantage of efficiency and within subject comparison, a crossover design may incorporate deficiencies that compromise study validity.<sup>111</sup> For example, a “carry-over of treatment effect” in crossover studies could result in a treatment-period interaction, thereby yielding a biased estimate of the treatment effect. Moreover, since blinding of patients to treatment is generally not possible, psychological influences cannot be overlooked when evaluating treatment efficacy in a crossover study. To preclude these methodological deficits, especially when comparing MRA therapy with CPAP, future randomized trials in oral-appliance therapy should preferably be of a parallel-group design. Moreover, a parallel design allows for easier long-term follow-up and determination of the precise indication of oral-appliance therapy in OSAHS management.

### Co-morbidity

Adverse effects of MRA therapy on the craniomandibular complex appear to be limited. In the clinical situation signs or symptoms of temporomandibular disorders resulting from MRA therapy are not commonly reported either.<sup>94,112</sup> It has been suggested that long-term evaluation of MRA therapy is needed to monitor any changes in craniomandibular status.<sup>112</sup> A four-year follow-up period of MRA therapy demonstrated only few adverse effects on the stomatognathic system.<sup>45</sup> It has been reported that serious adverse effects on the craniomandibular complex are the main reasons for discontinuing MRA therapy.<sup>67,68</sup> Conversely, orthodontic

side-effects were observed more frequently in MRA therapy. Although generally minor, a decreased dental overbite and overjet accompanied by a mesial shift in intermolar relationship was reported most uniformly. Patient-perceived changes in occlusion may be of additional value in detecting changes in dental occlusion. Other adverse effects on dental occlusion, such as a posterior open bite or reduced anterior mandibular crowding, may accompany these changes. The observed changes in dental occlusion are confirmed by cephalometric studies that also reported changes in overbite and overjet. Although not reported uniformly, cephalometric studies are also suggestive of changes in incisor inclination as a result of MRA therapy. These changes may be attributed to a labially directed force against the mandibular incisors and a lingually directed force against the maxillary incisors as the mandible attempts to return to a less constrained position.<sup>72</sup> The effect of long-term mandibular advancement on mandibular position was reported variably. Since in adult individuals skeletal alterations resulting from mandibular advancement are generally minimal,<sup>113</sup> changes in dental occlusion are most likely to result from a dentoalveolar effect of MRA therapy. Moreover, the observed shift in occlusion may be attributed to myostatic contracture of the lateral pterygoid muscle and failure of the mandibular condyles to fully reposition, following full-night mandibular protrusion.<sup>15,67</sup> This latter phenomenon may also explain the observed changes in anterior face height and condylar vertical position in the cephalometric studies. The available data suggest that dental and skeletal changes in MRA therapy may become more prominent over time.<sup>67,70,101</sup> It has been demonstrated that skeletal changes, that most likely relate to repositioning of the mandibular condyles, occur soon after the onset of treatment whereas dental changes appear to develop as treatment continues.<sup>101</sup>

On the basis of the available literature it appears that adverse effects of MRA therapy generally involve changes in dental occlusion. Since these changes appear to originate over longer treatment periods, they may go unnoticed by patients.<sup>67</sup> Most studies included in this review with respect to the co-morbidity of MRA therapy did not use a control group and recruited a non-homogenous patient population. Moreover, the use of various different appliances may obscure the findings. Despite these limitations, other methodological aspects of the studies included were generally of adequate quality. However, definite conclusions with respect to the adverse effects of long-term MRA therapy on the craniomandibular and craniofacial complex are not possible. Controlled studies are warranted addressing long-term co-morbidity of MRA therapy. Moreover, controlled studies should address the specific effects of MRA design, degree of mandibular protrusion and treatment duration on the occurrence and progression of adverse effects in MRA therapy.

## Concluding remarks

Randomized trials offer an evidence base for the use of oral appliances in the treatment of OSAHS. Oral appliances are effective in the treatment of OSAHS, although a placebo effect should be considered. MRA therapy generally yields superior results to other types of oral appliances in the treatment of OSAHS. Although definite conclusions are not possible, efficacy of MRA therapy appears to be related to the degree of mandibular advancement. Moreover, appliance design like the amount of bite-opening or the means of mandibular fixation may affect subjective parameters of success. Although short-term results indicate that MRA therapy should be preferred to UPPP, definite conclusions cannot be drawn. Superior results with respect to physiological outcomes indicate that CPAP should be preferred to MRA therapy. However, a clear patient preference for MRA therapy indicates that CPAP should not be considered ideal in the treatment of all OSAHS patients. In order to optimize methodological quality, future randomized trials in MRA therapy should incorporate a parallel-group design—a design which may clarify the specific indication of MRA therapy in OSAHS management. Moreover, important outcomes of MRA therapy like long-term efficacy, performance, cardiovascular status and objective compliance monitoring should be compared with other treatment modalities like CPAP. In order to compare different trials in MRA therapy, a consensus on the definition of treatment success is needed. Although generally not serious, MRA therapy may result in adverse effects on the craniomandibular and craniofacial complex. Adverse effects on the craniofacial complex appear most often in MRA therapy and generally involve changes in dental occlusion. However, the lack of controlled studies related to co-morbidity precludes any definite conclusions. Controlled studies are needed to address the long-term adverse effects of MRA therapy. Although it can not be excluded that efficacy or co-morbidity of oral-appliance therapy is influenced by the specific appliance design, it can be concluded that MRA therapy is a viable treatment modality for OSAHS.

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