Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review

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CRD summary
This review assessed the efficacy and safety of oral appliances (OAs) in obstructive sleep apnoea-hypopnoea syndrome. The authors concluded that OAs are a feasible treatment, although continuous positive airway pressure (CPAP) appeared more effective and adverse effects were reported with OAs. The review was reasonably well conducted, but there was insufficient evidence to directly compare CPAP with mandibular repositioning appliances and to support the authors' conclusions.

Authors' objectives
To evaluate the efficacy and safety of oral appliance (OA) therapy in patients with the obstructive sleep apnoea-hypopnoea syndrome (OSAHS).

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane CENTRAL Register were searched from inception to 2002 using the reported search terms. In addition, experts were contacted for details of unpublished or ongoing studies and reference lists of reviews and eligible studies were screened. No language restrictions were applied to the searches, but studies in Hebrew and Asian languages were excluded from the review. Studies reported as abstracts were also excluded. The authors were unable to include one identified 'in press' study.

Study selection
Study designs of evaluations included in the review
Controlled clinical trials were eligible for the evaluation of efficacy. Studies evaluating co-morbidity did not need to have a control group. Case reports were excluded. The duration of the included studies evaluating co-morbidity ranged from 6 months to a mean of 4 years.

Specific interventions included in the review
Efficacy studies that compared OA therapy using a mandibular repositioning appliance (MRA) with any conservative, surgical or noninvasive treatment (including no treatment or placebo intervention) were eligible for inclusion. Studies evaluating co-morbidity did not require a control treatment group. The review of efficacy compared one or two-piece MRAs with continuous positive pressure airway pressure (CPAP), control therapy (designed to increase vertical opening without advancing the mandible), appliances with variability in mandibular advancement and bite opening, appliances with variability in design and uvulopalatopharyngoplasty (UPPP).

Participants included in the review
Studies evaluating efficacy were eligible if they included patients aged 21 years or over who had been diagnosed with OSAHS. OSAHS was defined as an Apnoea-Hypopnoea Index (AHI) or Respiratory Disturbance Index (RDI) score of greater than 5. Studies evaluating co-morbidity could include mixed groups of patients (i.e. OSAHS and snoring patients). The mean age and body mass index of the participants in the included studies ranged, respectively, from 44 to 57.6 years and from 26.9 to 32 kg/m2.

Outcomes assessed in the review
Studies evaluating efficacy were eligible for inclusion if they primarily used AHI or RDI for assessment during a full-night sleep study. Studies evaluating co-morbidity were eligible if they primarily objectively assessed side-effects related to either the craniomandibular or craniofacial complex. Studies that assessed patient-perceived co-morbidity were excluded. The review also assessed outcomes reported on the Epworth Sleepiness Scale (ESS), physiological measures, quality of life, sleepiness scores, and behavioural or cognitive function measures.
How were decisions on the relevance of primary studies made?
Titles and abstracts were screened for relevance, then full-text articles retrieved to decide whether the study was eligible. The authors did not state how many reviewers performed the selection.

Assessment of study quality
Studies evaluating efficacy were assessed using criteria developed by Sindhu et al. for the assessment of randomised controlled trials (RCTs). The criteria were based on 15 fields: control group; randomisation; measurement of outcomes; study design; conclusions; intention-to-treat analysis; statistical analysis; adherence to study protocol; blinding; research question; losses to follow-up; outcomes; reporting of findings; patient compliance; and remaining variables. The maximum possible score was 100 points. Two reviewers, blinded to the title, authors and journal, independently assessed the validity of efficacy studies. Any disagreements were resolved through discussion with the aid of a third reviewer. Studies scoring at least 47 out of 100 were classified as 'methodologically sound'; this value was determined in a consensus meeting.

Studies evaluating co-morbidity were classified as having poor, adequate or good validity in a consensus meeting.

Data extraction
Two reviewers independently extracted the data. Any disagreements were resolved by consensus. For each study, the number of patients included and completing the study and the reported percentage of treatment success were extracted. For efficacy studies judged to be 'methodologically sound', effect sizes (ES) with 95% confidence intervals (CIs) were calculated for the AHI/RDI and the ESS. For studies evaluating co-morbidity, patient-reported compliance and adverse effects of interest were extracted.

Methods of synthesis
How were the studies combined?
The efficacy studies were grouped according to control treatment. Pooled ESs with 95% CIs for AHI/RDI and ESS were calculated using a random-effects model (DerSimonian and Laird) for the methodologically sound studies. Other outcomes reported in the efficacy studies were discussed.

Findings from studies evaluating co-morbidity were discussed separately.

How were differences between studies investigated?
No formal assessment of statistical heterogeneity was reported. Forest plots were presented for the meta-analyses of efficacy outcomes.

Results of the review
Sixteen efficacy studies (including 14 crossover studies) were included in the review (n=511): 13 RCTs (n=473) and 3 non-randomised controlled trials (n=38). Thirteen studies (12 RCTs and one non-randomised controlled trial) were included in meta-analyses. Thirteen studies (n=677) evaluated co-morbidity: a controlled clinical trial (n=92) and 12 case series (n=585).

Efficacy.
Thirteen of the included efficacy studies were awarded 47 or more points during the quality assessment and were deemed methodologically sound. However, most studies did not fully describe the method of randomisation. Blinding of the patients and therapists was not often feasible, but most studies did not report reasons for not blinding the outcome assessor. Other flaws included the lack of intention-to-treat analysis.

MRA versus control therapy (4 studies): the meta-analysis (3 trials, n=134) showed that MRAs significantly improved the AHI compared with control (ES -0.96, 95% CI: -1.49, -0.42). There was no significant difference in the ESS between MRA and control therapy.
Variability in mandibular advancement and bite opening (1 study, n=24): the only identified study had an overall inadequate methodological quality and an ES was not calculated.

Variability in appliance design (3 studies, n=8, n=24 and n=26): the AHI was not calculated for one study due to the inadequate quality score; neither of the other 2 studies individually reported any significant difference between MRA and other appliances in the ESs of the AHI.

MRA versus UPPP (1 study, n=95): the study reported that the MRA significantly improved the AHI compared with UPPP (ES -0.47, 95% CI: -0.91, -0.02).

MRA versus CPAP (6 studies, n=169): the meta-analysis showed that CPAP significantly improved the AHI compared with MRA (ES 0.83, 95% CI: 0.59, 1.06). There was no significant difference in the ESS between CPAP and MRA.

Co-morbidity.

Craniomandibular complex: changes associated with MRAs included increased mouth opening in 28% (1 study). Other reported changes appeared to be non significant or minor. Craniofacial complex: changes associated with MRA were found./ These included a significant decrease in dental overbite and overjet associated with MRA treatment (5 studies), which was confirmed using cephalometry in 3 studies, although one shorter term study showed no significant change in dental occlusion; a mesial shift of the mandibular first molars relative to the maxillary first molars (4 studies); a significant decrease in maxillary intercanine width in one study but no significant inter-arch changes in another study. There was no consistency among studies regarding changes in the inclination of upper and lower incisors, changes in mandibular position and changes in upper face height. Two studies demonstrated increased lower face height.

Authors' conclusions
Findings suggest that, although CPAP appeared more effective and MRA therapy has been associated with adverse effects, MRA was a feasible treatment for adults with particularly mild to moderate OSAHS. Further research is required.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design; the inclusion criteria for studies evaluating co-morbidity were broad. The reviewers did not state whether or not co-morbidity was reported in any of the controlled efficacy studies. Several relevant sources were searched and some attempts were made to minimise publication and language bias. Methods were used to minimise reviewer errors and bias in the assessment of validity and extraction of data, but it was unclear whether similar steps were taken at the study selection stage. The validity of the efficacy studies was assessed and results were reported. However, the quality assessment tool was designed for RCTs and might not have been appropriate for the included non-randomised studies; its appropriateness for assessing crossover studies (which formed most of the evidence) was not discussed.

Given that little information on the participants was presented, the clinical comparability of the studies could not be adequately assessed. The comparability of treatment effects between studies also could not be adequately assessed since, although forest plots were presented, statistical heterogeneity was not formally assessed. Where the results for the AHI and ESS differed there was no discussion of potential reasons for these differences. Most of the studies had small sample sizes (range 7 to 85 for efficacy studies) and were potentially underpowered to reliably detect a treatment difference. The review did not compare the adverse effects of CPAP with MRAs, thus their relative safety could not be judged. There was insufficient evidence to directly compare the advantages and disadvantages of CPAP versus MRA. The recommendations for additional research appear reasonable in view of the limited quality of the evidence, particularly about co-morbidities.

Implications of the review for practice and research
Practice: The authors stated that MRA treatment should be supervised by physicians with experience in sleep-disordered breathing.
Research: The authors stated the need for controlled studies (preferably parallel-group studies) to examine the specific indications for MRAs in OA therapy, the effects of MRA on long-term co-morbidity, and the effects of particular aspects of MRA design, degree of mandibular protrusion and the duration of treatment. Future studies should use a ‘true placebo’ rather than an intra-oral control device, so that the placebo effects of OA, if any exist, can be determined. Definitions for 'successful' treatment need to be standardised. The authors suggested defining 'successful treatment' as the correction of RDI to physiological levels (i.e. RDI <5); 'partial response' as a satisfactory improvement in symptoms with a 50% or greater reduction in the RDI, but a post-treatment RDI of 20 or less (since higher values are associated with greater mortality); and 'treatment and compliance failures' as patients not meeting criteria for success or partial success, or unable to use MRA.

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