An update on mandibular advancement devices for the treatment of obstructive sleep apnoea hypopnoea syndrome

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Abstract: Continuous positive airway pressure (CPAP) remains the gold standard treatment for obstructive sleep apnoea hypopnoea syndrome (OSAHS). However, the high efficacy of CPAP is offset by intolerance and poor compliance, which can undermine effectiveness. This means that alternatives to CPAP are also necessary. In recent years, oral appliances have emerged as the leading alternative to CPAP. There is now a strong body of evidence supporting their use in OSAHS and clinical guidelines now recommend their use in mild OSAHS and in more severe cases when CPAP fails. These devices are by no means a homogenous group as they differ greatly in both design and action. The most commonly used appliances are mandibular advancement devices (MAD) that increase airway diameter with soft tissue displacement achieved by mandibular protrusion. Despite the growing evidence, there are still barriers to MAD provision. Their effectiveness can be difficult to predict and there is debate about the required level of design sophistication. These uncertainties prevent more widespread inclusion of MAD within clinical sleep services. This review will focus on the efficacy, effectiveness, design features, side-effects of and patient selection for MAD therapy. Comparison will also be made between MAD and CPAP therapy.

Keywords: Obstructive sleep apnoea; sleep apnoea; mandibular advancement devices (MAD); oral appliances

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Introduction

Obstructive sleep apnoea hypopnoea syndrome (OSAHS) is a common sleep disorder characterised by intermittent upper airway collapse resulting in oxygen desaturation and sleep fragmentation. Excessive daytime sleepiness (EDS) is associated with cognitive impairment, mood disturbance and decreased quality of life (QoL). OSAHS is also linked with increased risk of road traffic accidents, cardiovascular disease and all-cause mortality (1,2). It affects 2–7% of adults (3) and an estimated 1% of UK men have severe OSAHS (4). Many cases go untreated due to not being diagnosed or intolerance of treatment. The consequences are estimated to cost the NHS around £432 million each year (2,5).

The pathogenesis of OSAHS is a complex interaction of multiple factors including pharyngeal anatomy, dilator muscle dysfunction and reduced lung volume (6). Whilst the relative contributions of these mechanisms vary between patients, the common result is sleep related upper airway collapse. The gold standard treatment remains continuous positive airway pressure (CPAP) therapy (7). It pressurises the upper airway to prevent collapse, reducing the frequency of apnoeas and hypopnoeas. However, CPAP effectiveness is limited by intolerance and poor compliance, with failure rates of 46–83% (8). There is a pressing need for alternatives to CPAP.

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and action. Nevertheless, the tongue is affected by all the appliances, either directly by forward movement of the muscle, or indirectly by advancing the mandible. The most commonly used appliances are mandibular advancement devices (MAD) and there is now a strong body of evidence supporting their use in OSAHS. Clinical guidelines recommend MAD ahead of CPAP in mild OSAHS and in more severe OSAHS when CPAP is refused or not tolerated (7,9,10). However, there are still barriers to MAD provision. Their effectiveness can be difficult to predict and there is still debate about the required level of design sophistication. These uncertainties prevent more widespread inclusion of MAD within clinical sleep services.

This review will focus on the efficacy, effectiveness, design features, side-effects of and patient selection for MAD therapy. Comparison will also be made between MAD and CPAP therapy.

**Mechanism of action of MAD**

MAD prevent upper airway collapse by protruding the mandible forward, thus altering the jaw and tongue position. They are also referred to in the literature as mandibular advancement splints (MAS) or mandibular repositioning appliances (MRA). Both video endoscopy and magnetic resonance imaging (MRI)-guided studies have determined that these devices predominantly increase the volume of the airway at the level of the velopharynx (11,12). The airway space is mostly enlarged laterally, thought to be due to traction on soft tissue connections between the pharynx and the mandibular ramus (13).

It was previously thought that even an inactive oral appliance (i.e., not protruding the mandible) may reduce apnoeic episodes. However, numerous randomised controlled trials (RCT) have established the efficacy of MAD over placebo including inactive appliances (14-16). The lack of significant difference between the inactive appliances and a no intervention control in one study is further evidence that the mechanism of action is through mandibular protrusion (16).

**Efficacy of MAD**

Treatment objectives for OSAHS address both the physiological and symptomatic aspects of the disease. The physiological goals target obstructive events, sleep fragmentation and oxygen desaturation. Symptomatic goals target snoring, sleepiness, QoL and possibly comorbidities. However, even published studies that share treatment objectives can vary in their definition of treatment success. This variability complicates the interpretation of efficacy. The apnoea-hypopnoea index (AHI) is the number of apnoea and hypopnoea events per hour of sleep. Most studies define treatment success as achieving a certain AHI target (usually ≤5–10/hour) or a certain percentage reduction in AHI (usually 50%). Studies since 2005 that looked at therapy with bespoke MADs (custom made from dental impressions) have reported mean AHI reductions of between 30% and 72%. Reviewing the data of these studies revealed a complete response (AHI <5) or partial response (≥50% reduction in AHI from baseline, but AHI >5) of between 45% and 100% (Figure 1) (15-19). Studies with higher response rates recruited patients with lower AHI at baseline. Blanco et al. (15) reported a 100% response rate, however the study had limitations due to small sample size and a high proportion of subjects withdrawing from the trial.

Apart from reductions in AHI, studies have also shown that MAD can improve the arousal index, oxygen saturation parameters and increase Rapid eye movement (REM) sleep duration (20-22). Partners of those on MAD therapy also benefit from reduction in snoring (15,20-22).

**Health outcomes of MAD**

EDS is reduced by MAD treatment. When measured subjectively using the Epworth Sleepiness score (ESS) all recent studies have shown a significant improvement in EDS with MAD treatment compared to inactive appliances.
(14-16,20-22). Published objective sleepiness outcomes are few and results vary. An early study (20) found that MAD improved mean sleep latency on Multiple Sleep Latency Test (MSLT) compared to an inactive appliance. However, when examining alertness with the Maintenance of Wakefulness Test, another study found no effects of either CPAP or MAD on mean sleep latency compared to placebo (23). In a more recent study both CPAP and MAD improved Oxford sleep resistance test scores to a similar extent (24). The varying results are probably a function of the different tests used, and variability in treatment implementation and compliance between studies.

Earlier meta-analyses were inconclusive about the effects of MAD therapy on QoL (25), but this may have been due to small studies and inconsistent methodologies. More recently, both generic and disease specific QoL measures have been shown to improve with MAD when compared to inactive controls (18). Perceived health status and QoL questionnaires specific for OSAHS showed considerable improvements after MAD (15). Generic questionnaires such as the Short Form 36 (SF-36) have also showed improvement in multiple studies (16,26).

Systolic and diastolic blood pressure (BP) have been shown to improve with MAD treatment (14,27). This is especially the case in hypertensive patients. A study with long follow-up data reported that positive effects on BP persisted for up to 4.5 years (28). BP benefits are not seen in all OSA intervention studies, including those testing CPAP. A well-designed pragmatic RCT comparing CPAP to MAD showed no effect on BP for either treatment in moderate to severe OSAHS (29). However, a recent meta-analysis demonstrated an overall benefit of MAD therapy to BP (30).

MAD compared to CPAP

CPAP is considered the gold standard treatment for OSAHS. It is highly efficacious in reducing obstructive events as measured by the AHI and can improve EDS, QoL and BP. Although efficacious, CPAP effectiveness is often limited by low adherence. When applying the popular minimum acceptable CPAP compliance threshold of 4 hours per night, failure rates have ranged from 29% to 83% depending on the study population (8,31).

Numerous studies have compared MAD to CPAP. Most have recruited patients with mild-moderate OSAHS, although more severe disease has also featured (25,29,32,33). Many of these papers have fed into meta-analyses, and a recent one examined the results of all trials comparing MAD to CPAP (34). All studies used AHI as the primary outcome of efficacy with multiple secondary outcomes including oxygen desaturation index (ODI) and arousal index. Results consistently demonstrate that CPAP is more effective than MADs at reducing sleep disordered breathing and achieving complete control of OSAHS (AHI ≤5) (34).

Despite the greater effect of CPAP on objective polysomnographic parameters, it does not appear to be more effective at achieving better health outcomes. It seems that the higher efficacy of CPAP is offset by greater MAD compliance. Phillips et al. (29) showed that CPAP and MAD achieved similar improvements in EDS and QoL. Average MAD compliance was 6.5 hours/night compared to 5.2 for CPAP (P<0.0001). These results are consistent with other studies (23,24,32), supporting the hypothesis that MAD and CPAP have similar clinical effectiveness due to greater MAD compliance achieving net similar AHI reduction (35,36).

Adherence also influences health economics. The cost effectiveness of MAD and CPAP in mild to moderate OSA was recently reviewed by investigators who included data from the TOMADO study. Sensitivity analysis found that MAD becomes more cost effective than CPAP when CPAP compliance drops below 90% of MAD usage. Therefore, it is important to determine factors influencing compliance and to employ a patient-centred approach when deciding which therapy to initiate (37). A focus group-based study interviewing CPAP and MAD users found that the four most important factors determining choice of treatment were device effectiveness, transportability, embarrassment and cost (38). This may explain the higher nightly MAD usage frequently reported in trials and why patients often prefer MAD to CPAP (39,40).

Design features influencing the efficacy of MAD

The design and sophistication of MAD vary greatly. Variables include adjustability, nature or extent of customisation and materials used; and they are not mutually exclusive. This complex heterogeneity undermines attempts to elucidate factors’ individual impacts on the effectiveness of specific appliances. The TOMADO study was a comprehensive RCT comparing three different non-adjustable MAD (18), but more work is needed in this area.

Non-adjustable, over-the-counter “boil and bite” appliances are the cheapest option available (Figure 2A). They are constructed of a thermoplastic material that becomes mouldable when warmed by immersion in hot
water. The user takes a mould of their teeth by biting into the softened material that then sets on cooling. Customised devices are constructed in a lab using dental impressions. The TOMADO study found that thermoplastic MAD could reduce AHI. However, they were less effective because they were poorly tolerated and fell out easily, so adherence was lower (18).

Custom made devices can either be a one-piece or an adjustable two-piece appliance. Upper and lower dental splints are fused in the one-piece device (monobloc), which is cheaper and easier to construct (Figure 2B). Although most of these appliances are a bespoke dentally produced device, “semi-bespoke” MAD, which require no specialist dental input, exist. The TOMADO study reported similar AHI reduction, tolerance and device retention with semi-bespoke MAD and dentally produced and fitted monoblocs. Semi-bespoke devices were found to be the most cost effective too, so the authors recommended that they be considered first choice when considering MAD therapy (41).

Adjustable two-piece devices come in separate upper and lower plates (Figure 2C). Construction requires additional specialist jaw articulation and is more expensive. Serially titrated mandibular protrusion is thought to increase treatment success by allowing gradual adaptation to optimal protrusion (42,43). The ability to titrate protrusion according to efficacy and tolerance is the key advantage of adjustable MAD (aMAD) and the main justification for their recommendation in clinical guidelines (10,44). However, there is a lack of supporting evidence. The degree of mandibular protrusion used in published studies has been highly variable, ranging from 50% to 80% of maximal protrusion (27,44). Existing studies that have compared so-called fixed MAD (fMAD) to aMAD have had methodological limitations and inconsistent findings (45-47). For example, one study comparing two devices set different protrusions for fMADs and aMADs, thus essentially comparing protrusions rather than devices. There is a need for a robust comparison of fMAD and aMADs.

Side effects of MAD

Most complications of MAD therapy are mild and temporary. They are nonetheless significant as they can limit device tolerance and effectiveness, so efforts are needed to mitigate this risk. Some authors have suggested that more side effects may be seen with greater levels of protrusion (48), but this has not been properly verified.

Short-term side effects usually occur during acclimatisation in the first few weeks of therapy. These include hypersalivation, dry mouth, dental pain, gingival irritation, myofascial pain and temporomandibular joint (TMJ) discomfort (49,50).

More information is needed on the incidence of long-
term side effects but they seem to mostly involve dentofacial changes. MAD use the patient’s dentition and alveolar ridges for retention when advancing the mandible forward. This invariably exerts reciprocal forces on the dentofacial structures. Changes in facial height and jaw relationship have been noted as early as 6 months into MAD use (51). Dental changes mainly relate to decreases in overbite and overjet as well as proclination of the lower incisors and retroclination of upper incisors (Figure 3) (51-56). A more recent paper reported how some patients undergoing MAD therapy experience occlusal alterations to posterior teeth (57). Appropriate planning and monitoring may avoid these effects as there is some evidence that an orthodontic MAD can increase overjet in those patients at risk of developing dentoalveolar changes (58). Despite the concerns about long-term dental side effects, it seems increasingly accepted that they may be a price worth paying for successful treatment of OSAHS (59).

Many studies have reported TMJ disorders complicating MAD use (50,58,60,61). However, these effects are transient and any pain appears to decrease in intensity with continued MAD use (61). In those with more noticeable TMJ pain, mandibular exercises may allow perseverance with MAD therapy until the discomfort improves (62,63).

There are some contraindications to MAD therapy. These include severe periodontal disease, severe pre-existing TMJ disorders, lack of adequate retention (inadequate dentition or implants) and severe gag reflex. Poor dexterity and other factors limiting hand function may also be relevant if they compromise device handling (43).

**Predictors of treatment success**

The unpredictability of response to MAD therapy is a significant barrier to the wider consideration of this treatment option by clinicians. Numerous studies have explored for clinical and sleep study predictors of treatment success. Younger age, lower body mass index (BMI) and smaller neck circumference have been related to successful MAD treatment (64-68). Female gender has also been suggested as a potential indicator of treatment success (64). In addition, polysomnographic parameters such as low AHI (64,66) and position dependent OSAH (69-71) have been proposed as predictors. However, none of these factors are sufficiently discriminatory. For example, successful treatment of OSAHS with MAD can be achieved in overweight patients and those with more severe disease (72,73).

Lateral cephalometric radiographs have also been tested. A retrognathic mandible, shorter soft palate and low-set hyoid bone have all been associated with favourable outcomes (74). However, these associations are weak and again cannot be relied on for clinical decision making. MRI with computational manipulation of the scans has been investigated (75). Although the science is promising, the costs undermine feasibility for most healthcare settings. Similarly, drug-induced sleep endoscopy continues to be explored as a predictive tool (76). Although effective in research settings and a few specialist centres this relatively expensive and intrusive investigation seems unlikely to be widely applied to routine clinical practice.

Perhaps a more promising method to predict treatment success is one in which mandibular advancement can be tested with a basic, cheap device before prescription of a more costly MAD. This has previously been explored with a thermoplastic MAD (17). Thermoplastic outcomes did not predict successful therapy with a customised MAD. However, the basic device was poorly tolerated and easily displaced. Furthermore, only around a third of patients were excessively sleepy at baseline and not all had significant OSA. More recent research has focused on titrating mandibular advancement during sleep studies in order to assess potential efficacy and determine optimal mandibular protrusion. Early prototyiptal studies have been promising (77,78), but again, these methods are resource expensive and seem...
unlikely to be widely adopted. Another recent innovation is adjustable thermoplastic MAD, which allow cheaper mandibular titration. A recent study showed these devices to be effective at reducing AHI in the short term (79). It remains to be seen whether they offer a long-term alternative to custom made adjustable MAD or whether they can be used to predict treatment response to the more expensive and longer lasting devices.

**Current guidelines**

Recommendations regarding the role of MAD therapy vary, but there are areas of agreement. Most clinical guidelines agree that MAD should be offered to patients with mild to moderate OSAHS and to those with more severe disease who do not want or cannot tolerate CPAP (7,9,10). They also state that MAD should be provided by qualified dentists who have had appropriate training in the field. Despite a lack of high level evidence, the ability to adjust protrusion according to efficacy and tolerance has meant that aMADs are increasingly recommended (10,43,80,81). Existing guidelines overlook semi-bespoke and thermoplastic adjustable devices. There is a need to update recommendations to reflect the latest evidence but continued research is also needed to address the uncertainties discussed in this article.

**Conclusions**

CPAP therapy is highly effective in OSAHS. However, this is often undermined by low adherence due to treatment intolerance. Cost effectiveness of CPAP is also less clear in milder disease. Historically, the heterogeneity of MAD therapy has contributed to uncertainty about its precise role. This continues but in recent years more evidence has emerged of the effectiveness of MAD therapy across the range of OSAHS severity. In milder disease, the data support MAD use as they are beneficial and cost-effective. In more severe cases, MAD should be considered for those who decline or cannot tolerate CPAP. High quality pragmatic research is needed to compare fixed to adjustable devices. More work is also needed to identify a simple and clinically feasible method of identifying patients likely to benefit from MAD therapy.

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**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

**References**


