Oral Appliance Treatment for Obstructive Sleep Apnea: An Update

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Conflict of Interest Statement

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PAC is a chief investigator on sponsored clinical trials in obstructive sleep apnea for ResMed Inc and Exploramed Inc. His department receives equipment support for oral appliance research from SomnoMed Ltd, and he has a pecuniary interest in the company from previous involvement in product development. He is a medical advisor to Exploramed Inc (a US medical device incubator) and Zephyr Sleep Technologies. He has received speaker fees / travel support from ResMed Inc Fisher & Paykel Healthcare.

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ABSTRACT

Oral appliances (OA) have emerged as an alternative to continuous positive airway pressure (CPAP) for Obstructive Sleep Apnoea (OSA) treatment. The most commonly used OA reduces upper airway collapse by advancing the mandible (OA_m). There is a strong evidence base demonstrating OA_m improve OSA in the majority of patients, including some with more severe disease. However OA_m are not efficacious for all, with approximately one third of patients experiencing no therapeutic benefit. OA_m are generally well tolerated, although short-term adverse effects during acclimatization are common. Long-term dental changes do occur, but these are for the most part subclinical and do not preclude continued use. Patients often prefer OA_m to gold-standard Continuous Positive Airway Pressure (CPAP) treatment. Head-to-head trials confirm CPAP is superior in reducing OSA parameters on polysomnography, however this greater efficacy does not necessarily translate into better health outcomes in clinical practice. Comparable effectiveness of OA_m and CPAP has been attributed to higher reported nightly use of OA_m, suggesting that inferiority in reducing apneic events may be counteracted by greater treatment adherence. Recently, significant advances in commercially available OA_m technologies have been made. Remotely controlled mandibular positioners have the potential to identify treatment responders and the level of therapeutic advancement required in single night titration polysomnography. Objective monitoring of OA_m adherence using small embedded temperature sensing data loggers is now available and will enhance clinical practice and research. These technologies will further enhance efficacy and effectiveness of OA_m treatment for OSA.
INTRODUCTION

Obstructive sleep apnoea (OSA) is a common sleep disorder characterized by recurring collapse of the upper airway during sleep, resulting in sleep fragmentation and oxygen desaturation. OSA is defined as the occurrence of 5 or more episodes of complete (apnoea) or partial (hypopnea) upper airway obstruction per hour of sleep (Apnoea-Hypopnea Index [AHI]) and is estimated to occur in around 24% of middle aged men and 9% of women ¹. Daytime symptoms such as sleepiness, cognitive impairment and effects on quality of life require appropriate treatment. Furthermore the association of OSA with increased risk of motor vehicle accidents, cardiovascular morbidity and all-cause mortality ²⁻³ emphasize the need for effective long-term treatment.

The gold standard treatment for OSA is to pneumatically splint open the upper airway during sleep using Continuous Positive Airway Pressure (CPAP). Although CPAP is highly efficacious in preventing upper airway collapse, patient acceptance, tolerance and adherence is often low, thereby reducing effectiveness ⁴. Hence there is a major need for effective alternative treatments.

Oral appliances (OA) are designed to improve upper airway configuration and prevent collapse through alteration of jaw and tongue position. The most common mechanism of action is to hold the lower jaw in a more anterior position (OAₘ). These appliances are variously termed ‘mandibular advancement devices (MAD)’, mandibular advancement splints (MAS)’ or mandibular repositioning appliances (MRA)’. Imaging studies show that mandibular advancement with OAₘ enlarges the upper airway space, most notably in the lateral dimension of the velopharyngeal region ⁵. Lateral expansion of the airway space is
likely mediated through lateral tissue movement via direct tissue connections between the lateral walls and the ramus of the mandible \(^6\). Various amounts of anterior tongue movement also occur with mandibular advancement \(^6\). Alternative OA designs which protrude the tongue instead of the mandible (tongue-retaining device [TRD]) are also available \(^7\)\(^-\)\(^9\). TRDs feature an extra-oral flexible bulb and hold the tongue forward by suction, preventing its collapse into the airway. TRDs may be less tolerated with inadequate device retention a potential issue reducing effectiveness \(^10\). TRD do not form part of the evidence base on which current recommendations for oral appliance treatment are made \(^11\) and are not be further discussed in this review. Current practice parameters of the American Academy of Sleep Medicine (AASM) indicate OA\(_m\) as a first line therapy in patients with mild to moderate OSA and in more severe OSA patients who fail treatment attempts with CPAP therapy \(^11\).

Recent advances in technologies including remotely controlled mandibular advancement sleep studies and objective adherence monitoring capabilities \(^12\)\(^-\)\(^13\) are likely to further enhance and support the effectiveness of OA\(_m\) in treatment of OSA. In light of such recent advances, an international registry has been established to initiate a large prospective cohort to study OA\(_m\) effectiveness and long-term treatment outcomes. The ORANGE-Registry (Oral Appliance Network on Global Effectiveness) is a partnership between centers with research interest and established expertise in OA\(_m\) treatment. ORANGE is comprised of a variety of specialists, including physicians, dentists and researchers from international centers including University of Sydney (Australia), University of Stanford and University of Pennsylvania (USA), Kaiser Permanente (CA-USA), Cambridge University (UK), Paris and Angers Hospital (France), Antwerp University (Belgium), Somnology Center and Kyushu
University (Japan), University of British Columbia, University of Montreal and Laval University (Canada), Groenningen University (Netherlands) and Umea University (Sweden).

This review was conducted within members of ORANGE to summarize the current evidence regarding efficacy and effectiveness of OA for the treatment of OSA as well as to highlight recent technological developments.

**Oral appliance designs and definitions of treatment success**

There are numerous differences in the design features of commercially available OA. Differences predominantly relate to the degree of customization to the patient’s dentition and one-piece (monobloc) designs (no mouth opening) versus two-piece design (separate upper and lower plates). Two-piece appliances also vary in permissible lateral jaw movement and in the coupling mechanisms which attach the two plates together. Other variations include the range of degree of advancement, amount of vertical opening, fabrication material and the amount of occlusal coverage.

Definitions of treatment success in reports of OA efficacy also vary. Treatment success is predominantly defined by a reduction in AHI with or without requirement for symptomatic improvement. Treatment success in terms of AHI are variously expressed as a reduction in treatment AHI below a specified value, such as less than 5 (resolution of OSA) or less than 10 (very mild disease) or by a percentage reduction in AHI from baseline which is deemed to be clinically significant (typically 50% AHI reduction).
There is now a large body of research that demonstrates efficacy of OA$_m$ in terms of reducing snoring and obstructive breathing events as well as showing beneficial effects on associated health outcomes such as daytime sleepiness.

**Oral appliances compared to inactive appliances**

Randomised controlled studies have established OA$_m$ efficacy by comparison to placebo or inactive appliance (does not provide mandibular advancement)$^{14-20}$. Four parallel group randomised controlled trials have compared a monobloc appliance (75% of maximum mandibular advancement) to a control device over treatment periods from 2 weeks to 3 months. All studies found in favour of the active appliance in reduction in AHI$^{14-15,17,20}$, Arousal Index$^{15}$ and improving oxygen saturation$^{20}$. Three crossover studies of active and inactive (single dental plate) OA$_m$ also confirm OSA improvement specific to the mandibular advancement device$^{16,18-19}$ with reductions in both NREM and REM AHI$^{21}$ and improvement in Arousal Index, oxygen saturation and REM sleep time. Reduced snoring was also found to be specifically related to the action of mandibular advancement both by objective measurement using a sound meter$^{19,16}$ and by subjective bed partner assessment$^{15,18}$. These inactive-device controlled studies confirm that OA$_m$ that jaw protrusion by OA$_m$ is the key mechanism by which treatment is delivered.

**Effects of oral appliance treatment on health outcomes**

Subjective daytime sleepiness, assessed by the Epworth Sleepiness Score (ESS), improves with OA$_m$ compared to inactive appliances in the majority of studies$^{14-20}$, although a placebo effect on ESS has been reported$^{16,18}$. Objectively measured sleepiness by the Multiple Sleep Latency Test (MSLT) was improved only with active OA$_m$.$^{16}$
Three placebo-controlled OAₘ studies have included health related quality of life questionnaires in assessment of OAₘ effectiveness. The Medical Outcome Survey Short Form 36 (SF-36) outcomes did not differ between OAₘ and inactive device in one study¹⁵, although the vitality domain improved in another²⁰. A large effect of OAₘ therapy in improvements on The Functional Outcomes of Sleep Questionnaire (FOSQ) has been reported¹⁵. OAₘ treatment also improved assessment on the Profile of Mood States (POMS) questionnaire, Vigor-Activity and Fatigue-Inertia scales²¹.

No differences in neurocognitive function by assessment of attention/working memory, verbal memory, visuospatial or executive functioning between control and active treatment was found in one crossover study²¹. However OAₘ treatment was associated with faster performance on tests of vigilance/psychomotor speed, although improvement did not correspond to reduced daytime sleepiness or AHI.

Blood pressure outcomes are reported in two placebo device-controlled studies¹⁴,²². A crossover study monitored 24-hour ambulatory blood pressure after 4 weeks of OAₘ and inactive appliance wear in 61 patients and found a reduction in 24-hour diastolic but not systolic blood pressure²². Awake blood pressure was reduced on average by 3.3 mmHg, although there was no effect on blood pressure measurements during sleep. A parallel group pilot study found a 1.8 mmHg reduction in 24 hour mean systolic blood pressure with OAₘ treatment compared to control, with a greater reduction of 2.6 mmHg in subgroup analysis of hypertensive patients¹⁴.
**Influence of oral appliance design features**

**Customisation of appliance**

OA$_m$ are generally customised devices fabricated from dental casts of a patient’s dentition and bite registrations by a dentist, which is associated with expense and time. A lower cost alternative is a thermoplastic or ‘boil and bite’ appliance. These devices are a thermoplastic polymer material, which becomes mouldable when heated in boiling water. A patient bites into the softened material and advances the lower jaw to approximately 50% of maximum and the device will set in this configuration with cooling. Direct comparison of the efficacy of thermoplastic and customised OA$_m$ devices in a cross-over study of 35 patients over four months of each device found post-treatment AHI was only reduced with the custom-made OA$_m$ $^{23}$. The thermoplastic device also showed a much lower rate of treatment success (60% vs. 31%). Lower adherence to the thermoplastic appliance was also evident, attributable to insufficient retention of the appliance during sleep. The overwhelming majority of patients (82%) preferred the customised OA$_m$ at the end of the study. Hence customisation to a patient’s dentition is a key component of treatment success.

**Degree of mandibular advancement**

Generally the greater the level of advancement, the better the treatment effect, although this must be balanced against potential increase in side effects. A study of three levels of advancement (2, 4 and 6mm) found dose dependence in improvement of overnight oximetry (25%, 48% and 65% of patients showing improvement (>50%) in desaturation respectively) $^{24}$. Assessment of pharyngeal collapsibility during mandibular advancement has also shown a dose-dependent effect in improvement of upper airway closing pressures $^{24}$. In a study of mild to moderate OSA patients randomised to either 50% or 75% of maximum
advancement there was no difference between these levels in treatment AHI or proportion of patients successfully treated (79% vs. 73%)\textsuperscript{25}. However in severe OSA, more patients achieved treatment success with 75% compared to 50% maximum advancement (52% vs. 31%)\textsuperscript{26}, suggesting maximising advancement may be more important in severe disease. A dose dependent effect of mandibular advancement was demonstrated using four randomised levels of advancement (0, 25, 50 and 75% maximum) with the efficacy of 50-75% advancement greater than 25% and 25% greater than 0%\textsuperscript{27}. However above 50% of maximum advancement there was an associated increase in reported side effects. A titration approach to determine optimal level of advancement with gradual increments over time is thought to optimise treatment outcome\textsuperscript{28}. Titration can be guided by a combination of both subjective symptomatic improvement and objective monitoring by overnight oximetry to find the optimally effective advancement level\textsuperscript{28}. A newly available remotely controlled mandibular titration device\textsuperscript{13} provides an objective mechanism by which to determine the maximal therapeutic level of mandibular protrusion during sleep. The target treatment protrusion identified by this method of sleep titration was found to result in effective treatment in 87% of patients predicted to be successfully treated OA\textsubscript{m} in an initial study. Identification of therapeutic protrusion level by this method may help reduce side effects produced by further unnecessary titration. Optimising mandibular advancement in individual patients is important for successful treatment, although no standardised titration procedure currently exists\textsuperscript{29}. In the clinical setting, a follow-up sleep study to objectively verify satisfactory treatment is often not conducted and this is an area by which to improve clinical outcomes.

\textit{Degree of vertical opening}
Opening of the bite occurs during OA<sub>m</sub> treatment as all appliances have a given thickness causing vertical jaw displacement. A crossover trial has compared two levels of vertical opening (4mm and 14mm, equivalent advancement) finding no detrimental impact on AHI, although patient preference was in favour of the smaller degree of mouth opening<sup>30</sup>. However, increased vertical mouth opening has an adverse effect on upper airway patency in the majority of OSA patients<sup>31</sup>. Therefore amount of bite opening should be minimised to improve patient tolerance and increase the beneficial effect on upper airway dimensions.

**Comparisons of different customised appliances**

Differences in reported OA<sub>m</sub> treatment efficacy potentially relate to different design features. There are a relatively limited number of trials which compare customised appliance designs for efficacy. However existing studies suggest different OA<sub>m</sub> designs are similarly effective in treating OSA. Two-piece appliances are thought to improve comfort and wearability as lateral movement and jaw opening is possible, however monobloc appliances can be cheaper and easier to manufacture. A comparison of a monobloc and two-piece OA<sub>m</sub> found no difference in AHI reduction, improved sleepiness or reported side effects, although patient preference in this study favoured the monobloc appliance<sup>32</sup>. A recent retrospective analysis of 805 patients using either an adjustable OA<sub>m</sub> (n=602) or a fixed device (n=203), found a higher treatment response rate for the adjustable device (56.8% vs. 47.0%)<sup>33</sup>. A comparison of two adjustable OAs with different retention mechanisms (one with occlusal coverage and firm dental retention, the other more passive retention with a looser attachment to the dental arches) found no differences in subjective symptoms, but the passive appliance resulted in greater reduction in treatment AHI, although the difference is unlikely clinically significant<sup>34</sup>. Two crossover studies have
compared two-piece adjustable appliances with different advancement mechanisms and found similar improvements in AHI, symptomatic improvements and side effects \(^{35-36}\).

New variations in customised OA\(_m\) designs may enhance effectiveness in the future. A recent cohort study tested the addition of tongue protrusion, via an anterior tongue bulb on a OA\(_m\) device and showed greater AHI reduction compared to mandibular advancement alone \(^{37}\). Simultaneous advancement of both the tongue and mandible, for example, may prove to increase therapeutic effect.

**Side effects of oral appliance treatment**

In initial acclimatisation to OA\(_m\) therapy, adverse side effects are commonly experienced. Adverse effects primarily include excessive salivation, mouth dryness, tooth pain, gum irritation, headaches and temporomandibular joint discomfort. Reported frequencies of side effects vary greatly \(^{38}\), potentially related to differences in device design. However adverse symptoms are usually transient, lasting around two months \(^{39}\). Temporomandibular disorder symptoms of pain and impairment in the initial treatment period tend to decrease over time and resolve after six to twelve months in the majority of patients \(^{39-40}\). Long-term persistence of side effects such as mouth dryness and tooth or jaw discomfort may lead to discontinuation of treatment \(^{41}\).

Assessment of dental changes with OA\(_m\) primarily relate to decreases in overbite and overjet \(^{42-47}\), retroclination of the upper incisor and procliation of the lower incisors \(^{43,46}\), changes in anterior-posterior occlusion and reduction in the number of occlusal contacts \(^{42,45-46}\). Overbite and overjet changes are evident at six months post treatment initiation \(^{46}\).
Duration of OA<sub>m</sub> use is reported to correlate with dental changes such as decreased overbite suggesting progressive changes to the dentition over time. However generally occlusal changes are negligible and in over half of patients actually represent an improvement on baseline occlusion. The initial type of bite, degree of mandibular advancement, adherence and oral health will influence the amount of bite-changes and discomfort that is produced during longer term treatment. Skeletal changes relating to prolonged OA<sub>m</sub> on lateral cephalometry, primarily report an increase in lower face height and a downward rotation of the mandible. Skeletal changes are probably a result of the changes in dentition that occur with wear of the OA<sub>m</sub>. Many patients are unaware of any changes in their bite and the majority of patients concur that positive effects of OSA treatment far outweigh any adverse effects related to dental changes.

**Long term effectiveness and adherence**

Overall long term efficacy of OA<sub>m</sub> treatment is fairly good. Repeat sleep studies show stability of AHI from 1 to 4 years after OA<sub>m</sub> implementation in treatment responders. Treatment AHI also has demonstrated stability between six monthly sleep studies. In one study OA<sub>m</sub> treatment response was maintained despite an increase in BMI over time. Improvements in health related quality of life and sleepiness symptoms are also sustained at long-term follow-up and continued improvement over time is noted. Diastolic and systolic blood pressure measurements are reduced after 2.5 to 4.5 years of OA<sub>m</sub> treatment. Although OA<sub>m</sub> treatment appears to remain efficacious, usage may drop off somewhat over time. 76% of patients report to be using their OA<sub>m</sub> after one year and 62% of patients after four years. In patients who continue to use their device at 5 years, self-reported adherence is good with over 90% of patients reporting usage rates of more than 4 nights per
week for more than half the night \textsuperscript{41}. Despite demonstrated long-term efficacy, the durability of different OA\textsubscript{m} devices and the potential need for continuous adjustment over time has not been systematically evaluated. Currently there is little knowledge of how often to follow-up patients on OA\textsubscript{m} treatment for device adjustment. More information about these aspects of OA\textsubscript{m} therapy could help improve long-term effectiveness and adherence.

\textbf{EFFICACY AND EFFECTIVENESS OF ORAL APPLIANCES COMPARED TO OTHER TREATMENTS}

\textbf{Oral appliances compared to CPAP}

To our knowledge there are currently 11 published randomised controlled trials which compare efficacy of OA\textsubscript{m} treatment with CPAP with polysomnographic outcomes (8 crossover trials, 3 parallel group trials) and variously evaluate aspects of clinical effectiveness with subjective and objective health outcome measures. Most studies have been limited to patients with mild-moderate OSA, although some did not include an upper AHI limit or allowed inclusion of patients with an AHI \( \leq 60 \) \textsuperscript{54-56}. The most recent study specifically enriched the sample with moderate-severe patients \textsuperscript{57}. Details of these studies are summarised in Table 2.

\textit{Polysomnographic indices}

General consensus from all trials to date is that both CPAP and OA improve sleep disordered breathing assessed in overnight sleep studies. However CPAP does so to a greater extent than OA\textsubscript{m}, with a higher percentage of patients experiencing complete resolution of OSA.

\textit{Apnoea Hypopnoea Index}
AHI improves on both CPAP and OA$_m$ treatment; however AHI is reduced to a greater extent with CPAP$^{54-62}$. Differences in the proportion of patients achieving treatment success (variously defined) are also in favour of CPAP. Studies which report a complete response to treatment (AHI $<$5/hr) indicate that nearly double the number of patients are successfully treated on CPAP compared to OA$_m$ (e.g. 34% CPAP vs. 19% OA$^{54}$, 73% vs. 43%$^{55}$, 75% vs. 40%$^{57}$). With success defined as a post-treatment AHI less than 10 events/hour, success rates for OA$_m$ are in the range of 30-85% and 62-100% for CPAP$^{27, 54-55, 59-60}$. In one crossover study including a placebo tablet treatment arm, 65% of patients achieved their best response with CPAP, 25% with OA$_m$ and 10% with placebo$^{58}$.

**Oxygen saturation**

Only one parallel trial has found an equal improvement in minimum arterial oxygen saturation with CPAP and OA$_m$ treatment$^{61}$. All other studies have report only CPAP improves minimum oxygen saturation$^{57-60, 62}$. In other oxygen measures, Oxygen Desaturation Index (ODI) remains higher and mean oxygen saturation lower on OA$_m$ treatment compared to CPAP$^{55, 57}$. CPAP treatment therefore appears to be superior in alleviating oxygen desaturation.

**Arousal Index**

Two studies have reported no difference between CPAP and OA$_m$ treatment in improving Arousal Index$^{27, 63}$. Neither treatment was found to decrease the number of awakenings compared to baseline in two crossover trials$^{59-60}$. A greater effect of CPAP in reducing Arousal Index has been reported in others$^{57-58, 61-62}$. Recent meta-analyses of these randomised trials found CPAP to be superior in reducing arousals from sleep.
**Health outcomes**

Health outcome measures have been included in most comparisons of OA\textsubscript{m} and CPAP treatment. Although CPAP is superior in reducing polysomnographic variables, the findings of subjective and objective health outcomes are not in favour of CPAP with improvements generally equivalent between treatments.

**Daytime sleepiness**

All trials reporting Epworth Sleepiness Score (ESS) show improvement after both OA\textsubscript{m} and CPAP. Two studies found a greater reduction in ESS after CPAP treatment by up to 4 points \textsuperscript{54, 61}. However the majority demonstrate no difference between OA\textsubscript{m} and CPAP treatments in reduction of subjective sleepiness \textsuperscript{27, 55-59, 61}. Recent meta-analyses have found no difference in ESS reduction between these treatments \textsuperscript{64-66}.

No differences in objectively measured daytime sleepiness have been reported in three crossover trials of CPAP and OA\textsubscript{m}. One study found no difference between OA\textsubscript{m} and CPAP in increased sleep onset latency during the Maintenance of Wakefulness Test (MWT) \textsuperscript{54}. Another study found no improvement with either CPAP or OA\textsubscript{m} on the MWT, although patients were not particularly sleepy at baseline \textsuperscript{58}. Equal improvement in performance on the Oxford sleep resistance (OSLER) test was found after two months treatment \textsuperscript{55}.

**Quality of life**

Health related quality of life outcomes, assessed by questionnaire, are relatively mixed in favouring either CPAP or OA\textsubscript{m} treatment. Of six studies incorporating the SF-36, two report
no difference in SF-36 scores. Three report in favour of CPAP, one showing better scores on health transition and mental (but not physical) component scores and another an improvement in 6 domains (excluding social functioning and mental health) compared to 3 domains (general health perceptions, vitality and emotional) with OA. The third study found only CPAP showed improvement compared to placebo treatment, although both treatment scores improved from baseline. Most recently OA were reported to perform better than CPAP in four of eight domains (bodily pain, vitality, social function, mental health) and the overall mental component score. OA treatment also improved more domains on the Nottingham Health Profile (NHP) with four of six domains (physical mobility, pain, emotional reaction and sleep) compared to two (emotional reaction and energy) on CPAP. In this crossover study there was a treatment-by-period effect for emotional reaction and subjective sleep quality with OA rating higher than CPAP when experienced as a second treatment but no difference between CPAP and OA as first treatments. A validated general health questionnaire administered to both OSA patients and their bed partners identified no differences between treatments by either self- or partner-assessment. The Functional Outcomes of Sleep Questionnaire (FOSQ) did not differ between CPAP and OA treatment in three studies although CPAP was superior in another. The Sleep Apnoea Quality of Life Index (SAQLI) did not differ between CPAP and OA treated patients. There have also been no reported differences between treatments in effects on anxiety and depression (Hospital Anxiety and Depression Score).

Cognitive performance

There was no difference in performance after CPAP and OA treatment in one administered cognitive battery (Performance IQ decrement score, Trails Making Test B, SteerClear).
Performance test, Paced Auditory Serial Addition Task [PASAT]) \(^{54}\). Another assessment with the Trails Making Test found Test A improved equally with both treatments but Test B only improved following CPAP treatment \(^{55}\). A placebo controlled study did not find any post-treatment improvement in a large number of cognitive tests (digit span backward, Trails Making B, Digit symbol substitution task, controlled word association task, Stroop color association test) although laspes on the Psychomotor Vigilance Task were reduced after CPAP but not OA\(_m\) treatment \(^{58}\). No post-treatment differences were detected between CPAP and OA\(_m\) in performance on the Aus-Ed driving simulator \(^{57}\).

**Blood pressure outcomes**

Blood pressure monitoring in a limited number of trials suggest no overt differences between CPAP and OA\(_m\) treatment in short term control of blood pressure. A parallel group study showed equivalent reduction in morning diastolic blood pressure between OA\(_m\) and CPAP treatment after 10 weeks \(^{61}\). Two crossover trials also report no difference between OA\(_m\) and CPAP treatment on blood pressure outcomes, although there was no reduction in blood pressure from baseline on either treatment \(^{57-58}\). However subgroup analysis of hypertensive patients have shown equivalent improvement in 24 hour blood pressure between OA\(_m\) and CPAP treatment \(^{57}\).

**Endothelial function**

Endothelium dysfunction is recognised as a key-early event which precedes or accelerates the development of atherosclerosis \(^{67}\) and may be predictive of future cardiovascular events \(^{68}\). Endothelial dysfunction has been proposed as a potential mechanism in the pathogenesis of cardiovascular complications of OSA \(^{69}\). A small randomised cross-over trial involving 12
OSA patients has demonstrated an equivalent increase in acetylcholine-induced vasodilation between 2 months of OA$_m$ and CPAP, with degree of improvement correlating with decrease in nocturnal oxygen desaturations $^{70}$.

**Cardiovascular morbidity**

Observational and randomised controlled trials have demonstrated beneficial impact of regular CPAP use on cardiovascular and metabolic outcomes in OSA $^{71-72}$. Although there are currently no randomised trials which compare cardiovascular morbidity between CPAP and OA$_m$ treatment, a recent non-concurrent cohort study monitored cardiovascular mortality in severe OSA patients on either CPAP or OA$_m$ treatment $^{73}$. The study followed 208 control subjects (AHI<5) and 570 severe OSA patients (177 CPAP treated, 72 OA$_m$ treated and 212 untreated) for a median time of 6.6 years. The cardiovascular mortality rate was highest in the un-treated OSA group and significantly lower in both treatment groups. There was no difference between CPAP and OA$_m$ in incidence of fatal cardiovascular events, despite a higher residual AHI in the OA$_m$-treated patients. There is a clear need for additional observational and randomised studies comparing the effect of OA$_m$ and CPAP treatments on cardio-metabolic outcomes and surrogate markers of cardiovascular risk.

**Treatment usage and patient preference**

Comparisons of treatment usage predominantly rely on self-reported adherence data. There was no difference in self-reported usage found between OA$_m$ and CPAP either in the number of nights of treatment use per week or hours per night in three studies $^{27, 54, 56, 59-60}$. Other studies report greater adherence to OA$_m$, with 1.1 nights/week and 1.9 hours/night more treatment time in patient diaries compared to objective CPAP usage data download $^{58}$. 
Furthermore based on definition of 4 hours/night for effective treatment, 43% of patients on CPAP and 76% of patients on OA_m show good adherence. Greater adherence has been reported for OA_m compared to self-reported CPAP usage. However it is known that self-report CPAP adherence significantly overestimates nightly and weekly usage compared to objective monitoring data^55, 57.

Overall there is preference for OA_m over CPAP treatment but with much variation. Four of six crossover trials asking for patient treatment preference at the end of the trial, found in favour of OA_m^55, 57, 59-60. In another study preference lay in favour of CPAP (44% vs. 30% preferring OA_m)^58 and in another preference was equally distributed between CPAP and OA^54. In the former study, OA_m preference was associated with lower levels of obesity and less symptoms, including sleepiness. A recent qualitative analysis of patient treatment preference and experience of OA_m and CPAP treatments has been conducted using focus groups of OSA patients on either form of treatment^74. CPAP and OA users described a similar amount of side effects, although the side effect profile differed between devices. The factors most frequently mentioned that influenced choice of treatment were effectiveness, transportability, embarrassment, cost, bed partner preference, access to power supply or hot water, convenience and impact on bite. Patient choice of treatment may be influenced by an individual’s personality, lifestyle, perceived stigma and financial status, although patients reported effectiveness of the treatment as paramount in their decision^74.

Combined oral appliance and CPAP therapy

Although OA_m and CPAP have been considered as alternative treatment pathways, there is scope for a patient to alternate between them as needed in situations such as travel when
CPAP may be inconvenient. Additionally there are some recent lines of evidence suggesting combining the two treatment modalities simultaneously may be of additional benefit. The effect of OA\textsubscript{m} in opening the upper airway has been explored as a means to reduce CPAP pressure, as high pressure requirement can lead to intolerance and reduced adherence in some patients. A pilot study of ten patients, partially treated by OA\textsubscript{m} but who failed CPAP due to intolerance to prescribed pressure, found auto-titration of CPAP pressure while wearing an OA\textsubscript{m} reduced average pressure requirement from 9.4 to 7.3 \textsuperscript{75}. A physiological study of upper airway mechanics at various CPAP pressures delivered under 3 conditions of 1) oronasal mask, 2) nasal mask and combined OA\textsubscript{m} and 3) nasal mask, showed that velopharyngeal resistance was reduced in the OA\textsubscript{m}/nasal mask condition (2) compared to CPAP alone \textsuperscript{76}. OA\textsubscript{m} may prove to be a useful adjunct to CPAP therapy in reducing pressure requirements and preventing issues of mouth opening, leaks and chin retraction which variously result from different CPAP masks.

**Oral appliances compared to surgery**

There is currently only one prospective randomised trial of OA\textsubscript{m} compared to surgical treatment for OSA \textsuperscript{77}. The surgical procedure used in this study was uvulopalatopharyngoplasty (UPPP), which involves removal of upper airway soft tissues including the uvula, soft palate, tonsils and adenoids. Ninety-five mild-moderate (Apnea Index >5 and <25 events/hr) OSA male patients were randomised to receive either UPPP or OA\textsubscript{m} treatment set to 50% of the patient’s maximum level of mandibular advancement. Both treatments significantly reduced sleep-disordered breathing events on polysomnography at 6 and 12 months, although at 12 months the OA\textsubscript{m} group showed a greater reduction in AHI. Complete treatment response (AHI ≥ 10 events/hour) also
occurred in a greater proportion of patients using OA$_m$ compared to the UPPP group (78% vs. 51%). At 4 year follow-up, AHI remained lower in the OA$_m$ group, with a complete response sustained in 63% compared to 33% of the UPPP treated group $^{52}$. In terms of symptoms, both surgical and OA$_m$ treatment reduced subjective daytime sleepiness assessed at 6 and 12 months $^{77}$. A greater reduction in sleepiness was initially observed with OA$_m$ treatment at 6 months but this was not sustained at 12 months. A quality of life assessment performed before treatment and at 1 year follow-up found improvement in all 3 quality of life domains (quality, vitality and contentment) with both treatments, however the UPPP-treated group showed significantly more contentment than the OA$_m$ group $^{78}$.

Maxillomandibular advancement (MMA) surgery, to enlarge the pharyngeal space by expanding the skeletal boundaries of the maxilla and mandible, is currently considered the most efficacious surgical procedure for treatment of OSA, particularly severe OSA $^{79-80}$. Although there are no randomised trials of MMA and OA$_m$, a French study offered MMA to 102 non-obese, severe OSA patients and treated those who refused surgery with an OA$_m$ $^{81}$. Polysomnography at 3 months found MMA reduced AHI (45 events/hr vs. 7 events/hr mean values, n=25) with a 74% surgery success rate (AHI<10/hr). OA$_m$ also reduced the AHI (41 events/hr vs. 22 events/hr mean values, n=23) with a lower success rate 30%, although a significant number of OA$_m$ patients did not complete the three month assessment. Hoekema and colleagues offered MMA to OSA patients who were successfully treated with an oral appliance (>50% reduction in AHI) $^{82}$. Four patients completed the surgery (of 43) and AHI was significantly reduced with a complete response (AHI<5/hr) in 3 of these patients. The
authors suggest response to OA\textsubscript{m} therapy may be a predictor of success of MMA surgery for OSA.

Overall, studies comparing OA\textsubscript{m} with surgical treatment for OSA are extremely limited. Such comparisons of effectiveness should also take into account adherence factors. Surgery, as an irreversible intervention, has 100% adherence over all hours of sleep, whereas device therapy is dependent on patient adherence to be effective. Therefore treatment comparisons need to take into account not only efficacy on treatment but the percentage of sleep time for which a removable device is used as a high proportion of sleep time not on treatment will reduce the overall effectiveness, even in a highly efficacious device\textsuperscript{83}.

**Patient selection and prediction of treatment success**

Consistent in all studies of OA\textsubscript{m} treatment efficacy is that OSA is not adequately alleviated in all patients and therefore OA\textsubscript{m} will have limited effectiveness in these patients. Table 1 summarises the proportion of OA\textsubscript{m} treatment responders, by various definitions, from randomised controlled OA\textsubscript{m} studies. Differences between studies likely relate to variations in definitions, appliance and patient factors. On average, a complete response (resolution of OSA or an AHI <5 events/hour) occurs in around 48% of patients with a range of 29-71% between studies (Table 1).

Individual variability in response to OA\textsubscript{m} treatment represents a significant clinical challenge as implementing therapy in patients that will ultimately not receive benefit is unsatisfactory from both a treatment and cost point of view. Therefore patient characteristics relating to treatment success and reliable prediction methods are a high research priority.
Various patient factors have been associated with treatment outcome. Less severe disease as well as supine-predominant OSA (a higher AHI in supine compared to lateral sleeping position) has been considered favourable for treatment success $^{15, 19-20, 53, 84}$. Younger age, female gender and less obesity (lower BMI and neck circumference) are also suggested as indicators of treatment success $^{19, 53, 85-87}$. Craniofacial features assessed by lateral cephalometry, including shorter soft palate length, lower hyoid bone position, greater angle between the cranial base and mandibular plane and a retrognathic mandible, are also associated with favourable treatment outcome $^{19, 86-89}$. Although various patient phenotypes have been related to a higher likelihood of treatment success, these are not universal.

Complete amelioration of OSA by OA$_m$ therapy can occur in severe patients and overweight patients $^{19, 26, 62}$. Anatomical characteristics appear to play a role in treatment outcome, however the relatively weak and somewhat inconsistent cephalometric data suggest that decisions based solely on these factors cannot be recommended $^{86}$.

Therefore reliable prediction tests are needed in order to discriminate treatment responders and non-responders. Although yet to be prospectively validated, various methods for prediction of OA$_m$ treatment outcome have been proposed. There are some promising techniques assessing anatomical and functional characteristics of the upper airway response which may prove to have clinical utility.

Approaches to selecting suitable patients for OA$_m$ treatment include imaging upper airway geometry and behaviour with and without simulated mandibular advancement. Nasendoscopy during drug-induced sleep has been used to visualise magnitude and patterns
of pharyngeal collapse without and with a mandibular advancement simulation bite. Patients with a greater improvement in pharyngeal patency under the mandibular advancement condition during drug induced sleep showed good sensitivity for treatment success. Drug-induced sleep endoscopy may have limitations, however awake nasendoscopy has also shown some predictive utility in demonstration of reduced upper airway collapsibility, simulated by the Mueller manoeuvre, with mandibular advancement. Computational methods to simulate changes in airflow patterns with mandibular advancement based on patient-specific upper airway geometries from magnetic resonance or computed tomography scans have also been considered to predict treatment outcome.

The region of pharyngeal airway collapse and its association with OA\textsubscript{m} treatment outcome has also been considered as a predictor using awake assessments of flow-volume loops and phrenic nerve stimulation. Other assessments of the airway during wakefulness have shown an association between higher nasal resistance and treatment failure with OA\textsubscript{m}. In OSA patients that have previously used CPAP treatment, a higher CPAP pressure requirement (>10.5 cm H\textsubscript{2}O) has been suggested as an indicator of lower likelihood of treatment success.

**Prediction of treatment success using a mandibular titration study**

Another approach to predicting OA\textsubscript{m} response is through a sleep study under the condition of mandibular advancement. This has been investigated by using a cheap ‘boil and bite’ OA\textsubscript{m}, however results were not indicative of treatment outcome with a customised OA\textsubscript{m}, limiting this approach as a reliable prediction method. Single night titration methods,
allowing advancement of the mandible during sleep, have shown more promise in indicating likely treatment success as well as therapeutic level of advancement in a small number of patients using prototype devices. This method involves use of a remotely controlled intraoral device during an attended sleep study to incrementally advance the mandible until sleep disordered breathing events are eliminated, analogous to a CPAP pressure titration study.

A significant advance in single-night titration methodology has occurred with recent development of a commercially available remotely controlled mandibular protrusion device. This protrusion device connects to upper and lower dental trays containing impressions of the patient’s dentition and advances the mandible by moving forward the lower tray during polysomnographic monitoring. This device has recently been tested as a prediction tool for OA treatment response in a prospective study of 67 patients. OSA patients were consecutively recruited with minimal exclusion criteria apart from severe obesity (BMI >40kgm²) and contraindications to OA. During the sleep titration the technologist remotely initiates forward movement of the lower dental tray in 0.2-0.6 mm increments in response to the appearance of apneas or hypopneas (halted in the event of an arousal until stable sleep had resumed). Protrusion is continued within the patient’s predetermined range of motion until respiratory events are eliminated from sleep (both REM and non-REM sleep stages and both lateral and supine body position) or until the patient’s maximal protrusive level is reached. This mandibular titration study was used to predict treatment response based on a set prediction rule of ≤1 respiratory event per 5 minutes of supine REM sleep. Patient’s who met this criterion were predicted successes and those with >1 event were predicted failures. All patients went on to use a OA set at either the effective protrusion
level from the titration night (predicted successes) or at a sham 70% of maximum protrusion (predicted failures). A follow-up sleep study wearing OA\textsubscript{m} was used to determine actual response with a stringent definition of therapeutic success of treatment AHI <10/hr plus 50% reduction in AHI from baseline. The mandibular titration prediction method correctly classified 30 of 32 patients as treatment responders. 5 of the 29 predicted failures were found to treatment responders. The prediction method showed a rate of 9% for inconclusive tests due to failure to reach maximal protrusion during the titration (3%) or insufficient REM sleep (6%). Overall the initial study using this device as a prediction tool shows good accuracy in identifying patients who will be fully treated by OA\textsubscript{m}. Interestingly, twenty of the patients correctly predicted to be treatment successes had OSA severity and BMI values above which would traditionally be considered appropriate for OA\textsubscript{m} treatment. Initial investigation of this single night titration device therefore shows good utility as a prediction tool as well as the likely therapeutic mandibular protrusion level and has potential to improve patient selection via a single laboratory sleep study.

**OBJECTIVE ADHERENCE MONITORS FOR ORAL APPLIANCES**

Mounting evidence suggests that OA\textsubscript{m} and CPAP treatment are comparatively effective in improving health outcomes, even in more severe OSA\textsuperscript{57}, presumably due to greater overall usage of the OA\textsubscript{m} device compared to CPAP. It has been possible to routinely objectively monitor CPAP adherence by machine usage since 1988\textsuperscript{100}. However data from objective monitoring shows that less than half of CPAP users are good adherers, using the device for less than 4 hours/night on less than 70% of nights\textsuperscript{4}. Until recently adherence data for OA\textsubscript{m} therapy has essentially remained limited to patient self-report\textsuperscript{11,101}. Although subjective adherence reports suggest short-term adherence is relatively good\textsuperscript{23,60,63,101}, exceeds that
of CPAP, the discrepancy between subjective and objective CPAP usage suggests that better adherence to OA\textsubscript{m} cannot be confirmed in the absence of objective monitoring. A true objective comparison between OA\textsubscript{m} and CPAP treatment effectiveness to support the inference of inferior OA\textsubscript{m} efficacy mitigated by superior adherence has been hindered by the lack of objective adherence data for OA\textsubscript{m}.

The recent introduction of objective monitoring capabilities in OA\textsubscript{m} devices will be of great importance for both research and clinical purposes. In research, objective adherence monitoring will help exclude over-estimation by self-report bias. The hours and days in which a treatment is applied can be accurately monitored. Treatment usage time is important for adequate treatment and objective adherence data may be used to compare overall therapeutic effectiveness. The ‘mean disease alleviation (MDA)’ can be calculated which takes into consideration not only the efficacy of treatment but the percentage of TST. Therefore a more accurate comparison of different therapies can be made, albeit subjective assessment of TST may be necessary. This will be invaluable for research in establishing the role of OA\textsubscript{m} in treatment of OSA.

In clinical practice, adherence monitors may help encourage patients to use their device and objective data may help improve patient management. Furthermore adherence data may serve as a communication tool between physician and dentist. The ability to establish objective usage may also provide essential data for patients, for example in some countries commercial drivers are required to prove treatment usage for their reinstatement.

\textit{Adherence monitoring technology}
Until recently, there have been limited reports of adherence monitoring technology for OAₘ. Lowe and colleagues assessed an intra-oral temperature sensor for objective measurement of OAₘ adherence in a study of 8 OSA patients, however this device was never commercially available. Subsequently, a commercially available temperature data logger was reported in terms of safety and used to obtain objective data on OAₘ treatment adherence in 7 patients. However the dimensions and storage capacity of this particular temperature data logger were found to be problematic. Microsensor thermometers with on-chip integrated readout electronics, which are free of these issues, have been described in recent reports. These microsensors, embedded into the OAₘ, represent a significant technological advance and are commercially available. A recent technical report describes another novel patent-pending micro-recorder which also may be embedded into an OAₘ. The specifications of different adherence monitors suitable for OAₘ are described in Table 3.

**Objective monitoring of OAₘ adherence**

Vanderveken and colleagues recently describe the first 3-month prospective clinical trial in which the Theramon® monitor was used to covertly monitor OAₘ adherence in 51 consecutive OSA patients. The study found that the overall objective mean rate of OAₘ use was 6.6 ± 1.3 h per night with 84% of patients fulfilling the criteria of ‘regular users’ by completing at least 4 hours of active OAₘ treatment on more than 70% of the days of the week. At a one-year follow-up extension of the initial 3-month study, 89% of the 37 continuing OAₘ users were still ‘regular users’ with an overall rate of OAₘ use of 6.4 ± 1.7 per night. This objectively measured usage rate is relatively high compared to that with CPAP in which regular usage occurs in 58 to 78 % of patients.
Additionally objectively monitored OA\textsubscript{m} adherence shows reasonable concordance with subjective self-report\textsuperscript{12,104}. This contrasts CPAP treatment in which it has been consistently demonstrated that patients’ own report of duration of CPAP use is an overestimation by approximately one hour\textsuperscript{4,55,57}, corresponding to a significant amount of total treatment time. This suggests that there may be differences in the perceived and/or reported subjective assessment of usage between OA\textsubscript{m} and CPAP treatments, with subjective compliance more accurate. This new data on concordance between subjective and objective OA\textsubscript{m} adherence suggests that previous studies relying on self-reported OA\textsubscript{m} use may be reasonably indicative of actual usage.

**SUMMARY/CONCLUSIONS**

OA\textsubscript{m} are an effective treatment for OSA, not only improving AHI but also a variety of physiologic and behavioural outcomes. Recent comparative effectiveness trials have shown health outcomes between CPAP and OA\textsubscript{m} treatments are equivalent, even in severe OSA, despite greater efficacy of CPAP in reducing AHI. This likely reflects greater nightly adherence to OA\textsubscript{m} compared to CPAP therapy. Recent advances in technologies related to OA\textsubscript{m} treatment have the potential to further improve their efficacy and effectiveness in clinical practice. Selection of appropriate patients who will respond to OA\textsubscript{m} treatment is an ongoing barrier to use. The now commercially available remotely-controlled mandibular positioner offers a means to predict response from a single-night mandibular titration study and has shown good positive predictive value in initial testing. The advent of new adherence monitoring technology which can be routinely incorporated into OA\textsubscript{m} devices to objectively monitor treatment usage represents another advance in OSA treatment which will be
beneficial in practise and research. This will further help clarify the role of OAₘ in OSA treatment next to CPAP. Establishing best quality devices which are objectively validated in terms of both efficacy and durability in combination with recent advances in patient selection and treatment monitoring, will continue to optimise OAₘ as an effective and even first-line treatment for OSA.
REFERENCES


<table>
<thead>
<tr>
<th>Study</th>
<th>Oral appliance</th>
<th>Inclusion</th>
<th>Patients n (%male)</th>
<th>Pre-treatment AHI</th>
<th>Treatment success (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarab 2010 [25]</td>
<td>Two-piece (9.6 ± 2.1mm)</td>
<td>AHI 5-45 + ≥2 symptoms</td>
<td>17 (71%)</td>
<td>21.6 ± 11.1</td>
<td>71</td>
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<tr>
<td>Andren 2012 [12]</td>
<td>Monobloc (70-75% maximum advancement)</td>
<td>AHI &gt;10 + hypertension</td>
<td>30 (83%)</td>
<td>23 ± 16</td>
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<tr>
<td>Blanco 2005 [13]</td>
<td>Monobloc (75% maximum advancement)</td>
<td>AHI &gt;10 + ≥2 symptoms</td>
<td>8</td>
<td>33.8 ± 14.7</td>
<td>57</td>
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<td>Bloch 2000 [30]</td>
<td>Monobloc and Herbst (initial 75% of maximum advancement)</td>
<td>AHI&gt;5 + CPAP failure</td>
<td>24 (96%)</td>
<td>26.7 ± 3.3</td>
<td>-</td>
</tr>
<tr>
<td>Fleury 2004 [26]</td>
<td>Two-piece (128.9 ± 23.8% maximum advancement)</td>
<td>AHI&gt;5 + CPAP failure</td>
<td>40</td>
<td>46 ± 21</td>
<td>-</td>
</tr>
<tr>
<td>Gotsopoulos 2002 [14]</td>
<td>Two-piece (80±9% maximum advancement)</td>
<td>AHI &gt;10 + ≥2 symptoms</td>
<td>73 (81%)</td>
<td>27.1 ± 15.3</td>
<td>36</td>
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<tr>
<td>Mehta 2001 [17]</td>
<td>Two-piece</td>
<td>AHI&gt;10</td>
<td>24</td>
<td>27±17</td>
<td>38</td>
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<tr>
<td>Study</td>
<td>Implant Type</td>
<td>AHI Condition</td>
<td>Cases</td>
<td>AHI Mean ± SD/Range</td>
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<tr>
<td>Petri 2008 [18]</td>
<td>Monobloc (74% range 64-85% maximum advancement)</td>
<td>AHI&gt;5</td>
<td>27</td>
<td>39.1 ± 23.8 (mild-moderate 44%, severe 56%)</td>
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<td>48</td>
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<tr>
<td>Pitsis 2001 [28]</td>
<td>Two-piece (87±4% advancement, 4mm/14mm vertical)</td>
<td>AHI&gt;5</td>
<td>23</td>
<td>21 ± 12 (range 6-47)</td>
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<td>26</td>
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<tr>
<td>Tegelberg 2003 [23]</td>
<td>Monobloc (75% maximum advancement)</td>
<td>AI 5-25 (mild-moderate)</td>
<td>26</td>
<td>18.9 ± 4.7^ (mild-moderate)</td>
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<td>52</td>
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All data presented as Mean ± Standard Deviation, unless ^Mean ± 95% Confidence Interval. AHI – Apnoea-Hypopnoea Index, AI – Apnoea Index, not reported (-).

Treatment success definitions: AHI<5 – treatment AHI < 5 events/hour, AHI<10 – treatment AHI < 10 events/hour, AHI≥50% - ≥50% reduction in treatment AHI from baseline AHI but treatment AHI remains above 5-10 events/hour.
Table 2. Oral appliances versus CPAP treatment: results from randomised controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects</th>
<th>Inclusion</th>
<th>Oral appliance</th>
<th>Treatment [washout] duration</th>
<th>Base-line AHI</th>
<th>Treatment AHI</th>
<th>OA vs. CPAP</th>
<th>Patient Preference</th>
</tr>
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<tbody>
<tr>
<td>Aarab 2011</td>
<td>parallel</td>
<td>57 (74%)</td>
<td>AHI 5-45 + ESS ≥ 10 Customised, Two-piece, set 25, 50 or 75% advancement depending on sleep study results at each level</td>
<td>24 weeks</td>
<td>CPAP: 20.9 ± 9.8</td>
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<td>↔</td>
<td>(p = 0.092)</td>
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<tr>
<td></td>
<td>[25]</td>
<td>(placebo</td>
<td>group included)</td>
<td></td>
<td>OA: 22.1 ± 10.8</td>
<td>1.4 ± 13.1</td>
<td>5.8 ± 14.9</td>
<td>↔</td>
<td>N/A – parallel groups</td>
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<tr>
<td></td>
<td></td>
<td>20 OA/ 18 CPAP</td>
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<tr>
<td>Barnes 2004</td>
<td>crossover</td>
<td>80 (79%)</td>
<td>AHI 5-30 Customised, 4 week titration to maximum comfortable advancement</td>
<td>3x12 weeks</td>
<td>21.5 ± 1.6^</td>
<td>4.8 ± 0.5^</td>
<td>14.0 ± 1.1^</td>
<td>↔</td>
<td>CPAP</td>
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<td>[61]</td>
<td>(placebo</td>
<td>[24]</td>
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<tr>
<td>Engleman 2002</td>
<td>crossover</td>
<td>48 (75%)</td>
<td>AHI ≥ 5/hr + ≥2 symptoms (including ESS ≥ 8) Customised, one-piece, 80% maximal protrusion, two deigns a) complete occlusal coverage or b) no occlusal coverage, assigned randomly</td>
<td>2x8 weeks [not reported]</td>
<td>31 ± 26</td>
<td>8 ± 6</td>
<td>15 ± 16</td>
<td>↔</td>
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<td>[57]</td>
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<td>[3]</td>
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<tr>
<td>Ferguson 1996</td>
<td>crossover</td>
<td>25 (89%)</td>
<td>AHI 15-50 + OSA symptoms Snore-Guard (Hays &amp; Meade Inc), maximum comfortable advancement</td>
<td>2x16 weeks</td>
<td>24.5 ± 8.8</td>
<td>3.6 ± 1.7</td>
<td>9.7 ± 7.3</td>
<td>CPAP</td>
<td>N/A</td>
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<td>[63]</td>
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<td>[2]</td>
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<tr>
<td>Ferguson 1997</td>
<td>crossover</td>
<td>20 (95%)</td>
<td>AHI 15-55 + OSA symptoms Customised, two-piece appliance, titration starting at 70% maximum advancement over 3 months</td>
<td>2x16 weeks</td>
<td>26.8 ± 11.9</td>
<td>4.0 ± 2.2</td>
<td>14.2 ± 14.7</td>
<td>CPAP</td>
<td>↔ OA</td>
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<td>[62]</td>
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<td>[4]</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>n (Percentage)</td>
<td>Inclusion Criteria</td>
<td>Treatment Details</td>
<td>Follow-up</td>
<td>AHI 10-60 + ≥2 Symptoms, BMI ≥ 35kg/m²</td>
<td>AMC™ (Artech Medical), Two-piece, advancement determined by single-night titration</td>
<td>2x8 weeks, 1 week</td>
<td>CPAP</td>
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<tr>
<td>Gagnadoux 2009 [58]</td>
<td>crossover</td>
<td>59 (78%)</td>
<td>[3]</td>
<td>[</td>
<td>2x8 weeks, 1 week</td>
<td>34 ± 13</td>
<td>2 (1-8)^#</td>
<td>6 (3-14)^#</td>
<td>CPAP</td>
</tr>
<tr>
<td>Hoekema 2008 [59]</td>
<td>parallel</td>
<td>103</td>
<td>(51 OA/52 CPAP)</td>
<td>[4]</td>
<td>8-12 weeks</td>
<td>CPAP: 40.3 ± 27.6</td>
<td>OA: 39.4 ± 30.8</td>
<td>2.4 ± 4.2</td>
<td>7.8 ± 14.4</td>
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<tr>
<td>Lam 2007 [64]</td>
<td>parallel (placebo group included)</td>
<td>101 (79%)</td>
<td>(34 OA/34 CPAP)</td>
<td>[10]</td>
<td>10 weeks (83% referred for concurrent weight loss program)</td>
<td>CPAP: 23.8 ± 1.9^</td>
<td>OA: 20.9 ± 1.7^</td>
<td>2.8 ± 1.1^</td>
<td>10.6 ± 1.7^</td>
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<tr>
<td>Phillips 2013 [60]</td>
<td>crossover</td>
<td>108 (81%)</td>
<td>[18]</td>
<td>2x4 weeks [2 weeks]</td>
<td>25.6 ± 12.3</td>
<td>4.5 ± 6.6</td>
<td>11.1 ± 12.1</td>
<td>CPAP</td>
<td>↔</td>
</tr>
<tr>
<td>Randerath 2002 [42]</td>
<td>crossover</td>
<td>20 (80%)</td>
<td>[</td>
<td>IST; Hinz; Herne, Germany, two piece, non-titratable, set to two thirds of maximum advancement</td>
<td>2x6 weeks [not reported]</td>
<td>17.5 ± 7.7</td>
<td>3.2 ± 2.9</td>
<td>13.8 ± 11.1</td>
<td>CPAP</td>
</tr>
<tr>
<td>Tan 2002 [65]</td>
<td>crossover</td>
<td>21 (83%)</td>
<td>[3]</td>
<td>2x8 weeks [2 weeks]</td>
<td>22.2 ± 9.6</td>
<td>3.1 ± 2.8</td>
<td>8.0 ± 10.9</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

↔ - equivalent between treatments, AHI – apnoea hypopnoea index, N/A – not applicable, not measured in study.

Data presented as Mean ± SD, unless denoted ^ (Mean ± SEM) or # (Median (interquartile range))
Table 3. Adherence monitors for oral appliances

<table>
<thead>
<tr>
<th></th>
<th>Thermocron® iButton® [89]</th>
<th>Theramon® [86, 90]</th>
<th>DentiTrac® [91]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td>16.25</td>
<td>4.3</td>
<td>4</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>17.35</td>
<td>13.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Width (mm)</td>
<td>5.8</td>
<td>9.0</td>
<td>8.5</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>3.3</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Sample frequency (x/h)</td>
<td>3</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>Storage capacity (days)</td>
<td>21</td>
<td>100</td>
<td>180</td>
</tr>
<tr>
<td>Battery life expectancy</td>
<td></td>
<td></td>
<td>&gt;2y</td>
</tr>
<tr>
<td>Temperature range</td>
<td>+15°C to +46°C</td>
<td>-25°C to +60°C</td>
<td></td>
</tr>
</tbody>
</table>