

Clinical effectiveness and cost-effectiveness results from the randomised controlled Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea (TOMADO) and long-term economic analysis of oral devices and continuous positive airway pressure

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Scientific summary

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Scientific summary

Background

Obstructive sleep apnoea–hypopnoea (OSAH) involves repeated interruption of airflow during sleep because of episodic collapse of the pharyngeal airway. Typically this results in oxygen desaturations and microarousals from sleep. When there is significant sleep disruption, then excessive daytime sleepiness (EDS) can occur.

Obstructive sleep apnoea–hypopnoea affects 2–7% of the adult population. Men have approximately double the risk of developing the condition compared with women and it increases with age. Obesity is a major risk factor for OSAH, particularly when adiposity is distributed around the neck and upper body, which suggests that OSAH incidence will rise with the increasing prevalence of obesity.

Obstructive sleep apnoea–hypopnoea is associated with increased risk of cardiovascular disease (CVD), including stroke, via a causal link with hypertension. EDS increases road traffic accident (RTA) risk and health-related quality of life (HRQoL) is also decreased. Health-care usage is almost doubled in OSAH, primarily as a result of the increased cost of treating CVD.

Continuous positive airway pressure (CPAP) therapy is the cornerstone of OSAH treatment. There is evidence that CPAP reduces respiratory events and EDS and increases cognitive function and HRQoL. There is some evidence for beneficial effects on blood pressure (BP), from which improvement in cardiovascular end points may be inferred. CPAP has been shown to be cost-effective for moderate to severe OSAH at a willingness-to-pay (WTP) threshold of £20,000 per quality-adjusted life-year (QALY), and clinical guidelines recommend it as first-line treatment in these patients.

The role of CPAP in the management of mild OSAH is less clear. CPAP requires a mask to be worn during sleep, which affects compliance and, therefore, effectiveness. There is a paucity of randomised trial evidence and the cost-effectiveness of CPAP appears more marginal in this group.

Mandibular advancement devices (MADs) are an alternative to CPAP in the treatment of OSAH. They are worn in the mouth during sleep, holding the mandible and tongue forward with the aim of maintaining upper airway patency. Available MADs represent a range of sophistication and cost. Reviews show that MADs are less efficacious than CPAP at reducing the apnoea–hypopnoea index (AHI), but are better than various placebos. Both CPAP and MADs improve EDS to a similar extent according to the Epworth Sleepiness Scale (ESS) score, and more than sham MADs and other placebos. Quality of life (QoL) has been understudied in MAD trials. A comprehensive economic analysis concluded that CPAP had a high probability of being more cost-effective than both MADs and conservative management (CM) in OSAH, at a £20,000 cost per QALY threshold. However, the evidence was from trials conducted in populations with moderate to severe OSAH. Recommendations from this study included the need to establish whether or not clinical effectiveness and cost-effectiveness vary between different types of MAD; the identification of patients likely to benefit from MAD treatment; and the assessment of HRQoL.

Objectives

1. To conduct a randomised controlled trial (RCT) [the Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea (TOMADO)] to assess whether or not MADs are clinically effective and cost-effective compared with no treatment in patients with mild to moderate OSAH, and to identify which one of three increasingly sophisticated and costly MADs is most clinically effective and cost-effective.
2. To update systematic reviews of RCTs of the effectiveness of MADs and/or CPAP in order to inform a long-term decision model.
3. To update and adapt a previously developed health economic decision model, incorporating results from TOMADO and other recently published studies to inform long-term cost-effectiveness in mild to moderate OSAH.

Methods

The Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea

TOMADO was an open-label, four-treatment, four-period, randomised crossover trial comparing the clinical effectiveness and cost-effectiveness of three types of MAD {[bespoke MAD (bMAD); NHS Oral-Maxillofacial Laboratory, Addenbrooke's Hospital, Cambridge, UK], semi-bespoke [SleepPro 2™ (SP2); Meditas Ltd, Winchester, UK] and over the counter [SleepPro 1™ (SP1); Meditas Ltd, Winchester, UK]} and a no-treatment control for patients with mild to moderate OSAH. Each 6-week period (4-week period for no-treatment arm) comprised a 2-week acclimatisation phase, followed by a 4-week treatment phase. A 1-week washout period followed active treatments. Eligible patients from the Respiratory Support and Sleep Centre at Papworth Hospital, Cambridge, UK, were ≥ 18 years of age with mild to moderate OSAH (AHI 5 events/hour to < 30 events/hour) and symptomatic daytime sleepiness (ESS score of ≥ 9). Patients did not require or had refused CPAP. The main exclusion criteria were predominantly central sleep apnoea; requirement for immediate CPAP; significant periodontal disease or tooth decay; partial or complete edentulism; and presence of fixed orthodontic devices.

The primary outcome was the AHI. EDS measured using the ESS was an important secondary outcome. Other outcomes were daytime BP, condition-specific [Functional Outcomes of Sleep Questionnaire (FOSQ) and Calgary Sleep Apnoea Quality of Life Index (SAQLI)] and generic [Short Form questionnaire-36 items and European Quality of Life-5 Dimensions (EQ-5D-3L)] HRQoL, side effects, resource use and cost-effectiveness.

A sample size of 90 was required to detect an effect size of one-third (5% two-sided alpha, 80% power, 20% loss to follow-up).

Randomisation was performed by the independent research unit at Papworth Hospital and treatment sequence was based on Williams' Latin squares designs.

Statistical analysis used 'intention to treat' and included period effects. Analysis used mixed-effects models based on either Poisson or Normal distributions to estimate treatment effects.

Trial-based economic analysis estimated cost utility during the 4-week periods from the perspective of the NHS. MAD costs came from NHS supply prices (SP1), private supply prices (SP2) and from the cost of materials and staff time for manufacture of the bMAD. Other unit costs for outpatient care including labour, capital and overheads, were taken from national estimates.

The EQ-5D-3L provided the base-case health-utility score for calculation of QALYs. Both probabilistic and deterministic sensitivity analyses were conducted.

Meta-analysis of clinical studies

We updated systematic reviews of RCTs in adult OSAH patients who included at least one group allocated to CPAP or MAD. All MADs were viewed as a single treatment, as were all CPAP technologies. For the update of the two existing systematic reviews from 2006 and 2008, three databases (MEDLINE, EMBASE and the Science Citation Index) along with resulting reference lists were searched from November 2006 and June 2008 to August 2013. Primary outcomes were AHI and ESS score, but daytime BP and disease-specific HRQoL results were also extracted. Three comparisons were investigated: MADs compared with CM; MADs compared with CPAP; and CPAP compared with CM. Random-effects meta-analyses were used to estimate treatment effects, both overall and stratified for baseline severity of OSAH.

Long-term cost-effectiveness

A previously developed model was used to assess the lifetime cost-utility of MADs and CPAP in patients with mild to moderate OSAH, from a NHS perspective based on differences in symptoms associated with OSAH and long-term sequelae. Additional searches of the databases listed above were used to update and adapt cardiovascular, RTA and compliance input values for the model. The TOMADO was sourced for utility estimates based on mapping ESS scores to EQ-5D-3L utilities and for device costs. The base case included a hypothetical cohort of 10,000 men, aged 51 years, with systolic BP of 130 mmHg, total cholesterol of 224 mg/dl and an ESS score of 11.9, in line with the TOMADO population averages. Costs were based on the SP2 and an assumed device lifetime of 12 months. Sensitivity analysis explored assumptions around the lifetime of the devices and their costs, ESS treatment effects, compliance, time horizon and effects on cardiovascular and RTA risks.

Results

The Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea-hypopnoea

Sixteen patients of the 90 recruited withdrew from the study and did not provide any outcomes. TOMADO showed that, for patients with mild to moderate OSAH, the AHI for each of the three non-adjustable MADs studied was significantly lower than with no treatment {relative risk 0.74 [95% confidence interval (CI) 0.62 to 0.89] for SP1, relative risk 0.67 (95% CI 0.59 to 0.76) for SP2, relative risk 0.64 (95% CI 0.55 to 0.76) for bMAD; $p < 0.001$ }. Differences between MADs were not statistically significant.

The effects of MADs on ESS score mirrored those for AHI, with reduction in ESS scores of 1.51 (95% CI 0.73 to 2.29) for SP1, 2.15 (95% CI 1.31 to 2.99) for SP2 and 2.37 (95% CI 1.53 to 3.22) for bMAD. SP2 and bMAD had significantly greater effects than SP1.

SleepPro 1 had shorter duration of use per night and greater likelihood of discontinuation during the treatment period. The SP1 was also less likely to be chosen as the preferred device by trial completers.

The relationship between MADs, sleepiness-related functioning and QoL (FOSQ and SAQLI) showed a similar pattern to that for AHI and ESS score, with significant effects for all MADs compared with no treatment, and SP1 performing less well than SP2 and bMAD. General HRQoL measures were largely insensitive to MAD treatment, with the exception that SP2 was associated with significantly higher Short Form questionnaire-6 Dimensions QALYs compared with control.

There were few serious adverse events (SAEs) during the study period and, of the four SAEs reported by four patients, three were short-term, cardiac-related events. Almost all patients reported at least one minor adverse event, with mouth discomfort and excess salivation being the main problems.

The trial-based cost-effectiveness analysis was limited by the short treatment period, but the improvements in HRQoL for all MADs compared with no treatment meant that all were cost-effective at a WTP of £20,000 per QALY. The SP2 was the most cost-effective MAD up to a WTP per QALY of £39,800.

Meta-analysis of clinical studies

The systematic review identified 12 studies including 629 patients comparing MAD with CM, 13 studies including 746 patients comparing MADs with CPAP and 52 studies including 5400 patients comparing CPAP with CM, with AHI or ESS score as one of the study end points. Study participants were predominantly middle-aged men (65–100% of participants were male; mean age range 44–59 years) who were overweight or obese. CPAP trials were generally conducted in patients with more severe OSAH according to AHI MAD trials. CM included sham devices, sham CPAP, placebo tablets, lifestyle advice and no treatment. Quality was variable, with many trials having < 50 patients and treatment periods generally short.

Heterogeneity between studies was variable and often unreliable because of the small number of studies available. Some heterogeneity could be explained by baseline severity, but unexplained heterogeneity remained.

Overall, compared with CM, both MADs and CPAP resulted in significant improvements in AHI [MAD -9.3 events/hour (95% CI -12.3 to -6.3 events/hour), $p < 0.001$; CPAP -25.4 events/hour (95% CI -30.7 to -20.1 events/hour), $p < 0.001$]. In direct comparisons of CPAP and MAD, the difference in effect between them was 7.0 events/hour (95% CI 5.4 to 8.7 events/hour; $p < 0.001$), in favour of CPAP. The reduction in AHI was strongly related to baseline severity. No trials compared CPAP with MAD trials in patients with mild OSAH according to AHI.

Excessive daytime sleepiness assessed by the ESS was less variable than AHI. Most trial populations were classed as having moderate baseline EDS. Overall, both MAD and CPAP resulted in a significant reduction in ESS score compared with CM [MAD 1.6 , 95% CI 0.8 to 2.5 ($p < 0.001$); CPAP 1.6 , 95% CI 0.65 to 2.53 ($p < 0.001$)]. The differences between the effects of MAD and CPAP were not significant in head-to-head comparisons (0.7 , 95% CI -0.1 to 1.4 ; $p = 0.093$). Estimated effects on EDS were strongly related to baseline OSAH severity and, to a lesser extent, baseline AHI. When trials of similar baseline characteristics were compared, there was little difference between the effects of MADs and CPAP on post-treatment ESS score. The meta-analysis provided little insight into the effect of treatment on daytime BP above previous meta-analyses.

With the exception of TOMADO, few additional trials contributed to the literature on HRQoL.

Long-term cost-effectiveness

In the base case, using the SP2 as the standard device, MADs were found to be more costly and more effective than CM in patients with mild to moderate OSAH, with an estimated incremental cost-effectiveness ratio (ICER) of £6687 per QALY. From a WTP of £15,367/QALY, CPAP is cost-effective, although the likelihood of MADs ($p = 0.48$) and CPAP ($p = 0.49$) being cost-effective is very similar. Although it was clear that both of these treatments were better than CM, there was substantial uncertainty in the choice between the two treatment options, with probabilities of being the most cost-effective, at a WTP of £20,000 per QALY, of 47% for MADs and 52% for CPAP.

When the average lifespan of the SP2 was increased from 12 months to 18 months, the ICER for CPAP compared with MAD became £44,066. The ICER for the SP1 compared with CM was £1552 and for the bMAD was £13,836. The ICER for CPAP compared with the SP1 was high, at £89,182, but CPAP was both cheaper and more effective than the bMAD. Differential compliance rates for CPAP reduced its cost-effectiveness, so that MADs become both less costly and more effective if compliance with CPAP is 90% of SP2.

Discussion

TOMADO was an important addition to the evidence on the use of MADs in mild to moderate OSAH. While all MADs were effective compared with CM, the semi-bespoke SP2 provides most of the benefit of a bespoke device at a lower cost and was the most cost-effective device tested. Comparisons of treatments across published trials suggest that CPAP has a much greater effect than MADs on AHI, but the effects on EDS are similar. These trials focus on populations with moderate to severe OSAH and there is evidence that the extent of treatment effects is strongly related to baseline severity.

In cost-effectiveness modelling, it is clear that both MADs and CPAP are cost-effective compared with CM, at a WTP threshold of £20,000 per QALY. However, for mild to moderate OSAH there is little to choose between the two treatment modalities. There is significant uncertainty related to assumptions about device costs, lifetimes, compliance and longer-term cardiovascular and RTA rates.

Conclusions

Implications for service

- CPAP remains the most clinically effective and cost-effective treatment for patients with moderate to severe OSAH based on reduction in AHI. For patients who are intolerant of CPAP, treatment with a MAD is also effective compared with CM.
- Both MADs and CPAP are effective treatments for patients with mild to moderate OSAH, and there is little to choose between them in terms of clinical effectiveness and cost-effectiveness.
- Of the three MADs investigated, the semi-bespoke SP2 is the most cost-effective in the short term and should be the first-choice device, with the bMAD reserved for patients who have difficulty producing the SP2 mould or whose dental eligibility is more marginal.

Implications for research priorities

- Pragmatic clinical effectiveness and cost-effectiveness comparisons of adjustable and non-adjustable MADs across the entire range of OSAH severity are still required.
- Head-to-head comparisons of CPAP and MADs in milder OSAH would reduce the uncertainty surrounding the current guidance that CPAP should be reserved as second-line treatment in these patients.
- Similarity of effects for CPAP and MAD on EDS may be as a result of differential adherence to treatment. However, there is limited information on this beyond short-term trials. Medium- to long-term compliance with MADs and CPAP should be monitored and reported.
- Observational studies of HRQoL over time to supplement existing trial data would be useful to understand the treatment outcomes of greatest relevance to patients.
- Further data on longer-term risk of CVD and its risk factors would reduce model uncertainty and improve the precision of estimates of clinical effectiveness and cost-effectiveness.

Trial registration

This trial is registered as ISRCTN02309506.

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