

Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis

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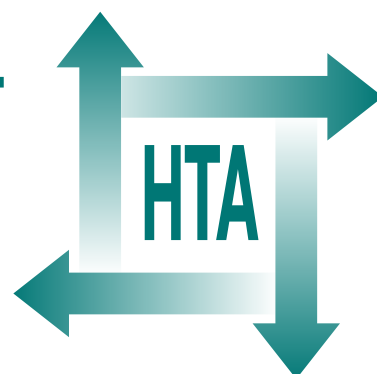
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Executive summary

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Executive summary

Background

Obstructive sleep apnoea–hypopnoea syndrome (OSAHS) is characterised by repeated, intermittent collapse and obstruction of the pharyngeal airway during sleep. This may result in brief awakening from sleep caused by increased respiratory effort. Recurrent arousal to restore airway functioning leads to a reduction in sleep quality. Untreated OSAHS is associated with increased daytime sleepiness, impairment of cognitive function and a reduction in health-related quality of life (HRQoL). As a result of increased daytime sleepiness and impaired concentration, there may be consequences for how effectively people can engage in work, home and leisure daytime activities. OSAHS has been associated with serious consequences such as increased risk of accidents and, if left untreated, it is a lifelong condition which may be a risk factor for hypertension, myocardial infarction and stroke. Owing to the association between OSAHS and obesity, the prevalence of OSAHS is expected to increase with increasing prevalence of obesity. The mainstay of medical treatment of OSAHS is administration of continuous positive airway pressure (CPAP) during sleep, although there are thought to be wide variations in the provision of CPAP treatment across the UK. CPAP devices are small, electric pumps that deliver air to the mouth and nose via a hose and soft plastic mask during sleep. The air pressure, which can be fixed or autotitrated, opens up the airway, particularly at pharyngeal level, preventing the soft tissue from collapsing. Excluding add-on expenses the cost of a CPAP machine is estimated at £280 and that of an autotitrating machine at £420.

Objectives

To determine the clinical effectiveness, safety and cost-effectiveness of CPAP devices for the treatment of OSAHS compared with the best supportive care, placebo and dental devices.

Methods

We conducted a systematic review of the clinical and cost-effectiveness literature. Fifteen electronic databases, including MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials, were searched up to November 2006 to identify primary studies. The contents pages of nine journals were searched from the beginning of 2005 to May 2007 as well as the conference proceedings for the 2005 and 2006 American, British and Australia and New Zealand Thoracic Society meetings. Industry submissions were searched for additional unpublished data. Randomised controlled trials (RCTs) comparing CPAP with best supportive/usual care (e.g. lifestyle advice and other conservative management), placebo, and dental devices in adults with a diagnosis of OSAHS of any severity were included. Different forms of CPAP were treated as a single technology.

The primary outcomes of interest were subjective daytime sleepiness assessed by the Epworth Sleepiness Scale (ESS) and objective sleepiness assessed by the Maintenance of Wakefulness Test (MWT) and the Multiple Sleep Latency Test (MSLT). Other outcomes of interest were blood pressure, cardiovascular events (CVEs), HRQoL, cognitive function and adverse events. The primary measure of cost-effectiveness was incremental cost per quality-adjusted life-year (QALY). Where sufficient clinical effectiveness data were available, they were pooled in a meta-analysis using a random-effects model. Studies in which the comparator was placebo or best supportive care were pooled separately from studies in which the comparator was dental devices. Where data sets included parallel and crossover trials these were pooled.

A new economic model was developed to make use of the available evidence on therapies for the treatment of OSAHS and to conform to the National Institute for Health and Clinical Excellence (NICE) scope. The cost-effectiveness of CPAP was compared with that of the use of dental

devices and conservative management. The costs and QALYs associated with the three treatments were compared over a lifetime time horizon. Costs and resource use were estimated from the National Health Service (NHS) and Personal Social Services (PSS) perspective for England and Wales and reported for the financial year 2005. Effectiveness was based on the RCT evidence on sleepiness symptoms (ESS), which was 'mapped' to utilities using individual patient data from a subset of studies; trial evidence on changes in blood pressure following intervention to estimate differences in the rates of CVEs over time; and non-randomised evidence assessing the difference in risk of road traffic accidents (RTAs) across treatments. Utilities were expressed on the basis of generic HRQoL instruments [the EQ-5D (EuroQoL-5 Dimensions) in the base-case analysis] valued using the public preferences associated with those instruments. The base-case analysis focused on a male aged 50. A series of subgroup and scenario analyses were also undertaken.

Results

The searches yielded 6325 citations, from which 48 relevant clinical effectiveness studies were identified, and 29 of these provided data on daytime sleepiness. The majority of studies included overweight or obese men with severe disease as measured by the apnoea-hypopnoea index (AHI) during sleep and had moderate to severe daytime sleepiness. The majority of the included RCTs did not report using an adequate method of allocation concealment or use an intention-to-treat analysis. Only the studies using a sham CPAP comparator were double-blinded. There was a statistically significant benefit with CPAP compared with control (placebo and conservative treatment/usual care) on the ESS [mean difference (MD) -2.7 points, 95% confidence interval (CI) -3.45 to -1.96]. However, there was high inconsistency in the treatment effect (statistical heterogeneity); this was reduced when trials were subgrouped based on mean symptom severity at baseline. The benefit with CPAP was greatest in the group of trials of severe symptoms (MD -5.0, 95% CI -6.5 to -3.5), and was progressively smaller with moderate (MD -2.3, 95% CI -3.0 to -1.6) and mild symptoms (MD -1.1, 95% CI -1.8 to -0.3). The treatment effect in all symptom severity groups was statistically significant. The benefit with CPAP on daytime sleepiness was robust across all the methodological subgroup analyses and sensitivity analyses. There was also a significant benefit with CPAP compared

with usual care on the MWT, which measures capacity to stay awake, but not on the MSLT, which measures capacity to fall asleep. The evidence for any benefit with CPAP compared with control was less clear on the secondary outcome measures, although there was some evidence of a beneficial impact on HRQoL and daytime mean arterial pressure (MAP). There was a lack of evidence on long-term outcomes such as number of strokes and cardiac events and a lack of direct evidence of an effect on RTAs.

There was no statistically significant difference between CPAP and dental devices (six trials) on the impact on daytime sleepiness (ESS) amongst a population with moderate symptom severity at baseline, although there was a small decrease in favour of CPAP (MD -0.9, 95% CI -2.1 to 0.4). There was moderate inconsistency in the treatment effect but the small number of trials limited exploration of this. There was no statistically significant difference between CPAP and dental devices on the other outcomes of interest, although again the number of trials available was very small.

A review of five studies evaluating the cost-effectiveness of CPAP was undertaken. ResMed (manufacturer's submission) estimated that, at year 1, the cost per QALY for CPAP compared with no CPAP is expected to exceed £20,000. Over the full 14-year time horizon CPAP was associated with lower costs and higher effects than no treatment and the cost-effectiveness-acceptability curve (CEAC) showed that, above a willingness to pay threshold of £2000 per QALY, CPAP was the optimal treatment strategy in all simulations. In the UK, Chilcott *et al.*⁴⁴ estimated that at 5 years the cost per QALY for CPAP compared with no CPAP is £3200. The three remaining studies examined the cost-effectiveness of CPAP in settings outside the UK and all found that CPAP appeared cost-effective for conventional thresholds.

All existing cost-effectiveness studies had several limitations which needed to be addressed in order to assess the value for money of these technologies. None used the full range of RCT evidence for estimating the impact of treatment on daytime sleepiness, blood pressure, HRQoL and other relevant outcomes. There was a lack of trial-based evidence to compare the utility associated with different treatments for OSAHS and limited data on the long-term impact of OSAHS on HRQoL, CVEs, RTAs and other outcomes. None of the evaluations examined all the comparators relevant to the review. Therefore a new economic model was developed.

Based on the new economic model, it was found that, on average, CPAP was associated with higher costs and benefits than were dental devices or conservative management. In the base-case analysis the incremental cost-effectiveness ratio (ICER) for CPAP compared with dental devices was £3899 for men and £4335 for women. The probability of CPAP being more cost-effective than dental devices or conservative management at a threshold of £20,000 per QALY was 0.78 and 0.80 for men and women respectively. Subgroup and scenario analyses found that the (ICER) of CPAP was consistently below £20,000 per QALY gained, with one exception: the ICER in a subgroup with mild disease in terms of baseline ESS score was estimated to be £20,585.

Discussion

There was clear evidence of a benefit with CPAP compared with placebo and conservative management/usual care on two of the three primary outcomes, one assessing subjective sleepiness and one objective measure of sleepiness. There was also some evidence of benefit on MAP and quality of life although this was less robust. On the basis of the York model, the available evidence suggests that, overall, CPAP is cost-effective compared with dental devices and conservative management assuming a cost-effectiveness threshold of £20,000 per QALY gained.

A number of uncertainties and caveats need to be borne in mind. These include:

- The relative treatment benefits with CPAP according to symptom severity are based on summary data and cannot be regarded as definitive. The estimates of cost-effectiveness by disease severity should consequently also be treated with caution. Furthermore, because it was not possible to estimate treatment effects on blood pressure or RTAs by baseline OSAHS severity, these effects have been removed entirely from the cost-effectiveness analysis by severity.
- The treatment effect for daytime sleepiness in mild symptomatic disease is based on only two studies and needs to be interpreted with some caution.
- Some of the analyses may have been underpowered and this was particularly true in relation to blood pressure.
- Dental devices may be a treatment option in moderate disease. However, there was

inconsistency in the treatment effect of CPAP compared with dental devices, possibly due to the variety of dental devices investigated. It remains unclear precisely what type of dental devices may be effective and in which populations with OSAHS. The effectiveness of dental devices compared with CPAP in mild and severe disease populations is unclear.

- Only two outcome measures from the clinical trial data [effect of treatment on ESS and systolic blood pressure (SBP)] were incorporated in the economic model. Potentially, other measures reported in the trials could impact on HRQoL independently of ESS, and this is not reflected in the current model. The model does not differentiate between conservative management, dental devices and CPAP in terms of the disutility associated with any undesirable side effects.
- The translation of health benefits in terms of ESS to utility scores was based on simple regression models. The effect of CPAP treatment on reducing RTAs was derived from observational studies. While some trials report the impact of CPAP on blood pressure, this outcome is infrequently reported, and the trials are too short in length to directly measure impact on CVEs, and so estimated changes in CVE rates are inferred from other published risk equations.

Conclusions

Implications for service provision

- CPAP is an effective treatment for OSAHS compared with conservative/usual care and placebo in populations with moderate to severe daytime sleepiness, and there may be benefits where the disease is mild.
- Dental devices may be a treatment option in moderate disease but some uncertainty remains.
- On average, CPAP was associated with higher costs and higher benefits than was conservative management. The incremental cost per QALY gained of CPAP was below £20,000 in the base-case analysis and most alternative scenarios. There was a high probability of CPAP being more cost-effective than dental devices and conservative management for a cost-effectiveness threshold of £20,000 per QALY gained.

Recommendations for research

- The expected value of further information calculated in the York economic model indicates that further research to reduce the uncertainty in the current evidence base would be potentially valuable.
- Further investigation of the effectiveness of CPAP for populations with mild sleepiness is required.
- Further trials comparing CPAP with dental devices may be useful.
- Further investigation of the effect of CPAP on hypertension would be beneficial, particularly

with respect to what populations might be expected to benefit, as would trials adequately powered to identify changes in CVEs.

Publication

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NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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