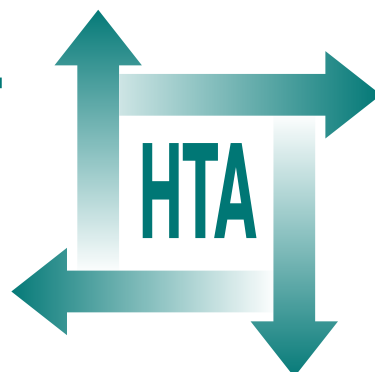


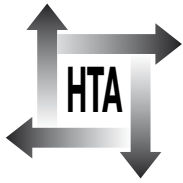
Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis

C McDaid, S Griffin, H Weatherly,
K Durée, M van der Burgt, S van Hout,
J Akers, RJO Davies, M Sculpher and
M Westwood 

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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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Abstract

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

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Objectives: To determine the clinical effectiveness, safety and cost-effectiveness of continuous positive airway pressure (CPAP) devices for the treatment of obstructive apnoea–hypopnoea syndrome (OSAHS), compared with the best supportive care, placebo and dental devices.

Data sources: The main search was of fifteen electronic databases, including MEDLINE, EMBASE and the Cochrane Library, up to November 2006.

Review methods: Randomised controlled trials (RCTs) comparing CPAP with best supportive/usual care, placebo, and dental devices in adults with a diagnosis of OSAHS were included. 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). A new economic model was developed to assess incremental cost per quality-adjusted life-year (QALY). The cost-effectiveness of CPAP was compared with that of the use of dental devices and conservative management. The costs and QALYs were compared over a lifetime time horizon. 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. Utilities were expressed on the basis of generic HRQoL instruments [the EQ-5D (EuroQoL-5 Dimensions) in the base-case analysis]. 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, 29 of these providing data on 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% CI –3.45 to –1.96]. However, there was statistical heterogeneity, which was reduced when trials were subgrouped by severity of disease. There was also a significant benefit with CPAP compared with usual care on the MWT. There was a non-statistically significant difference between CPAP and dental devices (six trials) in the impact on daytime sleepiness (ESS) among a population with moderate symptom severity at baseline (MD –0.9, 95% CI –2.1 to 0.4). A review of five studies evaluating the cost-effectiveness of CPAP was undertaken. All existing cost-effectiveness studies had limitations; therefore a new economic model was developed, based on which it was found that, on average, CPAP was associated with higher costs and benefits than dental devices or 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.

Conclusions: CPAP is an effective and cost-effective treatment for OSAHS compared with conservative/usual care and placebo in populations with moderate

to severe daytime sleepiness, and there may be benefits when the disease is mild. Dental devices may be a treatment option in moderate disease but some uncertainty remains. Further research would

be potentially valuable, particularly investigation of the effectiveness of CPAP for populations with mild sleepiness and further trials comparing CPAP with dental devices.



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*Due to the extensive nature of the appendices, these are available only in electronic format. The PDF file of the full report is available at www.ncchta.org/project/1592.asp. It will also be available on *HTA on CD* (see the inside front cover for full details).





Glossary and list of abbreviations

Glossary

Apnoea The cessation of airflow during sleep as the result of an obstruction, preventing air from entering the lungs. Arbitrarily defined in adults as a 10-second breathing pause.

Auto-positive airway pressure A type of continuous positive airway pressure (CPAP) machine that monitors changes in breathing and compensates automatically by making appropriate adjustments in pressure.

Continuous positive airway pressure (CPAP) Device used to treat sleep apnoea that delivers a stream of compressed air at a prescribed pressure via a nose or full-face mask and hose, splinting the airway (keeping it open under air pressure) so that unobstructed breathing becomes possible.

Cost-benefit analysis An attempt to give a monetary value to the consequences of the alternative interventions. In this way, the consequences can be more easily weighed against the costs of the intervention. This involves measuring individuals' 'willingness to pay' for given outcomes and can present difficulties.

Cost-consequence analysis Costs and health effects are reported separately.

Cost-effectiveness acceptability curve (CEAC) A graphical representation of the probability of an intervention being cost-effective over a range of monetary values against society's willingness to pay for an additional unit of health gain.

Cost-effectiveness analysis The consequences of the alternatives are measured in natural units, such as years of life gained. These consequences are not given a monetary value.

Cost-minimisation When two alternatives are found to have equal efficacy or outcomes

(consequences), i.e. the only difference between the two is cost. This is sometimes considered to be a subtype of cost-effectiveness analysis.

Cost-utility analysis The consequences of alternatives are measured in 'health state preferences', which are given a weighting score. In this type of analysis, different consequences are valued in comparison with each other, and the outcomes (e.g. life-years gained) are adjusted by the weighting assigned. In this way, an attempt is made to value the quality of life associated with the outcome so that life-years gained become quality-adjusted life-years gained.

Disutility The reduction in utility in comparison with a healthy population.

Hypopnoea Reduction of airflow during sleep. Arbitrarily defined in adults as a 10-second breathing event where there is continuous breathing but ventilation is reduced by at least 50%.

Mandibular advancement device Dental device that holds the lower jaw and tongue forward to allow more space to breathe and to prevent snoring.

Markov chain Monte Carlo (MCMC) A mathematical model containing a finite number of mutually exclusive and exhaustive health states, with uniform time periods, in which the probability of movement from one state to another depends on the current state and remains constant over time.

Mixed treatment comparison A form of meta-analysis used to strengthen inference concerning the relative efficacy of two treatments. It uses data based on direct comparisons (A versus B and B versus C trials) and indirect comparisons (A versus C trials), and also facilitates simultaneous inference

regarding all treatments in order to select those most appropriate.

Odds ratio A way of comparing whether the probability of a certain event is the same for two groups; refers to the ratio of the number of people having an event to the number not having an event.

Oxygen desaturation Less than the normal amount of oxygen carried by haemoglobin in the blood. Values below 90% are considered abnormal.

Polysomnography Procedure involved in the evaluation of sleep disorders, often conducted overnight, that consists of a simultaneous recording of multiple physiological parameters related to sleep and wakefulness.

Quality of life (health-related quality of life) A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity as well as other factors that might affect their physical, mental and social well-being.

Quality-adjusted life-year (QALY) An index of health gain whereby survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Random-effects model A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-study variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

Sensitivity analysis A mathematical method that examines uncertainty associated with parameters estimated into the analysis to test

the robustness of the analysis findings. In one-way sensitivity analysis each parameter is varied individually, and in multi-way analysis two or more parameters are varied at the same time. Threshold analysis identifies the critical values above or below which the results of a study vary and analysis of extremes is used to examine the most pessimistic and the most optimistic scenarios. Finally, probabilistic sensitivity analysis attributes distributions of probabilities to uncertain variables that are incorporated within a model.

Standard gamble Measuring a health-state utility by comparing life in a particular given health state to a gamble with a probability that perfect health is the outcome or that immediate death is the outcome. The probability is varied until a point of indifference between the two choices (i.e. until the preference for the given health state is equal to the preference for the gamble).

Time trade-off Measuring a health state by trading off life-years in a state of less than perfect health for a shorter lifespan in a state of perfect health.

Utility A measure of the strength of an individual's preference for a given health state or outcome. Utilities assign numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health), and provide a single number that summarises health-related quality of life.

Weighted mean difference (in meta-analysis) A method of meta-analysis used to combine measures on a continuous scale, where the mean, standard deviation and sample size in each group are known. The weight given to each study is determined by the precision of its estimate of effect and is equal to the inverse of the variance. This method assumes that all the trials have measured the outcome on the same scale.

List of abbreviations

ABPM	ambulatory blood pressure monitoring	ESS	Epworth Sleepiness Scale
AHI	apnoea–hypopnoea index	EVPI	expected value of perfect information
APAP	autotitrating positive airway pressure	FCI	Functional Capacity Index
BMI	body mass index	FLP	Functional Limitations Profile
BRMA	bivariate random-effects meta-analysis	FOSQ	Functional Outcomes of Sleep Questionnaire
BSJ	Brief Symptom Inventory	GHQ	General Health Questionnaire
CEAC	cost-effectiveness acceptability curve	GRISS	Golombok Rust Inventory of Sexual Satisfaction
CHD	coronary heart disease	HADS	Hospital Anxiety and Depression Scale
CI	confidence interval	HCHS	Hospital and Community Health Services
CNS	central nervous system	HODaR	Health Outcomes Data Repository
COWAT	Controlled Oral Word Association Test	HRQoL	health-related quality of life
CPAP	continuous positive airway pressure	HTA	Health Technology Assessment
CRD	Centre for Reviews and Dissemination	ICER	incremental cost-effectiveness ratio
CVD	cardiovascular disease	IHD	ischaemic heart disease
CVE	cardiovascular event	IQR	interquartile range
DBP	diastolic blood pressure	ITT	intention-to-treat
DSST	Digit Symbol Substitution Test	MAIS	Maximum Abbreviated Injury Scale
DVT	Digit Vigilance Test	MAP	mean arterial pressure
EQ-5D	EuroQoL-5 Dimensions	MCAR	missing completely at random

MD	mean difference	PSG	polysomnography
MeSH	medical subject heading	QALY	quality-adjusted life-year
MSLT	Multiple Sleep Latency Test	RCT	randomised controlled trial
MWT	Maintenance of Wakefulness Test	RDI	respiratory disturbance index
NA	not applicable	RTA	road traffic accident
nCPAP	nasal continuous positive airway pressure	SAQLI	sleep apnoea quality of life index
NHP	Nottingham Health Profile	SBP	systolic blood pressure
NICE	National Institute for Health and Clinical Excellence	SD	standard deviation
NR	not reported	SE	standard error
OA	oral appliance	SF-36	Medical Outcomes Study 36-item Short Form Health Survey
OLS	ordinary least squares	TAP	Thornton Adjustable Positioner
OP	oral placebo	TMT	Trail Making Task
OR	odds ratio	UDA	unit of dental activity
OSAHS	obstructive sleep apnoea–hypopnoea syndrome	UMACL	University of Wales Institute of Science and Technology Mood Adjective Checklist
OSAS	obstructive sleep apnoea syndrome	WAIS	Wechsler Adult Intelligence Scale
PASAT	Paced Auditory Serial Addition Task	WMD	weighted mean difference
POMS	Profile of Mood State		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



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.

Chapter I

Background

Description of health problem

Definition of obstructive sleep apnoea–hypopnoea syndrome

Obstructive sleep apnoea–hypopnoea is characterised by repeated, intermittent collapse and obstruction of the pharyngeal airway during sleep. Airway collapse can be complete, with total obstruction of the airway lumen and no respiratory airflow (apnoea), or partial with reduced respiratory airflow, arbitrarily often defined as at least a 50% reduction (hypopnoea). Pharyngeal patency (keeping the airway opened) depends on dilator muscles which contract during each inspiration to prevent the upper airway being closed by suction. The upper airway collapses due to falling muscle tone in the dilating muscles with sleep, leading to narrowing or total obstruction. This may result in brief awakening from sleep caused by increased respiratory effort. Recurrent arousal required to restore airway patency results in fragmentation of normal sleep architecture (structure) and a reduction in sleep quality. When obstructive sleep-disordered breathing is accompanied by clinical symptoms such as excessive daytime sleepiness, this is known as obstructive sleep apnoea–hypopnoea syndrome (OSAHS).^{1–3}

The most commonly reported symptoms of OSAHS are excessive daytime sleepiness, loud snoring and unrefreshing sleep.⁴ Other frequent symptoms are nocturnal choking, nocturia, witnessed apnoeas and morning headaches. Less commonly reported symptoms include reduced libido and enuresis.⁴

Classification of disease severity

Diagnosis of OSHAS is usually based on recordings of multiple physiological signals during sleep polysomnography (PSG). These include the apnoea–hypopnoea index (AHI), and repetitive oxygen desaturation indices. The AHI is the frequency of apnoeas and hypopnoeas per hour of sleep; a typical cut-off for positive diagnosis is between 5 and 10 events per hour. The AHI is also used to categorise severity. Whilst definitions regarding the severity of OSAHS vary between

sleep centres, recommendations for cut-offs suggest the following severity classification:⁵ mild OSAHS (AHI 5–15 events per hour of sleep); moderate OSAHS (AHI 15–30 events per hour of sleep); and severe OSAHS (AHI > 30 events per hour of sleep). Oxygen desaturation is calculated as the number of events causing a drop in arterial oxygen saturation per hour. Typically a diagnostic cut-off of > 4% drop is used to define an oxygen desaturation event, with thresholds approximating hypoxic dips per hour of 5–10 (mild), 10–30 (moderate) and greater than 30 (severe). The number of events can vary from night to night for individuals and these cut-off points for disease severity are considered arbitrary.^{1,4} None of these measures takes into account the severity of other symptoms such as daytime sleepiness. This is considered important as the daytime consequences of OSAHS are often of more concern to the patient than are nocturnal events.

Daytime sleepiness

Several tools are available for measuring sleepiness, both subjectively and objectively. The Epworth Sleepiness Scale (ESS) is the most frequently used assessment of daytime sleepiness. This short questionnaire measures the general level of daytime sleepiness based on the subjective probability of falling asleep in a variety of situations.⁶ The participant rates his or her likelihood of falling asleep in eight different daily situations, such as while sitting reading or while sitting inactive in a public place. The score range is from 0 to 24 and the higher the score the greater the sleepiness. A score of seven or less is regarded as normal sleepiness; a score of 16 or more indicates substantial daytime sleepiness. Average normal scores of 5.9 [standard deviation (SD) 2.2] with a range from 0 to 10⁶ and 7.6 (SD 3.9)⁷ have been obtained in different populations without sleep disorder. The validity of the scale as a test of propensity to sleep has been established.⁶ Reliability is reasonably high and the scale has high internal consistency (Cronbach's alpha 0.88).⁷ The score distribution appears to be approximately normal in OSAHS and normal populations.^{6,7}

The most commonly used objective measures of daytime sleepiness are the Maintenance of Wakefulness Test (MWT), which measures the

capacity to stay awake, and the Multiple Sleep Latency Test (MSLT), which measures the propensity to fall asleep in favourable conditions.⁸ The MWT is a 40-minute test that measures the capacity to remain awake in conditions supposedly ideal for falling sleep. If participants do not fall asleep during the test, they achieve the maximum score. The MSLT assesses the tendency to fall asleep during four or five tests at 2-hourly intervals throughout the day in conditions conducive to sleep. Both tests use a polysomnogram to establish when the participant has fallen asleep. An additional measure is the Osler test, a simplified version of the MWT, which uses a behavioural test rather than electroencephalograph recordings to define sleep onset.⁹ The score derived from all these tests is the time taken to fall asleep in minutes (sleep latency). Precise normative data on time taken to fall asleep have been difficult to establish for the MWT and MSLT as many factors may affect sleep latency, such as age, prior total sleep time and variations in the testing protocol.⁸ The 'normal' sleep latency for MSLT is around 10 minutes with an SD range of 2–19 minutes.⁸ On the MWT, the mean time taken to fall asleep in a population without sleep disorder was estimated at 35.24 minutes [standard error (SE) 0.98], though this varied with age.⁸ Both the MSLT and MWT are relatively poor at discriminating between sleepy and non-sleepy populations as a result of the overlap of sleep latency time in these populations. However, they are sensitive to conditions expected to increase or decrease sleepiness.⁸ Performance on both tests can be affected by physiological factors such as age and circadian rhythms; psychological factors such as anxiety and depression; and test protocol factors such as the extent of activity prior to testing and the specific instructions given. The correlation between the MSLT and MWT is weak, probably because they measure different aspects of sleepiness. The MWT can have limited ability to discriminate the most alert individuals due to a ceiling effect; the MSLT can have limited ability to discriminate the most sleepy individuals due to a floor effect.

Epidemiology

The severity of sleeping upper airway collapse is a continuous variable in the community and ranges from normality, through postural and continuous snoring, postural and continuous repetitive obstructive apnoeas associated with excessive sleepiness (i.e. OSAHS) and ultimately, in the most severe cases, to daytime hypercapnic ventilatory failure, cor pulmonale and death. The

major daytime symptom of the disease (excessive daytime sleepiness) also ranges from normality to very severe, disabling excessive somnolence. The severity of daytime sleepiness is moderately correlated with the objective severity of disease quantified from the number of episodes of airway obstruction per hour during sleep.¹⁰ The treatment of obstructive sleep apnoea is targeted mainly at controlling its symptoms (particularly excessive daytime sleepiness) and consequences (such as hypertension/vascular risk), through correction of the breathing disturbance. It is therefore appropriate that disease severity should primarily be stratified using symptom severity rather than the number of episodes of airway obstruction at night.

At least 1% of men in the UK have severe obstructive sleep apnoea with both marked objective respiratory abnormality at night and substantial excessive daytime somnolence, and about 6% of men have objectively detectable disease of lesser severity.¹¹ The prevalence of the disease in the normal community depends on the exact definition of an episode of airway obstruction.¹¹ The standard definitions of an obstructive apnoea, hypopnoea or > 4% oxygen desaturation episode, used to define disease severity for this analysis, are the most frequently used disease definitions. Using these indices, it is possible to define broad disease severity subgroups, such as the mild, moderate and severe definitions used in this report. However, the variation in the absolute number of identified respiratory events produced by modest alterations in sleep study scoring definitions means that the boundaries of these groups are necessarily arbitrary and they need to be applied to clinical practice with a degree of pragmatic common sense.

The main aetiological factor for adult obstructive sleep apnoea is obesity, particularly upper body and neck obesity. Fat deposition in these areas causes airway narrowing and ultimately collapse, although the severity of obesity required to cause airway collapse depends on associated features such as facial shape and jaw structure. Therefore, the prevalence of disease varies markedly with population obesity levels¹¹ and minimising the prevalence of OSAHS is an important potential benefit of population weight reduction strategies. Other common risk factors are enlarged tonsils and adenoids, and craniofacial abnormalities. OSAHS has also been associated with endocrine conditions such as hypothyroidism and acromegaly.

Outcomes associated with OSAHS

The major treatment goal in OSAHS is improvement in daytime sleepiness. As well as being symptomatically unpleasant, excessive sleepiness impairs function on tasks requiring vigilance such as driving, and can result in loss of employment when it causes recurrent unwanted sleep in the work environment. OSAHS is also associated with other negative consequences: deterioration in cognitive function (especially in those tasks requiring concentration, such as driving), changes in mood or personality, and impaired quality of life. Such impairments may be mediated by the severity of daytime sleepiness.¹² Other associated outcomes, with potentially major health resource implications, are hypertension, cardiovascular disease, cerebrovascular disease and stroke. A systematic review of the health effects of OSAHS concluded that OSAHS causes daytime sleepiness and possibly road traffic accidents (RTAs) but that the epidemiological evidence for a causal link with other adverse health outcomes is weak.¹³ A key limitation of the evidence was the failure to sufficiently take into account the potential confounding effects of factors such as obesity and smoking and to establish a causal time sequence.¹³ However, new epidemiological research has been published in the 10 years since that review, rendering it out of date, and a re-evaluation is required that incorporates the new research, although this is beyond the scope of the current review.

Cognitive function

Reported cognitive-related impairments with OSAHS include difficulties in work efficiency and performing new tasks, memory disturbance and concentration problems,¹² although there is contradictory evidence regarding these effects in a population with mild to moderate disease.¹⁴ Difficulties related to attention, memory and learning and executive performance have also been reported.¹² A systematic review of the field found that the most common aspects of executive function to be affected by OSAHS were working memory, phonological fluency, cognitive flexibility and planning (particularly non-verbal planning).¹⁵

Accidents including road accidents

There is also evidence that symptoms of daytime sleepiness and impaired concentration arising from untreated OSAHS pose a significantly increased risk of automobile accidents and injury in the workplace. Sleepiness while driving is a recognised risk factor in road traffic and occupational accidents.¹⁶ Studies of simulated driving tasks show

that participants with OSAHS perform as poorly as alcohol-impaired participants.^{17,18} A recent systematic review found an increased risk of motor vehicle collisions in drivers with OSAHS compared with those without OSAHS although the size of the estimated increased risk varied among studies.¹⁹ The UK Driver and Vehicle Licensing Authority (DVLA) does not allow people who are prone to sleepiness that may impair vigilance while driving to hold a driving licence.

Health-related quality of life

Given the known effects of sleep apnoea on daytime sleepiness and cognitive function, an effect on measures of quality of life would be expected; a systematic review found that OSAHS significantly contributes to impairment of health-related quality of life (HRQoL).²⁰ It is therefore desirable to assess the impact of treatments of sleep apnoea, such as CPAP, upon quality of life. The concept of HRQoL typically refers to an individual's perception of function in at least one of four domains: somatic sensation, physical function, emotional state and social interaction.²¹ The consequences of sleep apnoea for HRQoL include the detrimental effects on physical, mental and social function, including excessive tiredness and decreased energy, decreased concentration and memory, depressive symptoms and relationship difficulties.

A number of generic instruments have been developed to measure HRQoL. These include the Medical Outcomes Study 36-item Short Form Health Survey (SF-36),²² the Nottingham Health Profile (NHP)²³ and the EuroQol-5 Dimensions (EQ-5D).²⁴ Such instruments measure HRQoL in a standardised way that allows for comparisons across studies and conditions. However, these instruments have not been designed to specifically address the aspects of life affected by OSAHS, and as a consequence the criticism has been made that they may be less sensitive to important improvements experienced with treatment than would be a condition-specific instrument. For instance, most generic instruments do not include sleep as a specific dimension; only the NHP (Part 1) includes a sleep-specific dimension.

The two condition-specific instruments most commonly used to assess the HRQoL of people with sleep apnoea are the Functional Outcomes of Sleep Questionnaire (FOSQ)²⁵ and the sleep apnoea quality of life index (SAQLI).²⁶ These are considered to have high acceptability and relevance for both patients and clinicians, and because they are disorder specific they are thought to be highly sensitive to change. The FOSQ, designed to detect

the impact of disorders of excessive sleepiness on physical, mental and social functioning on everyday activities, contains 30 items grouped into five subscales: activity level, vigilance, intimacy and sexual relationships, general productivity and social outcome. Respondents are able to indicate whether lack of engagement with any of the items was a consequence of something other than sleepiness. One weakness of this instrument is that it does not measure experience of symptoms or overall well-being. In addition to a total score, the FOSQ generates a mean score for each subscale; low scores indicate poorer HRQoL. The SAQLI, designed specifically for use in clinical trials with patients experiencing sleep apnoea, contains 35 items grouped into four dimensions: daily function, social interactions, emotional functioning and symptoms. An additional domain, treatment-related symptoms, can also be added to capture the impact of treatment side effects. The SAQLI generates a total score; a low score indicates poor HRQoL. A drawback of this instrument is that it was designed to be interviewer led, although it has been used as a self-completed measure.

Cardiovascular disease

Based on three recent overviews of the evidence establishing a link between OSAHS and cardiovascular disease, the evidence seems strongest in respect of OSAHS as a risk factor for hypertension.²⁷⁻²⁹ There is also evidence linking OSAHS with stroke and cardiac disease, although considerable uncertainties about whether it is an independent risk factor remain.^{4,27,28}

Current service provision

The mainstay of medical treatment of OSAHS is administration of continuous positive airway pressure (CPAP) during sleep. There are thought to be wide variations in the provision of CPAP treatment across the United Kingdom. Dental devices (also known as oral appliances) represent the main alternative group of treatments, although these are generally used only in individuals with mild to moderate OSAHS. Evidence for lifestyle modification as an efficacious treatment is weak;³⁰ however, lifestyle management is often recommended as an adjunct to other treatments, including conservative options such as weight loss, avoidance of alcohol or sedative medication, improved sleep hygiene and use of a lateral sleeping position. In the severely obese, bariatric surgery has sometimes been used to achieve weight loss.⁴ Other treatment options, such as surgery

or drugs, are rarely used, and recent Cochrane reviews do not support their use for treatment of OSAHS.^{31,32}

Description of technology under assessment

CPAP devices

CPAP devices are small, electric pumps that deliver air to the nose or mouth 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. Fixed CPAP devices deliver air at a fixed optimal pressure, usually identified by earlier observation and titration during sleep, while autotitrating CPAP devices increase pressure, as needed, to maintain airway patency, or decrease pressure if no events are detected, over a set period of time. As the minimum effective pressure delivered is automatically adjusted in autotitrating CPAP devices, the mean pressure is often lower than that from optimal fixed pressure in CPAP units. Originally developed for patients with OSAHS, CPAP is increasingly being investigated for use in populations with serious co-morbidities such as Alzheimer's disease³³ and heart failure.³⁴⁻³⁶

It is difficult to obtain a precise estimate from the literature on rates of patient adherence to CPAP treatment. There are variations in how long-term adherence or compliance is defined, as well as in the methods used in epidemiological studies, and the influence of patient awareness that their compliance is being assessed also requires consideration.³⁷ There are two aspects that are of relevance when considering adherence: initial acceptance of treatment and long-term adherence (frequency of use as well as number of hours of use per night). Adherences among those accepting treatment of over 70%,³⁸ and 80%^{39,40} after 1 year, have been reported, although lower rates have also been reported. Reasons for discontinuation relate primarily to physical discomfort, nasal dryness and congestion, difficulty in adapting to the pressure, dislodgement during sleep, and the social consequences of using the unit. Some patients may discontinue because they achieve an improvement in symptoms through, for example, weight loss or tonsillectomy. Serious side effects from CPAP are thought to be very rare.

A number of variations of the technology have been developed, mainly with the aim of improving adherence. The primary variations have involved

the use of humidifiers, which have been shown to prevent upper airway dryness associated with CPAP use;⁴¹ and autotitrating and bi-level CPAP, which aim to vary the pressure depending on need during the night and therefore reduce both the pressure required and associated side effects. Lower treatment pressures have been reported with autotitrating than with fixed CPAP but no clinically important changes in adherence or other outcomes have been found,^{37,42} although one systematic review concluded that auto-CPAP may be of benefit in certain subgroups, as yet undefined.³⁷ Similarly, there is no evidence of increased adherence with humidified CPAP, although a need for further research has been noted.³⁷ Variations in the CPAP delivery interface, such as type of mask, have also been developed. A recent systematic review found a paucity of research on the impact of different masks, making it difficult to determine the best interface, but suggested that nasal pillows or the Oracle oral interface are potentially useful alternatives when patients are unable to tolerate the nasal mask.⁴³ For the purposes of this technology assessment report all types of CPAP device are treated as a single intervention.

Current usage in the UK

There are no routine data available on current use. Expert opinion estimates that approximately 20,000 of the probable 180,000 patients with OSAHS are using CPAP devices. Chilcott *et al.*⁴⁴ highlighted concerns about (1) the haphazard and sporadic provision of CPAP devices throughout the UK and (2) the potential scale of long-term costs related to provision of new devices and maintenance of an expanding pool of CPAP devices. Focusing on the Trent Region, the authors suggested that there is a great deal of variation in the pattern and range of services that are available in Trent for diagnosing and treating OSAHS. They gave the example that if 60 new CPAP devices are provided each year, as estimated in clinics in Leicester and Nottingham, the discounted cost of new investigations and maintenance of the existing pool of CPAP devices would increase exponentially. They reported the cost of a new, standard CPAP machine as £250 (no price year given) and estimated that, at that time, the annual maintenance and patient follow-up costs amount to an additional £250 per year. The cost of an initial investigation ranges from £370 to £790 per person investigated. They estimated that initial year 1 costs of about £60,000 in the Trent Region may rise to annual costs of £95,000 in year 5 and £115,000 in year 10.

Dental devices

Dental devices, also known as oral appliances, are designed to maintain the patency of the pharyngeal airway and prevent the lumen from collapsing during sleep by holding the tongue or mandible forward, thereby enlarging the posterior airspace. There are two main types – tongue repositioning devices and mandibular repositioning devices – although the latter is most commonly used for OSAHS.⁴⁵ Mandibular repositioning dental devices are either one-piece, holding the mandible in a fixed anterior position, or two-piece, allowing some movement of the mandible.⁴⁵ They can be custom-made or pre-fabricated; variations in design are available. Most side effects of treatment are reported to be minor and temporary, e.g. excessive salivation, although some are more significant, e.g. bite changes.⁴⁶ Owing to the perception that the increases in pharyngeal patency achievable with mandibular devices are modest and the lack of high-quality evidence available on their effectiveness, dental devices are currently considered appropriate for use only in mild to moderate OSAHS (where airway collapse is more easily reversed), or in patients who do not wish to use CPAP.⁴⁷

Previous systematic reviews

A number of recent systematic reviews have evaluated the effectiveness of CPAP as a treatment for OSAHS.^{13,48–50} In addition, there have been systematic reviews underpinning guidelines in a number of countries, which are not discussed here. The earliest review, published ten years ago, concluded that there was a paucity of robust evidence for a clinical benefit and the cost-effectiveness of CPAP.¹³ A key deficit identified was the lack of trials using a placebo that was indistinguishable from CPAP as, at that time, a pill placebo was being used. A considerable number of trials have been published subsequently. A systematic review in 2003 identified 12 trials; CPAP was compared with oral placebo, conservative therapy such as lifestyle changes and sham CPAP (a device identical to CPAP set at a non-therapeutic pressure).⁴⁹ The review investigated subjective sleepiness (ESS) and objective sleepiness (MSLT and MWT). When estimates from individual studies were pooled, there was a statistically significant improvement in the ESS score of 2.94 points (95% CI 1.61–4.26) with CPAP compared with control. There was evidence of variation in the treatment

effect which remained unexplained by age, sex, body mass index (BMI), location of study or mean hours of CPAP use. Variations by study baseline disease severity and methodological quality were not investigated. The MSLT and MWT were pooled, which would seem inappropriate in view of the poor correlation between these measures. A more recent review identified a smaller number of relevant trials ($n = 7$) due to tighter inclusion criteria; again the comparators were oral placebo, conservative treatment and sham CPAP.⁴⁸ When estimates from individual studies were pooled, there was a statistically significant improvement on the ESS of 1.2 points (95% CI 0.5–1.9) with CPAP compared with control in patients with mild to moderate OSAHS. There was also a statistically significant improvement in sleep latency on the MWT of 2.1 minutes (95% CI 0.5–3.7) with CPAP compared with control, but no statistically significant difference on the MSLT.

The most recent and comprehensive systematic review (a Cochrane review) concluded that CPAP was effective in reducing objective and subjective symptoms of sleepiness, and improving quality of life in individuals with moderate and severe OSAHS.⁵⁰ Evidence was available from 36 trials and substantially more evidence was available from trials using sham CPAP as a comparator than had been the case in the earlier reviews. Compared with placebo (sham CPAP, oral placebo and conservative treatment), there was a statistically significant improvement in favour of CPAP of 3.83 points on the ESS (95% CI 3.09–4.57) from parallel trials and 1.92 points (95% CI 1.25–2.59) from crossover trials, although there was evidence of statistical heterogeneity (variation in the treatment effect) across the trials. There was a statistically significant benefit with CPAP compared with control in sleep latency on the MSLT (1.25 minutes, 95% CI 0.18–2.32) and on the MWT (2.36 minutes, 95% CI 0.31–4.40) from crossover trials.

Although this was a good-quality review, the current review provides an update, which includes additional studies, as well as an alternative approach to the meta-analyses; the Cochrane review analysed the data from crossover trials and parallel trials separately. While this is an appropriate approach, it does reduce the power of any subgroup analyses to investigate the influence of factors such as disease severity on treatment outcomes.⁵⁰ Such an approach also results in two treatment effects (one for parallel trials and one for crossover trials) for each outcome for use in the economic modelling. The current review uses an established method to combine the results of parallel and crossover trials for which sufficient data are available.^{51,52}

Systematic reviews have also been conducted on the efficacy of dental devices. The Cochrane review discussed above found that CPAP was more effective than dental devices in reducing respiratory disturbances during sleep, although no difference was shown between the treatment groups in daytime symptoms such as sleepiness.⁵⁰ A second Cochrane review, which was last updated in June 2005, compared dental devices with placebo devices that were similar devices placed in the mouth but which did not cause the mandible to protrude.⁵³ When parallel studies were pooled, there was a statistically significant improvement with dental devices compared with control devices on the ESS (MD –2.09, 95% CI –3.8 to –0.37), although there was high statistical heterogeneity. Crossover trials also showed a statistically significant benefit on the ESS (MD –1.81, 95% CI –2.72 to –0.90). An earlier systematic review reported a statistically significant improvement on the AHI but reported contradictory results from trials on subjective sleepiness (ESS).⁴⁵

Chapter 2

Definition of decision problem

Decision problem

Untreated OSAHS is associated with increased daytime sleepiness, impairment of cognitive function and a reduction in quality of life. Owing to increased sleepiness and impaired concentration it may have consequences for how effectively people can engage in work, home and leisure daytime activities. It has been associated with serious consequences such as increased risk of accidents and, if left untreated, it is a lifelong condition that may be a risk factor for hypertension, myocardial infarction and stroke. As a result of the association between OSAHS and obesity, the prevalence of OSAHS is expected to increase with increasing prevalence of obesity.

There is evidence from previous systematic reviews that CPAP is an effective treatment for some of the outcomes associated with OSAHS. It is the recommended first choice of treatment for moderate or severe OSAHS. Surgery and drug therapy are generally not recommended. Treatment options for mild OSAHS include conservative options such as weight loss, avoidance of alcohol or sedative medication, improved sleep hygiene and use of a lateral sleeping position. Dental devices are also considered to be a treatment option for mild to moderate disease.

However, provision of CPAP for OSAHS is variable across the UK. This is thought to be due to a combination of lack of facilities for diagnosis and treatment and a lack of recognition of the significant morbidity associated with OSAHS. An evaluation of the clinical benefit and cost-effectiveness of CPAP is required. The main focus of interest is how CPAP compares with placebo, conservative therapy and dental devices and not how different types of CPAP devices vary in effectiveness. Therefore, different CPAP devices should be treated as one technology. If the data are available, the question of whether there are subgroups of people for whom CPAP is particularly appropriate should be investigated.

Overall aims and objectives of assessment

The aim of this review was to determine the clinical effectiveness, safety, and cost-effectiveness of continuous positive airway pressure (CPAP) devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome (OSAHS) compared with best supportive care, placebo and dental devices.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

Search strategy

The search terms used to capture the concepts of sleep apnoea and CPAP were arrived at by discussion with reviewers and experts. These search terms were then adapted for each individual database and relevant thesaurus terms used where possible. The search strategies used for each database are included in Appendix 1.

A range of databases and websites were searched to identify existing systematic reviews and guidelines on CPAP for sleep apnoea:

- Cochrane Database of Systematic Reviews (Cochrane Library 2006 issue 3) (www.thecochranelibrary.com)
- Database of Abstracts of Reviews of Effects [Centre for Review and Dissemination's (CRD) administration version of the database]
- Health Technology Assessment Database (CRD administration version of the database)
- Scottish Intercollegiate Guidelines Network (www.sign.ac.uk)
- National Guideline Clearinghouse (www.guideline.gov/)
- National Research Register (2006 issue 3) (www.update-software.com/National/)
- Health Services/Technology Assessment Text (HSTAT) (www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat)
- Turning Research into Practice Database (Trip) (www.tripdatabase.com/)
- Health Evidence Bulletins Wales (<http://hebw.cf.ac.uk/index.html>)
- Clinical Evidence (www.clinicalevidence.com)
- National Library for Health Guidelines Finder (www.library.nhs.uk/guidelinesfinder/).

Further databases were searched to identify primary studies:

- MEDLINE (1996 to November week 3 2006) (OVID)
- MEDLINE In-Process & Other Non-Indexed Citations (28 November 2006) (OVID)
- EMBASE (1980 to 2006 week 47) (OVID)

- Cochrane Central Register of Controlled Trials (Cochrane Library 2006 issue 4) (www.thecochranelibrary.com)
- CINAHL (1982 to November week 3 2006) (OVID)
- Science Citation Index (1900 to 25 November 2006) (Web of Knowledge)
- ISI Proceedings Science & Technology (1990 to 25 November 2006) (Web of Knowledge)
- Zetoc Conferences (1993 to 29 November 2006) (<http://zetoc.mimas.ac.uk/>)
- SIGLE (1980 to March 2005) (SilverPlatter)
- Index to Theses (1716 to 16 October 2006) (www.theses.com/)
- NHS Economic Evaluation Database (NHS EED) (CRD internal administration system 13 January 2007)
- Health Economic Evaluations Database (HEED) (1995 to January 2007) (CD-ROM)
- Health Technology Assessment (HTA) database (CRD internal administration system 13 January 2007)
- EconLit (1969 to October 2006) (SilverPlatter)
- EconPapers (<http://econpapers.repec.org/>).

The contents pages of the following journals (selected by the review team based on included references from a previous systematic review on this topic) were also hand searched to identify reports that might not have been indexed by the electronic databases. In addition, electronic alerts were set up for each journal so that the contents page could be scanned as the latest edition was published:

- *Thorax* [2005 vol 60(1) to vol 62(4)]
- *Sleep Medicine* [2005 vol 6(6) to vol 7(1)]
- *European Respiratory Journal* [2005 vol 26(5) to vol 29(4)]
- *Sleep* [2005 vol 28(11) to vol 29(12)]
- *Respiratory Medicine* [2005 vol 99(11) to vol 101(5)]
- *QJM* [2005 vol 98(11) to vol 100(3)]
- *Journal of Internal Medicine* [2005 vol 258(5) to vol 261(4)]
- *Journal of Sleep Research* [2005 vol 14(4) to vol 16(1)]
- *European Journal of Orthodontics* [2005 vol 27(6) to vol 29(1)].

The following conference proceedings were also scanned for relevant abstracts. This selection was based on recommendations from the Cochrane Airways Group:

- American Thoracic Society international conferences 2005 and 2006 (www.thoracic.org/)
- British Thoracic Society winter meeting 2006 (2005 winter meeting abstracts are published as part of the journal *Thorax* and therefore searched electronically) (www.brit-thoracic.org.uk/)
- Thoracic Society of Australia and New Zealand annual scientific meetings 2005 and 2006 (www.thoracic.org.au/).

The industry submissions were also searched for any additional unpublished data. No additional studies were identified.

Inclusion and exclusion criteria

Titles and abstracts identified from the searches were independently screened for relevance by two reviewers and disagreements were resolved by consensus. The full papers were ordered for all potentially relevant studies. Full papers were screened independently by two reviewers based on the inclusion criteria below. Disagreements were resolved by consensus and, if necessary, a third reviewer was consulted. Studies in any language (published or unpublished or in abstract form only) were included in the review if they met the following criteria.

Population

Studies of adults (16 years or older) with a diagnosis of predominantly obstructive sleep apnoea, confirmed by use of an appropriate tool (e.g. a respiratory polysomnographic sleep study, analysed by an appropriately qualified respiratory physician, from which a standard severity criterion such as the API or arterial oxygen desaturation index was derived), were included. Populations with disease of any severity were eligible. Studies of participants with central nervous system (CNS) dysfunction (e.g. stroke or dementia such as Alzheimer's disease) and heart failure were excluded. Both of these conditions can produce disorders of breathing control that are central in origin (i.e. breathing is interrupted by a lack of effort due to dysfunction in the part of the brain that controls breathing), in addition to OSAHS, making it difficult to determine OSAHS. Because of the complexities of differentiating obstructive from central sleep apnoea and the potential for a mixture of these disorders to complicate the

interpretation of outcomes, studies conducted specifically in these patient groups were excluded. However, studies of general population groups that may have included some patients with these co-morbid conditions were included.

Intervention and comparators

Studies of fixed CPAP or autotitrating CPAP therapy were eligible for inclusion provided the treatment was of at least 1 week's duration. For the purposes of this review, fixed and autotitrating CPAP were treated as the same intervention; studies comparing the two technologies were not eligible for inclusion. Relevant comparators were best supportive/usual care (including conservative intervention such as lifestyle advice regarding weight loss, alcohol consumption and sleep hygiene as well as sleep posture advice or treatment), placebo (including placebo pill and sham CPAP) and dental devices. For sham CPAP the subtherapeutic pressure used varies between studies. We included studies in which it was stated sham CPAP was used and did not exclude studies based on the specific subtherapeutic pressure used.

Outcomes

The following outcomes were included.

Primary outcomes

- Subjective sleepiness as assessed by the ESS
- Objective sleepiness as assessed by the MWT, Osler test, MSLT or equivalent measure.

Secondary outcomes

- Blood pressure (mean day and night blood pressure were assessed separately as the mechanisms and patterns of daytime and night-time blood pressure disturbance in OSAHS vary, and the relationship between daytime blood pressure and vascular risk has been more clearly described in other studies)
- Cardiovascular disease (e.g. myocardial infarction, stroke)
- Accidents (e.g. driving, occupational), although it was thought unlikely that such data would be found in randomised controlled trials (RCTs)
- Quality of life, where it was measured using a standardised scale
- Mood, anxiety and depression, where they were measured using a standardised scale
- Simulated driving performance
- Neuropsychological functioning
- AHI/desaturation rate
- Any complications or adverse effects of treatment.

Outcomes such as changes to sleep architecture (e.g. rapid eye movement sleep, slow-wave sleep, sleep efficiency) were not considered.

Study design

RCTs using a parallel or crossover design were included. In this field there is no standard practice as to whether a washout period is used in crossover trials and, if so, how long the washout period should be. Because the effect of CPAP in relation to daytime sleepiness is thought to be short-lived, the risk of carryover was not considered to be a serious problem.

Data extraction

The authors of the recent systematic review by Giles *et al.*⁵⁰ provided the extracted data from their review to avoid duplication of work. This also included some unpublished data. These data had been independently extracted by two reviewers. Data from the new studies, as well as any additional data required from the studies previously extracted by Giles *et al.*, were extracted by one reviewer and checked by another. Discrepancies were resolved by discussion and, if necessary, a third reviewer was consulted. Where there were multiple publications from the same study, the main publication for each study was identified and data were extracted from that paper. Where additional relevant outcomes were available in a related paper these were also extracted. For some of the studies cognitive outcomes were reported for only a subset of participants from the main study. These data were extracted. Where only a conference abstract was available, authors were contacted for further data. Where necessary, authors were contacted to clarify whether published studies had any overlapping patients or to obtain missing data such as standard errors from a paired analysis in crossover trials or where data were only available in graphs.

Data were extracted into Review Manager (RevMan) and into a standard form in Microsoft Word. Data extracted included patient characteristics (age, sex, severity of OSAHS, BMI), details of the intervention (fixed or autotitrating CPAP, use of humidifier), comparator (details of placebo, conservative management or dental device), adherence (usually reported as the average number of hours the machine was running at night), length of follow-up, outcomes as identified above and study quality.

Predominantly end point data were reported in the trials, except for blood pressure, for which a mixture of change and end point data were

reported. Where both end point and change data were reported, preference was given to end point data for all outcomes except blood pressure, in which case change data were used (provided the variance for the change score was reported). Where only change data were reported, the variance was imputed if necessary. Change scores may be less efficient than end point data in some situations as they have two sources of measurement error (at baseline and follow-up).⁵⁴ However, unlike end point values, the use of change scores removes a component of between-person variability.⁵⁴ Whether the between-person variation is increased or reduced by using an end point or change score depends on the size of the correlation between baseline and follow-up; therefore, it is important to specify in advance which measure will be used.⁵⁵ Use of change from baseline scores in crossover trials may increase the variation.⁵² The decision was made in advance to use change data for blood pressure where they were available, as this outcome was being used in the economic model, and change in blood pressure was preferred to end point for use in this model. All outcomes were continuous data and the mean difference (MD) between CPAP and comparator was calculated for each outcome.

Paired data were extracted from crossover trials where available. If the SD or SE from a paired analysis was not reported, the SE was imputed from the *t*-statistic, the *p*-value or the CI from a paired analysis.⁵² For one crossover study it was necessary to impute the SE for blood pressure:⁵² a within-person correlation of 0.5 was used and a within-person correlation of 0.1 and 0.9 for a sensitivity analysis.⁵⁶ It is generally recommended that when analysing a crossover trial the method of testing first for a carryover effect and then analysing only the data from the first sequence period as though it were data from a parallel trial should be avoided.⁵² In the studies we included, in a few instances there was evidence of a carryover effect into the second period, but the authors reported only data from the first sequence of the crossover trial and these data were treated as data from a parallel trial. These are not ideal data but, where these were the only data available they were used in the review.

Owing to time limitations and the quantity of cognitive data from crossover trials it was not feasible to impute data for a paired analysis, where these were not reported, for all the cognitive outcomes. Where three or more studies were available for potential pooling, the SE was estimated where data were available as above. For the other cognitive outcome measures the mean end value at follow-up and the SD for the

intervention and control group with the associated *p*-value were extracted. Where available, the SD or SE from a paired analysis was extracted.

Quality assessment

Study quality was assessed on the basis of criteria from CRD Report No. 4 and additional criteria were used to assess crossover trials (see Study quality, below). The criteria assessed were broad in anticipation that a narrative synthesis may have been necessary. Quality was assessed by one reviewer and checked by another. Discrepancies were resolved by discussion and, if necessary, a third reviewer was consulted.

Data analysis

Where sufficient data were available, they were pooled in quantitative syntheses using a random-effects model. Studies comparing CPAP with placebo or best supportive/usual care were pooled separately from studies comparing CPAP with dental devices. Where data sets included both study designs, parallel and crossover trials were pooled.⁵¹ The generic inverse variance method in RevMan was used to pool data sets which included both parallel and crossover designs, or only crossover trials. When only parallel trials were being pooled the weighted mean difference (WMD) method in RevMan was used. To transform the parallel data for entry into the generic inverse variance facility, the SE for the MD was calculated from the 95% CI. This was calculated using the formula $SE = (\text{upper confidence limit} - \text{lower confidence limit})/3.92$. This method assumes a sample size of at least 30; however, given the number of outcomes and studies included in the review it was not considered feasible in the time available to use the *t*-statistic.

Statistical heterogeneity between trials was assessed using the I^2 statistic.⁵⁷ Five sources of potential clinical and methodological heterogeneity were identified a priori as being of priority: baseline disease severity, baseline daytime sleepiness, study design, type of placebo and study quality. We planned to investigate these for the primary outcomes using subgroup analysis, as clinically important variations in the magnitude of treatment effects are likely in different severity groups. The subgroups specified in advance were as follows:

- population subgroups
 - baseline disease severity, as classified using the AHI or the desaturation rate using the mean baseline score for each study: mild (AHI 5–14/hour or oxygen desaturation

rate 5–10/hour), moderate (AHI 15–30/hour or oxygen desaturation rate 10–30/hour) and severe (AHI > 30/hour or oxygen desaturation rate > 30/hour)

- baseline symptom severity, as classified using the mean baseline ESS score for each study: mild (0–9 points), moderate (10–15 points) and severe (16–24 points)
- comparator subgroups
 - sham CPAP, oral placebo and best supportive care
- study design subgroups
 - parallel and crossover
 - end point data and change from baseline data.

We planned to investigate the influence of study quality on the treatment effect by pooling studies with adequate concealment of allocation separately from those with inadequate or unclear adequacy of concealment. This analysis was limited due to the small number of studies that reported an adequate method of concealing treatment allocation.

The pooling of the primary outcomes and blood pressure were rerun using a fixed-effect model to test the impact of the model of analysis used. The robustness of the findings for these outcomes was also investigated by assessing the impact on the treatment effect of removing each study singly.

Where no new data were identified for specific outcomes subsequent to the review by Giles *et al.*⁵⁰ we reported the analysis based on the data sets from that review, although we report the pooling from a random-effects model, combining crossover and parallel designs, as per our protocol rather than a fixed-effect model and separate analyses by study design, as used by the earlier review.

The risk of publication bias was not formally assessed.

Results of review of clinical effectiveness

Quantity and quality of research available

The searches identified 6325 potentially relevant references (*Figure 1*). On the basis of screening titles and abstracts, 235 full papers were ordered for further assessment. Inclusion screening of full papers identified 48 individual relevant studies. Eighteen of these were new studies or provided additional data subsequent to the review by Giles *et al.*⁵⁰ Four were available at the time of the review by

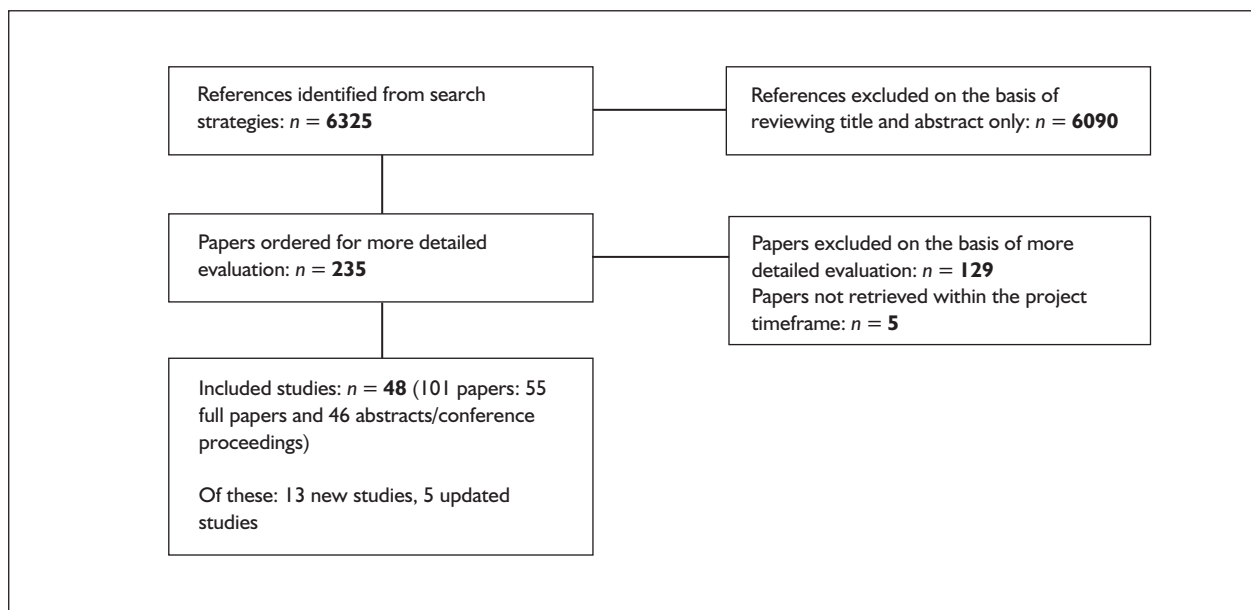


FIGURE 1 Study selection.

Giles *et al.*, but were classified as additional studies due to the different inclusion criteria used by the two reviews;^{58–61} two provided additional data as only abstracts had been available at the time of the earlier review;^{56,62} and 11 had become available since the earlier review had been completed.^{63–73}

Three of the new studies were available in abstract form only and did not provide sufficient data for inclusion in the analysis.^{69,71,72} Three studies that had been included in the review by Giles *et al.* were excluded because they focused on participants with CNS dysfunction or heart failure, and these populations were not considered in the current review.^{74–76} Details of the included studies and their related papers are provided in Appendix 5. For the purpose of simplicity the main papers from individual studies are referred to in the main body of the report although data from more than one paper may have been used.

Study characteristics

The characteristics of the included studies are summarised in *Table 1*. This table focuses on the study characteristics that were used for the subgroup analyses: severity of daytime sleepiness at baseline (ESS), baseline disease severity (AHI), comparator and study design (parallel and crossover). Further details of study characteristics, including baseline data, are reported in Appendix 5.

Intervention and comparators

Forty-six of the 48 included studies that used fixed pressure CPAP. The remaining two studies used

autotitrating pressure CPAP.^{67,77} Three studies used humidified CPAP^{73,78,79} and in two studies the use of a humidifier was optional.^{80,81} All CPAP interventions were treated as a single class in the analysis.

There were three three-arm trials: CPAP versus oral placebo and dental device;⁸² CPAP versus conservative/usual care and dental device;⁷⁰ and CPAP versus sham CPAP and supplemental oxygen.⁷³

CPAP was compared with sham CPAP (18 studies);^{56,58,62–68,73,77,79,83–88} oral placebo (nine studies);^{78,82,89–95} conservative/usual care (eight studies);^{59,69,70,96–100} dental devices (12 studies);^{70,72,80–82,101–107} and posture-related devices (three studies).^{60,61,108}

Where sham CPAP was used as placebo, the subtherapeutic pressure ranged from 0 to 4 cmH₂O. Where reported, the majority of studies ($n = 12$) used a pressure of 2 cmH₂O or less; two used a pressure of between 3 and 4 cmH₂O.^{64,84} In the studies using oral placebo an inactive tablet was used and participants were told that the tablet was intended to improve their airway function. The information provided on usual care/conservative treatment as a comparator was limited, but generally included dietary advice, dietary advice or referral to weight loss programmes, or advice on sleep hygiene and sleep posture.

Where reported, there were two main types of dental devices used in the included studies, one-

piece non-adjustable devices;^{70,81,103} and two-piece adjustable devices.^{72,80,82,101,102,105} In four of these studies incremental mandibular advancement was used until symptoms abated or further advancement was uncomfortable.^{72,80,82,102} In one study some participants used a one-piece and some used a two-piece device.¹⁰⁶

Studies which compared CPAP with some form of device to control sleeping position used a backpack with a soft ball inside to prevent a supine position while sleeping;¹⁰⁸ a shoulder–head elevation pillow to maintain an upright position (60°) while sleeping;⁶⁰ or a cervicomandibular collar to retain the head in a natural position and to prevent the jaw from opening during sleep.⁶¹

Participants

The participants in the included studies were predominantly middle-aged, male and overweight or obese. The mean age in the CPAP and comparison groups at baseline ranged from 44 to 58 years. With the exception of one study,⁹⁸ the majority of participants in the included studies were male; the proportion of female participants ranged from 0% to 48%. Based on the mean BMI (where reported) ten studies were of an overweight population (BMI 25–30 kg/m²) and 30 were of an obese population (BMI 30.1–40 kg/m²); the highest mean BMI at baseline was 40.1 kg/m².⁸⁸ Two studies were of patients who were being treated for another primary disease: type 2 diabetes⁶⁷ and headache symptoms.⁹⁸ Two studies specifically recruited patients with hypertension.^{65,68}

Table 1 provides details of baseline disease severity for the individual studies. Based on mean baseline daytime sleepiness, as reported by participants using the ESS, the majority of studies were of participants experiencing moderate sleepiness ($n = 27$); five of the included studies were of participants with severe daytime sleepiness and two were of participants with mild sleepiness. Symptom severity, as defined by the ESS, was not available for 14 studies. Based on disease severity at baseline, defined by AHI [or 4% oxygen desaturation or the respiratory disturbance index (RDI)], the majority of studies ($n = 26$) investigated a population with severe OSAHS, 15 investigated a population with moderate disease, and three investigated a population with mild disease. One study recruited patients with OSAHS that was mild in the lateral sleep position and severe in the supine position.¹⁰⁸ Disease severity, as defined by AHI or equivalent, was not available for three studies.

Study design

All the included studies were RCTs. There were 26 crossover trials, two partial crossover trials (only one group was crossed over in the second sequence) and 20 parallel trials. Only the data from the first sequence before crossover were used from the partial crossover trials.^{85,86} For one crossover trial the outcome data appeared to be from the first sequence and these data were treated as parallel data.⁶³ For some individual outcomes, only the data from the first sequence of the crossover trials were reported in the papers due to detection of a carryover effect, and these were treated as parallel data in the synthesis. Studies using oral placebo as a comparator were exclusively of crossover design, as were the trials in which the comparator was postural therapy. This was also the dominant study design for trials comparing dental devices with CPAP. Parallel trials were the dominant design used in trials comparing CPAP with sham CPAP or conservative/usual treatment.

Treatment duration varied. The majority of studies were between 4 and 12 weeks' duration. There were six studies of less than 4 weeks' duration^{58,73,79,85,91,108} and four of longer than 12 weeks' duration.^{80,81,99,100} Participants were assessed at the end of treatment.

Study quality

The following checklist was used to assess the methodological quality of included studies.

Criteria

1. Was the method used to assign participants to treatment groups or the sequence of treatments really random (e.g. computer generated or random number table)?
2. Was treatment allocation concealed?
3. Were the groups similar at baseline in terms of ESS and AHI?
4. If not, were adjustments made for differences in the treatment groups?
5. Did the analysis include an intention-to-treat (ITT) analysis?
6. Were appropriate methods used to account for missing data in the ITT analysis?
7. What proportion of participants was lost to follow-up for the primary outcomes?
8. Was the study described as blind or double-blind?
9. Who was blinded?
10. Were the participants CPAP naïve?
11. Was an appropriate analysis, using paired data, conducted? (Crossover trials only.)
12. Was there a treatment by period interaction? (Crossover trials only.)

TABLE 1 Characteristics of included studies

Study details	Number randomised (N)	Target population	Disease severity [AHI, mean (SD)]	Severity of sleepiness, [ESS, mean (SD)]	Treatment duration (weeks)
CPAP vs sham CPAP					
<i>Parallel trials</i>					
^{a,b} Arias et al., 2006 ⁶³	23	AHI ≥ 10 and ESS ≥ 10	Severe, I 44.1 (29.3)	NR	12
Barbé et al., 2001 ⁸³	55	AHI ≥ 30 and no or mild daytime sleepiness	Severe, I 54 (16.2), C 57 (20)	Mild, I 7 (2.2), C 7 (2)	6
Becker et al., 2003 ¹⁰⁹	60	AHI ≥ 5 and ESS ≥ 10	Severe, I 62.5 (17.8), C 65 (26.7)	Moderate, I 14.4 (2.5), C 14.1 (3.2)	9
^a Campos-Rodriguez et al., 2006 ⁶⁵	72	AHI ≥ 10 and hypertension	Severe, I 58.3 (24.6), C 59.5 (21.7)	Moderate, I 15 (3.9), C 13.6 (3.6)	4
^c Dimsdale et al., 2000 ⁵⁸	39?	RDI > 15 with or without hypertension	Severe, I RDI 53.6 (SD 23.2), C 41.7 (SD 25.6)	NR	1
^d Henke et al., 2001 ⁸⁵	45	AHI > 10 with daytime sleepiness or AHI > 20 with or without daytime sleepiness	Severe, I 62.1 (27.4), C 68.1 (25.2)	Severe, I 16.4 (5.6), C 16 (4.8)	2
^a Hui et al., 2006 ⁶⁴	56	AHI ≥ 5 and daytime sleepiness or two other symptoms	Severe, I 32.9 (SE 3.2), C 29.5 (SE 3.1)	Moderate, I 10.7 (5.3), C 11.6 (5.3)	12
Jenkinson et al., 1999 ⁷⁷	107	Men with > 10 episodes per hour of greater than 4% drop in SaO ₂ and ESS ≥ 10	Moderate, I median 32.9 (15.5–63.4), ^e dips per hour > 4% SaO ₂ , C 28.5 (10.7–68.7)	Severe, I median 16 (10.7–21.7), ^e C 17 (10–23)	4
^c Norman et al., 2006 ⁷³	46	AHI > 15 with or without hypertension	Severe, I 66.1 (SE 29.1), C 53.9 (29.8)	Moderate, I 12 (5.5), C 12 (6.6)	2
Pepperell et al., 2002 ⁸⁷	118	Men with ≥ 10 episodes per hour of greater than 4% drop in SaO ₂ and ESS ≥ 10	Severe, I 38 (19.8), dips per hour > 4% SaO ₂ , C 35.9 (19.6)	Severe, I 16.3 (3.3), C 16 (3.1)	4
^a Spicuzza et al., 2006 ⁶⁶	25	Moderate to severe OSAHS	Severe, I 55.3 (11.9), C 59.2 (17.3)	NR	4
^a West et al., 2006 ⁶⁷	42	Men with type 2 diabetes and > 10 episodes per hour of greater than 4% drop in SaO ₂ and ESS ≥ 9	Severe, I 33.1 (21.6), dips per hour > 4% SaO ₂ , C 39.1 (24.8)	Moderate, I 14.7 (3.5), C 13.6 (3.5)	12

continued

TABLE I Characteristics of included studies

Study details	Number randomised (N)	Target population	Disease severity [AHI, mean (SD)]	Severity of sleepiness, [ESS, mean (SD)]	Treatment duration (weeks)
Crossover trials					
^a Arias <i>et al.</i> , 2005 ⁵⁶	27	Men with AHI ≥ 10 and ESS ≥ 10	Severe, 44 (27.5)	NR	12
^a Coughlin <i>et al.</i> , 2007 ⁶²	35	RDI > 15 and ESS ≥ 10 or two other symptoms	Severe, RDI 39.7 (13.8)	Moderate, 13.8 (4.9)	6
^a Cross <i>et al.</i> , 2005, ⁸⁸ Abstract	10	Two major symptoms of OSAHS and > 20 episodes per hour of greater than 4% drop in SaO ₂	Severe, 63 (26)	NR	6
Marshall <i>et al.</i> , 2005 ⁷⁹	31	AHI 5–30, habitual snoring or nocturnal choking and at least one symptom of daytime sleepiness or ESS ≥ 8	Moderate, 21.6 (7.5)	Moderate, 12.5 (4.3)	3
^a Robinson <i>et al.</i> , 2006 ⁶⁸	35	Patients with hypertension and > 10 episodes per hour of greater than 4% drop in SaO ₂ and ESS < 10	Moderate, median 28.1 (IQR 18.0–38.0), dips per hour > 4% SaO ₂	Mild, Median 5.3 (IQR 3.0–7.0)	4
CPAP vs oral placebo					
<i>Crossover trials</i>					
Barnes <i>et al.</i> , 2002 ⁸⁹	42	AHI 5–30 and symptoms of OSAHS	Mild, 12.9 (6.3)	Moderate, 11.2 (5)	8
Barnes <i>et al.</i> , 2004 ⁸²	114	AHI 5–30	Moderate, 21.3 (13.6)	Moderate, 10.7 (6.5)	12
Engleman <i>et al.</i> , 1994 ⁹⁰	35	AHI ≥ 5 and at least two symptoms of OSAHS	Moderate, median 28 (range 7–129)	NR	4
Engleman <i>et al.</i> , 1996 ⁹¹	16	AHI ≥ 5 and at least two symptoms of OSAHS	Severe, 49 (32.5)	NR	3
Engleman <i>et al.</i> , 1997 ⁹²	18	AHI 5–14.9 and at least two symptoms of OSAHS	Mild, 11 (4)	Moderate, 14 (4)	4
Engleman <i>et al.</i> , 1998 ⁹³	23	AHI ≥ 15 and at least two symptoms of obstructive sleep apnoea	Severe, 43 (37)	Moderate, 12 (4)	4
Engleman <i>et al.</i> , 1999 ⁷⁸	37	AHI 5–14.9 and at least two symptoms of OSAHS including daytime sleepiness (ESS ≥ 8 or reported sleepiness while driving)	Mild, 10 (3)	Moderate, 13 (3)	4
Faccenda <i>et al.</i> , 2001 ⁹⁴	71	AHI ≥ 15 and at least two symptoms of OSAHS	Severe, median 35 (range 15–129)	Moderate, median 15 (range 6–14)	4
McArdle <i>et al.</i> , 2001 ⁹⁵	23	AHI > 15 and at least two symptoms of OSAHS	Severe, median 40 (IQR 25–65)	Moderate, median 14 (IQR 10–17)	4

TABLE 1 Characteristics of included studies

Study details	Number randomised (N)	Target population	Disease severity [AHI, mean (SD)]	Severity of sleepiness, [ESS, mean (SD)]	Treatment duration (weeks)
CPAP vs conservative/usual care					
<i>Parallel trials</i>					
Ballester <i>et al.</i> , 1999 ⁹⁶	105	AHI > 15 and severe clinical symptoms or AHI > 30 and mild to moderate symptoms	Severe, I 55 (22.3), C 58 (18.3)	Moderate, I 12.1 (5.0), C 11.4 (6.1)	12
Chakravorty <i>et al.</i> , 2002 ⁹⁷	71	AHI > 15	Severe, I 55 (28.7), C 35 (19.1)	Severe, I 16 (5.6), C 14 (4.2)	12
^a Drager <i>et al.</i> , 2006, ⁶⁹ Abstract	16	AHI > 30, normotensive	Severe, I 54 (8), C 65 (13)	NR	12
^a Lam <i>et al.</i> , 2007 ⁷⁰	101	AHI 5–40 or AHI 5–20 along with ESS > 9	Moderate, I 23.8 (11.1), C 19.3 (10.9)	Moderate, I 12 (5.8), C 12 (5.8)	10
Lim <i>et al.</i> , 2005, ¹¹⁰ Abstract	23	Primary headache symptoms and AHI ≥ 5	NR	NR	4
Lojander <i>et al.</i> , 1996 ⁹⁹	44	Diagnosis of OSAHS and BMI < 40 kg/m ²	Moderate	NR	52
Monasterio <i>et al.</i> , 2001 ¹⁰⁰	142	AHI 10–30 and absence of severe daytime sleepiness	Moderate, I 20 (6), C 21 (6)	Moderate, I 12.1 (4.9), C 13.2 (4.3)	24
^c Redline <i>et al.</i> , 1998 ⁵⁹	111	RDI 5–30 and absence of 'pathological sleepiness'	Moderate, I RDI 14.6 (9.8), C 11.8 (9.6)	Moderate, I 10.4 (4.3), C 10.6 (5.6)	8
CPAP vs posture-related device					
<i>Crossover trials</i>					
Jokic <i>et al.</i> , 1999 ¹⁰⁸	14	AHI < 15 in the lateral position and AHI in the supine sleep position at least twice that in the lateral position	Severe, (supine) 63.8 (148.9), mild (lateral) 4.9 (SE 4.1)	Moderate, I 3 (SD 1.3)	2
^c Skinner <i>et al.</i> , 2004 ⁶⁰	14	AHI 10–60 and daytime symptoms of obstructive sleep apnoea	Moderate, 27 (12)	Moderate, I 1.9 (4.6)	4
^c Skinner <i>et al.</i> , 2004 ⁶¹	10	AHI 10–60 and mild to moderate OSAHS	Moderate, 29.4 (13.4)	Moderate, I 3.2 (SD 4.9)	4
CPAP vs dental devices					
<i>Parallel trials</i>					
^f Fleetham <i>et al.</i> , 2002 ¹⁰¹	101	AHI > 10	Severe, I 37.6 (22.8), C 38.7 (22.2)	Moderate, I 12.8 (4.1), C 11.1 (4.9)	12
^a Hoekema <i>et al.</i> , 2006 ¹⁰²	103	Adults with a diagnosis of OSAHS	NR	NR	8
^a Lam <i>et al.</i> , 2007 ⁷⁰	101	AHI 5–40 or AHI 5–20 along with ESS > 9	Moderate, I 23.8 (11.1), C 20.9 (9.9)	Moderate, I 12 (5.8), C 12 (5.8)	10

continued

TABLE 1 Characteristics of included studies

Study details	Number randomised (N)	Target population	Disease severity [AHI, mean (SD)]	Severity of sleepiness, [ESS, mean (SD)]	Treatment duration (weeks)
<i>Crossover trials</i>					
Barnes <i>et al.</i> , 2004 ⁸²	114	AHI 5–30	Moderate, 21.3 (13.6)	Moderate, 10.7 (6.5)	12
^a Cibele <i>et al.</i> , 2006 ⁷² Abstract	13	AHI ≥20	Severe, 45.5 (SD 28)	Moderate, 10.6 (SD 4)	4
Ferguson <i>et al.</i> , 1996 ⁸¹	27	AHI 15–50	Moderate, 24.5 (8.8)	NR	16
Engleman <i>et al.</i> , 2002 ¹⁰³	51	AHI ≥5 and two or more symptoms of OSAHS, including sleepiness (ESS ≥8 or sleepiness while driving)	Severe, 31 (26)	Moderate, 14 (4)	8
Ferguson <i>et al.</i> , 1997 ⁸⁰	24	AHI 15–55	Moderate, 26.8 (11.9)	Moderate, 10.3 (3.1), C 11.0 (3.8)	16
L' Estrange <i>et al.</i> , 1999, ¹⁰⁴ Abstract	15	AHI > 50	Severe, 63.7 (10)	Moderate, 17.2 (3.8)	8
^f Olson <i>et al.</i> , 2002 ¹⁰⁷	24	AHI > 15 and AI > 5 or AHI > 5 and AI > 15	NR	NR	6
Randerath <i>et al.</i> , 2002 ¹⁰⁵	20	AHI 5–30 and clinical symptoms of OSAHS	Moderate, 17.5 (7.7)	NR	6
Tan <i>et al.</i> , 2002 ¹⁰⁶	24	AHI < 50	Moderate, 22.2 (9.6)	Moderate, 13.4 (4.6)	8
AHI, apnoea–hypopnoea index; AI, Arousal Index ; C, Comparator; ESS, Epworth Sleepiness Scale; I, Intervention (CPAP); IQR, interquartile range; NR, not reported; OSAHS, obstructive sleep apnoea–hypopnoea syndrome; RDI, respiratory disturbance index.					
^a Additional data since the review by Giles <i>et al.</i> ⁵⁰					
^b Data reported for first arm of crossover only.					
^c New data due to different inclusion criteria.					
^d Partial crossover, first arm data extracted only.					
^e 5th–95th centile.					
^f unpublished data obtained from the systematic review by Giles <i>et al.</i> ⁵⁰					

Full details of the quality assessment are presented in Appendix 3. Eighteen of 48 studies reported an adequate method of random sequence generation. The majority of studies did not report, or reported suboptimal methods of allocation concealment, with five studies reporting adequate allocation concealment, defined according to Cochrane criteria.^{62,77,87,95,109} As a consequence of the comparators used, only the 18 studies using sham CPAP were double-blinded; other comparators are visibly different and cannot therefore be double-blinded. Fourteen studies reported that participants were CPAP naïve; of these, 11 studies used sham CPAP as a comparator. It was unclear in the remaining studies using sham CPAP whether participants were CPAP naïve. ITT analysis was defined as all randomised patients included in the analysis within the treatment group to which

they were randomised. Although a number of studies described themselves as being ITT, only four studies^{61,82,87,106} used ITT analysis according to this criterion. The majority of studies reported loss to follow-up; with the exception of a few studies^{82,85,89,97,99,104,109} this was low (< 20%), with little difference between treatment arms. Of the 26 crossover studies included in the review, 19 reported an appropriate analysis using paired data. Fifteen studies evaluated the possibility of carryover effects, with four studies^{89,90,92,93} reporting carryover effects in primary or secondary outcomes.

Assessment of effectiveness

The primary outcomes of interest for clinical effectiveness were subjective daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS)

and objective sleepiness as assessed by the Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT) or Osler test.

Epworth Sleepiness Scale CPAP versus placebo or conservative/usual care

Data were available for the ESS from 23 trials (1334 participants). When all the studies were pooled there was a statistically significant benefit with CPAP compared with placebo/usual care for daytime sleepiness as measured by the ESS (MD -2.7, 95% CI -3.5 to -2.0). However, heterogeneity

was high ($I^2 = 71\%$) and this treatment effect is unlikely to be generalisable. The heterogeneity was investigated using subgroup analysis.

Clinical subgroup analyses

When studies were grouped by severity of daytime sleepiness at baseline (mild, moderate or severe, as defined by the ESS), heterogeneity was reduced. Although there was still evidence of moderate heterogeneity within the subgroups, with the exception of two studies, the direction of the effect was consistently in favour of CPAP (Figure 2). There was a statistically significant improvement

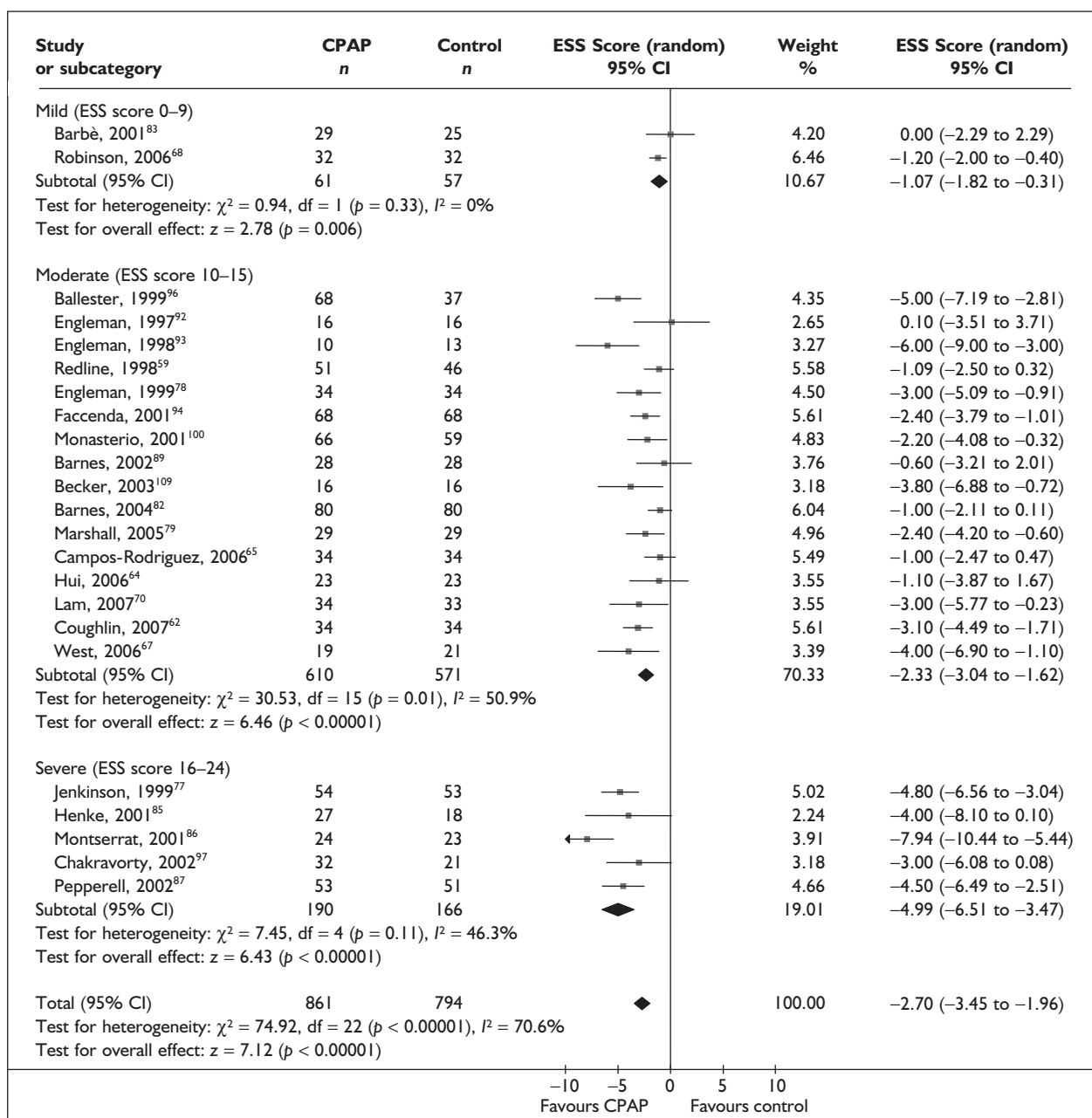


FIGURE 2 Epworth Sleepiness Scale (CPAP versus placebo/usual care), stratified by severity of sleepiness at baseline (ESS).

in symptoms of daytime sleepiness with CPAP treatment compared with placebo or usual care for all levels of disease severity. The improvement was greatest in trials in which baseline sleepiness was severe (MD -5.0, 95% CI -6.5 to -3.5) and was consecutively smaller with moderate (MD -2.3, 95% CI -3.0 to -1.6) and mild severity (MD -1.1, 95% CI -1.8 to -0.3). The estimate of treatment effect for studies of mild sleepiness at baseline is based on only two studies, one which reported no difference between CPAP and placebo and one which reported a small but statistically significant improvement in favour of CPAP.

When studies were grouped by disease severity (AHI) at baseline there was a statistically significant improvement in daytime sleepiness with CPAP compared with placebo or usual care in trials of severe and moderate disease populations but not mild disease (Figure 3). As with the subgroup analysis based on ESS, the treatment effect was largest in the severe disease population and the treatment effect was consecutively smaller with moderate and mild disease. There was moderate to high statistical heterogeneity in the subgroup analyses of trials of severe ($I^2 = 71\%$) and moderate ($I^2 = 65\%$) disease. Only three trials were available

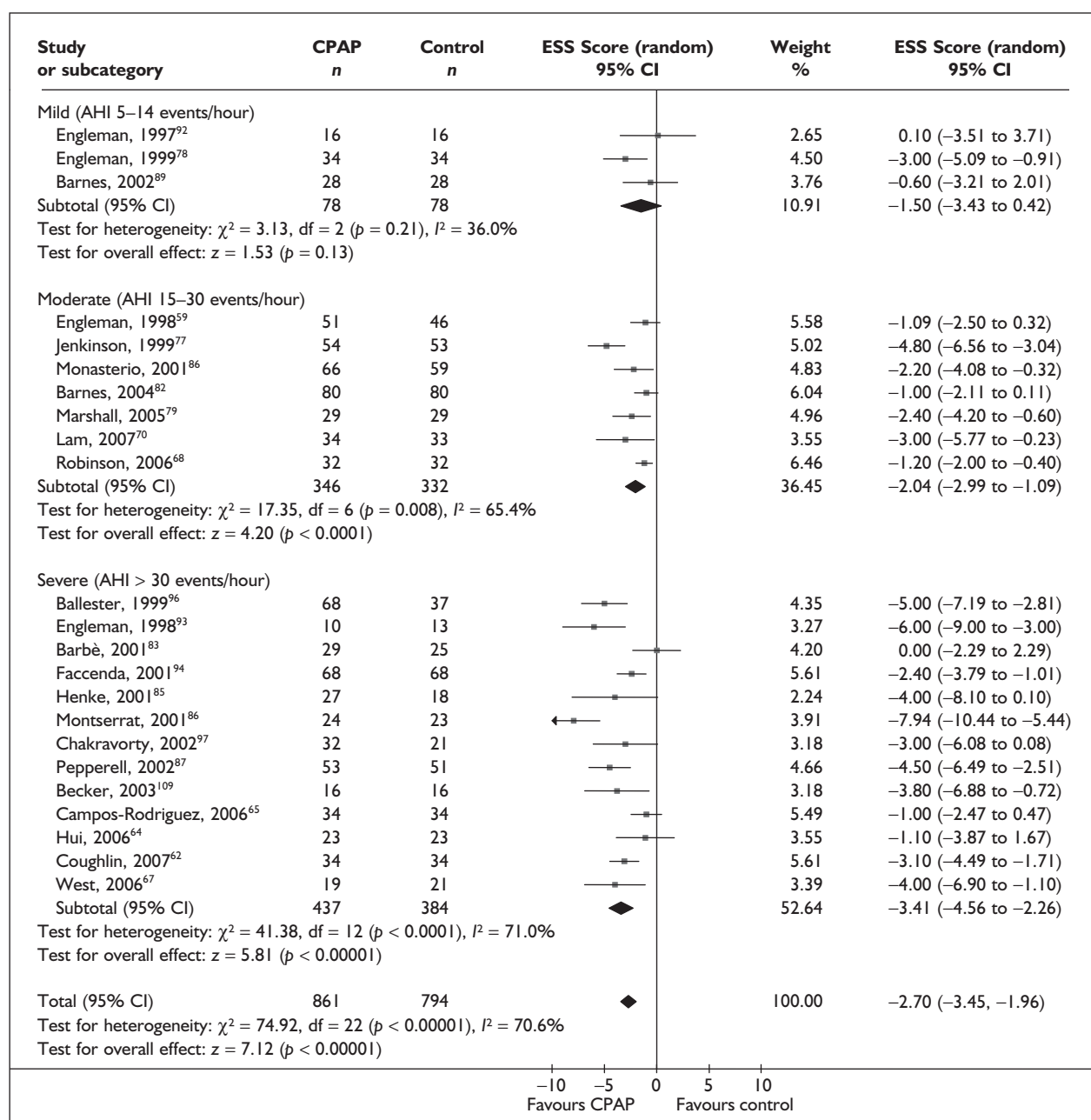


FIGURE 3 Epworth Sleepiness Scale (CPAP versus placebo/usual care), stratified by disease severity at baseline (AHI or oxygen desaturation dip rate).

for the analysis of mild disease and there was low statistical heterogeneity.

Other subgroup analyses

The variation in treatment effect with study design (parallel and crossover trials), type of data (end point and change scores) and comparator (sham CPAP, oral placebo and conservative/usual care) was also investigated. Each subgroup analysis was conducted for the whole data set. There was a statistically significant improvement in symptoms of daytime sleepiness (ESS) with CPAP over the comparator in each of the subgroups investigated and the treatment effects in the subgroups were consistent with each other, i.e. the 95% confidence intervals overlapped (see Appendix 4, Table 41).

Four of the five studies that reported an adequate method of concealment of allocation reported ESS as an outcome.^{62,77,87,109} When these four studies were pooled, the treatment effect was consistent with the treatment effect from the overall analysis (MD -3.5, 95% CI -4.5 to -2.5). There was no statistical heterogeneity ($I^2 = 0\%$).

Further subgroup analyses were conducted on the subset of studies using sham CPAP as a comparator on a *post hoc* basis. Blinding of participants is particularly useful in reducing bias when subjective outcome measures such as ESS are being used. Participant blinding was possible only in the studies in which a sham CPAP was used as the comparator. Effectively, sham CPAP provides the best placebo. Therefore, further subgroup analysis was conducted on the subset of studies using sham or placebo CPAP. Studies comparing CPAP with sham CPAP were grouped by mean symptom severity at baseline (ESS) and disease severity at baseline (AHI). There was a high degree of statistical heterogeneity ($I^2 > 75\%$) in the analyses based on the mean AHI at baseline and the treatment effect is unlikely to be generalisable. When the 12 studies of CPAP versus sham CPAP were grouped based on baseline ESS the findings were similar to the subgroup analysis of symptom severity conducted on the complete data set (CPAP versus oral placebo, sham placebo and usual care) (see Appendix 4, Figure 21). The benefit of CPAP was largest in the trials in which mean baseline sleepiness was severe (MD -5.4, 95% CI -7.0 to -3.7, $I^2 = 46\%$) and was consecutively smaller in trials of moderate (MD -2.4, 95% CI -3.4 to -1.4, $I^2 = 31\%$) and mild (MD -1.1, 95% CI -1.8 to -0.3, $I^2 = 0\%$) daytime sleepiness at baseline. Statistical heterogeneity within subgroups was low to moderate.

Sensitivity analyses

The effect of removing individual trials from the meta-analyses in which studies were subgrouped by mean baseline severity of sleepiness was investigated. The removal of individual studies resulted in only minor variations in the size of treatment effect in the severe and moderate subjective sleepiness at baseline subgroups and the difference between CPAP and control remained statistically significant (see Appendix 4, Table 42).

Using a fixed-effect model rather than a random-effects model did not result in any substantive changes to the results (see Appendix 4, Table 41).

CPAP versus dental devices

Data were available for the ESS from six trials ($n = 337$). All of these trials comprised populations with moderate daytime sleepiness (ESS) at baseline. There was no statistically significant difference in the impact on daytime sleepiness (ESS) between CPAP and dental devices (MD -0.9, 95% CI -2.1 to 0.4) (Figure 4). There was evidence of moderate statistical heterogeneity ($I^2 = 60\%$) and the treatment effect ranged from MD -4.0 in favour of CPAP to a small treatment effect in favour of dental devices (MD 0.4).

Clinical subgroup analyses

When studies were subgrouped on the basis of baseline disease severity (AHI), the findings were not substantially altered, although this analysis was limited by the small number of studies in the severe disease category and no studies in the mild group. There was no statistically significant difference between CPAP and dental devices in either the severe or moderate disease subgroup (see Appendix 4, Table 43). The treatment effects in the severe and moderate disease severity subgroups were consistent with each other, i.e. the 95% confidence intervals overlapped. The two trials of patients with severe disease were contradictory: one reported a statistically significant mean improvement of 4 points on the ESS (95% CI -6.3 to -1.7) with CPAP compared with dental devices and the other trial reported no statistically significant difference (MD 0.4, 95% CI -1.6 to 2.0).

Other subgroup analyses

The findings were similar within the subgroups of crossover and parallel trials, although these analyses were limited by the small number of trials. There was no statistically significant difference between CPAP and dental devices in either the crossover or parallel subgroup (see Appendix 4, Table 43).

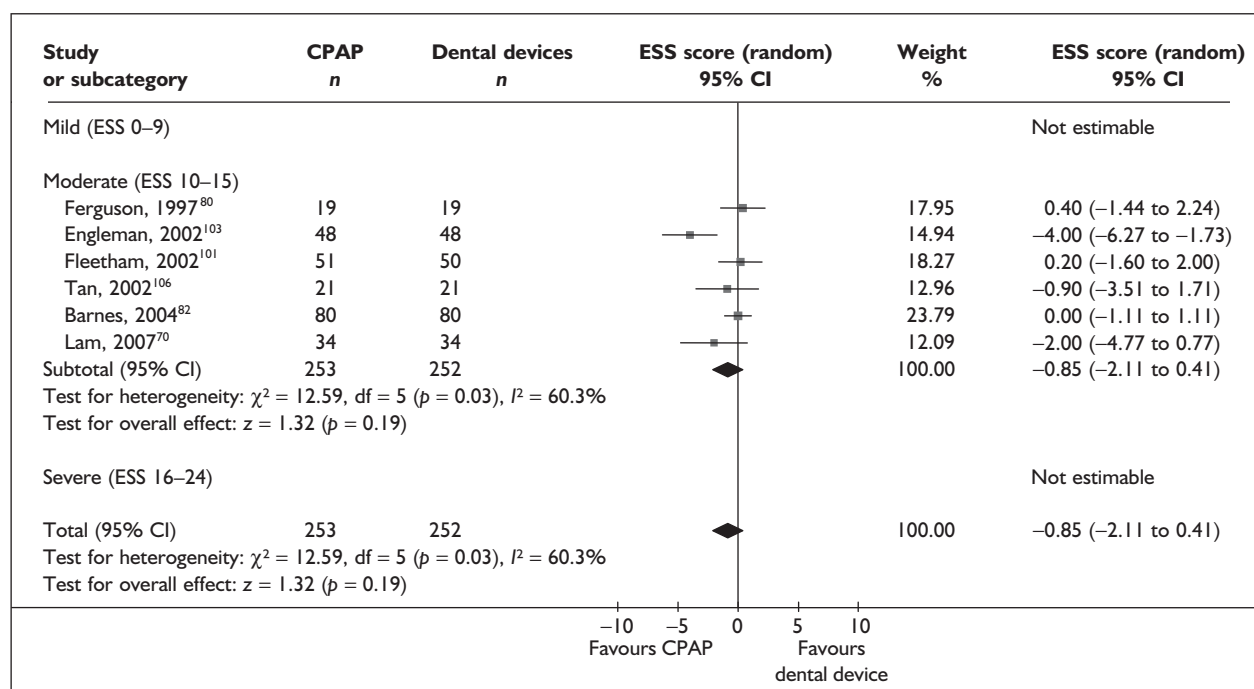


FIGURE 4 Epworth Sleepiness Scale (CPAP versus dental devices), stratified by severity of sleepiness at baseline (ESS).

Sensitivity analyses

The effect of removing individual trials from the meta-analysis of the whole data set was investigated. The removal of individual studies did not substantially alter the findings; the pooled effect size ranged from –0.1 to –1.2 and the effect remained not statistically significant (see Appendix 4, Table 44). The removal of one study that used two different dental devices dramatically reduced the statistical heterogeneity.¹⁰³ The use of a fixed-effect model did not substantially alter the findings (see Appendix 4, Table 43).

We conducted a *post hoc* sensitivity analysis to investigate the impact on the treatment effect of removing studies from the analysis that used a one-piece dental device,^{70,103,106} which is generally viewed as inferior to a two-piece adjustable device. The findings were not substantially altered, although the effect size moved in favour of dental devices (MD 0.13, 95% CI –0.71 to 0.97). When the two studies that specifically reported using incremental mandibular advancement with a two-piece device^{80,82} were pooled, the findings were not substantially altered (MD 0.11, 95% CI –0.84 to 1.06), although the effect size moved in favour of dental devices.

CPAP versus postural therapy

Data were available for the ESS from three small crossover trials (*n* = 36),^{60,61,108} the studies were not pooled for an overall treatment effect because of

differences in the comparators used. Symptom severity was moderate in all three trial populations. No statistically significant differences were found between CPAP and postural therapy (consisting of a backpack with a soft ball inside) on the ESS in patients with positional OSAHS (i.e. AHI while sleeping on the back was two or more times the AHI during sleep in the lateral position) (MD –1.5 (95% CI –2.9 to 0.8)). Similarly, there was no statistically significant difference between CPAP and a shoulder–head elevation pillow (*p* = 0.69 for difference in change)⁶⁰ or a cervicomandibular support collar⁶¹ (*p* = 0.22 for difference in change) on the Scottish National Sleep Survey Questionnaire. Only overall baseline ESS scores were reported for the last two studies so change scores and the corresponding mean difference could not be calculated.

Maintenance of Wakefulness Test

CPAP versus placebo or conservative/usual care

Outcome data were available from five studies (*n* = 287) on the MWT. One of these studies used the Osler test.⁶⁷ There was a benefit with CPAP compared with placebo/usual care in the length of time participants could stay awake in a setting conducive to sleep (MD 3.3 minutes, 95% CI 1.3–5.3) and this was statistically significant (Figure 5). Statistical heterogeneity was low (*I*² = 11%) and the treatment effect was consistently in favour of CPAP being beneficial.

Clinical subgroup analyses

The subgroup analysis by severity of daytime sleepiness at baseline (ESS) was limited by only one study being available in the severe symptom severity group and none being available in the mild group. When studies were subgrouped there was a statistically significant improvement with CPAP compared with control in the single severe study (MD 6.5 minutes, 95% CI 2.6–10.4) and the moderate subgroup (MD 2.3 minutes, 95% CI 0.4–4.3) (see Figure 5). The benefit was greatest in the study in which symptoms were severe at baseline. The subgroup analysis by baseline disease severity (AHI) was limited by having only a single study in the mild and severe disease groups. The difference between CPAP and control was not statistically significant for the single studies of mild and severe daytime sleepiness at baseline. The treatment benefit was greatest with moderate disease and the difference between CPAP and control was statistically significant, although this analysis was limited by the small number of studies available (see Appendix 4, Table 45).

Other subgroup analyses

The variation in treatment effect with study design (parallel and crossover trials) was also investigated. In both subgroups there was a

statistically significant benefit with CPAP compared with control. The treatment effect from the pooled crossover trials was smaller than that from parallel trials, although the 95% confidence intervals overlapped (see Appendix 4, Table 45).

Sensitivity analyses

The effect of removing individual trials from the meta-analysis was investigated. The statistically significant benefit of CPAP over placebo/usual care remained when individual studies were removed from the pooled analysis although the effect size ranged from 2.3 to 4.4 (see Appendix 4, Table 46). Using a fixed-effect rather than a random-effects model did not lead to any substantive changes to the results (see Appendix 4, Table 45).

CPAP versus dental devices

Data were available from two crossover trials ($n = 128$) on the MWT (Figure 6). In both studies baseline severity of daytime sleepiness (ESS) was classified as moderate. Neither study showed a statistically significant difference between CPAP and dental devices in the length of time participants could stay awake in a setting conducive to sleep (MD 0.7 minutes, 95% CI –1.6 to 2.9). The studies reported consistent findings.

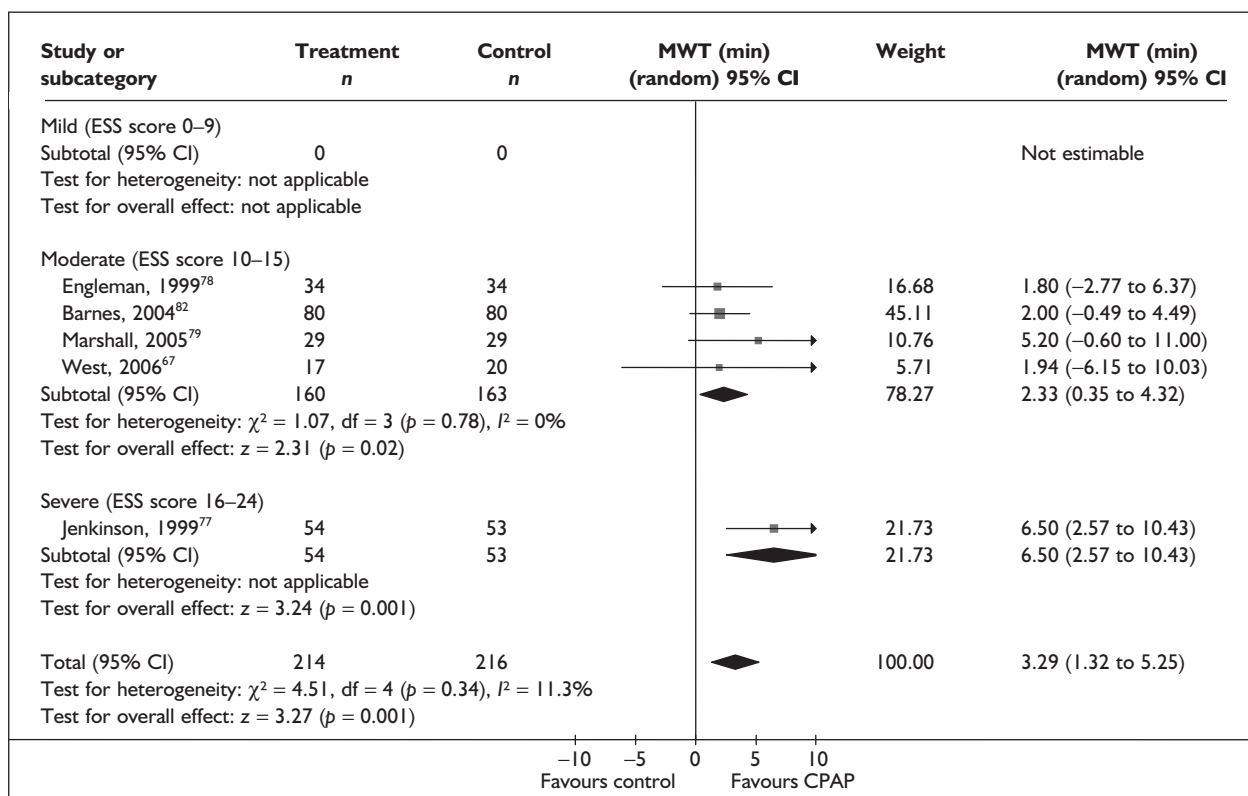


FIGURE 5 Maintenance of Wakefulness Test (CPAP versus placebo), stratified by severity of sleepiness at baseline (ESS).

CPAP versus postural therapy

Data were available for the MWT from one small crossover trial¹⁰⁸ ($n = 13$). There was no statistically significant difference between CPAP and postural therapy in the length of time participants could stay awake (MD 1.7 minutes, 95% CI -1.9 to 5.3, $p = 0.32$).

Multiple Sleep Latency Test

CPAP versus placebo or conservative/usual care

Outcome data were available from seven trials on the MSLT ($n = 331$). There was no statistically significant difference between CPAP and placebo/usual care in the length of time it took participants to fall asleep in surroundings conducive to sleep (MD 0.6 minutes, CI -0.7 to 1.9). There was evidence of moderate heterogeneity ($I^2 = 46\%$) (Figure 7).

Clinical subgroup analyses

The subgroup analysis by severity of daytime sleepiness at baseline (ESS) was limited by only one study being available in the severe and mild symptom severity groups and because one study could not be classified (see Figure 7). There was no statistically significant difference between CPAP and control in the one trial of severe disease severity (MD -6.1, 95% CI -27.3 to 15.1) and the direction of the treatment effect favoured the control group. There was no statistically significant difference between CPAP and control in the moderate subgroup (MD 0.2, 95% CI -1.8 to 2.2) or in the single trial of mild symptom severity (MD 2.0, 95% CI -0.8 to 4.8). When studies were subgrouped by baseline disease severity (AHI) there was a statistically significant benefit with CPAP compared with placebo/usual care for studies of a severe disease population (MD 2.3, 95% CI 0.9-3.7, $I^2 = 0\%$) but not for those with mild- or moderate-severity disease (see Appendix 4, Table 47).

Other subgroup analyses

The pooled treatment effects estimated by crossover and parallel trials separately were similar; there was no statistically significant difference between CPAP and control in either subgroup (see Appendix 4, Table 47).

Sensitivity analyses

The effect of removing individual trials from the meta-analysis was investigated. When the Monasterio *et al.* trial¹⁰⁰ was removed from the pooling, there was a statistically significant benefit in favour of CPAP (MD 1.2, 95% CI 0.0-2.4). Removing the other individual studies from the pooling did not change the overall result and the finding of no statistically significant difference between CPAP and control remained; the effect size ranged from 0 to 0.9 minutes when the individual studies were removed (see Appendix 4, Table 48). Using a fixed-effect rather than a random-effects model did not lead to any substantive changes to the results (see Appendix 4, Table 47).

CPAP versus dental devices

No data were available for the MSLT.

CPAP versus postural therapy

No data were available for the MSLT.

Summary of sleepiness outcomes

CPAP compared with control

The primary outcome of interest in the review was subjective sleepiness. Data were available on the ESS from 23 trials. Overall, CPAP reduced daytime sleepiness by a small amount compared with control; the effect probably varies among different groups of people. The average reduction on the ESS was 2.7 points, but might be anywhere between 2.0 and 3.5 points. There was considerable variation or inconsistency in the treatment effect (statistical heterogeneity); therefore some caution

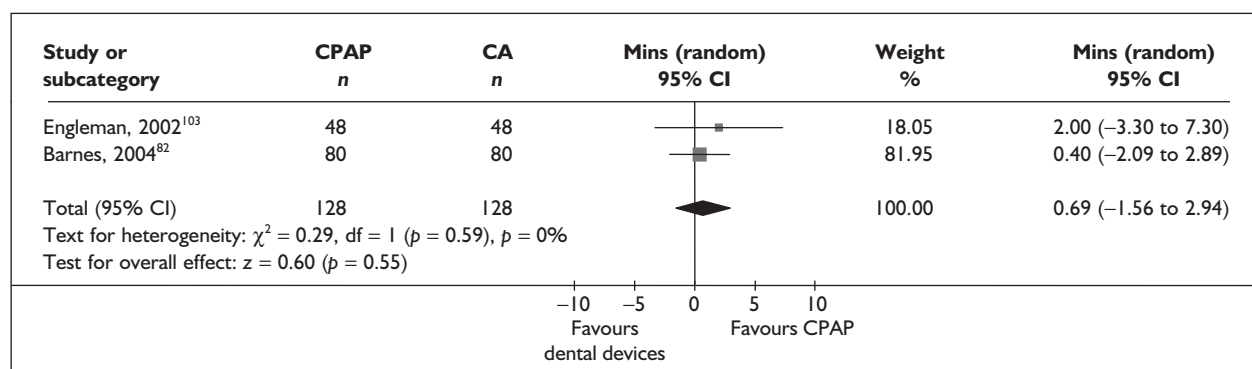


FIGURE 6 Maintenance of Wakefulness Test (CPAP versus dental devices).

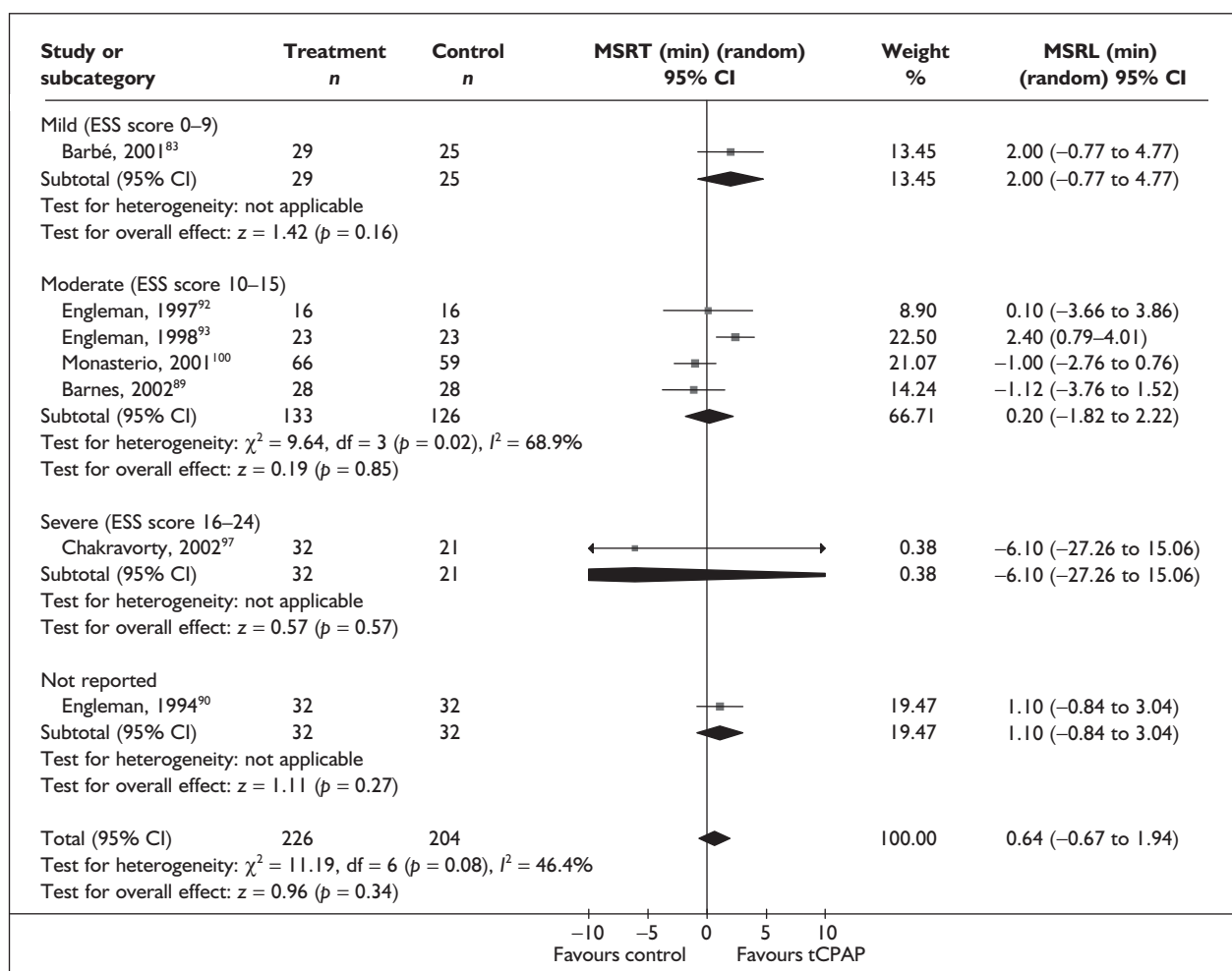


FIGURE 7 Multiple Sleep Latency Test (CPAP versus placebo), stratified by severity of sleepiness at baseline (ESS).

is needed in applying this result to all populations. Variation was reduced when studies were grouped based on baseline symptom severity and there was a trend towards a greater treatment effect with greater baseline symptom severity. It is not surprising that there would be less of a difference between CPAP and control in a population that reports only mild sleepiness at baseline.

In a severely symptomatic population the average reduction on the ESS was 5 points, but might be anywhere between 3.5 and 6.6 points; in a moderate symptom severity population the average reduction was 2.3 points, but might be anywhere between 1.6 and 3.0 points; and in mild severity the average reduction was 1.1 points, but might range anywhere between 0.3 and 1.8 points. When studies were subgrouped by disease severity at baseline, as measured by the AHI, there was a broadly similar trend. Although the definitions of disease and symptom severity used were based on current guidelines, these are arbitrary

definitions and interpretation of the results for these subgroups needs to be carried out with that in mind.

The benefit with CPAP compared with control was robust across all the methodological subgroup analyses (trial design, type of data, comparator, quality) and sensitivity analyses investigating the influence of individual trials and use of a fixed-effect model.

Objective sleepiness was assessed using the MWT and MSRT. Data from the MWT were available from five trials. The length of time participants could stay awake in surroundings conducive to sleep as measured by the MWT was greater with CPAP compared with control. The average reduction in sleep latency with CPAP than with control was 3.3 minutes, but might be anywhere between 1.3 and 5.3 minutes. There was a trend towards a greater treatment effect with greater symptom severity, although this analysis was

limited by the availability of only one study of a severe symptom severity population and none of a mild population. The benefit with CPAP compared with control was robust across the methodological subgroup analysis (trial design) and sensitivity analyses investigating the influence of individual trials and use of a fixed-effect model. The investigation of methodological factors was limited by the small number of trials available. There was no statistically significant difference between CPAP and control in how quickly participants could fall asleep in surroundings conducive to sleep when seven trials were pooled (MSLT).

CPAP compared with dental devices

Data were available from six trials. In a population with moderate daytime sleepiness at baseline, there was no statistically significant difference between CPAP and dental devices in the impact on daytime sleepiness. The treatment effect probably varies among different groups of people. The average effect was a reduction in sleepiness of less than one ESS point (0.9) with CPAP compared with dental devices, but might be anywhere between an increase in sleepiness of about half a point (0.4) to a decrease in sleepiness of 2.1 points. There was moderate variation in the treatment effect (statistical heterogeneity); therefore some caution needs to be taken in generalising this to all populations. The finding of no statistically significant difference between CPAP and dental devices was robust across subgroup analysis by disease severity (AHI) and trial design and sensitivity analyses investigating the influence of individual trials and use of a fixed-effect model. The investigation of methodological factors was limited by the small number of trials available.

There was no statistically significant difference between CPAP and dental devices in length of time participants could stay awake in surroundings conducive to sleep as measured by the MWT, though this is based on only two studies. No data were available for the MSLT.

Daytime blood pressure

Daytime blood pressure was the primary blood pressure outcome of interest and these data are reported below. A brief summary of the effects of treatment on night-time and 24-hour blood pressure is given below and the full data are reported in Appendix 4.

Fifteen studies reported outcome data for daytime blood pressure (Table 2); 12 used ambulatory blood pressure monitoring (ABPM) over 24 hours^{56,63–65,68,}

^{82–84,87,89,91,94} and three used conventional clinic blood pressure monitoring.^{62,70,100} Data were reported in graphs only for two additional studies, from which it was not possible to obtain an accurate variance estimate.^{58,73} Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were reported. Where daytime blood pressure was reported, four studies reported SBP, DBP and MAP,^{62,64,84,91} four reported MAP only,^{65,68,70,87} and five reported SBP and DBP but not MAP.^{56,63,83,89,100} The proportion of hypertensive patients ranged from 15% to 100% and, where reported, antihypertensive medication remained unchanged throughout the studies.

CPAP versus placebo/usual care

Daytime mean arterial pressure (using ABPM)

Data were available on daytime MAP for six trials ($n = 309$). There was an improvement in daytime MAP with CPAP compared with placebo/usual care (MD -2.1 mmHg, 95% CI -4.3 to 0.0) and this was statistically significant (Figure 8). There was moderate statistical heterogeneity ($I^2 = 59\%$).

Clinical subgroup analyses There was some evidence of a variation in treatment effect with severity of sleepiness at baseline (ESS), but this analysis was limited by the small number of trials (see Figure 8); only one trial each of severe and moderate baseline sleepiness was available. The single trial of severely symptomatic patients showed the largest treatment effect in favour of CPAP (MD -4.2 mmHg, 95% CI -6.4 to -2.0) and the difference between CPAP and control was statistically significant (see Figure 8). The difference between CPAP and control was not statistically significant for the moderate subgroup (MD -3.4 mmHg, 95% CI -7.9 to 1.2); the one trial of mild disease severity also reported no statistically significant difference between CPAP and control (MD 1.1 mmHg, 95% CI -2.9 to 5.1) (see Figure 8). Therefore, the overall treatment effect appears to be dominated by the one trial of severely symptomatic patients. When studies were grouped by disease severity at baseline (AHI) the treatment effect was largest with severe disease and there was a statistically significant difference in favour of CPAP; however, only one trial was available of moderate disease and none of mild disease (see Appendix 4, Table 49).

Other subgroup analyses Studies were subgrouped based on whether they were crossover or parallel and whether end point or change data were used. This analysis was limited by four of the six trials being parallel trials using change data (see Appendix 4, Table 49). For the subgroup of parallel

TABLE 2 Summary of blood pressure data reported in included studies

Study details	Baseline daytime BP [mean (SD)]	% (n) patients hypertensive at baseline	How BP was measured	Ambulatory blood pressure monitoring (ABPM)									Conventional clinic BP			
				Daytime MAP	Daytime SBP	Daytime DBP	Night MAP	Night-time SBP	Night-time DBP	24-hour MAP	24-hour SBP	24-hour DBP	Morning MAP	Evening MAP		
CPAP vs sham CPAP																
Arias et al., 2005 ⁵⁶	SBP 127 (9), DBP 79 (5)		24-hour ABPM using oscillometric method; every 30 minutes 8 a.m.–11 p.m. and every 60 minutes 11 p.m.–8 a.m.; patients asked to be measured no later than 11 p.m. (end point data)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Arias et al., 2006 ⁶³	SBP 127 (9), DBP 79 (5)		24-hour ABPM using oscillometric method (end point data)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Barbé et al., 2001 ⁸³	CPAP: SBP 130 (11), DBP 82 (5); Control: SBP 127 (10), DBP 80 (10)		24-hour ABPM; at least 60 data points taken for each participant; daytime 8 a.m. to 11 p.m. (end point data)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Becker et al., 2003 ⁸⁴	CPAP: MAP 104 (16), SBP 140 (18), DBP 86 (16); Control: MAP 104 (12), SBP 141 (14), DBP 85 (12)	CPAP: 50% (n = 8); Control: 81% (n = 13); on medication or office BP ≥ 160 and/or 90 mmHg; BP medication unchanged	ABPM measured over 20 hours using 1-minute recordings; night-time BP calculated for hours in bed and on treatment and daytime BP for remaining 12 hours (change and end point data)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Campos-Rodriguez et al., 2006 ⁶⁵	CPAP: MAP 101 (11); Control: MAP 99 (10)	100% (> 140/90 mmHg in three independent measurements); BP medication unchanged	24-hour ABPM using 30-minute recordings (change and end point data)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

continued

TABLE 2 Summary of blood pressure data reported in included studies

Study details	Baseline daytime BP [mean (SD)]	% (n) patients hypertensive at baseline	How BP was measured	Ambulatory blood pressure monitoring (ABPM)								Conventional clinic BP			
				Daytime MAP	Daytime SBP	Daytime DBP	Night MAP	Night-time SBP	Night-time DBP	24-hour MAP	24-hour SBP	24-hour DBP	Morning MAP	Evening MAP	
Coughlin <i>et al.</i> , 2007 ⁶²		79% (n = 27) (resting BP of 140/90 mmHg)	Waking BP measured between 8 a.m. and 11 a.m. in supine position after 5-minute rest; recorded as mean of three measurements taken at 1-minute intervals using automatic oscillometric digital BP monitor (end point data)											✓ (MAP; SBP; DBP)	
Hui <i>et al.</i> , 2006 ⁶⁴	MAP 98 (11), SBP 128 (9), DBP 84 (9)	50% (n = 28) (BP > 140/90 on two occasions or using antihypertensive medication; medication unchanged)	24-hour ABPM as outpatients during normal activities; BP measured every 30 minutes for 48 hours and second 24 hours of data used; patients recorded time at which they went to bed and woke up to identify sleep and wake periods (change and end point data)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Pepperell <i>et al.</i> , 2002 ⁸⁷	CPAP: MAP 104 (10), Control: MAP 104 (11)	19% (n = 22) taking medication for hypertension	24-hour ABPM measured during normal daily activities (except driving); patients kept diary and pressed event monitor to identify sleep and wake periods (change data)	✓		✓			✓	✓	✓	✓	✓		
Robinson <i>et al.</i> , 2006 ⁶⁸	CPAP: MAP 106 (14); Control: MAP 109 (13)	100% (BP > 140/90 on 24-hour ABPM or taking hypertensive drugs); medication unchanged	24-hour ABPM measured during normal daily activities (except driving); patients kept diary and pressed event monitor to identify sleep and wake periods (change and end point data)	✓					✓		✓	✓	✓		

TABLE 2 Summary of blood pressure data reported in included studies

Study details	Baseline daytime BP [mean (SD)]	% (n) patients hypertensive at baseline	How BP was measured	Ambulatory blood pressure monitoring (ABPM)								Conventional clinic BP			
				Daytime MAP	Daytime SBP	Daytime DBP	Night MAP	Night-time SBP	Night-time DBP	24-hour MAP	24-hour SBP	24-hour DBP	Morning MAP	Evening MAP	
Monasterio et al., 2001 ¹⁰⁰	CPAP: SBP 126 (17), DBP 81 (12); Control: SBP 132 (17), DBP 84 (11)	NR	Office daytime arterial BP recorded (end point data)											✓ (SBP; DBP)	
CPAP vs dental devices															
Barnes et al., 2004 ⁸²	NR		See above				✓								
Lam et al., 2007 ⁷⁰	CPAP: See above; Dental device: SBP 127 (15), DBP 76 (12)		See above											✓	✓

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; NR, not reported; SBP, systolic blood pressure.

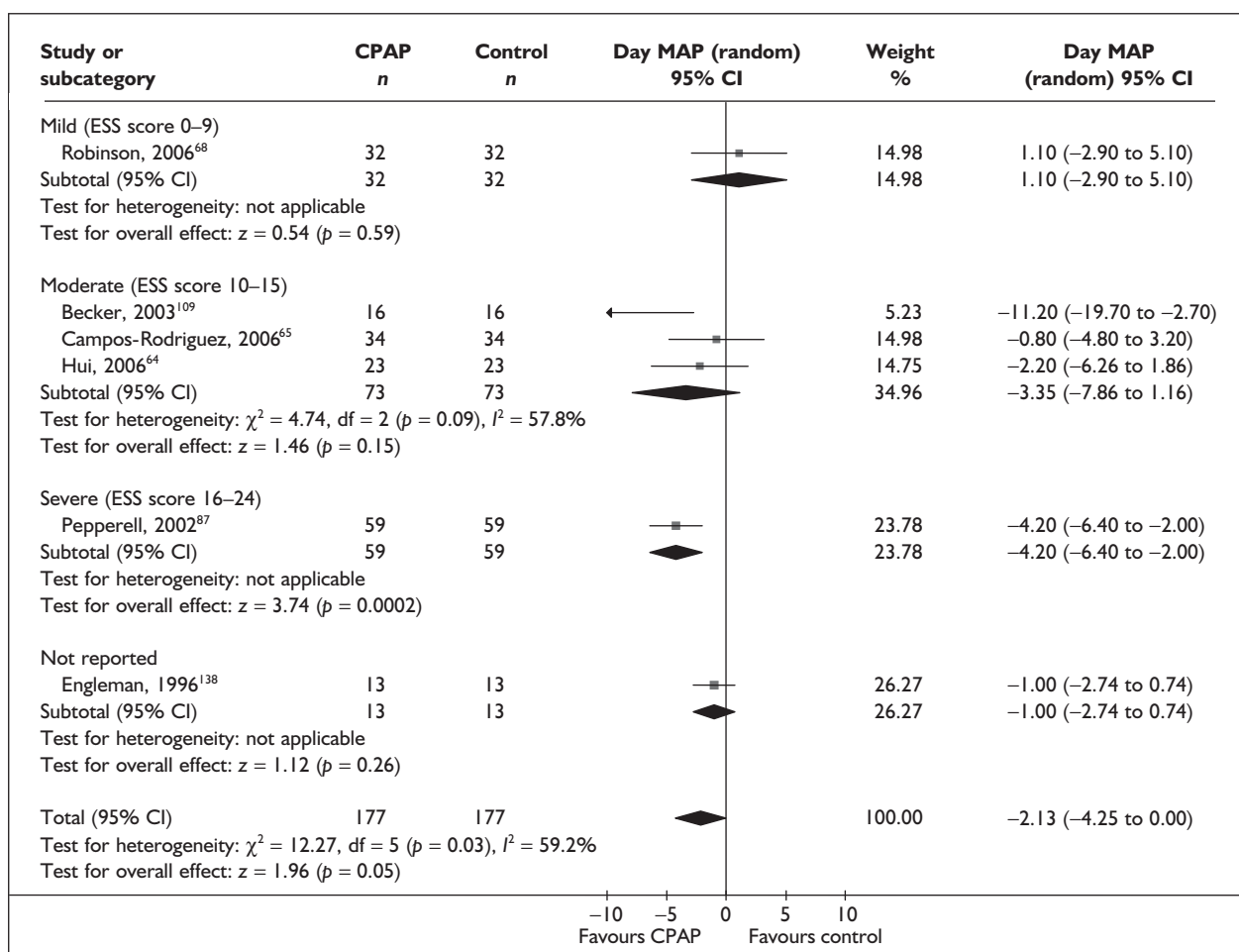


FIGURE 8 Daytime mean arterial pressure using ambulatory blood pressure monitoring (CPAP versus placebo/usual care), stratified by severity of sleepiness at baseline (ESS).

trials using change from baseline data there was a statistically significant improvement with CPAP compared with control. For the other two subgroups consisting of single studies there was no statistically significant difference between groups. The MAP treatment effect ranged from 1.1 mmHg to –3.5 mmHg (see Appendix 4, Table 49).

Sensitivity analyses When studies were individually removed from the analysis the treatment effect ranged from –1.4 mmHg to –2.7 mmHg and remained statistically significant in only one instance (see Appendix 4, Table 50). There was no substantial change in the MAP results using a fixed-effect model (see Appendix 4, Table 49).

Daytime systolic and diastolic blood pressure (using ABPM)

Data were available on daytime SBP and DBP from seven trials ($n = 220$). There was no statistically significant difference between CPAP and control for

SBP although there was a small decrease in SBP in favour of CPAP (MD –1.1 mmHg, 95% CI –3.4 to 1.2) (Figure 9). There was no evidence of statistical heterogeneity. Similarly, there was no statistically significant difference between CPAP and control for DBP although there was a small decrease in favour of CPAP (MD –1.2 mmHg, 95% CI –2.9 to 0.5); heterogeneity was low ($I^2 = 29\%$) (Figure 10).

Clinical subgroup analyses The mean baseline daytime sleepiness (ESS) was not reported for three trials^{56,63,91} and in the remaining trials the populations were classified as having symptoms of moderate severity at baseline. Therefore, it was not possible to explore the difference in treatment effect with different symptom severity at baseline for SBP or DBP. With the exception of one trial,⁸⁹ in which the population was classified as having disease of mild severity (AHI), the study populations were all classified as having severe disease. When the single mild disease severity

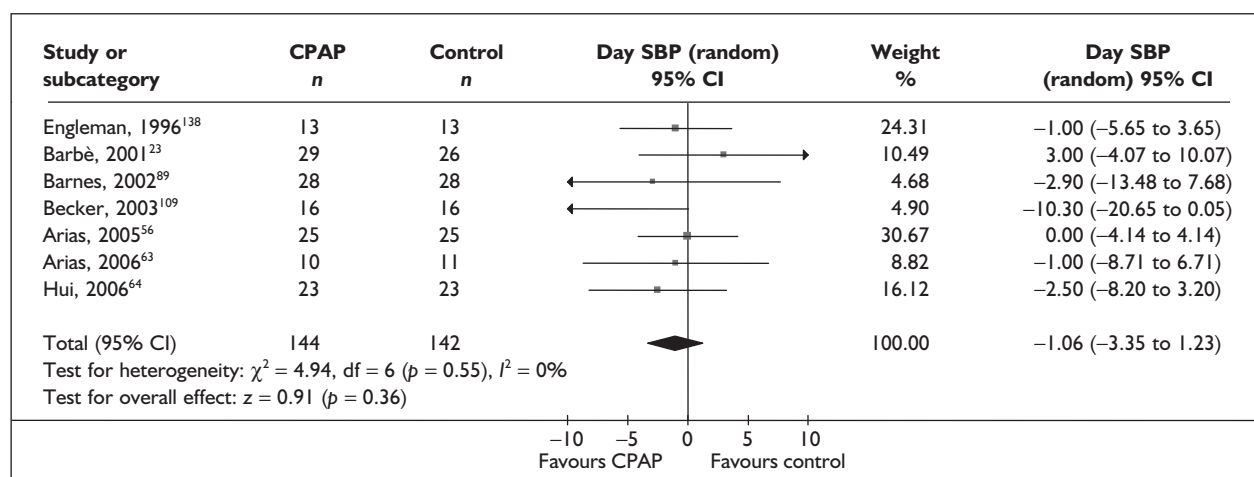


FIGURE 9 Daytime systolic blood pressure using ambulatory blood pressure monitoring (CPAP versus placebo/usual care).

(AHI) study was removed from the analyses for SBP and DBP, the difference between CPAP and control remained not statistically significant (see Appendix 4, Tables 51 and 52).

Other subgroup analyses The treatment effects in the crossover and parallel subgroups and the end point data and change data subgroups were consistent with each other, i.e. the 95% confidence intervals overlapped. The SBP treatment effect ranged from 1.2 for parallel trials using end point data to -5.2 for parallel trials using change from baseline data although the difference between CPAP and control was not statistically significant in any of the subgroups (see Appendix 4, Table 51). The DBP treatment effect ranged from 0.5 for parallel trials using end point data to -5.7 for parallel trials using change from baseline data although the difference between CPAP and control was not statistically

significant in any of the subgroups (see Appendix 4, Table 52). These analyses are limited by the small number of studies in each of the subgroups.

Sensitivity analyses The finding of no statistically significant difference between CPAP and control for SBP and DBP did not alter when a fixed-effect model was used. For DBP the treatment effect was smaller using a fixed-effect model and there was no substantial change for the SBP results using a fixed-effect model (see Appendix 4, Tables 51 and 52).

The SE for the MD in systolic and diastolic blood pressure for Arias *et al.* 2005⁵⁶ was imputed based on an estimated within-person correlation of 0.5. The meta-analyses were rerun using an SE based on an assumed within-person correlation of 0.1 and 0.9. For SBP this altered the treatment effect slightly but the finding of no statistically significant

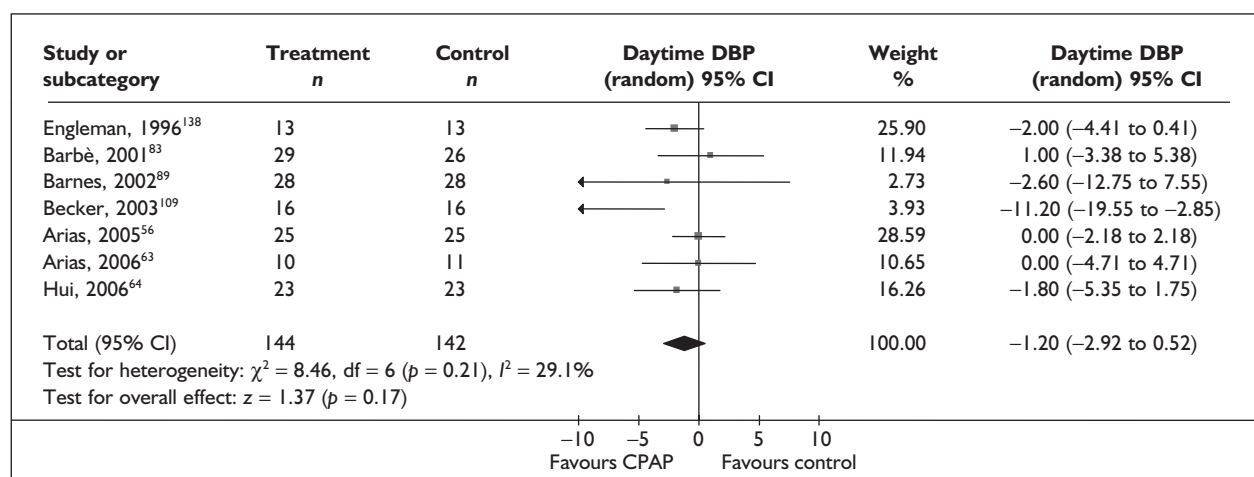


FIGURE 10 Daytime diastolic blood pressure using ambulatory blood pressure monitoring (CPAP versus placebo/usual care).

difference between CPAP and control did not change: assuming a within-patient correlation of 0.1 gave an SE of 2.75 for the study and the overall pooled treatment effect was -1.2 mmHg (95% CI -3.7 to 1.2); assuming a correlation of 0.9 gave an SE of 1.18 for the study and the overall pooled estimate was -0.6 mmHg (95% CI -2.4 to 1.1). Similarly, for DBP the treatment effect was slightly altered but the finding of no statistically significant difference between CPAP and control did not change: assuming a within-patient correlation of 0.1 gave an SE of 1.48 and the overall pooled treatment effect was -1.3 mmHg (95% CI -3.1 to 0.5); assuming a correlation of 0.9 gave an SE of 0.53 and the overall treatment effect was -1.1 mmHg (95% CI -2.7 to 0.6).

Conventional clinic blood pressure

Three studies ($n = 226$) used conventional or clinic daytime blood pressure: one study reported waking blood pressure recorded as the mean of three measurements taken at 1-minute intervals between 8 a.m and 11 a.m.;⁶² one study used a similar method to record morning (8–9 a.m.) and evening

(8–9 p.m.) blood pressure⁷⁰ and one provided very little information.¹⁰⁰ The populations in all three studies were classified as having moderate daytime sleepiness at baseline. There was an improvement in daytime SBP (MD -6.62 mmHg, 95% CI -9.48 to -3.76) and DBP (MD -3.47 mmHg, 95% CI -6.27 to -0.68) with CPAP compared with placebo/usual care and these were both statistically significant (Figures 11 and 12). Statistical heterogeneity was low ($I^2 = 0\%$ and 33% for SBP and DBP respectively).

CPAP versus dental devices

No studies were found that reported daytime ABPM. One study reported morning and evening blood pressure in a population with moderate sleepiness and moderate disease severity at baseline (see Table 2).⁷⁰ This study (a parallel trial, $n = 68$) found no statistically significant difference between CPAP and dental devices in terms of morning SBP (MD -2.9 mmHg, 95% CI -11.0 to 5.2), evening SBP (MD -4.9 mmHg, 95% CI -14.8 to 5.0), morning DBP (MD -1.6 mmHg, 95% CI -7.4 to 4.2) and evening DBP (MD -1.9 mmHg, 95% CI -7.6 to 3.8).

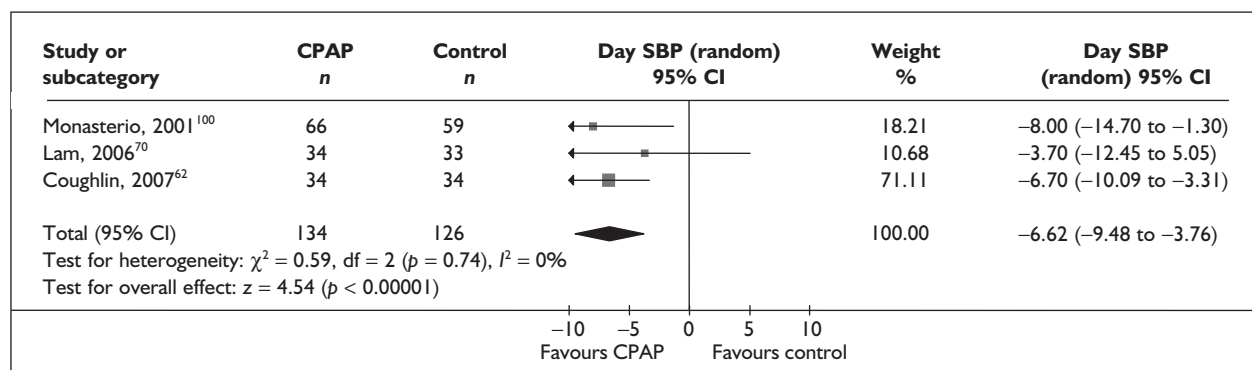


FIGURE 11 Daytime conventional systolic blood pressure (CPAP versus placebo/usual care).

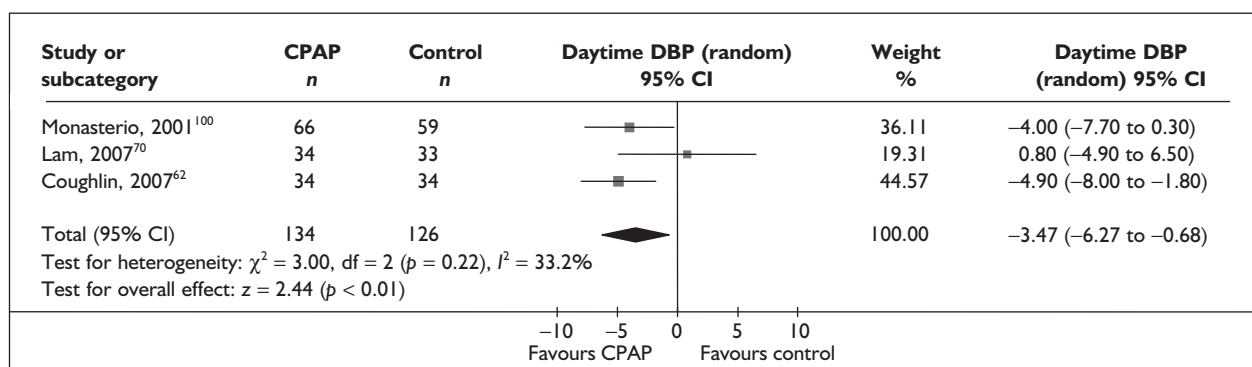


FIGURE 12 Daytime conventional diastolic blood pressure (CPAP versus placebo/usual care).

Night-time and 24-hour blood pressure CPAP versus placebo or conservative/usual care

Data were available on night-time MAP from six trials ($n = 309$).^{64,65,68,87,91,109} Overall, there was an improvement in night-time MAP with CPAP compared with placebo/usual care (MD -3.0 mmHg, 95% CI -4.7 to -1.4) and this was statistically significant. There was no statistical heterogeneity. The pooled treatment effects estimated by crossover and parallel trials and end point and change data separately were similar (see Appendix 4, *Figure 23*).

Data on SBP and DBP were available from seven trials ($n = 220$).^{56,63,64,83,89,109,138} There was no statistically significant difference between CPAP and control for night-time SBP (MD -2.9 mmHg, 95% CI -5.8 to 0.1) or DBP (MD -1.3 mmHg, 95% CI -3.2 to 0.7) (see Appendix 4, *Figures 24* and *25*).

Data on 24-hour blood pressure were available in one study that did not report daytime and night-time pressure separately (a crossover trial, $n = 68$ participants).⁹⁴ There was a statistically significant benefit with CPAP compared with oral placebo on 24-hour DBP (MD -1.5 mmHg, 95% CI -2.9 to -0.1); there was no statistically significant difference in 24-hour SBP (MD -1.3 mmHg, 95% CI -3.3 to 0.7); or 24-hour MAP (MD -1.0 mmHg, 95% CI -2.6 to 0.6).

CPAP versus dental devices

One study reported 24-hour blood pressure (crossover trial, $n = 80$) in a population with moderate symptom severity and moderate disease severity at baseline.⁸² There was no statistically significant difference between CPAP and dental devices for 24-hour SBP (MD 0.6 mmHg, 95% CI -2.5 to 3.7) or DBP (MD 0.4 mmHg, 95% CI -1.7 to 2.5).

Summary of blood pressure outcomes

Data were available from 15 trials. Studies using 24-hour ABPM were considered separately from those using conventional clinic-based measures. Daytime and night-time blood pressure were assessed separately as the mechanisms and patterns of daytime and night-time blood pressure disturbance in OSAHS vary and the relationship between daytime blood pressure and vascular risk has been more clearly described in the literature.

CPAP versus control

Six trials reported MAP using ABPM. There was a statistically significant reduction in MAP with CPAP compared with control; the size of the effect

probably varies among different groups of people. The average reduction in MAP was 2.1 mmHg, but might be anywhere between no reduction and 4.3 mmHg. There was moderate inconsistency in the treatment effect (statistical heterogeneity), but due to the small number of studies it was not possible to adequately investigate sources of this variation. Only one study was available of severely symptomatic patients and the overall treatment effect did seem to be dominated by this trial. There was no substantial change in the MAP results when a fixed-effect model was used as a sensitivity analysis. However, when individual studies were removed from the analysis the treatment effect remained statistically significant in only one instance, indicating a possible lack of statistical power due to the small number of participants.

There was no statistically significant difference between CPAP and control for SBP or DBP (measured using ABPM). The treatment effect probably varies among different groups of people. The average effect for SBP was a decrease of 1.1 mmHg with CPAP, but might be anywhere between a decrease of 3.4 mmHg and an increase of 1.2 mmHg compared with control. The average effect for DBP was a decrease of 1.2 mmHg with CPAP, but might be anywhere between a decrease of 2.9 mmHg and an increase of 0.5 mmHg compared with control. There was no inconsistency in the treatment effect (statistical heterogeneity). It was not possible to investigate whether the treatment effect varied with disease or symptom severity at baseline due to limitations in the data available. When a fixed-effect model was used, the findings were not substantially altered, except that the treatment effect for DBP was smaller. The pooling of three studies reporting conventional clinic blood pressure showed a large and statistically significant improvement in SBP and DBP with CPAP compared with control.

The results for night-time blood pressure were similar to those for daytime blood pressure. There was a statistically significant improvement in night-time MAP (using ABPM) but not SBP and DBP. The magnitude of the effects was broadly similar.

CPAP versus dental devices

Only one study was available that reported daytime blood pressure (morning and evening blood pressure using a conventional clinic method). This trial of a moderate symptom severity and moderate disease severity population found no statistically significant difference between CPAP and dental devices. Another trial that did not report daytime and night-time blood pressure separately reported

TABLE 3 Quality of life measures

Quality of life measure	Number of crossover trials	Number of parallel trials
CPAP versus placebo/usual care		
EuroQol and standard gamble		1 ⁹⁷
Functional Outcomes of Sleep Questionnaire (subscales)	3 ^{79,89,94}	1 ⁸⁶
Functional Outcomes of Sleep Questionnaire (total score)	3 ^{79,89,94}	3 ^{83,86,100}
Nottingham Health Profile	4 ^{78,90,92,93}	2 ^{96,100}
Sleep apnoea quality of life index		2 ^{67,70}
SF-36 (subscales)	3 ^{78,79,89}	3 ^{70,77,86}
SF-36 (physical and mental component summary or total score)	1 ⁸²	3 ^{77,83,86}
CPAP versus dental devices		
Functional Outcomes of Sleep Questionnaire	2 ^{82,103}	
Golombok Rust Inventory of Sexual Satisfaction		1 ^{102a}
Sleep apnoea quality of life index		3 ^{70,101,107}
SF-36 (subscales)		1 ⁷⁰
SF-36 (Physical and mental component summary or total score)	2 ^{82,103}	

a The data are published in Hoekema et al., 2006.¹¹¹

no statistically significant difference in 24-hour SBP and DBP between the two interventions.

Health-related quality of life

The most commonly used quality of life measures were the FOSQ, SF-36 and NHP (Table 3). The majority of studies in which quality of life was assessed were of populations with moderate symptom severity (ESS) at baseline.

CPAP versus placebo or usual care

SF-36

Six studies reported the SF-36 subscales. There were three crossover trials ($n = 91$), all of moderate baseline symptom severity (ESS)^{78,79,89} and three parallel trials ($n = 215$), two of severe symptoms^{77,86} and one moderate.⁷⁰ There was no statistically significant benefit with CPAP compared with control on any of the subscales of the SF-36 although for two of the scales (vitality and physical roles) there was a trend towards improvement with CPAP (see Table 4 for the overall effect and Appendix 4, Figure 26, for the forest plots). However, the pooled estimates are likely to have limited generalisability as there was moderate to high heterogeneity in the analyses for most of the subscales and specifically for the vitality and physical role subscales. For these two subscales, the findings encompassed two studies reporting a statistically significant improvement with CPAP^{77,78}

and the remaining studies reporting no statistically significant difference between CPAP and control (see Appendix 4, Figure 26).

The treatment effects in the crossover and parallel subgroups were consistent with each other, i.e. the 95% confidence intervals overlapped (see Appendix 4, Figure 26). For bodily pain, general health and physical function there was a statistically significant benefit with CPAP compared with control for the parallel trial subgroup but not the crossover subgroup. This may be driven by two of the parallel trials being of populations with severe baseline symptoms. There was a statistically significant difference between CPAP and control for the physical component summary score but not the mental component summary scores [three trials, one of mild and two of severe symptoms (ESS)] or the total score (one trial, moderate symptom severity) (see Appendix 4, Figure 26).

Functional Outcomes of Sleep Questionnaire (FOSQ)

Four trials reported the FOSQ subscales: three crossover trials ($n = 125$) of moderate symptom severity at baseline^{79,89,94} and one parallel trial ($n = 47$) of severe symptom severity.⁸⁶ There was a statistically significant benefit with CPAP compared with control for the activity level and social outcome subscales of the FOSQ (see Table 5 for the overall effect and Appendix 4, Figure 27, for the

TABLE 4 SF-36 subscales (CPAP versus placebo/usual care)

SF-36 Subscale (six trials)	Mean difference (95% CI)	Statistical heterogeneity (I^2)
Bodily pain	4.3 (-0.9 to 9.5)	48%
Emotional role	-0.4 (-12.3 to 11.5)	72%
General health	3.2 (-0.4 to 6.7)	0%
Mental health	2.2 (-2.2 to 6.7)	52%
Physical function	2.6 (-0.6 to 5.9)	8%
Physical role	6.9 (-3.8 to 17.5)	63%
Social function	1.9 (-4.4 to 8.1)	57%
Vitality	7.3 (-0.3 to 14.9)	77%

forest plots). Statistical heterogeneity was low for both of these subscales. Statistical heterogeneity was high for general productivity ($I^2 = 70%$): there was a statistically significant benefit with CPAP compared with control for the parallel trial of severe symptom severity population but not for the subgroup of crossover, moderate disease trials. For activity level and social outcome the statistically significant benefit with CPAP did not appear to be dominated by the parallel trial of severe symptom severity (see Appendix 4, Figure 27).

Nottingham Health Profile (NHP)

Data from the NHP were reported in six studies, four of which reported NHP Part 2 (all crossover trials, $n = 105$), three of moderate symptom severity^{78,92,93} and one unclassified⁹⁰. There was a statistically significant benefit with CPAP compared with placebo/usual care on the NHP Part 2 (MD -1.7, 95% CI -2.9 to -0.5) (see Appendix 4, Figure 28). There was no statistical heterogeneity. Monasterio *et al.*¹⁰⁰ did not specify which part of the NHP they used but the data presented suggest that it was probably Part 1. There was no statistically significant difference between CPAP

and conservative treatment on NHP Part 1 (total score) in this parallel trial of a moderate symptom severity population (MD 0.0, 95% CI -5.8 to 5.8). Ballester *et al.* reported the six domains from NHP Part 1 but not the total score.⁹⁶ There was a statistically significant difference between CPAP and conservative treatment on the energy ($p = 0.03$) and social isolation ($p < 0.005$) domains but not the emotional reactions, sleep, physical mobility or pain domains.

Sleep apnoea quality of life index (SAQLI)

Data were available on the SAQLI from two parallel trials, of moderate symptom severity populations. One study ($n = 67$) reported all the subscales⁷⁰ and the overall score and one reported the overall score only ($n = 41$).⁶⁷ There was a statistically significant improvement with CPAP compared with conservative treatment on the daily functioning, emotional and symptoms subscales but not for the social interaction subscale (see Appendix 4, Figure 29). For the total score (A–D subscales) one study showed a significant benefit with CPAP compared with conservative treatment and one showed no significant difference between CPAP and sham

TABLE 5 FOSQ subscales (CPAP versus placebo/usual care)

FOSQ subscale (number of trials)	Mean difference (95% CI)	Statistical heterogeneity (I^2)
Activity level ($n = 4$)	0.2 (0.0–0.3)	34%
General productivity ($n = 4$)	0.1 (-0.1 to 0.3)	70%
Intimacy and sexual activity ($n = 4$)	0.3 (-0.4 to 0.9)	0%
Social outcome ($n = 4$)	0.2 (0.0 to 0.4)	0%
Vigilance ($n = 4$)	0.2 (-0.1 to 0.5)	76%
Total score ($n = 6$)		51%

FOSQ, Functional Outcomes of Sleep Questionnaire.

CPAP (see Appendix 4, *Figure 29*). When change data from the latter study were used instead of end point data the difference between CPAP and sham CPAP was statistically significant and in favour of CPAP ($p = 0.05$). There was no baseline imbalance between groups.

EuroQol and standard gamble utility

One study was available of a severely symptomatic population ($n = 53$).⁹⁷ There was no difference between CPAP and conservative treatment in quality of life at follow-up, as measured by the EuroQol thermometer (0–100) (MD 2.0, 95% CI –8.1 to 12.1). The EuroQol-derived utility was 0.77 (SD 0.18) for CPAP versus 0.77 (SD 0.09) for conservative treatment. There was a 0.04 utility gain in the CPAP group and no change in the conservative treatment group, although the CPAP group started from a poorer baseline (EuroQol 0.73 versus 0.77 for CPAP and control respectively) and had more severe OSAHS at baseline (AHI 55 versus 35 for CPAP and control respectively).

CPAP versus dental devices

Data were available from a small number of studies comparing CPAP with dental devices. Where reported, the studies were all of moderate symptom severity populations at baseline.

Functional Outcomes of Sleep Questionnaire

Data from the FOSQ were available from two studies (crossover, $n = 128$) of populations with moderate symptom severity.^{82,103} When both studies were pooled there was no difference between CPAP and dental devices in terms of quality of life as measured by the FOSQ (MD –0.5, 95% CI –1.4 to 0.5). These two studies had contradictory findings: one showed a statistically significant benefit with CPAP compared with dental devices and one found no difference between the two treatments (see Appendix 4, *Figure 30*).

Sleep apnoea quality of life index

One study (parallel, $n = 68$) reported subscale scores for the SAQLI as well as a summed score for A–D and A–E subscales.⁷⁰ Unpublished data were available from Giles *et al.* for two studies for a summed score,^{101,107} although it was unclear whether this was for subscales A–D or A–E, therefore these studies were pooled separately (see Appendix 4, *Figure 31*). Based on the summed score for the last two studies there was no difference between CPAP and dental devices (see Appendix 4, *Figure 32*). For the summed score for A–D, CPAP showed a benefit over dental devices in the third study. However, when treatment-related

symptoms were included to calculate the total score for A–E for this study, CPAP no longer showed a benefit over dental devices (see Appendix 4, *Figure 32*).

SF-36

One study reported the physical and mental component summary scores for SF-36 (crossover, $n = 80$), one reported the total score (crossover, $n = 80$) and one reported the subscale scores (parallel, $n = 68$). One study (see Appendix 4, *Figure 33*) reported a benefit with CPAP compared with dental devices on both the physical and mental component summary scores.¹⁰³ In contrast, one study reported no difference between CPAP and dental devices on the total score.⁸² For one study there was a statistically significant benefit with CPAP compared with dental devices on the bodily pain subscale of SF-36 but not on any of the other subscales (see Appendix 4, *Figure 34*).⁷⁰

Golombok Rust Inventory of Sexual Satisfaction (GRISS)

This outcome was reported in two related papers^{102,111} The included male participants ($n = 38$) who were in a heterosexual relationship and had more erectile dysfunction and sexual dissatisfaction than age-matched controls. There was no difference between CPAP and dental devices on any of the subscales at follow-up (see Appendix 4, *Figure 35*).

CPAP versus postural therapy

Data were available from two small crossover trials ($n = 23$).^{60,61} The studies were not pooled for an overall treatment effect due to differences in the comparators used, i.e. a shoulder–head elevation pillow⁶⁰ and a cervicomandibular support collar.⁶¹

Functional Outcomes of Sleep Questionnaire

No statistically significant difference was found when CPAP was compared with either the shoulder–head elevation pillow ($p = 0.93$ for difference in change) or the cervicomandibular support collar ($p = 0.85$ for difference in change). Only overall baseline scores were reported so change scores and the corresponding mean difference could not be calculated.

SF-36

The physical and mental component summary scores for the SF-36 were reported. There was no statistically significant difference in the impact on the summary physical component score between CPAP and the shoulder–head elevation pillow ($p = 0.74$ for difference in change) or the

cervicomandibular support collar ($p = 0.18$ for difference in change). Similarly, there was no statistically significant difference in the impact on the summary mental component score between CPAP and the shoulder–head elevation pillow ($p = 0.31$ for difference in change) or the cervicomandibular support collar ($p = 0.19$ for difference in change). Only overall baseline scores were reported so change scores and the corresponding mean difference could not be calculated.

Summary of HRQoL outcomes

The majority of studies assessing quality of life were of populations with moderate symptom severity at baseline. A variety of disease-specific and generic measures were used and only those measures reported in two or more studies are summarised here. The findings for quality of life were somewhat contradictory, which may have been related to factors such as different outcome measures used, or differences in the study population or aspects of study design. Exploration of sources of heterogeneity was limited by the small number of trials.

CPAP versus control

Six studies reported the SF-36 subscales. There was no statistically significant difference between CPAP and control on any of the SF-36 subscales. There was moderate to high variation or inconsistency in the treatment effect (statistical heterogeneity) for most of the subscales, therefore some caution needs to be taken in generalising these findings to all populations receiving CPAP. Although the treatment effects from the crossover and parallel trial subgroup analysis were consistent with each other, in that their 95% confidence intervals overlapped, for bodily pain, general health and physical function there was a statistically significant benefit with CPAP compared with control for the parallel trials but not for the crossover trials. This may have been driven by two of the parallel trials being of severe symptom populations. In contrast, on the other generic scale, the NHP Part 2, there was a statistically significant benefit with CPAP compared with control based on a pooling of four studies. The treatment effect probably varies among different groups of people. The average effect was a reduction of 1.7 points with CPAP compared with control, but might fall anywhere between 0.5 and 2.9 points. There was no variation or inconsistency (statistical heterogeneity) in the treatment effect.

The findings from the disease-specific measures were also somewhat contradictory, although only

a small number of studies were available. On the FOSQ (four trials), a disease-specific measure, there was a statistically significant benefit with CPAP compared with control for the activity level and social outcome subscales but not for general productivity, intimacy and sexual activity, vigilance or total score. Only two studies reported the SAQLI total score; one reported a significant benefit with CPAP compared with control and for one there was no statistically significant difference.

CPAP versus dental devices

For the majority of the quality of outcome measures only single studies were available. There was no statistically significant difference between CPAP and dental devices when two studies reporting the FOSQ and two studies reporting the SAQLI were pooled. Three studies reported the SF-36 but all used different scores and the findings were not consistent.

Psychological outcomes

There were very few new data available on psychological outcomes following the review by Giles *et al.*⁵⁰ One additional publication was available which reported the Profile of Mood State (POMS) from a 1-week study by the Dimsdale group⁵⁸ and the Brief Symptom Inventory from a 2-week study by Norman *et al.*⁷³

CPAP versus placebo/usual care

General Health Questionnaire-28 (GHQ-28)

Three studies reported on the GHQ-28 (all crossover, $n = 74$) and these were pooled.^{90,92,93} There was no statistically significant difference between CPAP and placebo (MD -1.4 , 95% CI -4.1 to 1.4), although this estimate is of limited value as it was derived from only three studies, with moderate to high statistical heterogeneity ($I^2 = 70\%$) (see Appendix 4, Figure 36).

Hospital Anxiety and Depression Scale (HADS)

Five studies reported on the HADS and these were pooled (all crossover, $n = 134$).^{79,90,92,93,112} There was no statistically significant difference between CPAP and placebo for the anxiety (MD -0.3 , 95% CI -1.2 to 0.5) or the depression (MD -0.9 , 95% CI -1.9 to 0.1) subscales. There was moderate statistical heterogeneity in both analyses ($I^2 = 45\%$ and 62% respectively) (see Appendix 4, Figures 37 and 38).

Brief Symptom Inventory (BSI)

One study reported the BSI global severity index and the BSI depression subscale (parallel, $n = 24$).⁷³ The standard deviation was estimated for the former but, because data were only presented as a low-scale graph, it was not possible to estimate

the standard deviation for the depression subscale. There was no statistically significant difference between CPAP and sham CPAP at follow-up for the global symptom index of the BSI (See Appendix 4, *Figure 39*).

Profile of Mood State (POMS)

One study reported the POMS (parallel, $n = 34$).⁵⁸ There was no statistically significant difference between CPAP and placebo on any of the POMS subscales or the total score (see Appendix 4, *Figure 40*).

University of Wales Institute of Science and Technology Mood Adjective Checklist (UMACL)

Three studies reported the energetic arousal score from the UMACL and these were pooled (all crossover, $n = 73$).^{92,93,112} There was a statistically significant benefit in favour of CPAP compared with placebo (MD 1.7, 95% CI -0.0 to 3.3) (see Appendix 4, *Figure 41*). There was no statistical heterogeneity in this analysis.

CPAP versus dental devices

Hospital Anxiety and Depression Scale

One study reported the HADS (crossover, $n = 48$).¹⁰³ There was no statistically significant difference between CPAP and dental devices for the anxiety or depression subscales (see Appendix 4, *Figures 42 and 43*).

Summary of psychological outcomes

CPAP versus control

Data were available for three psychological outcome measures from two or more studies. There was no statistically significant difference between CPAP and control on the GHQ-28 or the HADS. There was a statistically significant benefit in favour of CPAP compared with control on the energetic arousal score from the UMACL. There was no inconsistency (statistical heterogeneity) in the treatment effect.

CPAP versus dental devices

There was no statistically significant difference between CPAP and dental devices in one trial reporting the HADS.

Cognitive outcomes

Eighteen trials used formal testing to measure the effects of CPAP on cognitive function in adults with obstructive sleep apnoea. Ten of the studies used a crossover design,^{72,78,79,82,89,90,92,93,103,108} while eight used a parallel group design.^{58,73,77,83,85,100,102,113} Six trials compared CPAP with sham CPAP,^{58,73,77,79,83,85} six trials with oral placebo,^{78,82,89,90,92,93} four trials

with dental devices,^{72,82,102,103} two trials with conservative treatment^{100,113} and one trial with postural therapy.¹⁰⁸ Most of the studies included small sample sizes (range 14–125), with three studies reporting on a subgroup of the original randomised population.^{77,113,114} Based on mean ESS score at baseline (where reported), the majority of trials were of reported moderate symptom severity populations, two trials were of severely symptomatic populations and one trial studied mild symptom severity. Based on mean baseline AHI, seven study populations were classified as having severe disease,^{58,73,83,85,93,103,108} seven as having moderate disease^{77,79,82,90,100,102,113} and three as having mild disease.^{78,89,92}

A total of 28 different cognitive tests were used, examining several areas of cognition (administered as verbal, pen-and-paper or computer-based tasks), making comparisons across trials difficult. The areas of functioning assessed were attention or vigilance, psychomotor function, construction, verbal fluency, IQ decrement, memory and learning (see *Table 12*). Seventeen tests were used by two trials or fewer; even when tests were used by multiple trials the scales used were not always uniform.

Testing protocols may have a confounding effect on performance; therefore assessment procedures were examined. Some variation between testing protocols existed (see Appendix 4, *Table 54*). Testing protocol issues include order of test presentation, which is a particular issue with test batteries containing many different types of test,¹¹⁵ and time of day when fluctuations in performance and levels of alertness can occur in response to circadian rhythms. In addition, performance may be improved by prior exposure to testing stimuli and procedures, which can have a significant beneficial impact on test performance when tests are administered on more than one occasion. Use of stimulants, such as nicotine and caffeine, can also modify cognitive performance, as can mood and depression. Therefore, ideally, testing protocols should employ measures to minimise risks of possible confounding, or account for potential biases in the analysis.

Nine trials administered a familiarisation session prior to baseline assessment,^{78,82,85,89,90,92,108,114,116–118} and four trials used alternative test forms in subsequent sessions in an attempt to minimise learning effects.^{85,90,92,116} Thirteen trials reported the time of day that assessments were conducted (five in the afternoon, two in the morning, and

six across the course of the day).^{78,79,85,89,90,92,100,108,113,114,118} Eight trials reported administering tests in a standardised order in an attempt to control the impact of each test in relation to each other across the test session.^{78,79,90,92,93,108,114,118} Four trials assessed for, or attempted to minimise, the effects of stimulants such as caffeine or nicotine, or the effects of alcohol consumption or drug intake.^{83,90,108,114} No study specifically looked at the effect of mood in relation to cognitive function, although one trial⁸² stated that significant depression was present in 40% of the included participants. Level of baseline function, compared with normative standards, was reported in only one trial.⁸⁹ However, a number of papers^{79,83,100,113,117} indicated that many participants demonstrated normal values at baseline, highlighting the possibility of a ceiling effect.

All of these issues could affect the findings of the studies and should be considered when interpreting the results reported below. Owing to time limitations and the quantity of cognitive data from crossover trials it was not feasible to impute data for a paired analysis, where these were not reported, for all the cognitive outcomes. Where three or more studies were available for potential pooling the SE was estimated where appropriate data were available. A narrative synthesis was used where pooling was not feasible. Details of the individual study results are reported in Appendix 4, *Table 53*. Where end point data were not reported, change scores were used.

CPAP versus placebo or conservative/usual care

Simulated driving task

Seven studies used a simulated driving task.^{78,83,90,92,93,100,118} Daytime sleepiness, based on ESS scores at baseline, varied between study populations; in one study daytime sleepiness was classified as severe,¹¹⁸ in one it was classified as mild⁸³ and in four it was classified as moderate.^{78,92,93,100}

Six of the seven studies used the SteerClear simulated driving test.^{78,83,90,92,93,100} SteerClear is a computerised program that attempts to mimic different components of attention involved in driving a car; the program simulates a long and monotonous highway drive that presents a number of obstacles over a period of 30 minutes.

Two studies reported performance in terms of the percentage of obstacles hit^{83,100} and four reported the number of obstacles hit.^{78,90,92,93} These were treated separately.

There was no statistically significant difference between CPAP and oral placebo in terms of the percentage of obstacles hit (*Figure 13*), or in the number of obstacles hit (MD -5.74 , 95% CI -14.75 to 3.27) (*Figure 14*). There was no statistical heterogeneity ($I^2 = 0\%$) for trials reporting the number of obstacles hit.

One parallel group trial¹¹⁸ used a different simulated driving test, based on the work of Land and Horwood.¹¹⁹ This computerised program presents a white on black image (as in night driving) of the moving edges of the road with an image of the vehicle bonnet at the bottom of the screen. The primary object is to steer the centre of the vehicle as accurately as possible down the middle of the road for 30 minutes. In addition, single digits are displayed at each corner of the screen (digits change randomly at an interval of 8–10 seconds) and the participant is required to identify target digits by pressing a button on either side of the steering wheel. Baseline ESS was classified as moderate in both groups. An improvement in terms of steering performance was found with CPAP compared with sham CPAP, although not all differences were statistically significant: SD of position on road (median difference -0.1 , $p = 0.08$), SD of deterioration (median difference -0.2 , $p = 0.007$), and length of drive (minutes) (median difference -0.3 , $p = 0.08$). This was based on end point data as per the protocol; when difference in change was considered, a significant difference in favour of CPAP was found for SD position on road ($p = 0.03$) and length of drive ($p = 0.02$).

Trail Making Task (TMT)

The TMT is a task of complex attention given in two parts, A and B. Individuals are asked to draw lines to connect consecutively numbered circles on one work sheet (Part A), and then connect the same number of consecutively numbered and lettered circles on another work sheet, alternating between the two sequences (Part B); time taken to complete the task (seconds) and errors made are typically recorded. The test is sensitive to a range of mental processes including speed of processing and mental flexibility.

Eight studies (five parallel, three crossover, $n = 260$) reported on TMT Part A^{78,83,85,89,90,100,117,341} and 12 (six crossover, six parallel, $n = 406$) reported on TMT Part B.^{78,82,83,85,89,90,92,93,100,113,117,341}

TMT Part A The severity of daytime sleepiness was classified as moderate in four studies,^{78,89,100,341} and in one study each was classified as mild⁸³

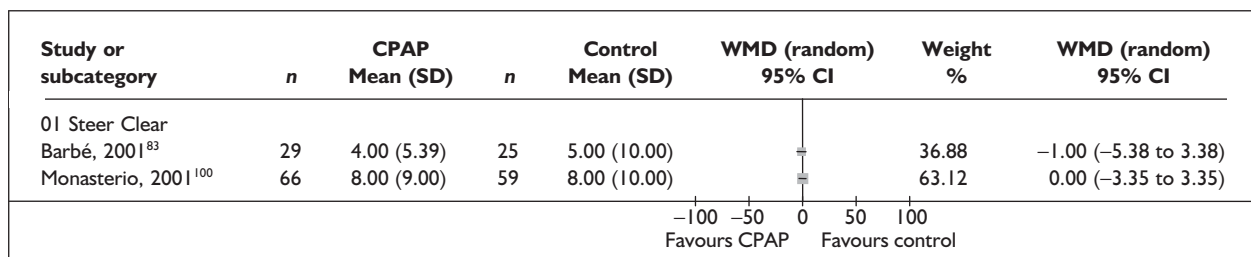


FIGURE 13 SteerClear (CPAP versus placebo/usual care), percentage of obstacles hit.

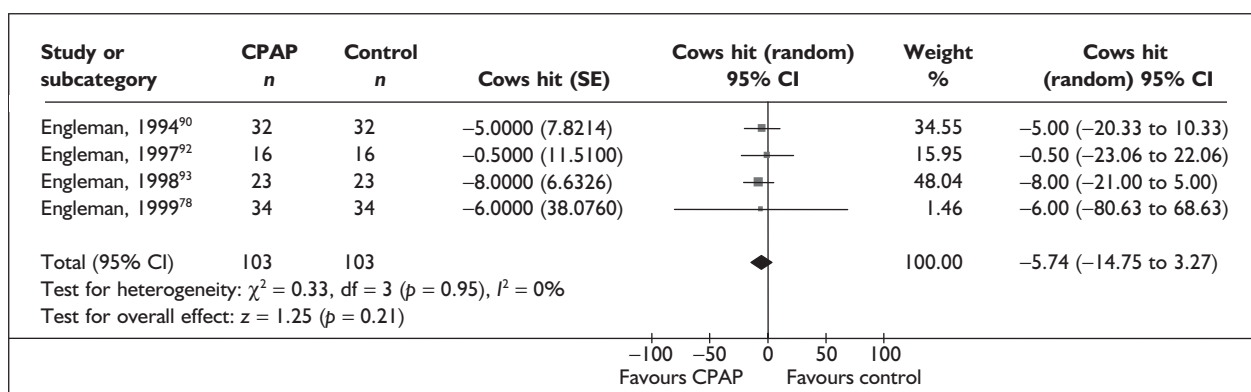


FIGURE 14 SteerClear (CPAP versus placebo/usual care), number of obstacles hit.

TABLE 6 Summary of TMT Part A data reported in included studies

Study	CPAP [mean (SD)]	Control [mean (SD)]	MD	p-Value
Crossover				
Barnes <i>et al.</i> , 2002 ⁸⁹	28.1 (NR)	27.6 (NR)	0.5	Not significant (precise p-value not reported)
Engleman <i>et al.</i> , 1994 ⁹⁰	NR	NR	NR	Not significant (precise p-value not reported)
Engleman <i>et al.</i> , 1999 ⁷⁸	26 (11)	29 (11)	-3.0	0.06
Parallel				
Barbé <i>et al.</i> , 2001 ⁸³	47 (NR)	47 (NR)	0	> 0.20
Dimsdale <i>et al.</i> , 2000 ^{58,117}	27.4 (NR)	27.4 (NR)	0	NR
Henke <i>et al.</i> , 2001 ⁸⁵	Only available in graph			Not significant (precise p-value not reported)
Monasterio <i>et al.</i> , 2001 ¹⁰⁰	49 (19)	49 (20)	0	0.76
Norman <i>et al.</i> , 2006 ^{73,341}	26.5 (NR)	21.7 (NR)	4.9	0.49 (relates to time \times treatment interaction for three treatment groups)
NR, not reported.				

and severe⁸⁵; two studies did not report symptom severity.^{58,90} None of the studies showed a significant difference between CPAP and control in the length of time it took to complete TMT Part A (Table 6). None of the studies reported adequate allocation concealment, and it was unclear whether groups were similar at baseline in four of the included studies.^{78,89,90,100}

Five trials (three crossover, two parallel) did not report sufficient data to calculate a variance.^{78,85,89,90,341} Therefore, only three of the eight trials reporting TMT Part A were used to generate a pooled estimate of treatment effect and are displayed on the forest plot below (Figure 15). When data from these three parallel group trials ($n = 215$) were pooled, no statistically significant between-group difference was found (MD 0.0, 95% CI -2.5 to 2.5). There was no statistical heterogeneity ($I^2 = 0\%$). Given that only a proportion of the available studies could be pooled, caution needs to be taken in interpreting the pooled effect.

TMT Part B Where reported, the populations in the majority of trials were classified as having moderate baseline daytime sleepiness,^{78,82,89,92,93,100,341} and in one study each as having mild⁸³ and severe⁸⁵ daytime sleepiness. One trial reported a significant difference in favour of CPAP compared with oral placebo in the length of time taken to complete the task; no statistically significant between-group differences were found

in the other trials (Table 7). Half of the studies did not report adequate allocation concealment, and it is unclear if the trials had sufficient power to detect a treatment effect.

Seven trials did not report sufficient data or used different scales; therefore, only data from two crossover^{90,93} and three parallel^{83,100,117} trials were pooled ($n = 328$) for TMT Part B (Figure 16). There was a statistically significant benefit with CPAP compared with control for time (seconds) taken to complete TMT Part B (MD -9.1, 95% CI -14.9 to -3.1). There was low statistical heterogeneity ($I^2 = 34\%$). However, as only a proportion of the studies were pooled, the treatment effect may not be generalisable.

Wechsler Adult Intelligence Scale (WAIS) Digit Symbol Substitution Test (DSST)

Ten studies used the DSST, a test of complex attention (five parallel and five crossover, $n = 488$).^{73,78,82,83,85,89,90,93,100,117} In this test of attention and processing, respondents are given a code table displaying the correspondence between pairs of digits (from 1 to 9) and symbols, and then asked to fill in blank squares with the symbol that is paired to the digit displayed above the square. Six out of the eight studies reporting daytime sleepiness could be classified as moderate^{78,82,89,93,100,341} and one trial each classified the study population as having mild⁸³ and severe⁸⁵ daytime sleepiness. Two trials found a significant benefit of CPAP compared with control in the number of correct responses,^{78,90} and

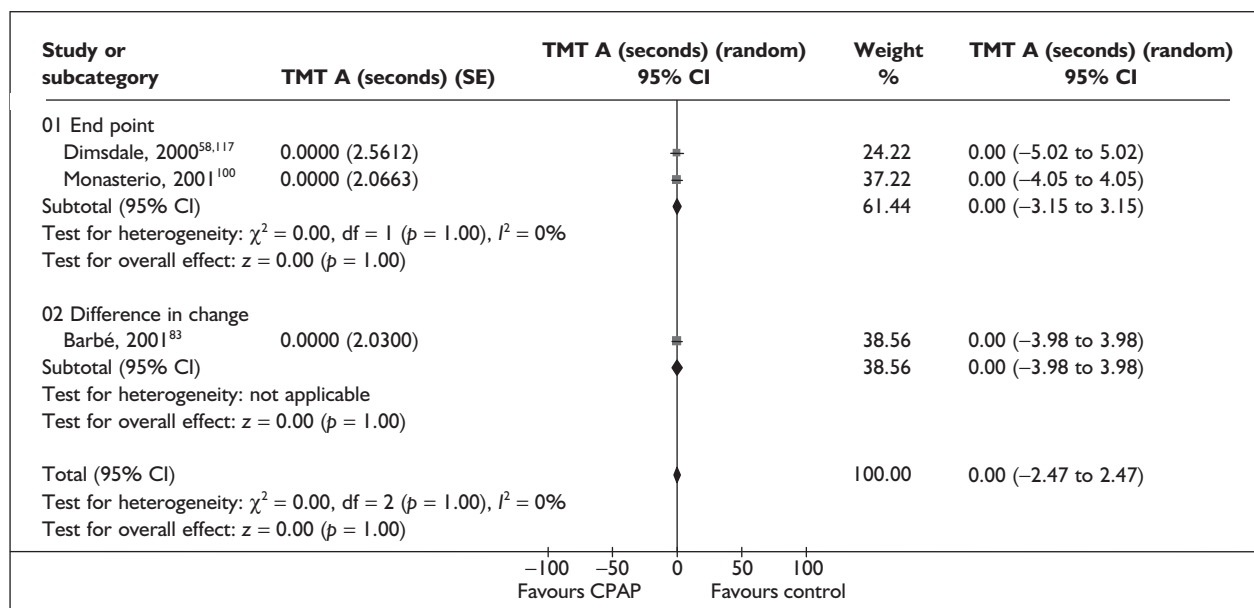
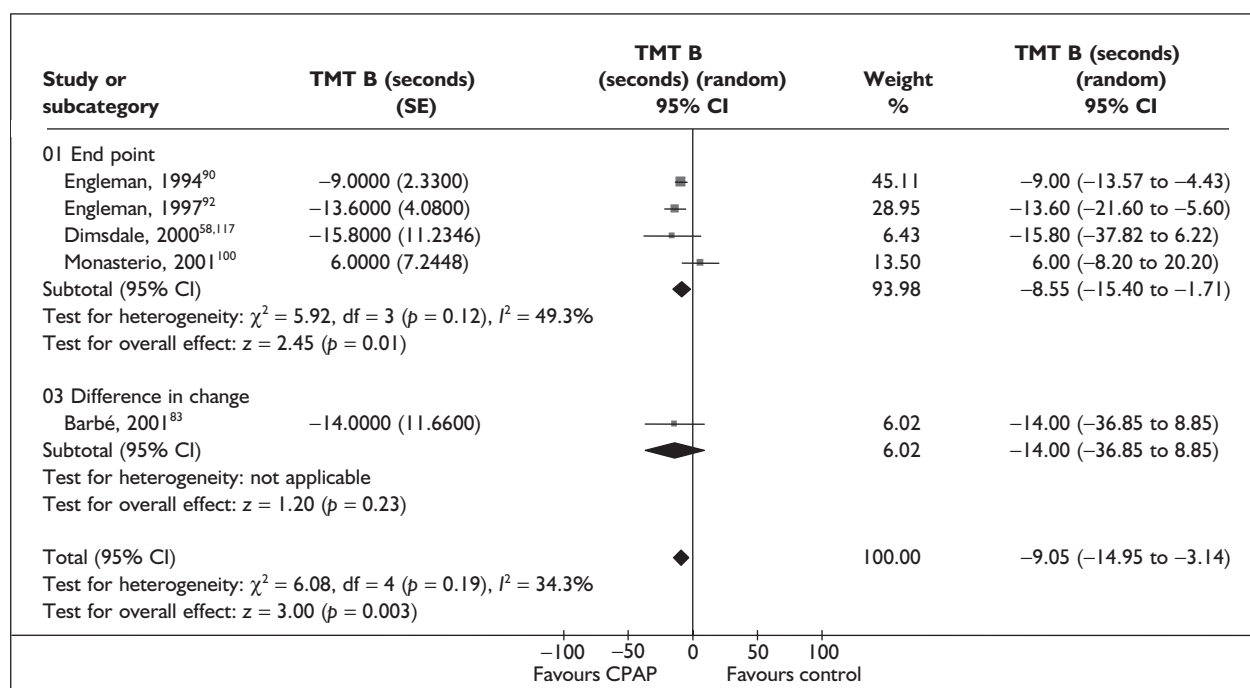


FIGURE 15 Trail Making Task Part A (CPAP versus placebo/usual care), stratified by type of data.

TABLE 7 Summary of TMT Part B data reported in included studies

Study	CPAP [mean (SD)]	Control [mean (SD)]	MD	p-Value
Crossover				
Barnes <i>et al.</i> , 2002 ⁸⁹	60.1 (NR)	65.2 (NR)	-5.1	Not significant (<i>p</i> -value not reported)
Barnes <i>et al.</i> , 2004 ⁸²	73.3 (29.5)	74.2 (32.2)	-0.9	Not significant (<i>p</i> -value not reported)
Engleman <i>et al.</i> , 1994 ⁹⁰	66 (28.3)	76 (28.3)	-10	0.02
Engleman <i>et al.</i> , 1997 ⁹²	64.1 (22)	77.7 (36.8)	-13.6	0.02
Engleman <i>et al.</i> , 1998 ⁹³	69 (32)	68 (32)	1.0	Not significant (<i>p</i> -value not reported)
Engleman <i>et al.</i> , 1999 ⁷⁸	63 (33)	65 (27)	-2	Not significant (<i>p</i> -value not reported)
Parallel				
Barbé <i>et al.</i> , 2001 ⁸³	96 (32.3)	110 (50)	-14.0	0.10
Dimsdale <i>et al.</i> , 2000 ^{58,117}	71.2 (31.8)	87 (34.8)	-15.8	Not significant (<i>p</i> -value not reported)
Henke <i>et al.</i> , 2001 ⁸⁵	Only available in graph			Not significant (<i>p</i> -value not reported)
Lojander <i>et al.</i> , 1999 ¹¹³	130, median	75, median		NR
Monasterio <i>et al.</i> , 2001 ¹⁰⁰	106 (42)	100 (39)	6.0	0.15 (difference in change based on median values)
NR, not reported.				

**FIGURE 16** Trail Making Task Part B (CPAP versus placebo/usual care), stratified by type of data.

one trial found a significant difference in change from baseline in favour of placebo;⁸⁹ no significant between-group differences were found in the other trials (Table 8). None of the trials reported adequate allocation concealment.

Four studies did not provide sufficient data to calculate a variance and one trial used a different scale; therefore, only five trials (three crossover and two parallel, $n = 170$) were pooled (Figure 17);^{78,83,90,93,117} no statistically significant benefit with CPAP was found compared with control in terms of the number of correct responses (MD 0.2, 95% CI -0.6 to 1.0). There was no statistical heterogeneity ($I^2 = 0\%$).

Paced Auditory Serial Addition Task (PASAT)

Seven studies used the PASAT test of vigilance.^{78,82,83,90,92,93,100} In this computerised task, a series of digits are presented at a set rate and the respondent is asked to add the numbers in pairs, such that each number is added to the one that immediately precedes it. Presentation rates range from 1 to 4 seconds. Different formats have been developed, for example the PASAT 1.2 and the PASAT 2.4, which are thought to be more difficult than the standard PASAT 1 and PASAT 2. One study reported outcomes for the PASAT 1.2,⁸² six studies for the PASAT 2,^{78,83,90,92,93,100} one study for

the PASAT 2.4,⁸² two studies for the PASAT 3,^{83,100} and two studies for the PASAT 4.^{83,90}

Daytime sleepiness was reported for six trial populations; five populations were classified as moderate^{78,90,92,93,100} and one trial as mild.⁸³ One crossover trial⁷⁸ found a significant benefit in favour of CPAP in the number of correct responses made; no statistically significant between-group differences were found in any of the other trials (Table 9). None of the studies reported adequate allocation concealment, and one study reported a significant treatment by period interaction for the PASAT 2⁹⁰ indicating a potential carryover effect of treatment.

Data from three or more trials were available for PASAT 1 and PASAT 2. Of the three studies reporting PASAT 1, two studies^{82,83} did not provide sufficient data to calculate a variance for pooling, and, of the six studies reporting the PASAT 2, two studies did not provide sufficient data to calculate a variance.^{90,92} Two crossover and two parallel trials were therefore pooled ($n = 234$) for PASAT 2 (Figure 18). No statistically significant benefit was found with CPAP compared with control for number of correct responses made (MD 2.30, 95% CI 0.24–4.37); statistical heterogeneity was low ($I^2 = 25\%$).

TABLE 8 Summary of Wechsler Adult Intelligence Digit Symbol Substitution Test data reported in included studies

Study	CPAP [mean (SD)]	Control [mean (SD)]	MD	p-Value
Crossover				
Barnes <i>et al.</i> , 2002 ⁸⁹	47.3 (NR)	48 (NR)	-0.7	0.07 (difference in change)
Barnes <i>et al.</i> , 2004 ⁸²	47.3 (3.6)	46.8 (3.6)	0.5	Not significant (p-value not reported)
Engleman <i>et al.</i> , 1994 ⁹⁰	52 (11.3)	51 (11.3)	1	0.05
Engleman <i>et al.</i> , 1998 ⁹³	52 (13)	52 (14)	0	Not significant (p-value not reported)
Engleman <i>et al.</i> , 1999 ⁷⁸	59 (12)	57 (14)	2	0.0004
Parallel				
Barbé <i>et al.</i> , 2001 ⁸³	43 (16.2)	47 (20)	-4	> 0.20 (difference in change)
Dimsdale <i>et al.</i> , 2000 ^{58,117}	53.2 (11.2)	53.5 (12)	-0.3	Not significant (p-value not reported)
Henke <i>et al.</i> , 2001 ⁸⁵	Only available in graph			A binary variable of improved or not improved was assessed; not significant (p-value not reported)
Monasterio <i>et al.</i> , 2001 ¹⁰⁰	9 (3) scaled score	9 (2)	0	0.97 (difference in change, based on median values)
Norman <i>et al.</i> , 2006 ^{73,341}	73.8 (NR)	68.7 (NR)	5.1	0.26 (based on time × treatment interaction for three-armed trial)
NR, not reported.				

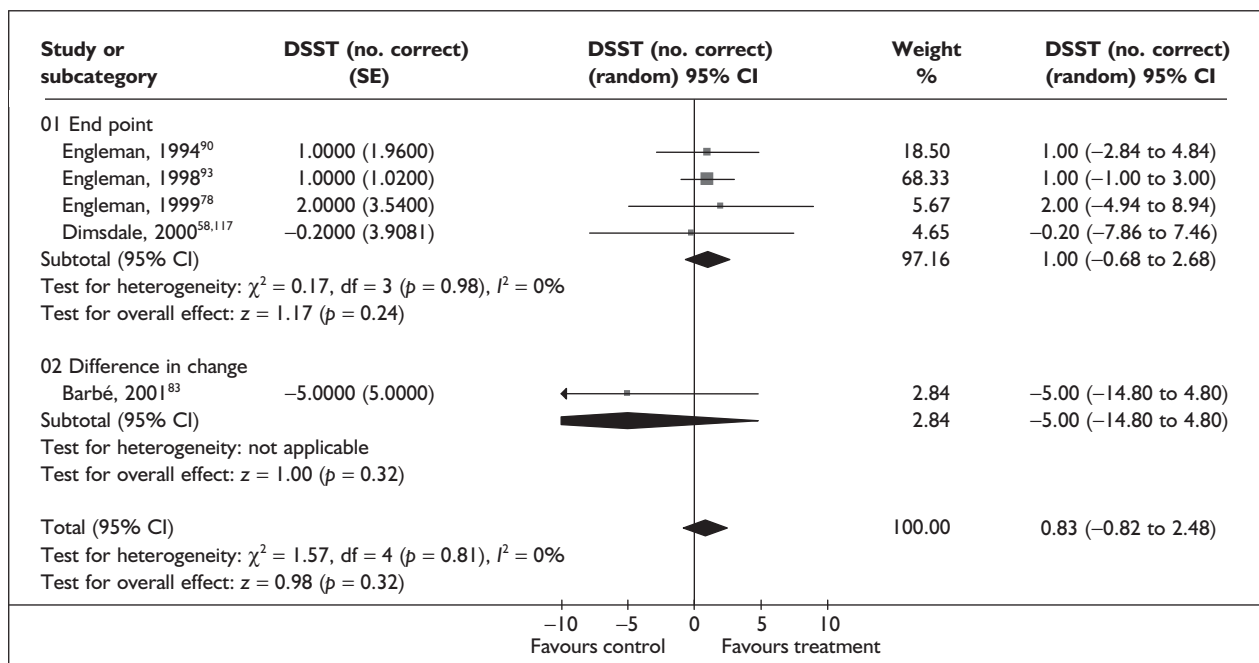


FIGURE 17 Wechsler Adult Intelligence Digit Symbol Substitution Test (CPAP versus placebo/usual care), stratified by type of data.

TABLE 9 Summary of PASAT data reported in included studies

Study	CPAP [mean (SD)]	Control [mean (SD)]	MD	p-Value
Crossover				
Barnes <i>et al.</i> , 2004 ⁸²	PASAT 1.2: 2.9 (0.9)	3.4 (0.9)	-0.5	Not significant (precise p -value not reported)
	PASAT 2.4: 3.8 (1.8)	3.7 (0.9)	0.1	Not significant (precise p -value not reported)
Engleman <i>et al.</i> , 1994 ⁹⁰	NR	NR	NR	Not significant (precise p -value not reported)
Engleman <i>et al.</i> , 1997 ⁹²	PASAT 2: 37.8 (13.2)	35.3 (11.2)	2.5	Not significant (precise p -value not reported)
Engleman <i>et al.</i> , 1998 ⁹³	PASAT 2: 37 (11)	35 (11)	2	Not significant (precise p -value not reported)
Engleman <i>et al.</i> , 1999 ⁷⁸	PASAT 2: 40 (11)	36 (14)	4	0.02
Parallel				
Barbé <i>et al.</i> , 2001 ⁸³	PASAT 1: 15 (5.4)	15 (5)	0	> 0.20 (difference in change)
	PASAT 2: 16 (5.4)	15 (5)	1	0.04
	PASAT 3: 12 (5.4)	12 (5)	0	0.09
	PASAT 4: 5 (5.4)	5 (5)	0	> 0.20
Monasterio <i>et al.</i> , 2001 ¹⁰⁰	PASAT 1: 5 (4)	5 (3)	0	0.32 (based on data for median values)
	PASAT 2: 12(4)	12 (4)	0	0.12
	PASAT 3: 15 (4)	15 (4)	0	0.20
	PASAT 4: 14 (4)	16 (4)	-2	0.20

PASAT, Paced Auditory Serial Addition Task.

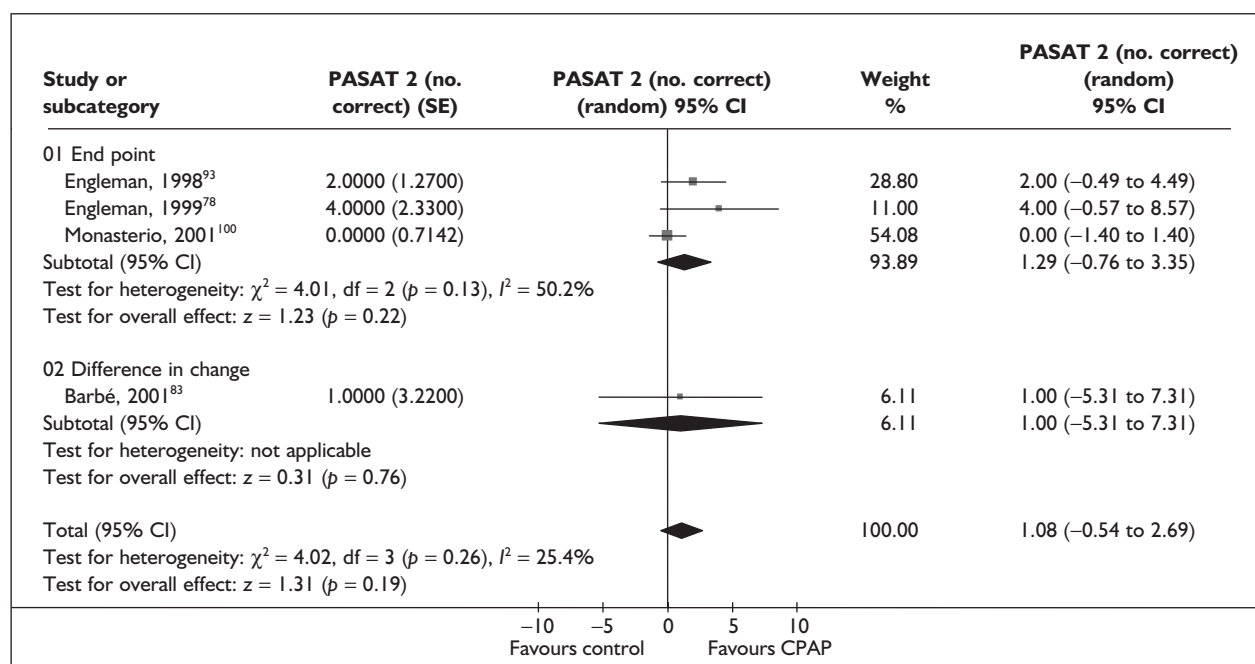


FIGURE 18 Paced Auditory Serial Addition Task (PASAT) 2 (second presentation rate) (CPAP versus placebo/usual care), stratified by type of data.

Verbal fluency

Nine trials assessed verbal fluency; there are a variety of verbal fluency tests in use and each is designed to measure the speed and flexibility of verbal thought processes. Six trials used the Controlled Oral Word Association Test (COWAT).^{82,85,89,90,92,93} The remaining trials did not specify the test used.^{58,73,100} Insufficient reported data, and uncertainty as to whether instruments were measuring the same thing, meant that these studies were not pooled (Table 10).

One small crossover study ($n = 28$)⁸⁹ reported a significant improvement in the number of correct words in the CPAP group compared with the oral placebo group. However, an order effect was found; individuals receiving placebo in the first treatment period had no significant change with either treatment. No significant differences between treatment groups were found in the remaining studies.

Digit Vigilance Test (DVT)

Two parallel group trials used the DVT, which is a measure of sustained attention and psychomotor speed, using a rapid visual tracking task (Table 11).^{117,341} Only one trial reported baseline ESS,³⁴¹ which was classified as moderate; both trials reported severe AHI scores. Time by treatment interactions showed a significant improvement specific to CPAP for time taken to complete the task, but not errors made, in a 2-week study

($n = 31$) comparing CPAP with supplemental oxygen and placebo.³⁴¹ A 1-week study ($n = 36$) found a significant difference between CPAP and sham CPAP in the number of errors made;¹¹⁷ however, after controlling for pre-treatment differences, no significant difference between groups was found. A summary of the results is presented in Table 11.

Other cognitive tests

A number of additional cognitive tests were also used by individual studies, including Stroop colour and word test, psychomotor vigilance, brief visuospatial memory and a concentration endurance test; however, no statistically significant between-group differences were found. It was unclear whether most of these studies were appropriately powered to detect an effect. In addition, few trials reported adequate allocation concealment, baseline comparisons were not always reported and intention-to-treat analysis was seldom conducted. Results for these studies are presented in Appendix 4, Table 53.

CPAP versus dental devices

Cognitive outcomes were reported in four studies (two crossover and two parallel group trials, $n = 160$).^{72,82,103,114} Where reported, symptom severity was classified as moderate, and in all but one trial¹⁰³ disease severity was also reported as moderate. There were no statistically significant differences between treatment groups on any of

TABLE 10 Summary of data for verbal fluency tests reported in included studies

Study	CPAP [mean (SD)]	Control [mean (SD)]	MD	p-Value
Crossover				
Barnes <i>et al.</i> , 2002 ⁸⁹	38.7 (NR) COWAT: no. correct	36 (NR)	2.7	0.02 (difference in change)
Barnes <i>et al.</i> , 2004 ⁸²	46.5 (10.7) COWAT	46.3 (8.9)	0.2	NR
Engleman <i>et al.</i> , 1994 ⁹⁰	NR COWAT	NR	NR	Not significant (precise p-value not reported)
Engleman <i>et al.</i> , 1997 ⁹²	38.5 (14.0) COWAT: no. correct	39.2 (12.4)	-0.7	Not significant (precise p-value not reported)
Engleman <i>et al.</i> , 1998 ⁹³	41 (12) COWAT: no. correct	42 (11)	-1	Not significant (precise p-value not reported)
Parallel				
Dimsdale <i>et al.</i> , 2000 ^{58,117}	44.5 (12.1) No. correct	37.3 (12.8)	7.2	NR
Henke <i>et al.</i> , 2001 ⁸⁵	NR COWAT	NR	NR	Not significant (precise p-value not reported)
Monasterio <i>et al.</i> , 2001 ¹⁰⁰	69 (27) Percentile	70 (29)	-1	0.53 (based on data for median values)
Norman <i>et al.</i> , 2006 ^{73,341}	40.9 (NR) Total score	45.5 (NR)	-4	0.15 (relates to time × treatment interaction from a three-arm trial)
COWAT, Controlled Oral Word Association Test; NR, not reported.				

TABLE 11 Summary of Digit Vigilance Test data reported in the included studies

Study	CPAP [mean (SD)]	Control [mean (SD)]	MD	p-Value
Parallel				
Dimsdale <i>et al.</i> , 2000 ^{58,117}	Time: 6.9 (1.3)	Time: 6.6 (1.6)	0.3	NR
	Errors: 10.1 (11.6)	Errors: 12.3 (12.4)	-2.2	0.49
Norman <i>et al.</i> , 2006 ^{73,341}	Time: 312.3 (NR)	Time: 303.1 (NR)	9.2	0.02 (relates to time × treatment interaction from a three-arm trial)
	Errors: 7.2 (NR)	Errors: 10.6 (NR)	-3.4	0.08 (relates to time × treatment interaction from a three-arm trial)
NR, not reported.				

TABLE 12 List of cognitive tests reported by individual studies

Cognitive test	Barbé et al., 2001 ⁸³	Barnes et al., 2002 ⁸⁹	Barnes et al., 2004 ⁸²	Cibele et al., 2006 ⁷²	^d Dimsdale et al., 2000 ⁵⁸	Engleman et al., 1994 ⁹⁰	Engleman et al., 1997 ⁹²	Engleman et al., 1998 ⁹³
Tests of attention								
CET								
DO					✓			
DVT					✓			
PVT		✓	✓	✓				
RT (8-C)							✓	✓
RVIP							✓	✓
Stroop		✓	✓		✓			
TMT	✓	✓	✓		✓		✓	✓
PASAT	✓		✓			✓	✓	✓
BW								
SteerClear	✓					✓	✓	✓
Other driving tests								
Tests of verbal fluency								
COWAT		✓	✓			✓ ^a	✓ ^a	✓ ^a
VFT					✓			
Tests of memory								
BVM								
BVRT							✓	✓
CT								
HVL								
WMS	✓	✓(s)						
WPMR		✓						
MDT								
Tests of motor performance								
PP								
FTT								
Tests of construction								
CFD								
Copying								
CFT								
Neurocognitive test batteries								
WAIS	✓(s)	✓(s)	✓(s)		✓(s)	✓(s)	✓(s)	✓(s)
IQ decrement						✓	✓	✓

BVM, brief verbal memory test; BVRT, Benton Visual Retention Test; BW, Bourdon–Wiersma test; CET, Continuous Endurance Test; CFD, clock-face drawing task; CFT, complex figure test; COWAT, Controlled Oral Word Association Test; CT, Consonant Triagram; DO, Digit Ordering; DVT, Digit Vigilance Test; FTT, finger tapping test; HVL, Hopkins Verbal Learning test; IQ, intelligence quotient; MDT, memory distractor task; PASAT, Paced Auditory Serial Addition Task; PP, Purdue Pegboard test; PVT, Psychomotor Vigilance Test; RT-8C, Eight Choice Reaction Time Test; s, subscales used; TMT, Trail Making Task; VFT, verbal fluency test; WAIS: Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale; WPMR, word paired memory recall.

Engleman et al., 1999 ⁷⁸	Engleman et al., 2002 ¹⁰³	Henke et al., 2001 ⁸⁵	^e Hoekema et al., 2006 ¹⁰²	^f Jenkinson et al., 1999 ⁷⁷	Jokic et al., 1999 ¹⁰⁸	Lojander et al., 1999 ¹¹³	Marshall et al., 2005 ⁷⁹	Monasterio et al., 2001 ¹⁰⁰	^g Norman et al., 2006 ⁷³
					✓				
							✓		✓
✓	✓	✓			✓	✓		✓	✓
✓	✓					✓		✓	
✓	✓	✓ ^c						✓	
			✓	✓					
		✓							
								✓	✓
									✓
					✓	✓			
					✓	✓		✓(s)	✓
						✓			
					✓	✓			
						✓			
						✓			
		✓ ^{b,c}							
✓(s)	✓(s)	✓(s) ^c				✓(s)		✓(s)	✓(s)
	✓								

- a Borkowski's Controlled Oral Word Association Test.
 b Medical College of Georgia Complex Figure Recall Test.
 c Results presented in graph format only.
 d Related paper ref. 117.
 e Related paper ref. 114.
 f Related paper ref. 118.
 g Related paper ref. 341.

the cognitive tests assessed (see Appendix 4, Table 53). None of these trials reported appropriate allocation concealment, and only one trial⁸² reported adequate randomisation methods and used intention-to-treat analysis.

CPAP versus postural therapy

Data were available for one small crossover study ($n = 14$).¹⁰⁸ No statistically significant between-group differences were found on any of the cognitive tests administered (see Appendix 4, Table 53). It is unclear whether performance differences at baseline existed, or whether the study was appropriately powered to detect an effect.

Apnoea–hypopnoea index

CPAP versus placebo/usual care

Nine studies reported the AHI at follow-up.^{66,70,73,82,85,87,97,100,109} There was high statistical heterogeneity ($I^2 = 97\%$) and any pooled effect is likely to be meaningless. All the studies reported a statistically significant reduction in the AHI with CPAP compared with placebo/usual care and the effect size ranged from -9.2 (95% CI -18.3 to -0.1) to -60.0 (95% CI -72.1 to -47.5) (see Appendix 4, Figure 44).

CPAP versus dental devices

Nine studies reported the AHI at follow-up.^{70,80–82,103,105–107,119} There was a statistically significant reduction in AHI in favour of CPAP compared with dental devices (MD -8.4 , 95% CI -10.5 to -6.3) (see Appendix 4, Figure 45). Statistical heterogeneity was low to moderate ($I^2 = 40\%$).

CPAP versus postural therapy

Data were available for the AHI from three small crossover trials ($n = 36$).^{60,61,108} There was a statistically significant benefit with CPAP on the AHI compared with postural therapy (shoulder–head elevation pillow, MD 15.5 , $p = 0.008$; cervicomandibular support collar, MD in change 16.8 , $p = 0.001$; backpack with soft ball inside, MD 6.1 , 95% CI 2.0 – 10.2 , $p = 0.007$).

Adverse effects

Reporting of adverse effects was patchy across studies. Reported adverse effects with CPAP were related mainly to discomfort with the equipment (e.g. machine noise, a feeling of pressure and mask discomfort), dry mouth and stuffy or runny nose (Table 13). Reported adverse effects with use of dental devices were related mainly to excess salivation, tooth discomfort and temporomandibular joint discomfort.

CPAP versus postural therapy

Data were available from two trials ($n = 23$).^{60,61} No statistically significant difference in the overall number of self-reported adverse events was found when CPAP was compared with a shoulder–head elevation pillow (MD -0.8 , $p = 0.16$). However, there were significantly fewer self-reported adverse events with a cervicomandibular support collar than with CPAP (MD in change 4.2 , $p = 0.01$). Type of adverse event and indication of perceived severity were not reported in either study.

Patient preference

New data were not found regarding patient preference for CPAP compared with dental devices. Giles *et al.* highlighted the difficulties in interpreting the data they found: preferences can be measured only when participants receive both treatment options (i.e. in crossover trials), leading to possible order effects.⁵⁰ It was not considered appropriate to pool the data.⁵⁰ Based on two studies ($n = 15$) of patients who had a successful outcome with both treatments there was a preference for CPAP. When all patients were considered (four studies, $n = 164$), in one study participants showed a statistically significant preference for dental devices over CPAP, but there was no statistically significant difference in the other studies and they did not show a consistent direction for preference.⁵⁰ Participants were more likely to withdraw while using dental devices than with CPAP [odds ratio (OR) 0.46 , 95% CI 0.25 – 0.84] (see Appendix 4, Figure 46).

TABLE 13 Adverse effects

Effect	Study	CPAP (n/N)	Control (n/N)	Dental device (n/N)
Mask discomfort or other problems with mask/headgear	Engleman <i>et al.</i> , 1999 ⁷⁸	8/34	0/34	–
Machine noise	Lojander <i>et al.</i> , 1996 ⁹⁹	2/13	0/20	–
	Lam <i>et al.</i> , 2007 ⁷⁰	8/34	–	0/34
Sleep disturbance	Engleman <i>et al.</i> , 1999 ⁷⁸	8/34	0/34	–
	Engleman <i>et al.</i> , 2002 ¹⁰³	16/48	–	12/48
	Lojander <i>et al.</i> , 1996 ⁹⁹	1/13	0/20	–
Difficulty falling asleep with prescribed pressure	Engleman <i>et al.</i> , 1999 ⁷⁸	1/34	0/34	–
Feeling of pressure	Lam <i>et al.</i> , 2007 ⁷⁰	11/34	–	0/34
Pressure (on face)	Randerath <i>et al.</i> , 2002 ¹⁰⁵	8/19	–	2/19
Pressure (in mouth)	Randerath <i>et al.</i> , 2002 ¹⁰⁵	0/19	–	2/19
Early awakening	Engleman <i>et al.</i> , 1999 ⁷⁸	1/34	0/34	–
Residual sleepiness	Engleman <i>et al.</i> , 1999 ⁷⁸	0/34	3/34	–
Dry throat/nose/mouth	Engleman <i>et al.</i> , 1999 ⁷⁸	4/34	0/34	–
	Engleman <i>et al.</i> , 2002 ¹⁰³	5/48	–	0/48
	Lojander <i>et al.</i> , 1996 ⁹⁹	2/13	0/20	–
	Lam <i>et al.</i> , 2007 ⁷⁰	16/34	–	11/34
Rhinorrhoea	Lojander <i>et al.</i> , 1996 ⁹⁹	7/13	0/20	–
Skin irritation or abrasion	Redline <i>et al.</i> , 1998 ⁵⁹	2/51	0/46	–
	Lam <i>et al.</i> , 2007 ⁷⁰	7/34	–	0/34
Minor nosebleeds (related to nasal spray)	Redline <i>et al.</i> , 1998 ⁵⁹	1/51	2/46	–
Use of antibiotics during intervention period	Redline <i>et al.</i> , 1998 ⁵⁹	7/51	2/46	–
Excess salivation	Engleman <i>et al.</i> , 2002 ¹⁰³	0/48	–	9/48
	Lam <i>et al.</i> , 2007 ⁷⁰	0/34	–	19/34
Tooth discomfort	Lam <i>et al.</i> , 2007 ⁷⁰	0/34	–	11/34
Tooth damage	Engleman <i>et al.</i> , 2002 ¹⁰³	0/48	–	3/48
Temporomandibular joint discomfort	Engleman <i>et al.</i> , 2002 ¹⁰³	0/48	–	33/48
	Lam <i>et al.</i> , 2007 ⁷⁰	0/34	–	13/34
	Randerath <i>et al.</i> , 2002 ¹⁰⁵	0/19	–	8/19
Removal of appliance during sleep	Engleman <i>et al.</i> , 2002 ¹⁰³	7/48	–	19/48
Leakage	Engleman <i>et al.</i> , 2002 ¹⁰³	11/48	–	0/48
Stuffy nose	Engleman <i>et al.</i> , 2002 ¹⁰³	8/48	–	0/48
Inconvenience	Engleman <i>et al.</i> , 2002 ¹⁰³	6/48	–	0/48
Side-effect severity				
None	Ferguson <i>et al.</i> , 1996 ⁸¹	11/25	–	10/21
	Ferguson <i>et al.</i> , 1997 ⁸⁰	10/20	–	7/20
Mild	Ferguson <i>et al.</i> , 1996 ⁸¹	1/25	–	9/21
	Ferguson <i>et al.</i> , 1997 ⁸⁰	4/20	–	9/20
Moderate	Ferguson <i>et al.</i> , 1996 ⁸¹	5/25	–	5/21
	Ferguson <i>et al.</i> , 1997 ⁸⁰	3/20	–	4/20
Severe	Ferguson <i>et al.</i> , 1996 ⁸¹	4/25	–	1/21
	Ferguson <i>et al.</i> , 1997 ⁸⁰	3/20	–	1/20

Chapter 4

Assessment of cost-effectiveness evidence

The examination of the cost-effectiveness of continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnoea–hypopnoea syndrome (OSAHS) comprises:

1. A systematic review of existing evidence on the cost-effectiveness of CPAP, against relevant comparators, including dental devices and conservative management. The review includes the manufacturer ResMed's submission¹²⁰ to the National Institute for Health and Clinical Excellence (NICE).
2. Employment of this systematic review to inform the development of an economic model to evaluate the cost-effectiveness of CPAP for the treatment of OSAHS.

Systematic review of existing cost-effectiveness evidence

Cost-effectiveness review methods

A systematic review of cost-effectiveness studies was undertaken to compare CPAP with other interventions routinely used for the treatment of OSAHS in the National Health Service (NHS). The review comprised manufacturer submissions to NICE and relevant, published cost-effectiveness analyses. To obtain the latter, papers obtained from the clinical effectiveness review (see Chapter 3) were scanned to check whether they included cost-effectiveness data. In addition, several economic databases were searched for cost-effectiveness studies as listed below (for full details see Appendix 1, Cost-effectiveness searches).

- MEDLINE and in process MEDLINE and other non-indexed citations (1950–Jan 10 2007) (OVID)
- EMBASE (1980–2007 week 1) (OVID)
- Cochrane Central Register of Controlled Trials (Cochrane Library 2006, issue 4) (www.thecochranelibrary.com)
- NHS Economic Evaluation Database (NHS EED) (CRD internal administration system 13/1/07)

- Health Economic Evaluations Database (HEED) (1995–Jan 2007) (CD-ROM)
- HTA database (CRD internal administration system 13/1/07)
- EconLit (1969–2006/10) (SilverPlatter)
- EconPapers (<http://econpapers.repec.org/>).

A broad range of studies was considered in the assessment of cost-effectiveness, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Studies were included in the cost-effectiveness review if they considered the costs and outcomes associated with two or more interventions in the treatment of OSAHS. Therefore, studies based on cost–consequence analysis, cost–utility analysis, cost-effectiveness analysis, cost minimisation analysis and cost–benefit analysis were eligible for inclusion.

Data were extracted using a data extraction form that was developed for use in previous technology assessment reviews. The quality of the cost-effectiveness studies was assessed based on a checklist developed by Drummond *et al.* (2005)¹²¹ and which reflects the criteria for economic evaluation detailed in the methodological guidance developed by NICE (www.nice.org.uk/) (see Appendix 6 for economic evaluation data extraction table and *Table 40* for economic evaluation quality assessment table).

Cost-effectiveness review results

The above searches identified four full economic evaluations for inclusion in the cost-effectiveness review of published studies.^{44,122,123,124} One manufacturer (ResMed) submitted a full cost-effectiveness study to NICE.¹²⁰ Two manufacturers, Fisher Paykel Ltd¹²⁵ and Respironics (UK) Ltd,¹²⁶ submitted a partial economic evaluation. Full economic evaluations, including ResMed's submission and the four published economic evaluations (i.e. Ayas *et al.*¹²², Mar *et al.*¹²³, the Trent Report by Chilcott *et al.*⁴⁴ and Tousignant *et al.*¹²⁴), are reviewed next and reported in *Table 40*. These are followed by an overall summary of the cost-effectiveness evidence base.

Review of manufacturers' submissions
ResMed model¹²⁰

Overview ResMed performed a cost-utility analysis comparing CPAP using fixed pressure and CPAP using autotitrated pressure with a 'do nothing' alternative for the treatment of patients with severe OSAHS.¹²⁰ The hypothetical patient population depicted by the model consisted of 55-year-old patients with severe OSAHS as defined by an AHI > 30 and daytime sleepiness represented by a score of 12 on the ESS. The analysis was undertaken from the NHS and PSS perspective.

ResMed produced a cohort-based Markov model with a 14-year time horizon and each Markov cycle lasted a year.¹²⁰ Patients enter the model following an initial outpatient visit or a diagnostic sleep study test. Treatment begins 8.4 months after whichever visit takes place first. For each year in the model patients can remain event free in the severe OSAHS state, or can have a non-fatal or fatal stroke, a cardiovascular event (CVE), e.g. myocardial infarction or a road traffic accident (RTA), as illustrated in *Figure 19*. In each subsequent year patients who have had a non-fatal CVE or an RTA can have a stroke, CVE or RTA. However, patients who have a stroke can no longer drive and, therefore, are not at subsequent risk of an RTA.

The primary measure of cost-effectiveness was incremental cost per quality-adjusted life-year (QALY) gained, and the secondary measure was cost per life-year gained. The QALY estimate incorporated the impact on health-related quality of life (HRQoL) of stroke, CVE and RTA. Effectiveness estimates and utilities were drawn from the HRQoL published literature and government statistics, and based on the authors' assumptions. Data on patient management and resource use were obtained from 19 clinicians throughout the UK who had relevant clinical experience. Unit cost data on CPAP treatment, and resource use associated with CVEs and RTAs, were obtained from list prices, the published literature and government statistics. The authors undertook several univariate sensitivity analyses and probabilistic sensitivity analysis to test the robustness of findings.

Summary of effectiveness data

For the base-case analysis, utility values for treated and untreated OSAHS were obtained from Mar *et al.*¹²³ In this study, a survey of 51 OSAHS patients who attended a sleep clinic in Spain was undertaken before the initiation of CPAP and 3 months after initiation of CPAP in order to generate 'do nothing' and nasal CPAP (nCPAP) utility values, respectively. The EQ-5D instrument

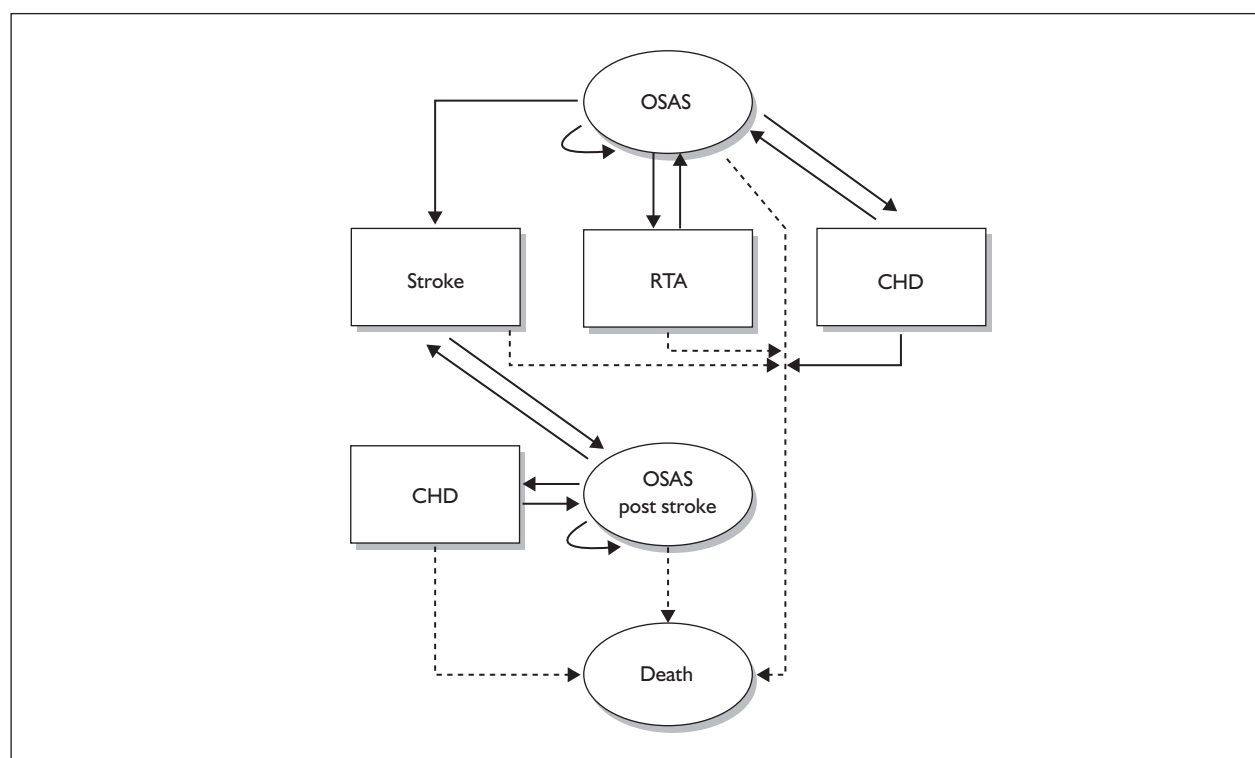


FIGURE 19 Structure of ResMed Model (adaptation of Figure 6.1, p. 9, v in ResMed submission).

(EuroQoL Group¹²⁷) was used to describe patient health states and completed data for 46 patients were obtained. These were then elicited using the time trade-off technique and valued based on UK societal preferences (Dolan *et al.*¹²⁸). No information was obtained on the HRQoL of OSAHS patients with stroke and coronary heart disease (CHD). To estimate these utilities, the authors assumed quality adjustment factors of 0.8 and 0.9 in relation to standard OSAS patient utilities (Table 14, based on Torrance *et al.*¹²⁹) To estimate utility associated with a non-fatal RTA, ResMed took the average utility for OSAHS and a non-fatal CVE in treated and untreated patients.

The annual incidence rates of fatal and non-fatal cardiovascular and cerebrovascular events in patients with severe OSAHS (AHI > 30) were calculated for CPAP-treated and untreated patients using the results of a long-term observational study by Marin *et al.*¹³⁰ The untreated patients comprised those who had refused CPAP treatment on initial referral to the sleep clinic. The baseline characteristics of these patients may differ compared with the treated patients for reasons other than chance, thus undermining the internal validity of the study results. Results were extrapolated from years 12–14. No method of extrapolation was reported. The authors justified the use of a 14-year time horizon because 14 is divisible by seven: the estimated NHS shelf-life of CPAP according to the authors. ResMed used the Mar *et al.*¹²³ study to estimate the ratio of CHD and stroke in patients with untreated severe OSAHS as 1.185 and 1.353 respectively compared with treated OSAHS. Therefore, they estimated the ratio of developing CHD to stroke as 1 : 1.13. Based on the same data, ResMed estimated the ratio of CHD to stroke in treated patients as 1 : 1. Thus, treatment with CPAP was assumed to reduce the incidence of CHD and stroke, and to reduce the proportion of

total CHD and stroke events. Using these estimates, ResMed calculated the annual risk of CVE and stroke.

To estimate the risk of an RTA, ResMed took the average risk increase of an RTA in patients with OSAHS based on two studies. One study assessed RTAs in patients with OSAHS before and after treatment with CPAP (George *et al.*).¹³¹ Patients were followed-up for at least 3 years. The other study (Mazza *et al.*¹³²) measured driving ability in OSAHS patients before and after CPAP treatment using a 'road safety platform' (i.e. a stretch of road to test driving ability). The risk of an RTA was estimated as 2.6 times greater than the risk among controls, whereas the risk among treated patients was assumed to be equivalent to that among controls. Using data from the Department of Transport¹³³ and assuming that all OSAHS patients were drivers of a licensed motor vehicle, ResMed estimated that the risk of an RTA among the control group and treated OSAHS patients was 0.009 per year and 0.023 per year for untreated OSAHS patients.

ResMed reviewed the published literature to obtain data on compliance among OSAHS patients with fixed CPAP. Compliance was defined as the percentage of patients with OSAHS of all severity levels who have not discontinued using their CPAP device. ResMed estimated that 79% of patients would continue to use CPAP after the first year of treatment, based on the results of four studies that followed patient compliance for at least 1 year.^{39,40,134,135} It took the average compliance across the studies, the follow-up time for which varied between 2 and 7 years. For patients who continued their use of the device for at least 1 year, it was assumed that there would be no further loss to compliance, based on expert clinical opinion. For autotitrating CPAP it was estimated

TABLE 14 ResMed utility values

Health state	Utility values	
	Untreated OSAS patients	nCPAP OSAS patients
OSAS	0.738	0.811
Non-fatal stroke	0.590	0.649
Non-fatal CHD	0.664	0.730
Non-fatal RTA	0.701	0.771

CHD, coronary heart disease; nCPAP, nasal continuous positive airway pressure; OSAS, obstructive sleep apnoea syndrome; RTA, road traffic accident.

that compliance would be 84%. The increase in compliance with autotitrating CPAP compared with fixed CPAP was based on expert opinion.

Summary of resource utilisation and cost data

The opinion of 19 clinical experts was sought in order to estimate the health-care resource use associated with the management of OSAHS in the UK. Resource use and unit costs were reported separately and these are detailed in *Tables 15* and *16* respectively. Unit costs were reported in 2005 prices and were based on list prices, ResMed estimates, the published literature and government statistics. Costs were calculated by multiplying the resource use by the relevant unit costs (*Table 17*). Confidence intervals were calculated based on the resource use estimates provided by clinical experts.

Examination of the electronic model submitted by ResMed revealed a number of modelling errors that may have affected the ability of the model to provide an accurate estimate of mean costs and QALYs. The beta distributions used to characterise the uncertainty around transition probabilities and utilities were mis-specified. The alpha and beta

parameters were correctly estimated from the mean and SD, but the scale parameter was set equal to the mean, effectively truncating the distributions at the mean. This meant that for the probabilistic analysis the mean and SD of every transition probability was lower than indicated by the source data. In addition, a number of other distributions were truncated; for example, the relative risk of an RTA was modelled as a normal distribution with mean = 2.6, SD = 0.26, and truncated at a lower limit of 2.4 and an upper limit of 2.9. The reason for the truncation is unclear, and it effectively reduces the uncertainty around the model input parameters. The uncertainties around resource use and cost data were characterised using normal distributions, which allow negative values to be drawn for simulations in the probabilistic analysis.

The numbers of CHD and stroke events were calculated as a proportion of the number of patients alive in the first year of the model for every cycle rather than as a proportion of those patients at risk at a given time point. This led to an overestimate of the number of events, as patients who die as the model progresses are not removed from the pool of those at risk.

TABLE 15 ResMed estimates of health-care resource use

Resource use	Probability (95% CI)
Probability of having an initial outpatient visit before a diagnostic sleep study	0.31 (0.11–0.51)
Probability of one outpatient visit after a diagnostic sleep study	0.69 (0.49–0.89)
Probability of having a home sleep study	0.75 (0.59–0.90)
Probability of having a home titration study	0.99 (0.97–1.00)
Probability of having a titration study in hospital	0.04 (0.00–0.05)
Probability of using CPAP (fixed) for titration	0.19 (0.01–0.36)
Probability of using CPAP (auto) for titration	0.81 (0.64–0.99)
Probability of seeing a consultant during the titration phase	0.40 (0.05–0.52)
Probability of seeing a specialist nurse during the titration phase	1.00 (0.53–1.00)
Probability of seeing a technician during the titration phase	0.48 (0.10–0.93)
Probability of having a humidifier	0.38 (0.22–0.50)
Probability of switching from fixed to autotitrating CPAP in the second year	0.06 (0.04–0.07)
Probability of switching from fixed to autotitrating CPAP in subsequent years	0.01 (0.00–0.02)
Probability of a non-compliant patient returning his or her machine	0.75 (0.50–1.00)
Probability of having a follow-up visit within 3 months of starting CPAP	0.75 (0.50–1.00)
Probability of having a follow-up visit within 4–6 months of starting CPAP	0.75 (0.75–1.00)
Probability of annual follow-up visits after starting CPAP with a consultant	0.13 (0.00–0.27)
Probability of annual follow-up visits after starting CPAP with a specialist nurse	0.61 (0.33–0.79)
Probability of annual follow-up visits after starting CPAP with a technician	0.26 (0.09–0.54)
Probability of a dead patient’s machine being returned	0.90 (0.75–1.00)

TABLE 16 ResMed unit costs

Resource	Cost	Source
Myocardial infarction episode	£1694.51	Department of Health, 2005 ¹³⁷
Home-based cardiac rehabilitation for the first year following a myocardial infarction	£3702.49	Taylor <i>et al.</i> , 2006 ¹³⁸
Stroke episode	£1667.23	Department of Health, 2005 ¹³⁷
Annual cost of stroke rehabilitation	£10,140	Department of Health, 2005 ¹³⁹
Initial outpatient visit with specialist	£115.00	Department of Health, 2005 ¹³⁷
Follow-up outpatient visit with specialist	£108.00	Department of Health, 2005 ¹³⁷
Initial sleep study	£115.35	Department of Health, 2005 ¹³⁷
Follow-up sleep study	£107.87	Department of Health, 2005 ¹³⁷
Specialist nurse visit (30-minute appointment)	£34.00	Department of Health, 2005 ¹³⁷
Technician visit (30-minute appointment)	£9.50	Department of Health, 2005 ¹³⁷
Fatal car accident	£5688.23	Department of Transport, 2004 ¹³³
Serious/slight car accident	£12,019.89	Department of Transport, 2004 ¹³³
CPAP S8 Escape	£280.00	ResMed ¹²¹
APAP S8 AutoSet Spirit	£410.00	ResMed ¹²¹
HumidAire H3i (Humidifier)	£150.00	ResMed ¹²¹
Ultra Mirage II Nasal (Mask)	£80.00	ResMed ¹²¹
Miscellaneous spare parts for CPAP	£100.00	Estimate
Cost of using CPAP (auto) for dose titration	£2.51	Estimate
Cost of using CPAP (fixed) for dose titration	£1.71	Estimate
Nightly cost of using Embletta X10 for a diagnostic sleep study	£6.69	Estimate

APAP, autotitrating positive airway pressure.
 NB The nightly cost of using an Embletta X10 (portable diagnostic device) is based on an acquisition cost of £6690, a shelf-life of 5 years and the device being used four nights a week for 50 weeks a year.

The proportion of males in the hypothetical patient population was modelled with uncertainty. Risks that differed according to gender, such as mortality risks, were averaged according to the proportion of males and females at the start of the model. Averaging over heterogeneous subgroups in this manner can produce misleading results. For example, as the risk of death is greater among men, the proportion of men in the hypothetical patient population would be expected to fall over time. By not reflecting this in the model the number of deaths will be overestimated.

A number of other minor errors were also found. The lack of internal validity indicates that the model results should be interpreted with caution.

Summary of cost-effectiveness

The expected outcomes associated with severe OSAHS at 14 years from commencement of treatment with CPAP compared with no treatment

are provided in *Table 18*. Based on the Markov model, differences in health gain between patients receiving CPAP and patients who are untreated becomes apparent after 2–3 years of treatment.

The primary cost driver in patients with severe OSAHS was managing stroke [i.e. 68% of the total cost for the no treatment group, 48% for the CPAP (fixed) and 45% for CPAP (auto) groups]. The secondary cost driver in untreated patients was the cost associated with managing RTAs (i.e. 23% of the total cost for the no treatment group), whereas in CPAP-treated patients it was the cost associated with the device itself [i.e. 22% for the CPAP (fixed) and 26% for CPAP (auto) groups].

Key results of the cost-effectiveness model are shown in *Table 19*. The incremental cost-effectiveness ratio (ICER) was based on deterministic analysis and over 14 years it was estimated that CPAP dominates no treatment (i.e.

TABLE 17 ResMed annual cost associated with CPAP

	CPAP (fixed)	CPAP (auto)
Year 1		
Initial outpatient visit	£35.65	£35.65
Diagnostic sleep study at home	£5.02	£5.02
Diagnostic sleep study at hospital	£115.35	£115.35
Follow-up outpatient visit after sleep study	£74.52	£74.52
Dose titration study (home)	£2.34	–
Dose titration study (inpatient)	£4.31	–
Consultant visit during titration phase	£43.20	–
Specialist nurse visit during titration phase	£38.08	–
Technician visit during titration phase	£90.25	–
CPAP machine	£280.00	£410.00
Mask	£80.00	£80.00
Humidifier	£57.00	£57.00
Sundries	£100.00	£100.00
Follow-up visit within 3 months of starting CPAP	£81.00	£81.00
Follow-up visit within 4–6 months of starting CPAP	£81.00	£81.00
Year 1 total	£1087.72	£1039.54
Years 2–7 and 9–14		
Follow-up outpatient visit	£37.25	£37.25
Replacement mask	£80.00	£80.00
Sundries	£100.00	£100.00
Total for each year (2–7 and 9–14)	£217.25	£217.25
Year 8		
Follow-up outpatient visit	£37.25	£37.25
Replacement CPAP machine	£280.00	£410.00
Replacement mask	£80.00	£80.00
Replacement humidifier	£57.00	£57.00
Sundries	£100.00	£100.00
Year 8 total	£554.25	£684.25

TABLE 18 ResMed probabilities of expected outcomes after 14 years

Outcome	No treatment	CPAP (fixed)	CPAP (auto)
CVE	0.57 (0.55–0.66)	0.74 (0.69–0.80)	0.78 (0.73–0.81)
Stroke	0.35 (0.20–0.53)	0.16 (0.08–0.26)	0.14 (0.07–0.25)
RTA	0.39 (0.23–0.60)	0.17 (0.08–0.29)	0.15 (0.07–0.28)
Event-free survival	0.30 (0.15–0.47)	0.63 (0.52–0.73)	0.68 (0.56–0.74)
QALYs	7.22 (6.85–7.62)	8.19 (7.79–8.69)	8.32 (7.97–8.81)

CVE, cardiovascular event; QALYs, quality-adjusted life-years; RTA, road traffic accident.

TABLE 19 Key ResMed model results at end of 14 years

Model result	CPAP (fixed)	CPAP (auto)	No treatment
Base case			
Cost per QALY gained compared with no treatment	–£1620 95% CI –£4123 to £259	–£1845 95% CI –£3936 to £37	–
Cost per life-year gained compared with no treatment	–£9215 95% CI –£19,824–£22,224	–£9845 95% CI –£18,530 to £218	–
Cost per event-free life-year gained	–£4813 95% CI –£10,195 to £1158	–£5441 95% CI –£10,005 to £135	–
Secondary analysis			
Cost per QALY gained compared with no treatment when clinical outcomes relating to cardiovascular and cerebrovascular events are excluded	£2311 95% CI £483–£3254	£2173 95% CI £460–£2912	–
Cost per QALY gained compared with no treatment when clinical outcomes relating to cardiovascular and cerebrovascular events and RTAs are excluded	£4551 95% CI £2259–£6597	£4219 95% C £2124–£5799	–
Expected alive	74%	78%	57%
Increased probability of survival compared with no treatment	26%	32%	–
Expected event-free survival	63%	68%	30%
Increased probability of event-free survival compared with no treatment	100%	113%	–
Reduction in relative risk of having a CVE compared with no treatment	55%	60%	–
Reduction in relative risk of having a stroke compared with no treatment	57%	63%	–
Reduction in relative risk of having an RTA compared with no treatment	36%	41%	–
Expected cost (NHS perspective) per patient	£9086 95% CI £6851–£11,117	£8622 95% CI £6712–£10,947	£10,645 95% CI £7912–£14,177
Reduction in NHS management costs compared with no treatment	15% (£1559)	19% (£2,023)	–
CVE, cardiovascular event; QALY, quality-adjusted life-year; RTA, road traffic accident.			

CPAP was associated with lower costs and higher effects than no treatment). However, at 1 year, the cost per QALY for CPAP is expected to exceed £20,000. After 2 years the expected cost per QALY gained is £10,000 or less, and after 11 years CPAP is the dominant treatment. CPAP (fixed) was compared with no treatment and CPAP (auto) was compared with no treatment. Based on this indirect analysis, the authors found that CPAP (auto) dominated CPAP (fixed).

Several univariate sensitivity analyses were undertaken and demonstrated that the cost-

effectiveness of CPAP was robust to changes in some input values. However, the model was sensitive to the following parameters: time to start of treatment, compliance rate with CPAP, risk of having a cardiovascular event or a cerebrovascular event, risk of having an RTA, utility for treated and untreated OSAHS, cost of managing a non-fatal RTA and cost of managing stroke rehabilitation.

The results of the univariate sensitivity analyses are reported in *Table 20*. No rationale was provided for the ranges over which input values were varied.

Cost-effectiveness acceptability curves (CEACs) were presented for CPAP (auto) and CPAP (fixed). Each was assessed in a pair-wise comparison against a 'do nothing' alternative. The CEAC showed that CPAP (auto) has a marginally higher probability of being cost-effective compared with a 'do nothing' option than CPAP (fixed) compared with a 'do nothing' option at a willingness to pay threshold of less than £5000 per QALY in all simulations.

Comments on methodology

Use of observational data

ResMed used the results of a before and after study (Mar *et al.*, 2003)¹²³ to examine the impact of no treatment compared with CPAP on HRQoL associated with sleepiness. There are numerous weaknesses associated with before and after data which might undermine results. A number of factors may bias and confound the results, for example a placebo effect, a Hawthorne effect, regression to the mean and/or co-intervention. As Chapter 3 demonstrates, a considerable RCT-based literature exists which examines the efficacy and effectiveness of CPAP compared with other therapies in the treatment of OSAHS. The study by Mar *et al.*¹²³ did not report the change in ESS or any other measure in the utility study that would have allowed comparison with the results of the systematic review of trial evidence in Chapter 3.

Choice of comparators

ResMed did not include the full range of comparators that are discussed in Chapter 3. For patients with diagnosed severe OSAHS it is not clear that a 'do nothing' option represents routine clinical practice. Incremental cost-effectiveness analysis examines the relative cost-effectiveness of treatment options. It is possible that by comparing CPAP with a 'do nothing' alternative, the comparative benefit of CPAP is increased, compared, for example, with dental devices. ResMed briefly describes the recent systematic review by Giles *et al.*⁵⁰ This review suggests that symptoms post treatment did not show a significant difference between CPAP and dental devices. However, Giles *et al.* also suggest that additional data are required.⁵⁰

Time horizon

ResMed modelled cost-effectiveness results over a 14-year time horizon. However, OSAHS is a chronic condition; therefore, given the NICE guidelines, it is appropriate to model the results for a lifetime horizon. ResMed used a 14-year time horizon for analytical convenience. It was assumed that the device life of CPAP was 7 years and a 14-year time horizon is a multiple of seven. The device life of

CPAP was not tested in the univariate sensitivity analysis. However, it was found that results were sensitive to the second most important cost driver in CPAP-treated patients: the cost associated with the device itself [i.e. 22% for CPAP (fixed) and 26% for CPAP (auto)]. Ayas *et al.*¹²² and Mar *et al.*¹²³ assumed the device life of CPAP to be 5 years. The shorter the device life, the greater the cost associated with the relevant treatment.

Errors in the model

There were shortcomings in the internal validity of the electronic model that may have led to inaccurate estimates of costs and QALYs.

Review of other NICE submissions (2007)

Fisher Pakyel Ltd and Respironics Ltd submitted partial economic evaluations that are not summarised here as they did not contain a full cost-effectiveness analysis.^{125,126}

Review of published economic evaluations

Review of Ayas *et al.*¹²²

Overview

Ayas *et al.*¹²² performed a cost-utility analysis comparing CPAP with a 'do nothing' alternative for the treatment of patients with moderate to severe OSAHS. The base-case analysis was patients aged between 25 and 54 years who were newly diagnosed with moderate to severe OSAHS, classified as having an AHI ≥ 15 events per hour. The analysis was undertaken from the US third-party payer perspective and the societal perspective.

The authors developed a Markov model with a 5-year time horizon. Each Markov cycle lasted 1 year. The primary outcome measure used in the analysis was incremental cost per QALY. The QALY estimate for CPAP incorporated the expected gains in HRQoL due to a reduction in RTAs. Effectiveness, utility and resource use estimates were obtained from the published literature and administrative databases. A number of univariate sensitivity analyses were undertaken. In addition, the authors undertook a probabilistic sensitivity analysis.

Summary of effectiveness data

For the base-case analysis, QALY estimates were obtained using utilities valued based on the standard gamble, in patients with OSAHS, pre and post CPAP therapy (Chakravorty *et al.*⁹⁷) Therefore, patient preferences rather than societal preferences were used for the valuations. Overall, a weighted average of the findings was obtained for patients

TABLE 20 ResMed model results of deterministic sensitivity analysis at end of 14 years

Scenario	Base-case value	Effect
Model results that are sensitive to input values		
Time to start of treatment: range 4.8 months to 12.0 months	8.400	Relative cost–utility changes marginally but CPAP (fixed) and CPAP (auto) remain dominant vs no treatment
Compliance rate with CPAP (fixed): range 0.5–1.0	0.790	Relative cost–utility of CPAP (fixed): range £703 to –£2543; at a compliance rate < 0.6 CPAP (fixed) is no longer dominant treatment; relative cost–utility of CPAP (auto) remains unchanged
Compliance rate with CPAP (auto): range 0.7–1.0	0.790	Relative cost–utility of CPAP (auto): range –£1,574 to –£2564; relative cost–utility of CPAP (fixed) remains unchanged
Risk of CVEs among treated and untreated patients: range 50% below to 75% above the base-case value	1.000	As risk increases, relative cost–utility of CPAP (fixed) ranges from £24 to –£2843, CPAP (auto) ranges from –£218 to –£2999; if risk falls to 60% below the base-case value, CPAP (fixed) ceases to be dominant
Ratio of CVEs to stroke among untreated OSAHS patients: range 1 : 4 to 1 : 0	0.47 : 0.53	As the ratio increases, the relative cost–utility of CPAP (fixed) ranges from –£404 to –£3534 and of CPAP (auto) ranges from –£870 to £3374
Risk of untreated OSAHS patients having an RTA: range 1.0–5.0 above background rate	2.600	As risk increases, relative cost–utility of CPAP (fixed) ranges from –£498 to –£3107 and of CPAP (auto) ranges from –£812 to £3244
Utility for untreated OSAHS: range 0.5–0.9	0.738	If utility falls below 0.68 CPAP ceases to be most cost-effective alternative, assuming treated OSAHS unchanged
Utility for treated OSAHS: range 0.5–0.9	0.811	If utility rises above 0.89 CPAP ceases to be most cost-effective alternative, assuming untreated OSAHS unchanged
Utility of non-fatal stroke in untreated OSAHS patients: range 0.5–0.9	0.590	As utility increases, relative cost–utility of CPAP (fixed) ranges from –£1532 to –£2020 and of CPAP (auto) ranges from –£1751 to –£2262
Utility of non-fatal stroke in treated OSAHS patients: range 0.5–0.9	0.649	As utility increases, relative cost–utility of CPAP (fixed) ranges from –£1694 to –£1510 and of CPAP (auto) ranges from –£1914 to £1739
Utility of non-fatal CVE in untreated OSAHS patients: range 0.5–0.9	0.664	As utility increases, relative cost–utility of CPAP (fixed) ranges from –£1565 to –£1708 and of CPAP (auto) ranges from –£1787 to £1936
Utility of non-fatal cardiovascular event in treated OSAHS patients: range 0.5–0.9	0.730	As utility increases, relative cost–utility of CPAP (fixed) ranges from –£1646 to –£1602 and of CPAP (auto) ranges from –£1858 to £1835
Utility of non-fatal RTA in untreated OSAHS patients: range 0.5–0.9	0.701	As utility increases, relative cost–utility of CPAP (fixed) ranges from –£1573 to –£1901 and of CPAP (auto) ranges from –£1792 to £1901
Utility of non-fatal RTA in treated OSAHS patients: range 0.5–0.9	0.771	As utility increases, relative cost–utility of CPAP (fixed) ranges from –£1649 to –£1607 and of CPAP (auto) ranges from –£1876 to £1831
NHS cost of cardiac rehabilitation in the first year following a non-fatal CVE: range £1851–£7404	£3702	As cost increases, relative cost–utility of CPAP (fixed) ranges from –£1445 to –£1970 and of CPAP (auto) ranges from –£1677 to –£2180
Annual NHS cost of stroke rehabilitation following non-fatal stroke: range £5070–£20,280	£10,140	As cost increases, relative cost–utility of CPAP (fixed) ranges from –£287 to –£4286 and of CPAP (auto) ranges from –£456 to £4623
NHS cost of managing a non-fatal RTA: range £6000–£22,000	£12,020	As cost increases, relative cost–utility of CPAP (fixed) ranges from –£1113 to –£2461 and of CPAP (auto) ranges from –£1384 to –£2609

continued

TABLE 20 ResMed model results of deterministic sensitivity analysis at end of 14 years

Scenario	Base-case value	Effect
Model results that are not sensitive to input values		
Per cent of OSAHS patients who are male: range 0.5–1.0	0.700	Relative effect unchanged
Probability of having a home diagnostic sleep study: range 0.5–1.0	0.750	Relative effect unchanged
Probability of having a home titration study: range 0.5–1.0	0.990	Relative effect unchanged
Probability of switching (fixed) to (auto) CPAP in the 2nd year: range 0.0–0.1	0.060	Relative effect unchanged
Probability of a clinician visit within 3 months of starting treatment: range 0.5–1.0	0.750	Relative effect unchanged
Probability of an annual visit with a consultant: range 0.0–0.5	0.130	Relative effect unchanged; relative cost–utility of CPAP (fixed) and CPAP (auto) changes marginally
Probability of an annual visit with a specialist nurse: range 0.4–1.0	0.610	Relative effect unchanged
Initial NHS cost of managing a CVE: range £1000–£2500	£1695	Relative effect unchanged; relative cost–utility of CPAP (fixed) and CPAP (auto) changes marginally
Initial NHS cost of managing an episode of stroke: range £1000–£2500	£1667	Relative effect unchanged; relative cost–utility of CPAP (fixed) and CPAP (auto) changes marginally
NHS cost of managing a fatal RTA: range £2000–£8000	£5688	Relative effect unchanged
Annual discount: rate 0–6%	3.5%	Relative effect unchanged; relative cost–utility of CPAP (fixed) and CPAP (auto) changes marginally
CVE, cardiovascular event; OSAHS, obstructive sleep apnoea–hypopnoea syndrome; RTA, road traffic accident.		

by age group and sex. These were adjusted for the impact of CPAP on RTAs and the impact of death due to natural causes, as explained below.

Estimates of effect were calculated based on the proportion of patients in one of six patient groups (i.e. ages 25–34, 35–44, 45–54 by sex), reflecting the distribution found in a sample of 99 patients with OSAHS: a distribution comparable to that in the United States. The probabilities of RTAs were stratified by the relevant patient groups. An RTA could either result in a fatality or property damage only or be injury related. The injury-related RTAs were stratified into one of five levels on the Maximum Abbreviated Injury Scale (MAIS), with scores ranging from one (minimal injury) to five (most severely injured). Of the patients having an RTA, the severity of injury was estimated as 85.6%, 10.5%, 3.3%, 0.4% and 0.2% for severity levels 1–5. RTA survivors in level 5 MAIS state were assumed to be unable to drive again and therefore were confined to a tunnel state in the model.

The effect of CPAP on RTAs was based on a random-effects meta-analysis of eight observational

studies in which actual RTAs were observed in patients pre and post initiation of CPAP (Table 21).^{131,136–142} It excluded driving simulator studies. A pooled reduction in RTA risk and an improvement in HRQoL due to CPAP were calculated by a random-effects meta-analysis using the inverse variance of the logarithm of the odds ratio. It was assumed that the RTA crash rate in OSAHS patients who received CPAP equalled that in the general population. The RTA rates in OSAHS patients who were *not* receiving CPAP were obtained taking the general population RTA rates and dividing these by the proportionate reduction in RTAs associated with CPAP therapy.

Based on one study (Chakravorty *et al.*⁹⁷) it was assumed that the average utility in patients receiving CPAP was 0.55, an increase in utility of 0.23 compared with baseline (no CPAP). The utilities were valued using the standard gamble. Quality weights for the five MAIS injury levels were obtained using the Functional Capacity Index (FCI), which used rating scale preferences from patients who had functional limitations exceeding

1 year. The FCI weights were applied using similar methods to those of Graham *et al.*¹⁴³

The transition probability of death was estimated by applying the yearly, sex-specific probability of an RTA death to the rate of death due to natural causes, based on US life tables.

Summary of resource utilisation and cost data

The base-case analysis included third-party payer, direct medical costs only. For the first year, the total cost of CPAP was calculated using the US Medicare fee schedule. For year 2 and year 5, ongoing annual CPAP cost components were included. The costs included those of the device and the time of medical and emergency specialists. For the first 15 months, rental fees were applied based on Medicare guidelines. Following this, patients incurred a rental fee. The CPAP machine was assumed to have a device life of 5 years.

For the analysis undertaken from a societal perspective, productivity losses associated with

RTAs were also included, e.g. losses in household and market productivity, and associated workplace costs were calculated using the human capital approach. Non-medical costs including legal costs and insurance administration costs were also included. Societal costs of RTAs were stratified by level of severity using the MAIS scale and were based on national data. Lifetime costs of RTA outcomes and costs were based on public sources. In addition, it was assumed that all RTA costs were uniformly distributed over a future of 40 years for all patient groups. Unit costs were reported separately from resource use. Costs were reported for the year 2003. A discount rate of 3% was applied to the costs and effects for the base-case analysis.

Patient compliance with CPAP was included in the analysis. A compliance rate of 70% was assumed, based on findings in one article (McArdle *et al.*³⁹) It was assumed that non-compliant patients incurred rental costs for the device and the cost of a single visit to their doctor over a 3-month period but did not benefit from the device over the period.

TABLE 21 Studies comparing rates of RTAs with and without CPAP therapy as used in the Ayas *et al.* model.¹²³

Source	Country	Number of patients	Mean AHI	Mean age	Definition of crash	Rates of RTA	
						CPAP	No CPAP
George, 2001 ¹³¹	Canada	210	54	52	From provincial insurance database	CPAP	No CPAP
Findley <i>et al.</i> , 1988 ¹³⁷	US	50	37	56	State DMV (injury or property damage > \$500)	0.06 per year	0.18 per year
Krieger <i>et al.</i> , 1997 ¹³⁶	France	547	59.8	56.6	Self-report	0 per year	0.07 per year
Engleman <i>et al.</i> , 1996 ¹³⁸	Scotland	215	47	53	Self-report (major incidents)	0.0256 per year	0.084 per year
Horstmann <i>et al.</i> , 2000 ¹³⁹	Switzerland	85	NA	NA	Self-report	0.001 per 16,000 km driven	0.005 per 16,000 km driven
Suratt and Findley, 1992 ¹⁴⁰	US	22	NA	NA	NS	2.7 per 1,000,000 km driven	10.6 per 1,000,000 km driven
Cassel <i>et al.</i> , 1996 ¹⁴¹	Germany	59	38.9	49	Self-report	0.023 per year	0.30 per year
Yamamoto <i>et al.</i> , 2000 ¹⁴²	Japan	39	55.7	48	Self-report	0.14 per 100,000 km driven	0.8 per 100,000 km driven

AHI, apnoea-hypopnoea index; DMV, Department of Motor Vehicles; RTA, road traffic accident.

Summary of cost-effectiveness

From a third-party payer perspective, CPAP was more costly and more effective than no CPAP and the ICER was \$3354 per QALY (95% CI \$1062 per QALY to \$9715 per QALY). From the societal perspective CPAP was also found to be more costly and more effective and had an ICER of \$314 (95% CI cost saving to \$6114). Based on the probabilistic sensitivity analysis, if the value of society's willingness to pay for a QALY is \$50,000, 100% of the 1000 Monte Carlo simulations favoured the cost-effectiveness of CPAP from the third-party payer and the societal perspective. From the societal perspective, 42% of the ICERs from the simulations indicated that CPAP was dominant, i.e. it was associated with lower costs and greater effects than was no treatment.

Based on the univariate sensitivity analyses, ICER estimates were shown to be robust to many assumptions associated with the parameter estimates chosen. The analytical perspective had a substantial influence on the ICER, resulting in a more than 10-fold higher ICER when comparing the third-party payer perspective with the societal perspective. The type of utility estimate used also had considerable influence on the ICER. When EQ-5D utility estimates were used in place of standard gamble estimates, the ICER estimate increased more than fivefold.

Comments on Ayas *et al.*¹²²

A single study (Chakravorty *et al.*⁹⁷) was used to measure the treatment effect of CPAP on sleepiness and hence HRQoL. This treatment effect was obtained from one arm of an RCT, with the pre-CPAP utility estimate used for the no treatment arm and the 3-month post-CPAP utility estimate used for the CPAP arm. As revealed by the systematic review (see Chapter 3), a considerable number of other data are available on the treatment effect of CPAP. Since only one arm of an RCT was used, in effect the data were subject to the same limitations associated with the before and after study design as mentioned in the discussion of the ResMed submission. It is worth noting that the mean change in ESS in the study arm used to inform the utility estimates was -8, which is considerably greater than the reduction with CPAP indicated by the weight of evidence incorporated in the systematic review in Chapter 3.

The impact of CPAP on RTAs was based on eight before and after studies, pre and post CPAP. Another influence that might undermine the results derived from this study design is referral bias. Patients may have been referred for suspected

sleep-disordered breathing because they were involved in an RTA, thereby falsely inflating rates prior to using CPAP. The authors undertook a sensitivity analysis, using the odds ratio of the lower end of the confidence interval, which gave an ICER of around \$3530 per QALY. The utility values were adjusted for various MAIS injury levels using the FCI. FCI weights represent rating scale preferences, whereas the NICE guidance focuses on choice-based measures of valuation.

For the base-case analysis, patient preferences were used to estimate utilities, based on the standard gamble technique. NICE methods guidance focuses on the use of societal preferences to inform health-care decision-making. However, it is worth noting that the authors applied EQ-5D estimates based on societal preferences in a sensitivity analysis.^{123,144} The resultant CPAP ICER was within ranges typically considered to be cost-effective.

CPAP is a chronic condition; therefore, it would have been appropriate to extrapolate results over the life course.

Review of Mar *et al.*¹²³

Overview

Mar *et al.*¹²³ performed a cost-utility analysis comparing nCPAP with a 'do nothing' alternative for the treatment of patients with OSAHS. The base case was defined as a 50-year-old male patient with moderate to severe OSAHS, classified as having an AHI ≥ 30 per hour and an ESS > 10 . The analysis was undertaken from the Spanish health-care system perspective.

The authors developed a semi-Markov (time-varying) model with a time horizon of 5 years and over the lifetime. Each Markov cycle lasted 1 year. The primary outcome measure used in the analysis was incremental cost per QALY. The QALY estimate for nCPAP incorporated the expected gains in HRQoL due to a reduction in stroke and CHD as well as the impact of these events on mortality and RTAs. At the end of each cycle patients could be in an OSAS state, have a non-fatal stroke or non-fatal CHD or die. During the cycle, patients could experience a temporary event: a stroke, CHD or an RTA. Cost estimates were also adjusted for the reduced risk of these three events. Effectiveness, utility and resource use estimates were obtained from the published literature and administrative databases. A number of univariate sensitivity analyses were undertaken. In addition, the authors undertook a probabilistic sensitivity analysis.

Summary of effectiveness data

The effect of CPAP on stroke, CHD, RTAs and HRQoL was incorporated in a series of steps. To model the reduced risk of stroke and CHD due to nCPAP compared with no CPAP, it was assumed that use of nCPAP returned blood pressure to its pre-OSAHS levels, as a consequence of the reduction in AHI by nCPAP. Based on an assessment of CVE risk, it was assumed that OSAHS patients with an AHI of greater than 30 had an increase in diastolic arterial pressure of 3.6 mmHg. It was estimated that increases in blood pressure were linearly correlated with the natural logarithm of the risk of stroke and CHD, based on MacMahon *et al.*¹⁴⁵ Therefore, applying this to the 3.6 mmHg increase in diastolic pressure, the natural logarithms of the risk could be obtained, thus estimating the relative risks of stroke and CHD. It was assumed that relative risk of these events remained constant at a given blood pressure and that absolute risk was best estimated by applying this relative risk to the baseline absolute risk for patient and age and sex using rates tables.

Mortality rates for stroke, CHD, RTAs and all causes by age and sex were based on an administrative database from the Basque country, Spain. The transition probabilities from OSAHS to death were based on the mortality rates of all causes, excluding stroke, CHD and RTAs. Age- and sex-specific mortality rates for the general population were multiplied by the corresponding relative risks to calculate the corrected rate for nCPAP and no CPAP groups (Table 22).

Utility values were obtained as described in Summary of effectiveness review for the ResMed submission (see pp. 54–5).

Summary of resource utilisation and cost data

The cost analysis was undertaken from the health-care perspective. The following direct costs were considered: costs of investigation, diagnosis and

treatment of OSAHS and costs attributable to CVE morbidity, costs associated with in-home technical maintenance and medical follow-up. The nCPAP was assumed to have a device life of 5 years.

Data relating to the last 5000 patients who had suspected OSAHS and who attended a sleep clinic (in the Basque country) were used to estimate the cost of diagnosis and the proportion of patients abandoning treatment during the first year. It was assumed that no benefits of treatment accrued to these patients.

Costs were reported for the year 2000 and were converted from Spanish pesetas to euros. A discount rate of 3% was applied to the costs and effects for the base-case analysis.

Summary of cost-effectiveness

The base-case analysis found that CPAP was more costly and more effective than no CPAP. The ICER for CPAP was €7861 per QALY over a 5-year time horizon and €4938 per QALY for the lifetime horizon.

Based on the univariate and multivariate sensitivity analyses, ICER estimates were robust to many assumptions associated with the parameter estimates chosen and remained in the region of €5000–€10,000. The only case where the ICER was found to exceed €20,000 per QALY was for a worst-case scenario analysis in which the authors used the lower limit of the CI obtained from the patient preference utility survey and a 5-year time horizon. As anticipated, the authors found that the cost-effectiveness ratio increases as the cost of nCPAP increases. For example, the authors assessed the impact of an increase in diagnostic costs on cost-effectiveness and the impact of two different types of diagnostic protocol on the ICER. As well as this, they presented disaggregated incremental effectiveness data (for CVE risk, RTAs and utility effect) and disaggregated incremental cost information for a 50-year-old male using nCPAP for both a 5-year and a lifespan time horizon. They

TABLE 22 Probability values used in the Mar *et al.*¹²³ model

Probabilities (relative risks)	Untreated OSAS patients	nCPAP OSAS patients
CHD	1.185	1.0
Stroke	1.353	1.0
Car accident	8.1	1.0
Death after stroke	1.1	1.1
Death after CHD	1.1	1.1

CHD, coronary heart disease; OSAS, obstructive sleep apnoea syndrome.

found that the results were very sensitive to the time horizon specified. Over the lifespan of the patient, improvements in quality of life accounted for 84% of the incremental effectiveness of nCPAP. The purchase and maintenance costs of nCPAP accounted for 86% of the overall incremental costs. When the time horizon was reduced to 5 years, these costs amounted to 98% and 61% of the overall incremental costs respectively.

Overall, therefore, the authors suggested that nCPAP is cost-effective in patients with an AHI ≥ 30 and who also exhibit symptoms of daytime sleepiness. The authors suggested that the improvement in HRQoL associated with nCPAP is the main force behind its clinical effectiveness, as measured in QALYs, being seven times greater than that of reduced CVE mortality, which in turn is seven times greater than that of decreased numbers of RTAs. The authors suggested that the remaining uncertainties about the impact of nCPAP on long-term mortality have relatively little impact on the clinical and economic efficiency of treatment.

Comments on Mar *et al.*¹²³

Data from a single survey, conducted as part of the study, were used to measure the treatment effect (in the form of change in sleepiness in terms of utilities) of CPAP versus no CPAP. As mentioned in the comments on the Ayas *et al.*¹²² study, a large number of other data were available but were not used to inform this estimate, and the data were based on a before and after design, which represents a weak source of evidence of effectiveness.

No account in the model was taken of the impact of an RTA on morbidity/utility or costs. It is not clear that the mortality rates for RTAs (or stroke or CHD) were related to OSAHS. Probabilistic sensitivity analysis was not undertaken.

Review of the Chilcott *et al.* Trent Report⁴⁴

Overview

The Trent Report, written by Chilcott *et al.*,⁴⁴ provided the foundation for the work undertaken by Mar *et al.*¹²³ A cost-utility analysis was undertaken which compared nCPAP with a 'do nothing' alternative for the treatment of patients with OSAS. Summary results were reported comparing nCPAP and dental devices. The authors undertook the analysis based on a review of the literature and using clinical opinion. The analysis was undertaken from the UK health-care system perspective. The primary outcome measure used in the analysis was incremental cost per QALY. Cost

estimates were also adjusted for the reduced risk of these three events. Effectiveness, utility, resource use estimates and costs were obtained from the published literature, administrative databases and clinical expert opinion. Several univariate sensitivity analyses were undertaken.

Summary of effectiveness data

No relevant utility data were available; therefore, an indirect approach was undertaken to estimate utilities. No data were reported on any change in ESS associated with treatment. The authors used SF-36 data generated by the Sleep Disorders Unit at the Royal Hallamshire Hospital in Sheffield. This involved a cohort study in which patients who were referred to the Unit for suspected OSAHS completed the SF-36 questionnaire before and after initiation of treatment, as reported in a conference abstract (Waterhouse *et al.*^{146,147}). Given that the data were not randomised, the authors attempted to validate them by comparing the results with data presented in Jenkinson *et al.*⁷⁷ They found that the before and after results were broadly similar for all SF-36 dimensions in the two studies. However, the population from the Waterhouse *et al.*¹⁴⁷ study appeared to have a lower initial baseline health status. The 1998 Brazier algorithm (Brazier *et al.*¹⁴⁸) (and another algorithm: no further details) was applied to the Waterhouse results to derive a preference-based single index measure of health. The QALY results at 1 year are reported in Table 23.

Summary of resource utilisation and cost data

The cost analysis was undertaken from the health-care perspective. As for the Mar *et al.*¹²³ analysis, the Trent Report considered the costs of investigation, diagnosis and treatment of OSAHS and maintenance and medical follow-up costs. In contrast to Mar *et al.*,¹²³ any costs attributable to CVE morbidity were not included in the analysis. The report did not mention the financial year of the cost data. The device life of nCPAP was estimated to be 5 years. A discount rate of 6% was applied to the costs and a discount rate of 1.5% was applied to effects for the base-case analysis.

Summary of cost-effectiveness

The results of the base-case analysis are reported in Table 24. The results were extrapolated on a time horizon of up to 5 years, assuming that the benefits accrued in the trial period were maintained.

Several univariate sensitivity analyses were undertaken, comprising impact of the analytical time horizon; costs of investigation for nCPAP;

long-term costs of maintenance, follow-up and other health-care resource usage; long-term impact of gross annual health-care costs; potential impact of improved mortality from use of nCPAP treatment; impact of uncertainty in morbidity benefits from nCPAP therapy; and discount rate. All estimates of cost-effectiveness over 1 year were < £16,000 per QALY gained.

The authors suggested that the cost-effectiveness of dental devices compared with no treatment was likely to be similar or worse than the cost-effectiveness of nCPAP therapy compared with no treatment. The costs of nCPAP and dental devices were similar. Based on two studies,^{80,149} they found small differences in clinical effectiveness and costs when comparing nCPAP with dental devices. The implied differences in costs and outcomes, and the considerable level of uncertainty associated with both, suggested to the authors that the incremental cost-effectiveness of nCPAP over dental advancement devices was likely to be highly uncertain.

Comments on the Trent Report

Data used to estimate effectiveness were short term and based on observational data (Waterhouse *et al.*, 2 weeks' duration;^{146,147} Jenkinson *et al.*, 4 weeks' duration⁷⁷). No account was taken of the potential impact of nCPAP on the risk of CVE or RTAs in terms of costs or effects. The analysis was deterministic.

Review of Tousignant *et al.*¹²⁴

Overview

Tousignant *et al.*¹²⁴ performed a cost-utility analysis retrospectively comparing the impact on HRQoL of pre-treatment with treatment using nCPAP. In this way nCPAP was compared with a 'do nothing' option in 19 patients with moderate to severe OSAHS. The study took place at a sleep clinic in Montreal, Canada.

Summary of effectiveness data

Patients attending a hospital sleep clinic (mean age 57 years, SD 10) and who had been receiving nCPAP treatment for an average of 9 months completed a standard gamble exercise. The health states valued were receiving treatment with nCPAP, pre-treatment, full health and immediate death. To assess the reliability of the results, patients completed the exercise on two occasions 2–3 weeks apart. The mean utility score for the pre-treatment health state was 0.63 (\pm 0.29) and the mean utility score for the nCPAP treatment health state was 0.87 (\pm 0.17). The intraclass correlation coefficients for the retest data were above 0.7 for both the treatment health state and pre-treatment health states. Patient life expectancy was estimated using Canadian life tables. The difference in utility pre and post treatment was multiplied by the life-years to calculate QALYs.

Summary of resource utilisation and cost data

The perspective of the cost analysis was not stated but appears to be the health-care system

TABLE 23 Gain in QALYs at 1 year in the Chilcott *et al.* Trent Report⁴⁴

	Mean	Lower 95% CI	Upper 95% CI
All study participants	0.10	0.07	0.12
Participants offered long-term nCPAP treatment	0.12	0.09	0.16

nCPAP, nasal continuous positive airway pressure; QALY, quality-adjusted life-year.

TABLE 24 Baseline cost per QALY gained in the Chilcott *et al.* Trent Report⁴⁴

Time horizon	Cost per QALY gained
1 month	£99,000
1 year	£8300
2 years	£5200
5 years	£3200

QALY, quality-adjusted life-year.

perspective. Costs included the cost of supplies and the rental and maintenance costs of the nCPAP device and associated devices (e.g. tubing and masks). It was estimated that the yearly cost of treating a patient in Quebec was CAN\$2348 (price year not given). Costs also included the cost of one overnight sleep study at the outset of treatment at CAN\$500, which included physician fees, technician salaries, supplies and amortisation of capital costs over 7 years. Alternatively, an ongoing cost of treatment per patient per year was estimated at CAN\$800.

Summary of cost-effectiveness

Based on the use of the different cost estimates (above) a high estimate of CAN\$9792 per QALY gained by nCPAP was calculated as well as a low estimate of CAN\$3397 per QALY gained. Three patients had particularly large treatment effects. The authors explored the impact of excluding the three patients on the cost–utility ratio. Without the three patients, based on the high cost estimate, the cost–utility ratio increased to CAN\$18,637 per QALY.

Comments on Tousignant *et al.*¹²⁴

As all the patients were currently receiving nCPAP therapy, their valuation of the pre-treatment health state was done retrospectively. Given this, it is difficult to ascertain the extent to which the difference in pre-treatment and treatment utility scores is a real difference reflecting the impact of nCPAP treatment and the extent to which it reflects some sort of measurement error due to bias in recall. In addition, the results may be unreliable due to the weaknesses associated with observational data. It appears that costs (and effects) were not discounted to present values. For the most part, resource use estimates were reported separately from costs. Only the impact of treatment effects over the short term was considered. The analysis was deterministic.

Discussion of manufacturers' submissions and published cost-effectiveness studies

Of the studies reviewed, none compared all therapies identified in the NICE scope, i.e. none compared CPAP with dental devices and conservative management. The NICE Reference Case states that costs included in the economic evaluation should be based on the NHS and PSS perspective. Only two studies (ResMed¹²⁰ and Chilcott *et al.*⁴⁴) examined the treatment of OSAHS in the UK NHS context, the others focusing on the US,¹²² Spanish¹²³ and Canadian¹²⁴ health-care systems.

The existing cost-effectiveness studies had several limitations that need to be addressed in order to assess the value for money of these technologies. The key limitations were:

- The cost-effectiveness studies did not use the full range of clinical trial 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.
- There were limited data (in terms of quantity and quality) on the long-term impact of OSAHS on HRQoL, CVE, RTAs and other outcomes.
- None of the evaluations examined all the comparators relevant to this review.

In an attempt to make full use of all of the available evidence on therapies for the treatment of OSAHS and in order to overcome some of the limitations noted above, a new cost-effectiveness model was developed.

York economic model

The objective of the York economic assessment was to assess the cost-effectiveness of CPAP by developing a clinically and economically appropriate decision model structured to characterise OSAHS and the impact of the different therapies. Several sources of evidence were used to inform the analysis. The model was developed using the methodological guidance for the NICE Reference Case (www.nice.org) as reported in *Table 25*. The development of the model was informed by research in the published literature including the clinical effectiveness systematic review reported in Chapter 3, published cost-effectiveness analyses, previously performed economic models and the advice of clinical experts participating in this technology assessment review. The methods used for decision modelling are based on those described in Briggs *et al.*¹⁵⁰

The new economic evaluation, undertaken by a team in York (and termed the York economic model from now on), is described in two parts. First, the methods used to perform the economic analysis are described; these comprise the structure of the model, the parameter estimates including a brief summary of the literature searches undertaken to inform the model, and the assumptions underlying the base-case analysis.

TABLE 25 Summary of NICE Reference Case

Element of health technology assessment	Reference case
Defining the decision problem	Scope developed by the Institute
Comparator	Alternative therapies routinely used in the NHS
Perspective on costs	NHS and PSS
Perspective on outcomes	All health effects on individuals
Types of economic evaluation	Cost-effectiveness analysis
Synthesis of evidence on outcomes	Based on a systematic review
Measure of health benefits	QALYs
Description of health states for calculation of QALYs	Health states described using a standardised and validated generic instrument
Methods of preference elicitation for health state valuation	Choice-based method, e.g. time trade-off, standard gamble (not rating scale)
Source of preference data	Representative sample of the public
Discount rate	Annual rate of 3.5% on both costs and health effects
Equity provision	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit

NICE, National Institute for Health and Clinical Excellence; PSS, Personal Social Services; QALYs, quality-adjusted life-years.

Second, the results of the base-case analysis are presented and the role of parameter uncertainty is investigated by means of a probabilistic sensitivity analysis.

Methods of York economic model

Overview

A cost–utility analysis was undertaken that compared CPAP with use of dental devices and conservative management, using comparators relevant to the NHS. The scope developed by NICE indicated that CPAP devices should be treated as a single class of intervention, and this was reflected in the modelling. However, in the secondary analysis, various adjuncts to CPAP, e.g. the use of a humidifier, were examined to assess their impact on the costs associated with CPAP. The costs and QALYs associated with CPAP, dental devices and conservative management were compared over a lifetime time horizon as OSAHS is a chronic condition. The cost of the resource use associated with each intervention was estimated from the NHS and PSS perspective for England and Wales. Costs relating to the financial year 2005 were reported.

The health effects of OSAHS, and the impacts of alternative treatments, were expressed in terms of QALYs. Given the dearth of HRQoL data

expressed in terms of utility in the randomised trials (see Chapter 3), it was necessary to estimate the relationships between clinical end points and QALYs using other data. Three clinical end points were related to QALYs. The first was difference in ESS between treatments; ESS was taken as the main measure of sleepiness given that it was reported in most trials, and in many it was the primary end point (see Chapter 3). The second clinical end point was differential treatment effect on blood pressure, which was reported in trials, and was related to CVE risks and hence to QALYs in the model. The third end point was differences in the risk of RTAs, which was based on non-randomised evidence and was related to QALYs in the model.

HRQoL in terms of utilities was expressed on the basis of generic HRQoL instruments, the EQ-5D and the SF-6D (a preference-based single-index measure for health, based on SF-36 and SF-12, allowing QALYs to be obtained for use in cost–utility analysis), and valued using the public preferences associated with those instruments. An annual discount rate of 3.5% was applied to costs and benefits to discount them to present values. The assumed target patient population is adults (16 years or older) with a diagnosis of OSAHS confirmed by use of an appropriate tool (e.g. the AHI or arterial oxygen desaturation index and the ESS). The model was run separately by age and

sex, given the availability of age- and sex-specific mortality data and CVE risks. The base-case analysis is based on a male aged 50, as the average age of patients in the RCTs was around 50 [at baseline the mean age range was 44–58 years (see Chapter 3)] and the majority of participants in the included RCT studies were male.

The following analyses were undertaken to explore the robustness of the findings in the York economic model.

Base-case analysis

- The base-case analysis compared the costs and QALYs of CPAP versus dental devices versus conservative management in a male aged 50 years.
- Subgroup analyses were undertaken by gender, OSAHS severity (as measured by ESS) and other relevant baseline patient characteristics.

Secondary analysis

- Scenario analyses undertaken to explore the impact on cost-effectiveness of:
 - excluding the impact of treatment on CVE
 - excluding the impact of treatment on RTAs
 - excluding the impact of treatment on both CVE and RTAs
 - change in ESS linked to SF-6D utility score rather than EQ-5D
 - relative risk reduction for CVE based on DBP and MacMahon *et al.*¹⁴⁵
 - autotitrating positive airway pressure (APAP) machine with 5-year life span and humidifier
 - treatment effects from bivariate random-effects meta-analysis (BRMA) (APBM only)
 - treatment effects from BRMA (APBM and office measurements).
- Subgroup analyses
 - for a cohort aged (35 and 65).
- Other relevant modelling assumptions.
- Uncertainty and value of information analysis.

The York economic model is fully probabilistic and the results from the model are presented probabilistically to reflect the implications of parameter uncertainty on decision uncertainty.

To inform research priorities, the expected value of perfect information (EVPI) was calculated for the decision problem.¹⁵⁰ This represents the value of obtaining perfect information on all the model parameters to eliminate the decision uncertainty

(given acceptance of the model structure and evidence base). The EVPI can be compared with the potential costs of additional research to indicate whether there is value in further research to reduce the decision uncertainty.

Structure of the York economic model

A Markov state transition cohort model was developed in Microsoft® Excel 2002 and the Bayesian evidence synthesis was undertaken using WinBUGS 1.4 (the WinBUGS code is reported in Appendix 8). The structure of the model is shown in *Figure 20*. The model characterises the patient's prognosis over his or her lifetime in terms of four health states: (1) OSAHS; (2) OSAHS post coronary heart disease (CHD); (3) OSAHS post stroke; and (4) death. Yearly cycles were chosen for the current model. The model records the ESS score of the hypothetical patient cohort and any change in ESS associated with treatment. As described in Chapter 3, the evidence suggests that interventions for OSAHS might have a beneficial effect on sleepiness, which may in turn affect the risk of RTAs. The trial data also describe the effect of treatment on blood pressure, which may in turn affect the incidence of CHD and stroke. Therefore, these events are included in the model. Based on the model structure, patients can remain in the initial OSAHS state until death. Alternatively, they could experience CHD, and those that survive move to an OSAHS post-CHD state that incorporates the increased mortality and morbidity associated with having had a first CHD event. They could then remain in this state until death, experience an RTA or have a stroke that may render them disabled.

Alternatively, they could experience a stroke from the initial OSAHS health state. Patients who survive a stroke enter an OSAHS post-stroke health state which incorporates the increased mortality and morbidity associated with having had a first stroke. Patients who are not disabled remain at risk of an RTA. In contrast, if they become disabled post stroke, it is assumed that they are no longer able to drive and therefore incur no further risk of a driving accident. Once in the OSAHS post-stroke health state it is assumed that they will remain in this health state until death, which could happen directly or following an RTA. The model does not record CHD events separately following a stroke.

Patients in the initial OSAHS state might at some point have an RTA which could be fatal or non-fatal. In the latter case they would return to the OSAHS state.

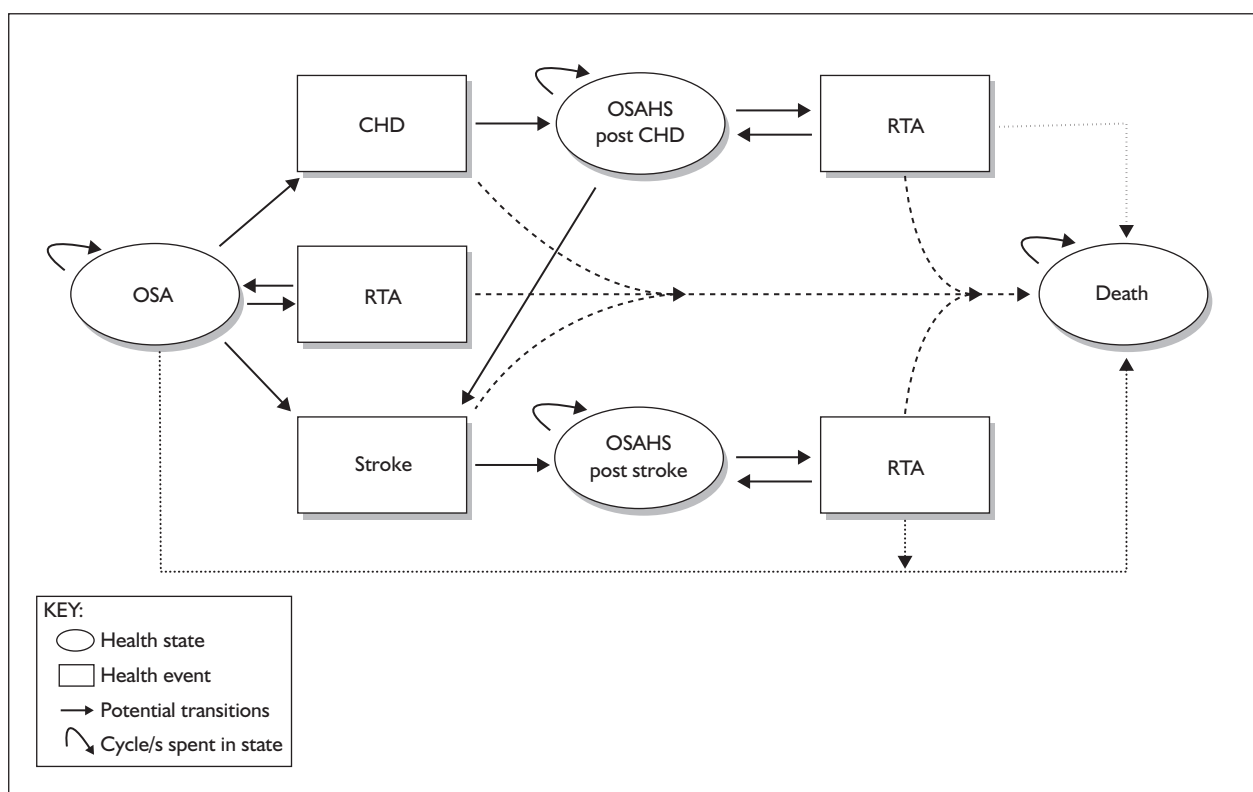


FIGURE 20 York economic model structure.

Parameter estimates for inclusion in the York economic model

This section reports the methods used to estimate parameters for the base-case analysis and secondary analyses. It describes the approach used to estimate the utility, resource use and costs associated with CPAP, dental devices and conservative management in the treatment of OSAHS.

The evidence used to populate the parameters of the economic model comprises the RCT data reviewed in Chapter 3 as well as relevant evidence from non-randomised trials, modelling studies, analyses of administrative databases and expert clinical opinion. In addition, individual patient data from three trials^{87,144,151} were obtained from the clinical experts on this technology assessment (RJOD/JS).

Several searches were undertaken to populate specific parameters of the economic model. Searches in MEDLINE were conducted to identify data to inform three elements of the model: (1) HRQoL studies, utilities and QALYs; (2) literature linking CVE, particularly stroke and CHD, to

OSAHS; and (3) literature linking RTAs to OSAHS. The search strategies are presented in Appendix 1, Cost-effectiveness searches.

Utility estimation for inclusion in the York economic model

As reviewed in Chapter 3, the evidence base on the effectiveness of CPAP in OSAHS consists of a number of randomised trials of varying designs (crossover and parallel), which display heterogeneity in their inclusion criteria and which report a considerable range of outcome measures covering sleepiness, HRQoL and blood pressure. Analysis was required to link the short-term outcome measures of clinical effectiveness to a preference-based measure of HRQoL in terms of utilities. The randomised trial data provided evidence on what can be viewed as intermediary outcomes in terms of sleepiness and blood pressure, but did not measure either treatment effects in terms of a reduction in the number of CVEs or a reduction in the risk of RTAs. Therefore, a model was required to link the available clinical data to long-term outcomes, HRQoL and costs in order to estimate the long-term cost-effectiveness of treatment with CPAP.

Valuing clinical effectiveness in terms of utility

The NICE Reference Case indicates that the measure of health outcome used in the cost-effectiveness analysis should be QALYs calculated with utility values derived from a validated generic, preference-based measure of HRQoL. The systematic review reported in Chapter 3 highlighted the measures used to describe the efficacy of treatments for OSAHS in RCTs, among which the ESS was the most frequently reported ($n = 27$ trials). Utility values and quality-adjusted survival were infrequently reported ($n = 1$ trial comparing CPAP to placebo) (Chakravorty *et al.*⁹⁷). Therefore, an additional literature search was undertaken, and this identified four other papers that contained potentially relevant HRQoL/utility data for inclusion in the model.

Table 26 reports key information on the four studies (see Appendix 7 for more details). Jenkinson *et al.*¹⁵² and Chakravorty *et al.*⁹⁷ also reported pre- and post-ESS scores. The former reported a pre-treatment ESS of 14 (SD 5) and a post-treatment score of 8.2 (SD 4.8). In a CPAP treatment arm,

Chakravorty *et al.*⁹⁷ reported a pre-treatment ESS of 16 (SD 6) and a post-treatment score of 8 (SD 6). In the lifestyle arm, Chakravorty *et al.*⁹⁷ reported a pre-treatment ESS of 14 (SD 4) and a post-treatment score of 11 (SD 5). Note that none of the studies reporting utility data assessed the use of dental devices.

In order to use the trial data and to allow a comparison between CPAP and dental devices, there was a need to link the data on clinical efficacy, in the form of the disease-specific ESS, to utility. Data on mean difference in ESS were available for 23 studies comparing CPAP with placebo and six studies comparing CPAP with dental devices. To achieve the link between change in ESS and change in utility, three sets of individual patient data were obtained, two that measured ESS and SF-36 profile in the same patients^{87,151} and one that measured ESS, SF-36 profile and EQ-5D in the same patients.¹⁴⁴ The SF-36 data were used to calculate utility values based on the SF-6D, using an algorithm developed by Brazier *et al.*¹⁵³ based on UK public preferences. The EQ-5D data were used to calculate utility based on general UK

TABLE 26 Summary of studies reporting utility data

Authors	Method	Study design	Utility values [mean (SD)]	Source of values
Tousignant <i>et al.</i> , 1994 ¹²⁴	SG	Retrospective before and after study. Patients did SG exercise twice (2–3 weeks apart) to assess reliability. Health states valued were: receiving nCPAP treatment and pre-treatment	Pre-treatment health state = 0.63 (0.29); nCPAP treatment health state = 0.87 (0.17)	Patients attending hospital sleep clinic who had been receiving nCPAP (for around 9 months) ($n = 19$)
Jenkinson <i>et al.</i> , 1997 ¹⁵²	EQ-5D	Before and after study. Patients completed EQ-5D before commencing treatment with nCPAP and 5 weeks later	Baseline EQ-5D index = 0.79 (0.21); post-treatment EQ-5D index = 0.84 (0.25)	Patients attending sleep clinic for nCPAP therapy ($n = 108$)
Chakravorty <i>et al.</i> , 2002 ⁹⁷	EQ-5D, SG	RCT comparing 3 months' treatment with CPAP with lifestyle management. EQ-5D and SG were completed before randomisation and at 3 months. In SG patients were asked whether they would choose their current state of health or treatment with two potential outcomes: complete cure or failure leading to a worst health state/death	<i>CPAP group</i> : SG pre-treatment = 0.32 (0.17); SG post-treatment = 0.55 (0.26); EQ-5D index pre-treatment = 0.73 (0.18); EQ-5D index post-treatment = 0.77 (0.18) <i>Lifestyle group</i> : SG pre-treatment = 0.31 (0.13); SG post-treatment = 0.35 (0.12); EQ-5D index pre-treatment = 0.77 (0.12); EQ-5D index post-treatment = 0.77 (0.09)	Patients referred to hospital sleep clinic ($n = 71$)
Mar <i>et al.</i> , 2003 ¹²³	EQ-5D	Before and after study. Patients completed EQ-5D pre-treatment and after using nCPAP for 3 months	Baseline EQ-5D index = 0.74; post-treatment EQ-5D index = 0.81	Patients referred to sleep unit ($n = 46$)

EQ-5D, EuroQol-5 Dimensions; nCPAP, nasal continuous positive airway pressure; SG, standard gamble.

population tariff values.¹²⁸ The three data sets were then used to develop prediction models to estimate the relationship between ESS and (1) utility values based on SF-6D and (2) utility scores based on EQ-5D.

A simple linear regression model was fitted to predict absolute utility scores from absolute ESS, controlling for baseline utility and baseline ESS. A larger number of observations were available with the SF-6D in comparison with the EQ-5D and, where multiple observations were available on the same patient, analyses were adjusted to reflect the dependence between repeated observations on the same individual. All variables were treated as continuous data, and baseline scores were centred prior to estimation. The use of ordinary least squares (OLS) regression relies on the assumption that the error terms are normally distributed. Assessment of the residuals estimated in both regressions revealed that this assumption appeared reasonable for utility scores based on the SF-6D (*Figure 21*). However, typically, EQ-5D scores do not follow a normal distribution, and as expected the EQ-5D scores in the data set formed a distribution skewed to the left, with a large number of observations clustered at a score of 1. *Figure 21* shows that the residuals from the regression of EQ-5D scores on ESS deviate somewhat from a normal distribution. Although OLS regression methods have been found to perform well when predicting

EQ-5D scores,¹⁵⁴ a generalised linear model was also fitted to the data to ascertain whether an alternative error distribution such as a gamma might produce a better fit. However, this model did not improve the fit on the basis of the Akaike Information Criterion and so the results from the OLS model were used for both the EQ-5D and the SF-6D.

The results of the regression analyses are shown in *Tables 27* and *28*. The models indicate that an increase of 1 point in ESS is associated with a fall in utility of 0.01 and this is true for both the SF-6D and EQ-5D instruments, the results of which were remarkably similar. A test was performed to see if there was evidence for a change in relationship between different levels of baseline ESS (i.e. a change in the slope of the regression line for particular cut-off values of ESS) but there was no evidence to support such a subgroup effect.

The Cholesky decomposition of the covariance matrix from the regressions was employed to characterise the uncertainty around the estimated coefficients and to reflect the correlation between coefficients in the probabilistic sensitivity analysis.¹⁵⁰ The baseline utility for the hypothetical patient population was predicted from the specified baseline ESS score. Changes in ESS associated with treatment were converted to changes in utility

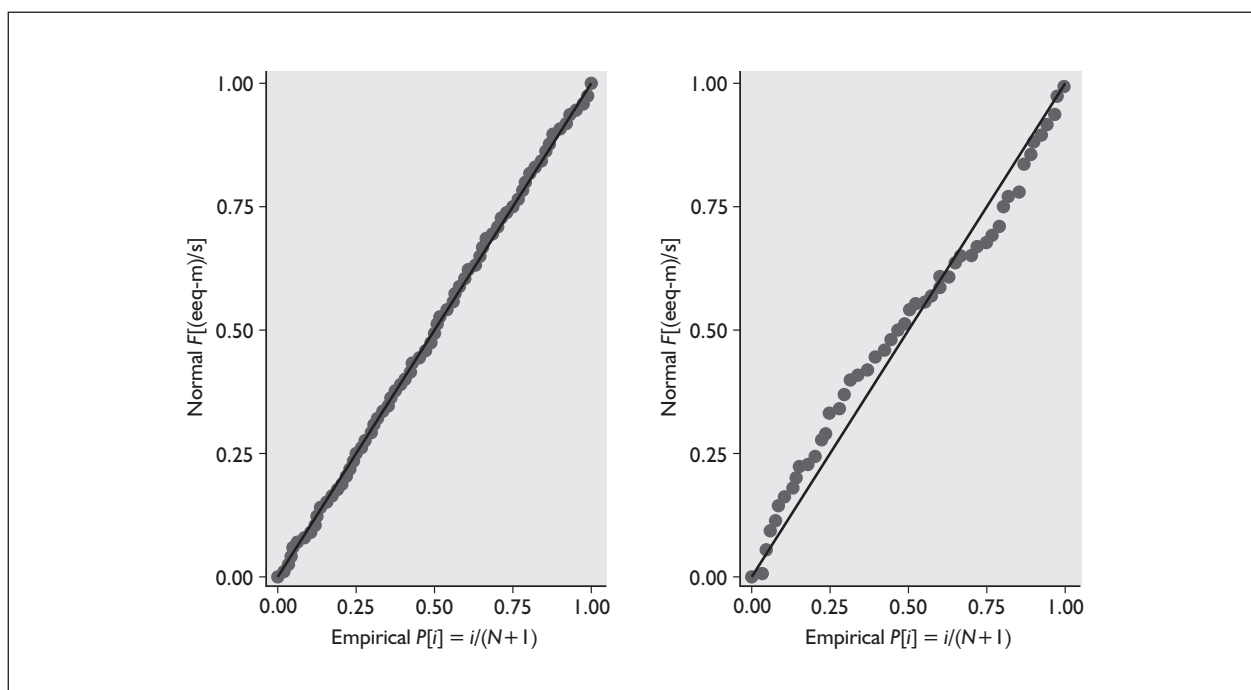


FIGURE 21 Standardised normal plot of residuals for use in York economic model.

TABLE 27 Predicting utility scores from ESS for use in York economic model

Utility	Coefficient	SE	p-Value	95% CI	
OLS model for utility based on SF-6D (n = 294)					
ESS	-0.0095213	0.0013849	0.000	-0.0122512	-0.0067915
Baseline ESS	0.0050331	0.0011942	0.000	0.0026791	0.0073871
Baseline utility	0.5588972	0.0534972	0.000	0.4534455	0.6643489
Constant	0.8067555	0.0115013	0.000	0.7840845	0.8294265
OLS model for utility based on EQ-5D (n = 94)					
ESS	-0.0096984	0.003947	0.016	-0.0175364	-0.0018604
Baseline ESS	0.0029526	0.0033693	0.383	-0.0037382	0.0096435
Baseline utility	0.6287684	0.1346153	0.000	0.3614492	0.8960877
Constant	0.8925207	0.0286109	0.000	0.8357052	0.9493363

ESS, Epworth Sleepiness Scale; OLS, ordinary least squares; SF-6D, a preference-based single-index measure for health, based on SF-36 and SF-12, allowing QALYs to be obtained for use in cost-utility analysis.

(utility increments) using the predicted relationship between ESS and utility.

The utility decrements associated with stroke, CHD and age were based on the regression analysis reported by Sullivan *et al.*¹⁵⁵ and are reported in Table 28. Utility decrements and increments can be applied to the baseline utility of the hypothetical cohort to reflect the utility associated with being in any health state in the model. The EQ-5D scores used in the analysis by Sullivan *et al.* were calculated using US community preferences. However, equivalent decrements were not available based on UK community preferences. The uncertainty around the utility decrements was characterised using a normal distribution, as the utility decrements are described by the coefficients

from a regression analysis. The standard errors are small enough that there is no risk of unsuitable values being selected in the probabilistic analysis.

The utility associated with experiencing an RTA was based on EQ-5D measures from the Health Outcomes Data Repository (HODaR).¹⁵⁶ HODaR recorded EQ-5D data for individuals 6 weeks after their inpatient episode (at Cardiff Hospital, UK) for injuries sustained from an RTA. Data were extracted for all patients who had a traffic accident as a motorcycle rider, an occupant of a three-wheeled motor vehicle, a car occupant or an occupant of a pick-up truck or a van [V20 to V59, International Classification of Diseases-10 (ICD-10) codes]. Results were found for 56 patients. A gamma distribution was used to characterise

TABLE 28 Utility scores for use in the York economic model

Utility	Mean	SD	Source
OSAHS untreated (baseline)	Baseline ESS × (-0.01 + 0.89) ^a		Estimated from prediction equation (see Table 27)
OSAHS treated with CPAP (change from baseline)	MD_ ESS _{CPAP_CM} × -0.01		Estimated from prediction equation (see Table 27)
OSAHS treated with dental devices (change from baseline)	MD_ ESS _{DD_CM} × -0.01		Estimated from prediction equation (see Table 27)
Stroke (absolute decrement)	-0.0524	0.0002	Sullivan and Ghushchyan, 2006 ¹⁵⁵
CHD (absolute decrement)	-0.0635	0.0001	Sullivan and Ghushchyan, 2006 ¹⁵⁵
RTA (absolute utility)	0.62	0.27	Currie <i>et al.</i> , 2005 ¹⁵⁶
Age decrement (per year)	-0.0007	0	Sullivan and Ghushchyan, 2006 ¹⁵⁵

CM, conservative management; CHD, coronary heart disease; DD, dental device; ESS, Epworth Sleepiness Scale; MD_ ESS, mean difference in ESS; OSAHS, obstructive sleep apnoea-hypopnoea syndrome; RTA, road traffic accident.
 a When using equation based on EQ-5D.

the uncertainty around the utility decrements associated with clinical events.

For the base-case analysis the effect of treatment on ESS was derived by pooling all of the available trial data to obtain an overall effect. However, in Chapter 3 it was noted that there was a high level of heterogeneity in this overall analysis that was reduced when trials were grouped by baseline severity of OSAHS. The treatment effects estimated by pooling trials grouped according to average baseline ESS (mild, moderate or severe) were applied in three separate analyses (see Chapter 3, *Figure 2*). These analyses cannot be interpreted as subgroup analyses reflecting differential treatment effects according to OSAHS severity as they are based on a study-level covariate in the form of average baseline ESS. In order to conduct a true subgroup analysis, trial data would have to be available that estimated the relationship at the patient level between baseline ESS and change in ESS with treatment.

Linking reduction in blood pressure to cardiovascular events

As noted above, the randomised trials provided information on the effect of CPAP on blood pressure but, for the economic model, the implications of this treatment effect for clinical events need to be estimated. The Framingham risk equations provide a link between risk factors such as blood pressure and the incidence of fatal and non-fatal CVDs. Published risk equations predict the risk of CHD and stroke¹⁵⁷ over a range of 4–12 years as a function of either SBP or DBP. Anderson *et al.*¹⁵⁷ state that, of the two alternative measures, SBP was the best predictor of stroke, and

therefore this was selected as the measure of blood pressure to be included in the economic model. We did not identify corresponding risk equations that incorporated MAP. The risk equations were estimated separately for men and women using the baseline characteristics of the hypothetical patient population shown in *Table 29*, which were determined from the RCT data where possible and based on plausible assumptions otherwise. It was also possible to incorporate the increased baseline risk associated with high BMI using the relative risk published by Mora *et al.*¹⁵⁸ However, as none of the relevant comparators demonstrated efficacy in terms of weight loss and reducing BMI, this was not included in the analysis.

It was assumed that the only risk factor affected by use of CPAP was blood pressure. The Framingham risk equations are based on Weibull models, and so the predicted risk is non-linear with respect to each risk factor. To determine whether the use of the mean change in blood pressure would bias the results, a check was performed on a set of individual patient data that reported change in blood pressure. The risk of CHD and stroke was predicted for each patient individually, and the mean of the individual predicted risks was compared with the risk based on the mean change in blood pressure for the whole group. The risks were found to be identical to two decimal places, and so it was felt that, although the equations are non-linear, the use of the mean change would not bias the model results.

In order to estimate the probability of CHD and stroke events per model cycle, a piece-wise exponential was assumed. The equations were used

TABLE 29 Hypothetical baseline patient characteristics for use in the risk equations of the York economic model

Age	50
SBP	130
Smoking (0 = no; 1 = yes)	1
Total cholesterol (mg/dl)	224
HDL-cholesterol (mg/dl)	43
Diabetes (0 = no; 1 = yes)	1
ECG-LVH (0 = no; 1 = yes)	0
Ten-year probability of stroke event	3.4% (male); 3.7% (female)
Ten-year probability of death from CVD	3.8% (male); 3.6% (female)
Ten-year probability of CHD	19.7% (male); 19.2% (female)
Ten-year probability of death from CHD	3.9% (male); 3.7% (female)

CHD, coronary heart disease; CVD, cardiovascular disease; ECG-LVH, electrocardiographic left ventricular hypertrophy; HDL, high-density lipoprotein; SBP, systolic blood pressure.

to predict the 4-year probability of an event every 4 years given the current age of the hypothetical patient cohort and starting from year 0. For the intervening years it was assumed that survival followed an exponential distribution, and so each 4-year probability was converted into a constant yearly probability to be applied over the relevant 4-year interval. When multiple equations from the Framingham set are used they should be applied in random order to take into account competing risks. However, in a cohort model structure the risk equations must be applied in the same order across the entire cohort for any given model cycle. This is relevant to patients in the initial state of the model who may experience either CHD or a stroke event. Rather than specify an order in which to apply the equations, the probability of any event was calculated by summing the hazards and then the proportion of events that were CHD or stroke events was calculated.

The relative risk reduction for CVE implied by the difference in SBP with CPAP compared with usual care is estimated to be relatively low using the Framingham risk equations (RR ≈ 0.98 for mean reduction in SBP of 1.06 mmHg). It has been posited that the Framingham risk equations may be subject to regression dilution bias when describing the relationship between a change in blood pressure and the change in risk of cardiovascular disease (CVD) events. Random fluctuations in blood pressure may cause the relationship between blood pressure and incidence of CVEs to be underestimated if the analysis is conducted on the basis of single baseline assessment of blood pressure. The Framingham risk equations specified in Anderson *et al.*¹⁵⁷ are based on the average of two office measurements of blood pressure (systolic or diastolic). MacMahon *et al.*¹⁴⁵ conducted an analysis to estimate the change in risk of stroke and CHD as a function of DBP in which they correct for regression dilution bias by incorporating data on usual DBP (average DBP over several years) as well as baseline DBP. Their results indicate that the percentage reduction in risk of stroke or CHD is approximately linearly related to DBP. They estimate that a 7.5 mmHg fall in DBP is associated with a 46% (SD 2%) reduction in risk of stroke and a 29% (SD 1%) reduction in risk of CHD. MacMahon *et al.* did not estimate the absolute risk of stroke or CHD events associated with particular levels of DBP. Therefore, a scenario analysis was conducted in which the baseline risks of stroke and CHD events were determined by the Framingham risk equations, but the change in risk associated with treatment was modelled using the relationship provided by MacMahon *et al.* The relative risk

reduction for CVE implied by the difference in DBP with CPAP compared with usual care is estimated to be higher based on the MacMahon *et al.* analysis in comparison with the Framingham risk equations (RR = 0.96 for CHD and RR = 0.94 for stroke given a mean reduction in DBP of 1.20 mmHg).

Evidence synthesis on change in ESS and SBP

The model incorporates data on the effectiveness of treatments for OSAHS in terms of change in ESS and change in SBP. The use of a BRMA allows the incorporation of the between- and within-study correlation in the treatment effect in these two end points.^{159,160} The between-study correlation is estimated in the meta-analysis on the basis of those studies that report both outcomes. However, none of the studies provided an estimate of the within-study correlation between the mean change in ESS and the mean change in SBP. As it was felt that these treatment effects might be correlated, a set of patient-level data were obtained from which an informative prior distribution for the within-study correlation could be estimated.^{87,144,151} Note that the assumption in the BRMA is that *treatment effects* on different outcomes may be correlated, and not that measures of ESS and blood pressure might themselves be correlated. The meta-analysis was performed in WinBUGS, and the code and data appear in Appendix 8.

The results of the BRMA are shown in *Table 30*. The estimate for the mean change in ESS is similar to that reported in Chapter 3. This is not surprising given the relatively small number of data points that inform this estimate. However, the estimate for the mean change in blood pressure differs somewhat from that reported in Chapter 3. This is because the BRMA in essence imputes the missing SBP for the 19 studies that did not report that end point on the basis of the observed between-study correlation. Only four trials reported both ESS and daytime SBP based on ABPM.^{64,83,89,109} This provides limited data to inform the estimation of the parameters of the BRMA relating to between-study correlation. For this reason the mean changes estimated in separate univariate meta-analyses in Chapter 3 were applied in the base-case analysis, and these were used regardless of whether the differences were statistically significant. The estimates from the BRMA were applied in a sensitivity analysis. Three additional trials reported both ESS and daytime SBP based on office measurements.^{62,70,100} While the absolute SBP recorded by ABPM may be expected to differ from that recorded by an office-

TABLE 30 Results of a BRMA for mean difference in ESS and mean difference in SBP (CPAP versus conservative management)

Measure	ESS [MD (SD)]	SBP [MD (SD)]
BRMA incorporating trials that report SBP based on ABPM	-2.65 (0.43)	-1.64 (1.72)
BRMA incorporating trials that report SBP based on ABPM or office measures	-2.62 (0.43)	-3.69 (1.55)

ABPM, ambulatory blood pressure monitoring; BRMA, bivariate random-effects meta-analysis; ESS, Epworth Sleepiness Scale; SBP, systolic blood pressure.

based measure, it could be argued that the *changes* in SBP may be comparable. If this assumption is acceptable, then a BRMA could be estimated based on seven trials that report both outcome measures, as shown in *Table 30*.

No trials reported change in daytime SBP based on ABPM for the comparison of CPAP with dental devices. For the base-case analysis, it was assumed that the ratio of the treatment effects on daytime SBP for CPAP and dental devices compared with placebo would be equal to the ratio of the observed treatment effects on ESS. The mean differences in ESS for CPAP versus conservative management ($MD_ESS_{CPAP_CM}$) and for CPAP versus dental devices ($MD_ESS_{CPAP_DD}$) were reported in Chapter 3. The mean difference in ESS for dental devices versus conservative management was calculated from this information using standard methods for an indirect comparison ($MD_ESS_{DD_CM} = MD_ESS_{CPAP_CM} - MD_ESS_{CPAP_DD}$) (Bucher *et al.*¹⁶¹). The mean difference in SBP for dental devices compared with conservative management was therefore calculated as $MD_SBP_{DD_CM} = MD_SBP_{CPAP_CM} \times (MD_ESS_{DD_CM} / MD_ESS_{CPAP_CM})$.

Where parameters were estimated in WinBUGS, the output from 10,000 Monte Carlo iterations was used directly to characterise the uncertainty around the estimated treatment effects and to incorporate the correlation between outcomes. The uncertainty around treatment effects estimated in the meta-analysis reported in Chapter 3 was characterised using a normal distribution.

Estimating the treatment effect of interventions on RTAs

To estimate the impact of CPAP on RTAs, the meta-analysis of before and after studies undertaken by Ayas *et al.*¹²² was updated (see *Table 21*). Only one additional study was found (Barbé *et al.*¹⁶²). Because this study reported a relative risk rather than an odds ratio (as in the Ayas *et al.* paper¹²²), the data reported on events and non-events were used to (re)calculate an odds ratio. The log odds ratios were then pooled by means of inverse variance weighting. The separate and pooled odds ratios are reported in *Table 31*. Note that, although the relative risk reduction of experiencing an RTA with CPAP treatment is high, the absolute baseline risk is very low.

The literature search did not identify any studies that assessed the impact of treatment with dental devices on RTAs. For the base-case analysis an adjusted odds ratio for dental devices compared with conservative management was estimated by applying the ratio of the treatment effects on ESS for CPAP and dental devices versus conservative management to the odds ratio for RTAs for CPAP versus conservative management.

It was assumed that patients left disabled following a first stroke event would no longer be at risk of an RTA. For the base-case analysis the proportion of first strokes that were disabling was estimated to be 30.9% based on the Second European Stroke Prevention Study (ESPS-2).¹⁶³ Note that the base-case analysis applies to patients who hold a driving

TABLE 31 Meta-analysis to calculate the RTA rates with CPAP compared with those without CPAP

Source	Odds ratio	Variance
Ayas <i>et al.</i> , 2006 ¹²² (based on eight studies)	0.15	0.00094
Barbé <i>et al.</i> , 2007 ¹⁶² (single study)	0.33	0.02075
Pooled data Ayas <i>et al.</i> , 2006 ¹²² and Barbé <i>et al.</i> , 2007 ¹⁶²	0.17	0.00098

RTA, road traffic accident.

TABLE 32 Treatment effects used to populate the York economic model

	CPAP vs CM [mean (SD)]	CPAP vs DD [mean (SD)]	DD vs CM [mean (SD)]
ESS (mean difference)			
Overall ^a	-2.7 (0.38)	-0.85 (0.64)	-1.85 ^b
Mild baseline severity (ESS)	-1.07 (0.39)	NA	NA
Moderate	-2.33 (0.36)	-0.85 (0.64)	-1.48 ^b
Severe	-4.99 (0.76)	NA	NA
Blood pressure (mean difference)			
SBP ^a	-1.06 (1.17)	NA	-0.73 ^b
DBP	-1.20 (0.88)	NA	-0.82 ^b
RTA (odds ratio) ^a	0.17 (0.001)	NA	0.25 ^b
CM, conservative management; DBP, diastolic blood pressure; DD, dental device; ESS, Epworth Sleepiness Scale; NA, not applicable; RTA, road traffic accident; SBP, systolic blood pressure.			
a Base-case analysis.			
b Derived parameter.			

licence. For OSAHS sufferers who do not drive the appropriate analysis is one in which the risk of RTA is excluded.

In summary, *Table 32* shows the treatment effects used to populate the York economic model.

Compliance

The long-term compliance with CPAP will have implications for the estimated effectiveness in the target population. The majority of the trial data were based on less than 12 weeks' follow-up. Given this, long-term compliance with CPAP was estimated on the basis of observational data provided by McArdle *et al.*³⁹ This study reported compliance over 6 years in a cohort of Scottish patients with a median age of 50 and an average ESS score at baseline of 12. The results indicated that 84% of patients continued to use CPAP 1 year after initiation of treatment, and that compliance was steady after a period of 4 years, with 68% of patients continuing treatment. The percentage of patients compliant at 2 and 3 years after treatment initiation was read from the survival curve (74% and 73% respectively) and these data were then used to model the rate of discontinuation from years 1 to 4 in the model. Patients discontinuing treatment were assumed to return immediately to the levels of ESS, SBP and utility associated with no treatment. In the base-case analysis it was assumed that 90% of patients who discontinued treatment with CPAP would return their machine. Equivalent data were not available for dental devices, and so in the base-case analysis it was assumed that

compliance with dental devices was equivalent to that for CPAP.

Mortality rates

Table 33 reports the parameters associated with CHD, stroke and RTAs.

The mortality rate for individuals who have not experienced CHD or stroke (by age and sex) was taken from the UK life tables of the Government Actuary Department (www.gad.gov.uk). For each age band, the all-cause hazard was reduced by the proportion of people dying of cardiovascular disease (CVD) or ischaemic heart disease (IHD) causes to get the hazard of death for non-CVD or non-IHD causes using methods developed by Chiang.¹⁶⁸ For patients who experienced CHD or stroke, an elevated mortality rate was used based on relative risks from the literature. For patients who experienced CHD and stroke, relative risks of death of 3.2¹⁶⁵ and 2.3,¹⁶⁴ respectively, were employed. These relative risks were applied to the non-cardiovascular/ischaemic heart disease mortality rates in the UK population (by age and sex).

Resource use and cost estimation for the York economic model

The costs of the three interventions for OSAHS included the initial costs of the interventions as well as the ongoing costs of care associated with the interventions. The costs included the cost of the devices, staff time and overheads associated with providing the interventions and the cost of other NHS health care and PSS related to OSAHS. Costs were reported in prices relating to 2005 and any

TABLE 33 Parameters associated with CHD, stroke, RTAs and death from other causes used in the York economic model^a

Parameter	Mean	95% CI	Source
CHD			
Relative risk of death following CHD	3.2	2.67–3.83	Rosengren <i>et al.</i> , 1998 ¹⁶⁵
Stroke			
Relative risk of death following stroke	2.3	2.0–2.7	Dennis <i>et al.</i> , 1993 ¹⁶⁴
RTAs			
Rate of non-fatal RTAs for male licence holders	0.0089	b	Department of Transport, 2004 ¹³³
Rate of non-fatal RTA for female licence holders	0.0082	b	Department of Transport, 2004 ¹³³
Rate of fatal RTA for male licence holders	0.00014	b	Department of Transport, 2004 ¹³³
Rate of fatal RTA for female licence holders	0.000060	b	Department of Transport, 2004 ¹³³
CHD, coronary heart disease; RTAs, road traffic accidents.			
a The following risks are not detailed in the table as they were estimated as age and sex dependent from national life tables (other cause mortality) or from the Framingham risk equation (risk of fatal and non-fatal stroke and fatal and non-fatal CHD).			
b Estimates based on population (rather than sample) data, therefore no uncertainty expressed.			

costs that related to previous years were uprated using the Hospital and Community Health Services (HCHS) pay and prices index (2006).¹⁶⁶

The review of the published cost-effectiveness studies identified limited information on resource use associated with CPAP treatment. Only one study related to the UK setting.⁴⁴ This study included the costs of investigation and diagnosis for OSAHS and nCPAP. In contrast, the York model includes adults who have already been diagnosed with OSAHS and therefore does not incorporate this cost. The current study attempts to take into account the impact of treatment in terms of the utilisation of other health-care resources comprising any health-care use due to stroke, CHD and RTAs. None of the existing published cost-effectiveness studies included the full range of relevant costs and none compared dental devices with CPAP for OSAHS in the UK.

The costs of CPAP, dental devices and conservative management used in the York economic model are shown in *Table 34*. The majority of CPAP costs and resource use were obtained from the ResMed submission, which was informed by a survey of 19 clinical experts. Other relevant data were obtained from published studies and from correspondence with clinical experts.

It was assumed that the CPAP machine has a device life of 7 years (which was the device life used by ResMed and confirmed by a clinical expert) and that a dental device lasts for 2 years (based on clinical opinion). The costs of the devices were expressed as equivalent annual costs¹²¹ using the public sector discount rate of 3.5%.

No published NHS cost of dental devices for the treatment of OSAHS was found; therefore, to fulfil the scope of the review, the cost was estimated based on clinical opinion. It was assumed that the dentist provided a Thornton Adjustable Positioner (TAP), a device that is commonly used for the treatment of OSAHS in the UK. Under the new NHS Dental Contract a course of treatment is classified into a treatment band. It is appropriate to classify TAP provision as Band 3 as such treatment requires laboratory work (www.ic.nhs.uk/). Twelve units of dental activity (UDAs) are applied to Band 3.¹⁶⁷ The national average reimbursement rate for a UDA is not known. The value of UDAs varies because of a number of factors, including the contract values negotiated locally by primary care trusts (PCTs), differences in the treatment patterns, treatment needs in different areas and the degree to which PCTs may have set broader service objectives for contractors that cannot be measured by units of dental activity (Department of Health, personal communication). Therefore, the value of a UDA was obtained from published material (Bath

TABLE 34 Costs and resource use associated with treatments for OSAHS included in the York economic model

Parameters	Costs (2006)	Probability [mean (SD)]	Number	Source
CPAP and APAP initial costs				
<i>Outpatient visit</i>				
Unit cost of outpatient (consultant) visit	£107.87			NHS reference costs 2006
Probability of having a follow-up outpatient visit		0.69 (0.3)		ResMed survey of clinicians
Total cost of follow-up outpatient visit	£74.52			
<i>Home titration</i>				
Probability of home titration		0.99 (0.01)		ResMed survey of clinicians
Probability of using APAP		0.81 (0.19)		ResMed survey of clinicians
APAP machine	£410			ResMed
Probability of using CPAP		0.19		ResMed survey of clinicians
CPAP machine	£280			ResMed
Number of times CPAP/APAP used for dose titration			163	
Total cost of home titration	£2.34			
<i>Inpatient titration</i>				
Probability of inpatient titration		0.01		Assume if not home titration must be inpatient titration (1-0.99)
Unit cost of sleep study follow up	£107.87			NHS reference costs 2006
Total cost of inpatient titration	£1.08			
<i>Titration by specialist nurse</i>				
Probability of seeing a specialist nurse for titration		1		Assumption
Unit cost of 30-minute appointment with specialist nurse	£34			NHS reference costs 2006
Total cost of titration by specialist nurse	£34			
<i>Titration by consultant</i>				
Probability of seeing a consultant for titration		0.4		ResMed survey of clinicians
Total cost of titration by consultant	£43.10			
Total cost of 30-minute appointment with technician	£9.50			
<i>Total initial costs (first year)</i>				
CPAP	£164.64			
APAP ^a	£108			
CPAP ongoing costs				
Interest rate			3.5%	NICE methods guidance
Estimated device life of CPAP			7 years	
Annual equivalent cost of CPAP device	£44.24			280/annuity factor
Annual equivalent cost of CPAP mask	£80			ResMed
Annual sundries	£15			Clinical opinion
Annual follow-up	£79			Clinical expert referring to NHS tariff

TABLE 34 Costs and resource use associated with treatments for OSAHS included in the York economic model

Parameters	Costs (2006)	Probability [mean (SD)]	Number	Source
Total CPAP ongoing costs (yearly)	£218.24			£44.24 + £80 + £15 + £79
APAP ongoing costs				
APAP machine	£410			ResMed
Humidifier	£150			ResMed
Estimated device life of APAP and humidifier			5 years	ResMed
Annual equivalent cost of APAP with humidifier	£100			560/annuity factor
Annual sundries	£100			ResMed
Annual equivalent cost of CPAP mask	£80			ResMed
Annual follow-up	£79			Clinical expert referring to NHS tariff
Total APAP ongoing costs (yearly) ^a	£359			£100 + £100 + £80 + £79
Dental device costs				
Estimated device life of dental device			2 years	
NHS cost of dental device and its provision	£250.92			12 units of dental activity × 20.91
Total dental device costs (yearly)	£128.82			
Dental device ongoing costs (yearly)				
Maintenance of dental device	£19.47			Edwards et al., 1999, ¹⁶⁸ cost of a consultant appointment
Conservative management cost				
One-off consultation with a GP	£21			Curtis and Netten, 2006 ¹⁶⁶
APAP, autotitrating positive airway pressure; OSAHS, obstructive sleep apnoea–hypopnoea syndrome.				
a Applied in sensitivity analysis.				
NB Some figures are approximate as reported to limited number of decimal places.				

TABLE 35 Mean costs associated with CHD, stroke and RTAs used in the York economic model

Parameter	Mean cost	SD	Source
CHD and stroke			
Cost of fatal CVE	£3021	367	Briggs et al., 2007 ¹⁶⁸
Acute cost of CHD	£9997	428	Briggs et al., 2007 ¹⁶⁸
Ongoing cost of CHD	£751	117	Briggs et al., 2007 ¹⁶⁸
Acute cost of stroke	£9067	294	Bravo et al., 2007 ¹⁶⁹
Ongoing cost of stroke	£2392	282	Bravo et al., 2007 ¹⁶⁹
RTA			
Cost of RTA (all injuries)	£2700	1643	Department of Transport, 2004 ¹³³
Cost of fatal RTA	£5450	1643	Department of Transport, 2004 ¹³³
CHD, coronary heart disease; CVE, cardiovascular event; RTA, road traffic accident.			

& North East Somerset Primary Care Trust: www.banes-pct.nhs.uk/about/BoardPapers/2007/May/Agenda%20Item%2010%20Annex%201.pdf. The average reimbursement per UDA was estimated to be £20.91; therefore, multiplied by 12 UDAs, this gives an estimate of approximately £251 for the total cost of a dental device. Based on clinical expert opinion, it was assumed that the patient would have a yearly check-up appointment.

The cost of non-compliance was determined by the proportion of CPAP machines not returned (10%) and the cost of dental devices no longer used. The data were entered probabilistically based on estimates of the service and resource use data obtained from ResMed’s survey of clinicians. The uncertainty around the probability distributions was characterised by beta distributions.

On the basis of clinical advice, conservative management was estimated as the cost of a one-off GP consultation during which the patient may receive advice on posture, dietary habits and lifestyle. A unit cost of a GP appointment was obtained from the Personal Social Services Research Unit (PSSRU) costs of health and social care report.¹⁶⁶

The unit costs associated with stroke, CHD and RTAs are reported in *Table 35*. Published references were used to estimate these parameters. The uncertainty around the costs was characterised by gamma distributions, where mean costs and SD were presented, and by normal distributions,

where the costs were based on coefficients from a regression analysis. The Department of Transport information regarding the costs of RTAs was presented as point estimates. In order to characterise the uncertainty around these estimates it was assumed that the SD would be equal to that reported by HODaR (Currie *et al.*¹⁵⁶) for the hospital cost associated with non-fatal RTAs (mean £2437, SD £1643).

Results of York economic model

Base-case analysis

The base-case analysis is based on a hypothetical cohort of men aged 50 with the baseline cardiovascular risk factors described in *Table 36*. In this cohort CPAP was associated with both higher costs and higher QALYs in comparison with treatment with dental devices or conservative management. The incremental cost-effectiveness of CPAP compared with dental devices is estimated to be £4000 per QALY. CPAP might therefore be considered cost-effective at a cost-effectiveness threshold per QALY of £20,000.

Similar results were obtained for a hypothetical cohort of women aged 50, as shown in *Table 37*.

For the base-case analysis the effect of CPAP on ESS was derived by pooling all of the available trial data to obtain an overall effect. The treatment effects estimated by pooling trials, grouped according to average baseline ESS (mild, moderate or severe), were applied in three separate analyses

TABLE 36 Base-case results from York economic model comparing costs and QALYs of conservative management, dental devices and CPAP in males aged 50

	Conservative management	Dental device	CPAP
Treatment costs	£21	£1726	£2465
RTA costs	£2201	£1138	£904
CVE costs	£5918	£5932	£5931
Total costs	£8140	£8797	£9301
Total QALYs	11.93	12.26	12.39
ICER		£2000	£3899
Probability of being cost-effective for threshold			
£10,000 per QALY	0.01	0.32	0.66
£20,000 per QALY	0.00	0.20	0.80
£30,000 per QALY	0.00	0.17	0.83

CVE, cardiovascular event; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RTA, road traffic accident.

TABLE 37 Results from York economic model comparing costs and QALYs of conservative management, dental devices and CPAP in females aged 50

	Conservative management	Dental device	CPAP
Treatment costs	£21	£1824	£2608
RTA costs	£2139	£1108	£878
CVE costs	£5840	£5829	£5820
Total costs	£7999	£8762	£9306
Total QALYs	12.71	13.02	13.15
ICER		£2432	£4335
Probability of being cost-effective for threshold			
£10,000 per QALY	0.02	0.33	0.64
£20,000 per QALY	0.01	0.21	0.78
£30,000 per QALY	0.00	0.17	0.83
CVE, cardiovascular event; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RTA, road traffic accident.			

and the results are shown in *Table 38*. Note that the trials comparing CPAP with dental devices all had a mean baseline ESS that would classify them as moderate OSAHS. Because it was not possible to estimate the differential effect of baseline severity of OSAHS on CVD and RTA risks, these risks have not been included in the results in *Table 38* (i.e. these cost-effectiveness results by severity include only treatment effects on ESS). It can be seen that cost-effectiveness varies according to severity, with CPAP most cost-effective (lower ICER) in severely affected patients. However, CPAP has an ICER below a cost-effectiveness threshold of £20,000 for moderate and severe levels using baseline ESS score. The ICER in a subgroup with mild disease was estimated to be £20,585.

Secondary analysis

There are a number of uncertainties over several of the modelling assumptions, and results are shown as a set of subgroup and scenario analyses in *Table 39*. In each case the variable or assumption altered from the base-case analysis is indicated in the title of the scenario analysis, and all other variables and

assumptions were left unchanged. It can be seen that, although ICERs for CPAP vary according to the different assumptions, they consistently fall below a threshold of £20,000 per QALY. The greatest effect on the CPAP ICER comes from applying the highest feasible acquisition cost for the treatment by including the costs of an APAP machine and a humidifier.

Value of information analysis

The base case per episode EVPI was estimated to be £183 (male) and £202 (female) for a cost-effectiveness threshold of £20,000 per QALY. Assuming a lifetime for the technology of 5 years and incidence of OSAHS of 0.1% in the UK population aged between 16 and 65 (39 million) gives an effective population of 0.18 million (<http://www.statistics.gov.uk/cci/nugget.asp?ID=949>). This corresponds to a population EVPI of £33 million (male). When CVE and RTA events were excluded from the model, the population EVPI rises to approximately £51 million (based on per episode EVPI of £277 in men).

TABLE 38 Results from the York economic model for subgroups grouped according to baseline severity of OSAHS as measured by ESS

	Conservative management	Dental device ^a	CPAP
Mild OSAHS, male aged 50 (mean baseline ESS = 7)			
Total cost	£21	NA	£2726
Total QALYs	14.56	NA	14.69
ICER			£20,585
<i>Probability of being cost-effective for threshold</i>			
£10,000 per QALY	0.95	NA	0.05
£20,000 per QALY	0.57	NA	0.43
£30,000 per QALY	0.32	NA	0.68
Moderate OSAHS, male aged 50 (mean baseline ESS = 13)			
Total cost	£21	£1906	£2726
Total QALYs	13.51	13.70	13.80
ICER		ED	£9391
<i>Probability of being cost-effective for threshold</i>			
£10,000 per QALY	0.40	0.24	0.36
£20,000 per QALY	0.09	0.21	0.70
£30,000 per QALY	0.04	0.18	0.78
Severe OSAHS, male aged 5 (mean baseline ESS = 16)			
Total cost	£21	NA	£2726
Total QALYs	13.01	NA	13.62
ICER			£4413
<i>Probability of being cost-effective for threshold</i>			
£10,000 per QALY	0.05	NA	0.95
£20,000 per QALY	0.02	NA	0.98
£30,000 per QALY	0.01	NA	0.99
ED, extended dominance; ESS, Epworth Sleepiness Scale; ICER, incremental cost-effectiveness ratio; NA, not applicable; OSAHS, obstructive sleep apnoea–apnoea syndrome; QALY, quality-adjusted life-year.			
a All of the trials comparing CPAP with dental devices were classified as moderate OSAHS based on average baseline ESS. NB Only differential treatment effects on ESS are included.			

TABLE 39 Results from the York economic model for a range of scenario and subgroup analyses

	Male			Female		
	CM	DD	CPAP	CM	DD	CPAP
Subgroup analysis						
<i>Cohort aged 35</i>						
Cost	£8521	£9356	£10,034	£8177	£9155	£9868
QALY	15.55	15.99	16.15	16.21	16.60	16.76
ICER		£1894	£4143		£2477	£4454
<i>Cohort aged 65</i>						
Cost	£5969	£6398	£6728	£5159	£5709	£6078
QALY	7.95	8.17	8.26	8.89	9.12	9.21
ICER		£1866	£2960		£2426	£3944
Scenario analysis						
<i>Change in ESS linked to SF-6D utility score rather than EQ-5D</i>						
Cost	£8129	£8781	£9295	£8003	£8761	£9307
QALY	10.66	10.95	11.06	11.35	11.62	11.74
ICER		£2258	£4451		£2748	£4669
<i>Relative risk reduction for CVE based on DBP and MacMahon et al., 1990¹⁴⁵</i>						
Cost	£8133	£8734	£9207	£7949	£8656	£9189
QALY	11.92	12.28	12.42	12.70	13.04	13.19
ICER		£1678	£3330		£2040	£3756
<i>Exclude CVE events from model</i>						
Cost	£2488	£3171	£3736	£2389	£3252	£3894
QALY	13.41	13.77	13.90	14.48	14.82	14.96
ICER		£1896	£4184		£2557	£4732
<i>Exclude CVE and RTA events from model</i>						
Cost	£21	£1906	£2726	£21	£2038	£2920
QALY	13.69	13.92	14.02	14.69	14.93	15.04
ICER		ED	£8098		ED	£8113
<i>APAP machine with 5-year life span and humidifier</i>						
Cost	£8150	£8816	£10,939	£7979	£8741	£11,036
QALY	11.92	12.25	12.38	12.70	13.01	13.14
ICER		£2017	£16,362		£2408	£18,356
<i>Treatment effects from BRMA (APBM only)</i>						
Cost	£8132	£8799	£9283	£7973	£8737	£9275
QALY	11.93	12.26	12.40	12.69	13.01	13.14
ICER		£2003	£3678		£2412	£4093
<i>Treatment effects from BRMA (APBM and office measurements)</i>						
Cost	£8139	£8771	£9237	£7989	£8728	£9222
QALY	11.92	12.27	12.42	12.70	13.04	13.19
ICER		£1787	£3097		£2170	£3249

APBM, ambulatory blood pressure monitoring; BRMA, bivariate random-effects meta-analysis; CM, conservative management; CVE, cardiovascular event; DBP, diastolic blood pressure; DD, dental device; ED, extended dominance; ESS, Epworth Sleepiness Scale; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RTA, road traffic accident.

TABLE 40 Economic evaluation quality assessment

Cost-effectiveness	Ayas et al., 2006 ¹²²	Mar et al., 2003 ¹²³	ResMed, 2007 ¹²⁰	Chilcott et al., 2000 ⁴⁴
Study question				
Were costs and effects examined?	✓	✓	✓	✓
Were alternatives compared?	✓	✓	✓	✓
Are viewpoint/s clearly stated?	✓	✓	✓	✓
Selection of alternatives				
All relevant alternatives were compared	✓	✓	✓	✓
For the alternatives compared are all clearly described?	✓	✓	✓	✓
The rationale for choosing the alternative programmes compared is stated	✓	✓	✓	✓
Form of evaluation				
The choice of form of economic evaluation is justified in relation to questions addressed	✓	✓	✓	✓
If a cost minimisation analysis is chosen, have equivalent outcomes been adequately demonstrated?	NA	NA	NA	NA
Effectiveness data				
The sources of effectiveness estimates used are stated	✓	✓	✓	✓
Effectiveness data are from RCTs or review of RCTs	X	X	X	X
Potential biases are identified	✓	✓	X	✓
Details of method of synthesis or meta-analysis of estimates are given	✓	✓	✓	✓
Costs				
All the important and relevant resource use is included	✓	✓	✓	✓
All the important and relevant resource use is measured accurately	✓	✓	✓	✓
Appropriate unit costs are estimated	✓	✓	✓	✓
Unit costs are reported separately from resource use data	✓	✓	✓	✓
If productivity costs are included, are they treated separately from other costs?	✓	NA	X	X
The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	✓	✓	X
Benefit measurement and valuation				
The primary outcome measure for the economic evaluation is clearly stated	✓	✓	✓	✓
Methods to value health states and other benefits are stated	✓	✓	✓	✓
Details of the individuals from whom valuations were obtained are given	✓	✓	✓	✓

TABLE 40 Economic evaluation quality assessment

Cost-effectiveness	Ayas et al., 2006 ¹²²	Mar et al., 2003 ¹²³	ResMed, 2007 ¹²⁰	Chilcott et al., 2000 ⁴⁴
Decision modelling				
Details of any model used are given	✓	✓	✓	NU
The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	✓	✓	NU
All model outputs are described adequately	✓	✓	✓	NU
Discounting				
Discount rates are used for both costs and benefits	✓	✓	✓	✓
Do discount rates accord with current NHS guidance?	X	X	✓	X
Allowance for uncertainty: stochastic analysis of patient-level data				
Details of statistical tests and confidence intervals are given for stochastic data	NA	NA	NA	NA
Uncertainty around cost-effectiveness estimates are expressed	NA	NA	NA	NA
Sensitivity analysis is used to assess uncertainty in non-stochastic variables and analytic methods	NA	NA	NA	NA
Allowance for uncertainty: stochastic analysis of decision models				
Are all appropriate input parameters included with uncertainty?	✓	✓	✓	NU
Is second-order uncertainty (uncertainty in means) included rather than first-order uncertainty (uncertainty between patients)?	✓	X	✓	NU
Are the probability distributions adequately detailed and appropriate?	✓	X	X	NU
Sensitivity analysis is used to assess uncertainty in non-stochastic variables (e.g. unit costs) and analytic decisions (e.g. methods to handle missing data)	✓	✓	✓	NU
Deterministic analysis				
The approach to sensitivity analysis is given	✓	✓	✓	✓
The choice of variables for sensitivity analysis is justified	✓	✓	✓	✓
The ranges over which the variables are varied are stated	✓	✓	✓	✓
Presentation of results				
Incremental analysis is reported using appropriate decision rules	✓	✓	✓	✓
Major outcomes are presented in a disaggregated as well as an aggregated form	✓	✓	✓	✓
They are applicable to the UK setting	X	X	✓	✓
✓, yes; X, no; NA, not applicable; NU, not undertaken.				

Chapter 5

Assessment of factors relevant to the NHS and other parties

It is unlikely that the implementation of CPAP as a treatment for OSAHS would have training requirements for clinicians that have major resource implications for the NHS. Consultant-level respiratory physicians are currently required to have completed a basic sleep apnoea training programme. Appropriate diagnosis is important and may have additional cost implications. The trials included in this technology assessment mainly used thorough diagnostic assessment (encompassing recordings of multiple physiological signals during sleep) to establish a diagnosis of OSAHS, and the findings of this review are applicable to a population where there has been an adequate diagnostic assessment. Trained staff and structured induction programmes

are another feature of specialist units. The detailed consideration of what would constitute an appropriate diagnostic assessment and the associated cost implications were outside the remit of this technology appraisal.

In practice, dental devices are unlikely to be provided under NHS dental care, and in regions where they may be available under the NHS waiting times for treatment may need consideration. The cost-effectiveness model in this appraisal (the York model) considered NHS costs and PSS costs; incorporating private costs of dental care would reduce the cost-effectiveness of dental devices.

Chapter 6

Discussion

Statement of principal findings

Clinical effectiveness

The clinical effectiveness and safety of CPAP compared with best supportive care, placebo and dental devices for the treatment of OSAHS was investigated using systematic review and meta-analyses. The majority of studies in the review included participants with moderate daytime symptom severity (ESS) at baseline, who were male and overweight or obese. Several studies excluded patients who reported sleepiness while driving; this may indirectly have led to most studies having a mean baseline symptom severity that was classified as moderate. When disease at baseline was classified based on the AHI, most included studies were classified as being of severe disease populations.

The mean age of participants in the included studies ranged from 44 to 58 years and the duration of follow-up in most studies was between 4 and 12 weeks. We excluded studies that were restricted to patients with serious co-morbid conditions such as heart failure or Alzheimer's disease; therefore, the findings may not be generalisable to those groups. Although 48 relevant studies were identified, the outcomes investigated varied and data for some outcomes were available from only a small number of studies. In general, there was inconsistency (statistical heterogeneity) in the treatment effect within groups of studies with the same comparators. Heterogeneity for the primary outcome of subjective sleepiness (as measured by the ESS) was reduced when studies were subgrouped based on mean severity of daytime symptoms at baseline, but not when subgrouping was based on the mean number of episodes of airway obstruction at night (AHI). This was possibly because ESS and AHI are not strongly correlated. It was considered appropriate to focus on the stratification of studies by symptom severity rather than the number of episodes of airway obstruction at night as the treatment of OSAHS is targeted mainly at controlling its symptoms and consequences, e.g. hypertension, rather than correcting the breathing disturbance itself. Any variation in the treatment effect discussed below is

in relation to disease severity based on severity of daytime symptoms at baseline, as measured by the ESS.

There was clear evidence of a benefit with CPAP compared with placebo, conservative treatment/ best supportive care, on two of the three primary outcomes, one assessing subjective symptoms of daytime sleepiness (ESS) and one objective measure of sleepiness (MWT). The benefit with CPAP on daytime sleepiness was robust across all the methodological subgroup analyses and sensitivity analyses. There was consistent evidence that the treatment effect increased with symptom severity at baseline. The evidence for any benefit with CPAP was less clear on the secondary outcome measures, although there was some evidence of a beneficial impact on quality of life and daytime MAP. The identified studies comparing CPAP with dental devices were in populations with symptoms of moderate severity. There was no statistically significant difference between CPAP and dental devices on any of the measures investigated. However, only a small number of studies was available and there was some inconsistency in the findings, making it difficult to draw firm conclusions. Despite obesity being an important aetiological factor for adult OSAHS, there were no studies directly comparing CPAP with weight loss interventions; where a weight loss programme was used, both the intervention and comparator group received this.

There was a lack of evidence on long-term outcomes such as stroke and cardiac events (with changes in event rates in the economic model being inferred from blood pressure changes rather than being measured directly), and a lack of direct evidence on RTAs and accidents in the workplace.

Daytime sleepiness

The primary outcome of interest for the clinical treatment of OSAHS is the control of excessive daytime sleepiness, for its symptomatic benefits and the consequences for tasks that require vigilance and the resistance of sleep onset, e.g. driving and employment performance. In this review, sleepiness was quantified as subjective daytime sleepiness as measured by the ESS and

objective sleepiness as measured by the MWT and MSLT. These objective and subjective measures of sleepiness were used as primary outcomes, as the daytime consequences of OSAHS are the primary concern for patients. There was evidence that CPAP was more effective than placebo or conservative treatment/usual care in reducing symptoms of daytime sleepiness as measured by the ESS and MWT but not the MSLT. There was no statistically significant difference between CPAP and dental devices or CPAP and postural therapy on any of the three primary outcomes in a population classified as having moderate symptom severity at baseline.

The random-effects model that we used for the statistical pooling assumes that the effect of treatment differs in different populations, but that these effects cluster around a mean. The estimated MD for daytime sleepiness in the overall pooling was 2.7 points on the ESS, but might be anywhere between 2.0 and 3.5. However, this probably has limited generalisability, due to high statistical heterogeneity or inconsistency in the treatment effect. Heterogeneity was reduced when estimates were generated for studies subgrouped by mean baseline symptom severity. The benefit with CPAP was greatest in the group of trials of severe symptoms (MD -5.0 points, 95% CI -6.5 to -3.5), and was smaller with moderate (MD -2.3 points, 95% CI -3.0 to -1.6) and mild symptoms (MD -1.1 points, 95% CI -1.8 to -0.3). These were all statistically significant. It is not surprising to find a smaller benefit in the studies of populations that only had mild sleepiness prior to treatment. The estimate for mild disease was based on only two trials; therefore, this finding may not be robust. Although there was still moderate statistical heterogeneity in the subgroups, the direction of the treatment effect was consistently in favour of CPAP, with the exception of two studies.

There was a statistically significant benefit with CPAP compared with placebo/usual care on the ability to stay awake in a setting conducive to sleep (MWT). It is not possible to make a firm conclusion about whether the benefit with CPAP varied by disease severity as there were no trials of mild symptom severity and only one of severe. There was a benefit with CPAP in the single trial of a severe symptom severity population, which was apparently greater than that in the group of trials of moderate disease symptoms. There was no statistically significant difference between CPAP and control in the length of time it took participants to fall asleep in a setting conducive to sleep (MSLT), for any level of disease severity. This

finding may have limited generalisability due to the evidence of inconsistency in the treatment effect which could not be adequately investigated. Again, only single trials were available of mild and severe symptomatic populations, making it impossible to draw firm conclusions about whether there may be a variation in the treatment effect in populations with different disease severity.

It is not surprising that the findings from the MSLT and MWT do not correspond, as, although the two tests appear to measure the same thing, time to onset of sleep, low correlations have been found between the two tests, implying that there is not a simple single dimension of sleepiness.¹⁷⁰ It has been suggested that the MSLT measures underlying arousal as well as propensity to sleep. American Academy of Sleep Medicine practice parameters state that use of MSLT is not routinely indicated for the diagnosis of OSAHS or for assessment of response to treatment.¹⁷¹ The ESS and MWT may be more clinically meaningful in that they measure the ability to resist sleep. This has potentially more applicability to real-life situations, in which the ability to resist sleep while driving or carrying out a daily activity is important, than does the length of time it takes a person to fall asleep, when instructed to do so, as measured by the MSLT.

There was no statistically significant difference between CPAP and dental devices amongst a population with moderate symptom severity at baseline (where reported). The treatment effect is likely to differ in different groups of people, based on the random-effects model used. The average effect was a reduction in sleepiness of less than 1 point (0.9) in favour of CPAP compared with dental devices, but might be anywhere between an increase in sleepiness of 0.4 points with CPAP and a decrease in sleepiness of 2.1 points. However, it is unclear how generalisable this is within a moderate disease population as there was evidence of moderate inconsistency (heterogeneity) in the treatment effect. The effectiveness of CPAP compared with dental devices in severe and mild severity populations could not be estimated due to a lack of studies investigating these populations. Overall it is difficult to draw firm, clinically useful conclusions from the studies comparing CPAP with dental devices and postural therapy. Assessment of the comparative clinical effectiveness of CPAP and dental devices or postural therapy is limited by the number and consistency of available data and by the spectrum of patients studied. The studies of postural therapy, in particular, were very small

trials and there was only one trial on each type of postural therapy.

Blood pressure

The studies assessing blood pressure had diverse populations; the proportion of hypertensive patients ranged from 15% to 100%. Day and night blood pressure were considered separately as the mechanisms and patterns of daytime and night-time blood pressure disturbance in OSAHS vary. Priority was given to daytime measures as the relationship between daytime blood pressure and vascular risk has been more clearly established and was more useful for the economic model. Based on studies using ABPM, there was a statistically significant benefit with CPAP compared with placebo/usual care in daytime MAP. Based on the random-effects pooling used, the size of the effect probably varies among different groups of people: the average reduction in daytime MAP was 2.1 mmHg, but might be anywhere between no reduction and 4.3 mmHg. When SBP and DBP were considered separately, the differences between CPAP and control were not statistically significant although there was a small decrease in both measures in favour of CPAP (MD -1.1 mmHg, 95% CI -3.4 to 1.2, and MD -1.2 mmHg, 95% CI -2.9 to 0.5, respectively). It should be noted that not all the trials in the analysis of MAP were the same as those in the SBP and DBP analyses. Therefore, the lack of a statistically significant effect for SBP and DBP may be due to differences in the study populations or methods.

The overall treatment effect for MAP did not appear to be robust. When individual studies were removed from the pooling the treatment effect remained statistically significant in only one instance. The analyses for all three blood pressure measures were based on a small number of trials and participants, and blood pressure was not always the primary outcome in the studies. Therefore, the risk of the analyses being underpowered to detect an effect is an important consideration. The subgroup analysis exploring variation in treatment effect with symptom severity was limited by the small number of trials available. The pooling of a small group of studies using conventional clinic blood pressure measurement showed a large and statistically significant improvement in SBP and DBP with CPAP compared with control. Given the evidence that a person's actual blood pressure is more accurately reflected by the repeated measurements of ABPM than by conventional clinic measures,¹⁷² the results of the studies using ABPM probably provide a more generalisable estimate of

the effect of treatment on blood pressure. However, there is always the possibility that there are important differences between these studies other than the method of blood pressure measurement.

Health-related quality of life (HRQoL)

There was evidence of a beneficial impact on HRQoL although the findings were somewhat inconsistent. This may have been related to a number of factors including the different types of quality of life outcome measures used, the small number of trials available or aspects of study design. It was not possible to explore these factors due to the small number of trials available. In general, the available data sets were too small to allow meaningful investigation of potential sources of heterogeneity. The included studies reporting these outcomes were of moderate and severely symptomatic populations; it is unclear whether similar benefits would be experienced by a mild disease population.

The most commonly reported quality of life measures were the FOSQ, the NHP and the SF-36, although the number of trials available for any single quality of life measure was small. Only one trial was identified that used a utility-based measure to inform the cost-effectiveness model. The majority of the trials were of moderate symptom severity populations (based on ESS). There was a statistically significant benefit with CPAP compared with placebo/usual care on the activity level and social outcome dimensions of the FOSQ (a condition-specific measure) when three trials of moderate disease and one of severe disease were pooled; and on the NHP (Part 2) in a moderate disease severity population. There was no statistically significant difference between CPAP and control on the SF-36 subscales. However, there was high inconsistency (statistical heterogeneity) for the emotional role and vitality subscales, limiting the reliability of these findings. It is therefore not appropriate to draw general conclusions from these analyses. When parallel and crossover trials were pooled separately, there was a benefit with CPAP compared with control on the SF-36 bodily pain, general health and physical function subscales in the parallel trial subgroup; this may have been driven by two trials of severely symptomatic populations.

Quality of life data regarding CPAP compared with dental devices (all moderate symptom severity) were inconsistent: on the FOSQ one study showed a statistically significant benefit with CPAP compared with dental devices and one found no

difference; there was no statistically significant benefit on the SAQLI with CPAP; and on the SF-36 one study reported a statistically significant benefit with CPAP compared with dental devices on the physical and mental component subscales, one reported a statistically significant benefit on the bodily pain subscale with CPAP and there was no statistically significant difference on the total score in one study. There was no statistically significant difference between CPAP and postural therapy in any quality of life measure studied.

Psychological and cognitive outcomes

Assessment of the effects of CPAP on psychological outcomes was limited by the small number of trials investigating these outcomes. Subgroup analysis by baseline symptom severity was not feasible. The most commonly used scales were the General Health Questionnaire-28 (GHQ-28), Hospital Anxiety and Depression Scale (HADS) and University of Wales Mood Adjective Checklist (UMACL). There was no statistically significant benefit with CPAP compared with placebo/usual care on the GHQ-28 or HADS. However, there was evidence of inconsistency in the treatment effect (statistical heterogeneity) which could not be explored, making any firm conclusions difficult. On the UMACL there was a statistically significant benefit with CPAP compared with placebo. There was no statistically significant difference between CPAP and dental devices in a single trial using HADS.

Despite the substantial number of trials investigating cognitive outcomes, interpretation was difficult due to the wide range of tests used, non-uniform use of the same scales, variation in testing protocols and the difficulty in assessing the risk of a ceiling effect due to lack of information on how baseline performance compared with normative performance. The findings were contradictory from trials for individual cognitive tests, with some showing a benefit with CPAP and others not.

Cost-effectiveness

Published evidence and company submissions

Only one manufacturer submitted a full economic evaluation of CPAP – ResMed. This analysis used decision modelling and evidence drawn from a range of sources to estimate the costs and QALYs associated with CPAP versus a ‘do nothing’ option. The company’s estimated cost-effectiveness over

14 years was that CPAP dominated no treatment (i.e. CPAP was associated with higher QALYs and lower costs), although this varied over shorter time horizons. Comparing CPAP (auto) and CPAP (fixed), the analysis suggested that the former dominated the latter. There are a number of methodological weaknesses associated with the ResMed analysis including the following:

- The results of a before and after study¹²³ were used to examine the impact of no treatment compared with CPAP on HRQoL (in terms of utilities) associated with sleepiness. There are numerous limitations to this type of study in estimating treatment effects. Furthermore the approach effectively ignores the considerable RCT-based literature examining the efficacy and effectiveness of CPAP compared with other therapies.
- ResMed did not include the full range of comparators and, at least for patients diagnosed with moderate/severe OSAHS, it is not clear that a ‘do nothing’ option represents typical clinical practice.
- ResMed modelled cost-effectiveness results over a 14-year time horizon. However, OSAHS is a chronic condition; therefore, it is appropriate to model the results for a lifetime horizon.
- There were shortcomings in the internal validity of the electronic model that may have led to inaccurate estimates of costs and QALYs.

Four published full economic evaluations of CPAP were identified and reviewed.^{44,122,123,124} Although they varied in terms of their detailed methods, there was moderate consistency in the estimates of cost-effectiveness with CPAP; estimates of the incremental cost per QALY gained with CPAP against no therapy ranged from about £1500 to £3000. These studies had several limitations including:

- the failure to use a full range of clinical trial evidence for estimating the impact of treatment on daytime sleepiness, blood pressure, HRQoL and other relevant outcomes
- a lack of evidence to compare the utility associated with different treatments for OSAHS
- limited evidence (in terms of quantity and quality) on the long-term impact of OSAHS on HRQoL, CVEs and RTAs
- the fact that none of the evaluations examined all the comparators relevant to this review.

York economic model

As a result of the limitations of existing cost-effectiveness studies of CPAP, a new model was developed. Its key features (compared with earlier models) were that it compared CPAP with relevant alternative treatment options (taken as conservative management and dental devices); it based the main estimate of effectiveness on the RCT evidence on sleepiness symptoms (based on the ESS), which were 'mapped' to utilities using individual patient data from a subset of studies; and it used trial evidence on changes in blood pressure following intervention to estimate differences in the rates of CVEs over time.

The York model found that, on average, CPAP was associated with higher costs and benefits compared with dental devices or conservative management. The incremental cost per QALY gained with CPAP, compared with dental devices, using base-case assumptions and an assumed age of 50 years, was £3899 for men and £4335 for women; the probability of CPAP being more cost-effective than dental devices and conservative management at a threshold of £20,000 per QALY was 0.78 and 0.80 for men and women respectively.

The York model is the first to compare CPAP with dental devices. It was noted earlier that differences between dental devices and CPAP in the effect on the ESS were not statistically significant. However, those differences were incorporated into the cost-effectiveness analysis and the uncertainty in these, as well as all other, parameters are reflected in the expressed decision uncertainty. The systematic review detailed in Chapter 3 included only trials in which CPAP was a comparator. As a consequence, trials comparing dental devices with placebo will not have been identified. Hence, the comparison between dental devices and conservative management is not based on the full range of available data. However, a recent systematic review of dental devices by Hoekema *et al.* identified few additional dental device versus placebo studies.¹⁷³

Clinically, the treatment effect on the ESS from CPAP, relative to conservative therapy, was greater in patients with greater baseline severity of OSAHS. When this was reflected in the cost-effectiveness analysis by looking at the cost-effectiveness of CPAP in separate severity groups, the ICER (probability of being cost-effective at a threshold of £20,000 per QALY) varied between £20,585 (0.43) and £4413 (0.98) in patients with mild and severe disease respectively. In mild and severe disease, it was only possible to compare the cost-effectiveness

of CPAP with conservative management given the absence of trials of dental devices in those patients. Furthermore, given the lack of evidence on the relative treatment effects of the alternative therapies on blood pressure and RTAs by baseline OSAHS severity, these estimates do not factor in differential effects on CVEs or RTAs, so are likely to be an underestimate.

A series of other subgroup and scenario analyses found that the ICER of CPAP was consistently below £20,000 per QALY gained (when there is no distinction between baseline severity of disease). Typically the cost-effectiveness of interventions was lower (i.e. the ICER was higher) in women than in men; this may be due to the fact that women have a lower baseline risk of CVD and RTAs, giving less potential for QALY gains. They also typically have a longer life expectancy, resulting in higher treatment costs compared with no treatment. CPAP remained cost-effective when the age of the hypothetical cohort was increased or decreased by 15 years. Although the target population for this appraisal is patients aged 16 or older, the clinical trials typically included older patients and so the results may not be generalisable to a younger cohort. As mentioned previously, the generalisability to cohorts older than the patient population included in the trials may be compromised by the presence of additional comorbidity in older people.

The greatest contribution to QALY gain was found to be the gain in utility associated with a reduction in ESS score with CPAP. The next most important factor in differentiating between the alternative treatments in terms of QALY gain was the rate of RTAs. The inclusion of CVEs reduced quality-adjusted survival by similar amounts for all three alternatives. A similar pattern was observed for costs, with the greatest difference between alternatives contributed by the cost of the device and associated care, followed by RTA costs and finally CVE costs.

The cost of the CPAP device is higher than the cost of dental devices or conservative management. However, the NHS and PSS costs of RTAs were lower with CPAP than with those relating to dental devices and conservative management as fewer events occur. The costs of CVD differed little between the alternative treatment strategies. A consequence of the reduced risk of fatal RTAs or fatal CVEs with CPAP was that more patients remained alive and at risk of a non-fatal CVE, partially offsetting any savings from a reduced

risk of events overall. Omitting the impact of CVD had little effect on the study results. Even when incorporating the larger relative risk reduction for CVEs implied by the MacMahon *et al.*¹⁴⁵ study, the reduction in blood pressure associated with CPAP contributed little to the estimation of its cost-effectiveness. When the impact of CVD and RTAs was omitted, the incremental cost of CPAP compared with usual care increased, but the ICER remained low at £8098. Note that the results of this analysis are relevant for patients who do not drive.

The per episode EVPI was high, indicating that the cost of decision uncertainty may be high. Reliable data relating to incidence of OSAHS were not found; therefore, the mortality rate of men aged 35 was used as an approximation (0.1%) in order to calculate the population EVPI, assuming a lifetime for the technology of 5 years. This indicated that the upper boundary for the value of further research was between £33 million and £50 million. Further investigation may be warranted to identify those parameters that contribute most to the decision uncertainty. Including the prevalent patient population in those able to benefit from additional research would increase the EVPI considerably. The indication is that the value of information gained from further research may well exceed the costs of undertaking that research.

Based on the regression analysis to predict utility scores, the EQ-5D and SF-6D utility models indicated that an increase of 1 point in ESS was associated with a decline in utility of 0.01. A crude comparison of the ESS and utility data from Chakravorty *et al.*⁹⁷ indicates that, for a 1-point drop in ESS, an increase in utility of 0.005 was found based on the EQ-5D valuations and 0.03 based on the standard gamble valuations. The 0.23 improvement in utility post treatment, on the basis of a before and after analysis of standard gamble valuations, has been used in a previous economic evaluation by Ayas *et al.*¹²² without an attempt to link in the available clinical evidence. The crude comparison of ESS and utility data from Jenkinson *et al.*¹⁵² indicated that, for a 1-point drop in ESS, an increase in utility was found of 0.009 based on the EQ-5D valuations. Therefore, our analysis seems to be in line with previously published estimates.

Hypothetically, the sensitivity of EQ-5D scores to changes in sleepiness could be limited as the instrument does not contain a question specifically directed at sleepiness or energy and wakefulness. However, the EQ-5D instrument could still capture the health effects of sleepiness, e.g. in terms

of its effects on usual activities or anxiety and depression. This analysis suggests that this concern may be unfounded, as employing the utility scores calculated from SF-6D, which does include a question about energy and vitality, produced strikingly similar results in the set of individual patient-level data available.

The York model considered NHS and PSS costs and, therefore, omitted any private costs of health care. In practice, however, according to our clinical experts, dental devices are infrequently provided under NHS dental care. Private costs of dental devices were estimated at an initial cost of over £600 which, if included in the analysis, would reduce the cost-effectiveness of dental devices.

Strengths and limitations of the assessment

Clinical effectiveness

While there is clear and robust evidence of a benefit with CPAP compared with placebo/usual care in relation to daytime sleepiness, the finding of a variation in the treatment effect with disease severity needs to be interpreted with some caution. The factors of interest investigated (except for one *post hoc* analysis) were specified in advance and the number of factors investigated was kept as small as possible. In addition, the findings from the subgroup analyses make clinical sense. However, the subgroup analyses are based on summary data and the comparisons are therefore observational and are not based on randomised comparisons as in a trial or an individual patient data analysis. Therefore, the trend of a treatment effect by disease severity should not be considered definitive. In addition, although the cut-off points used to define disease (AHI) and symptom severity (ESS) are based on those used clinically, these are arbitrary cut-off points. The subgroup analyses for other outcomes were limited by the small number of studies available. However, because disease and symptom severity are thought to be clinically important factors in the response to treatment we have tried to make clear the clinical populations to which the findings refer.

The subgroup analyses also do not account for any potential confounding between the factors investigated; for example, studies using a sham CPAP comparator were less likely to be crossover trials. Where the treatment effect varied between crossover and parallel trials, this may not have been due to the study design but may have been related

to the comparator used. There were other factors that may have had an influence on the treatment effect that it was not feasible to investigate, due to the limitations of the available data, such as study duration and the subtherapeutic pressure used for sham CPAP.

The findings for the primary outcome of subjective sleepiness were robust when only studies with adequate concealment of allocation were considered. However, the investigation of the impact of study quality (as defined by adequacy of concealment of allocation) on the findings was limited by the fact that only five studies reported that an adequate method had been used. It was also possible to investigate whether the findings were robust, for the ESS as an outcome measure, when only the studies using sham CPAP as a comparator were considered. Participant blinding was possible only in the studies in which CPAP was used as the comparator; effectively it provides the best placebo in this field. When only studies using a sham CPAP comparator were subgrouped by baseline symptom severity (ESS) the findings were similar to those using the complete data set subgrouped by baseline symptom severity (ESS), i.e. there was a statistically significant benefit with CPAP compared with sham CPAP for each of the three subgroups, and the treatment effect was largest for the severe symptom subgroup and was consecutively smaller for the moderate and mild groups. Only a small subset of studies included all the randomised patients in the analysis; therefore, as a group of studies there is a risk that the size of the treatment effect may have been slightly overestimated. It was not possible to investigate the impact of this; however, loss to follow-up was reasonably low in the majority of studies.

The benefit with CPAP compared with control on the ESS and MWT is consistent with previous systematic reviews.^{48,50} A previous subgroup analysis reported a more pronounced effect of CPAP in participants with moderate and severe symptoms at baseline, although this was apparent in parallel trials only.⁵⁰ A systematic review published just as the current review was completed reported 24-hour mean blood pressure, using ABPM, as a primary outcome.¹⁷⁴ A small but statistically significant decrease in 24-hour MAP of 1.7 mmHg was reported (MD -1.7 mmHg, 95% CI -2.7 to -0.7). There was a statistically significant decrease in daytime MAP of a similar magnitude to the current review (-1.8 mmHg, 95% CI -3.3 to -0.2) compared with 2.1 mmHg (MD -2.1, 95% CI -4.3 to 0.0) in the current review. Unlike the current

review, there was a significant improvement with CPAP compared with placebo for SBP [-2.3 mmHg, (95% CI -4.3 to -0.2) compared with -1.1 mmHg (95% CI -3.4 to 1.2)] in the current review and DBP [-2.9 mmHg, (95% CI -4.4 to -0.4) compared with -1.2 mmHg (95% CI -2.9 to 0.5)]. The recently published review used estimates for MAP from SBP and DBP where MAP was not reported and included data from two studies from which we could not get accurate estimates from the graphs and were not able to obtain the data from the authors. The additional power in the analysis may have been important in deriving a statistically significant benefit on SBP and DBP.

Cost-effectiveness

The York model is the first cost-effectiveness study to seek to reflect the implications for long-term costs and QALYs of a broad range of trial evidence on sleepiness and to compare all relevant treatment options in the NHS. It explores a range of scenarios and quantifies decision uncertainty and the EVPI. The analysis suggests that CPAP is cost-effective compared with dental devices and conservative management, assuming a cost-effectiveness threshold of £20,000, with one exception, i.e. the ICER in a subgroup with mild disease in terms of baseline ESS score was estimated to be £20,585.

This is consistent with previously published economic evaluations. However, the York model additionally provided an estimate of the value of further research, which indicated that the cost of the uncertainty associated with the model parameters was high. The EVPI was calculated based only on the incident patient population and does not incorporate uncertainty in model structure, modelling assumptions and data quality. Given this, it may underestimate the cost of the decision uncertainty. When interpreting the results of the York model some caveats must be borne in mind:

- The translation of health benefits in terms of ESS to utility scores was based on simple regression models derived from just three sets of patient-level data.
- The patient-level data on which the regression models were based came from predominantly patients receiving CPAP. To address this problem, future trials would ideally incorporate generic instruments to provide a direct measure of preference-based HRQoL.

- The effect of CPAP treatment on reducing RTAs was derived from observational studies. While it would not seem feasible to conduct an RCT to measure such a rare effect, it would be preferable to have been able to link this information in some way to the information obtained in the systematic review.
- 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.
- Only two outcome measures from the clinical trial data (effect of treatment on ESS and SBP) were incorporated in the economic model. Potentially some of the other measures reported in the trials could impact on HRQoL independently of ESS and this is not reflected in the current model. In particular, the model does not differentiate between conservative management, dental devices and CPAP in terms of the disutility associated with undesirable side effects from treatments themselves, which may be expected to differ between the technologies.
- The estimates of cost-effectiveness of CPAP by baseline severity in OSAHS should be considered with caution. Although there was clear heterogeneity in ESS treatment effects in the overall meta-analysis in Chapter 3, it was only possible to group trials by severity using average study-level data. 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 this analysis.

Uncertainties

- The effectiveness (and hence cost-effectiveness) of using CPAP to treat mild disease remains uncertain due to a paucity of research; the treatment effect for daytime sleepiness in the current review is based on only two studies.
- The relative treatment benefits with CPAP according to symptom severity are based on summary data and cannot be viewed as definitive.
- The patients studied in most trials tend to be middle-aged and predominantly male. It is unclear whether therapeutic benefits are similar in other groups, in particular the elderly, in whom cognitive impairment and cerebrovascular disease are more prevalent and the OSAHS may be complicated.
- There is evidence of a benefit with CPAP on MAP although this finding was not robust, possibly due to an underpowered analysis. In addition, it remains unclear in what patient groups this benefit might be expected to be found in terms of disease severity and blood pressure status at baseline.
- The evidence of a fall in MAP implies a reduction in cardiovascular risk, but this has not been directly studied and the magnitude of the risk for end-organ cardiovascular damage is therefore uncertain.
- Dental devices may be a treatment option in moderate disease. However, there was inconsistency in the treatment effect comparing CPAP and dental devices, possibly due to the variety of dental devices investigated. It remains unclear precisely what type of 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.

Other relevant factors

The trials included in this technology assessment mainly used thorough diagnostic assessment to establish a diagnosis of OSAHS and the findings of this review are applicable to a population in which there has been an adequate diagnostic assessment. In view of the diagnostic complexity of sleep apnoea, adequate diagnostic assessment should include a multichannel sleep study reported by an appropriately trained physician (such as a consultant respiratory physician). The detailed consideration of what would constitute an appropriate multichannel sleep study and the associated cost implications were outside the remit of this technology appraisal.

CPAP does not deal with one of the key underlying causes of the disease, which is obesity. It was not possible to assess the relative benefits of CPAP over weight loss interventions due to a lack of appropriate data. The main focus of the current review was CPAP for the treatment of OSAHS, but a recent systematic review comparing lifestyle interventions with placebo found no relevant studies and identified a need for research addressing obesity.³⁰

Chapter 7

Conclusions

Implications for service provision

- CPAP is an effective treatment for OSAHS compared with best supportive care and placebo in populations with moderate to severe symptoms and there may be benefits where the disease is mild. In populations with moderate to severe symptoms there is robust evidence of improvement in symptoms of daytime sleepiness.
- There is evidence of benefit in blood pressure and quality of life with CPAP, although some uncertainty remains about these outcomes.
- 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 were dental devices or conservative management. The probability of CPAP being more cost-effective than dental devices or conservative management was high for a cost-effectiveness threshold of £20,000 per QALY gained.

Suggested research priorities

- An EVPI analysis suggested that because the cost of any decision uncertainty may be high, the value of further research to investigate the parameters contributing most to the decision uncertainty may exceed the costs of that research.

- There is uncertainty about the effectiveness of CPAP for populations with OSAHS with mild daytime sleepiness and further investigation of the effectiveness of CPAP for this population is required.
- Although dental devices are not as cost-effective as CPAP, they do provide an alternative treatment option for patients who cannot tolerate CPAP. The trial evidence comparing dental devices with CPAP was not extensive and had some limitations; therefore, further trials may be useful. Given the heterogeneity of devices in use, the research should identify the most effective type and address whether there are specific patient groups that do or do not benefit.
- Further investigation of the effect of CPAP on hypertension and which populations might be expected to benefit in terms of OSAHS disease severity and normotensive and hypertensive patients would be beneficial.
- Currently changes in cardiovascular events have to be inferred from changes in blood pressure; therefore, clinical trials that are adequately powered to identify changes in CVEs would be beneficial.
- The populations studied in current trials are mostly male and middle-aged. Clinical trials to define treatment effects at the extremes of age (particularly in the elderly, in whom cardiovascular co-morbidity complicates assessment) and in women would be beneficial.
- More comprehensive data are required on side effects, and this information should be systematically obtained and reported in any future research.



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Contribution of authors

Catriona McDaid (Research Fellow) was involved in the clinical effectiveness part of the review, writing the protocol, study selection, data extraction, quality assessment, data analysis and report writing. Susan Griffin (Research Fellow) was involved in the cost-effectiveness section, study selection, development of the economic model and report writing. Helen Weatherly (Research Fellow) was involved in the cost-effectiveness section, study

selection, development of the economic model and report writing. Kate Durée (Research Fellow) was involved in the clinical effectiveness section including writing the protocol, study selection, data extraction, quality assessment, data analysis and report writing. Mariëlle van der Burgt (Visiting Researcher) was involved in the cost-effectiveness section, study selection, development of the economic model and report writing. Sue van Hout (Research Fellow) contributed to the quality of life section for the background and summarised the studies reporting utility data which were used to inform the economics section. Jo Akers (Information Officer) devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report. Robert Davies (Reader in Respiratory Medicine) provided technical and clinical advice and commented on drafts of the report. Mark Sculpher provided input at all stages of the review, commented on drafts of the report and took overall responsibility for the economic section. Marie Westwood (Reviews Manager) provided input at all stages of the review, commented on drafts of the report and took overall responsibility for the review.



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