The Continuous Positive Airway Pressure for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis

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Contents

Tables

Figures

1 Definition of terms and list of abbreviations

Glossary

Apnoea	The cessation of airflow during sleep, preventing air from entering the lungs caused by an obstruction. Arbitrarily defined in adults as a ten second breathing pause.
Auto-Positive Airways Pressure	A type of CPAP machine that monitors changes in breathing and compensates automatically by making appropriate adjustments in pressure
Cost-benefit analysis	An attempt to give the consequences of the alternative interventions a monetary value. In this way, the consequences can be more easily compared with the costs of the intervention. This involves measuring individuals' "willingness to pay" for given outcomes, and can be difficult.
Cost-consequence analysis	Costs are reported separately from health effects.
Cost-effectiveness analysis	The consequences of the alternatives are measured in natural units, such as years of life gained. The consequences are not given a monetary value.
Cost-effectiveness acceptability curves (CEAC)	A graphical representation of the probability of an intervention being cost effective over a range of monetary values for society's willingness to pay for an additional unit of health gain.
Cost-minimisation	When two alternatives are found to have equal efficacy or outcomes (consequences). Therefore, the only difference between the two is cost. This is sometimes considered to be a sub-type 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.
Continuous Positive Airways Pressure	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.
Disutility	The reduction in utility compared to a healthy population.
Hypopnoea	Reduction of airflow during sleep. Arbitrarily defined in adults as a ten 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 making more space to breathe and 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 and in which the probability of movement from one state to another depends on the current state and remains constant over time.
Mixed treatment comparison	Mixed treatment comparison is a form of meta-analysis used to strengthen inference concerning the relative efficacy of two treatments. It uses data based on direct comparisons (A vs. B and B vs. C trials) and indirect comparisons (A vs C trials) also, it facilitates simultaneous inference regarding all treatments in order to select the best treatments.
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 normal amount of oxygen carried by heamoglobin 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 physiologic 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 which might affect their physical, mental and social well-being.
Quality Adjusted Life Year (QALY)	An index of health gain where 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 parameter estimated into the analysis to test the robustness of the analysis findings. In one-way sensitivity analysis each parameter is varied individually, for 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 and 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 life span 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 trial have measured the outcome on the same scale.

List of abbreviations

AHI	Apnoea/Hyponoea Index
APAP	Autotitrating positive airway pressure
BMI	Body mass index
CHE	Centre for Health Economics
CI	Confidence interval
CPAP	Continuous Positive Airways Pressure
CMSC	Cervicomandibular Support Collar
CNS	Central Nervous System
CRD	Centre for Reviews and Dissemination
EVPI	Expected Value of Perfect Information
ESS	Epworth Sleepiness Scale
EQ-5D	EuroQoL – 5 dimensions
HTA	Health Technology Assessment
ITT	Intention-to-treat
IQR	Interquartile range
MD	Mean Difference
MeSH	Medical Subject Heading
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NA	Not applicable
NR	Not reported
OA	Oral appliance
OLS	Ordinary Least Squares regression
OP	Oral placebo
OR	Odds ratio
OSAHS	Obstructive Sleep Apnoea/Hypopnoea Syndrome
QALY	Quality-Adjusted Life-Years
QoL	Quality of Life
RCT	Randomized controlled trial
RTA	Road traffic accidents
SD	Standard deviation
SE	Standard error
SHEP	Shoulder-Head Elevation Pillow
WMD	Weighted mean difference
WTP	Willingness to pay

2 Executive summary

2.1 Background

Obstructive sleep apnoea-hypopnoea (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). Due to 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 life long condition which may be a risk factor for hypertension, myocardial infarction and stroke. Due to the association between OSAHS and obesity, the prevalence of OSAHS is expected to increase with increasing prevalence of obesity.

2.2 Objectives

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

2.3 Methods

We conducted a systematic review of the clinical and cost-effectiveness literature. Fifteen electronic databases were searched up to November 2006 to identify 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 (RCT) comparing CPAP to best supportive/usual care (e.g. lifestyle advice and other conservative management), placebo, or 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 outcomes (CVE), HRQoL, cognitive function and adverse events. The primary measure of cost-effectiveness was incremental cost per quality-adjusted life-years (QALY).

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 NICE scope. The cost-effectiveness of CPAP was compared to 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 NHS and 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 sub-set of studies; and trial evidence on changes in blood pressure following intervention to estimate differences in the rates of CVE over time; and non-randomised evidence assessing the difference in risk of RTA across treatments. Utilities were expressed on the basis of generic HRQoL instruments (the EQ-5D in the base-case analysis) valued using the public preferences associated with those instruments. The base-case analysis focussed on a male aged 50. A series of sub-group and scenario analyses were also undertaken.

2.4 Results

Forty-eight 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. There was a statistically significant benefit with CPAP compared to control (placebo and conservative treatment/usual care) on the ESS (MD -2.7, 95% CI: -3.45, -1.96). However, there was high inconsistency in the treatment effect (statistical heterogeneity); this was reduced when trials were sub-grouped based on mean symptom severity at baseline. The benefit with CPAP was greatest in the group of trials of severe symptoms (MD -5.0 points, 95% CI: -6.5,-3.5), and was progressively smaller with moderate (MD -2.3 points, 95% CI: -3.0, -1.6) and mild symptoms (MD -1.1 points, 95% CI: -1.8, -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 sub-group analyses and sensitivity analyses. There was also a significant benefit with CPAP compared to usual care on the MWT, which measures capacity to stay awake, but not the MSLT, which measures capacity to fall asleep. The evidence for any benefit with CPAP compared to 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 on road traffic accidents.

There was no statistically significant difference between CPAP and dental devices (six trials) in 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, 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 one, the cost per QALY for CPAP compared to 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 £2,000 per QALY, CPAP was the most optimal treatment strategy in all simulations. Relating to the UK, Chilcott et al estimated that at five years the cost per QALY for CPAP compared to no CPAP is £3,200. The three remaining cost-effectiveness 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 need to be addressed in order to assess the value for money of these technologies. None of the cost-effectiveness studies 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. There were limited data on the long-term impact of OSAHS on HRQoL, CVE, road traffic accidents (RTA) 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 compared to dental devices or conservative management. In the base-case the ICER for CPAP compared to dental devices was £3,899 for men and £4,335 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. Sub-group and scenario analyses found that the incremental cost-effectiveness ratio (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.

2.5 Discussion

There was clear evidence of a benefit with CPAP compared to 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 to 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 BP or RTA 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 to 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 to CPAP in mild and severe disease populations is unclear.
- Only two outcome measures from the clinical trial data (effect of treatment on ESS and 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. In particular the model does not differentiate between conservative management, dental devices and CPAP in terms of the disutility associated with any undesirable side effects from treatments themselves, which may be expected to differ between the technologies.

2.6 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 compared to 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 to 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 well as trials adequately powered to identify changes in CVE.

3 Background

3.1 Description of health problem

3.1.1 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 apopnoeas and morning headaches. Less commonly reported symptoms include reduced libido and enuresis.[4]

3.1.2 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 take 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 nocturnal events.

3.1.2.1 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 their 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 (SD 2.2) with a range from 0 to 10[6] and 7.6 (SD3.9)[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 Multiple 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 forty 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 score the maximum of 40 minutes. The MSLT assesses the tendency to fall asleep during four or five tests at two 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 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 a two standard deviation range of 2 to 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 (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

due to 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.

3.1.3 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 through 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 mainly targeted at controlling its symptoms (particularly excessive daytime sleepiness) and other consequences (such as hypertension/vascular risk), rather than correcting the breathing disturbance itself. 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 UK adult men 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 sub-groups, 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, though 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 levels[11] and minimising the prevalence of OSAHS is an important potential benefit of population weight reduction strategies.

3.1.4 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 where 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 large 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 but that the epidemiological evidence for a causal link with other adverse health outcomes was 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 ten years since that review, making it out of date, and a re-evaluation is required incorporating the new research, though this is beyond the scope of the current review.

- **Cognitive function**

Reported cognitive related impairments with OSAHS include difficulties in work efficiency, performing new tasks, memory disturbance and difficulties in concentrating;[12] though there is contradictory evidence regarding these effects in a population with mild to moderate disease.[14] Difficulties with 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 on tests of nonverbal planning).[15]

- **Accidents including road acidents**

There is also evidence that symptoms of daytime sleepiness and impaired concentration arising from untreated OSAHS pose a significant 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 to those without OSAHS though the size of the estimated increased risk varied amongst studies.[19] The UK Driving Licence authorities do not allow people 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 (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 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] they are considered to have high acceptability and relevance for both patients and clinicians, and because they are disorder specific they are though 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 measure 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; low score indicate poor HRQoL. A drawback of this measure is that it was designed to be interviewer-led, although it has been used as a self-completed instrument.

- **Cardiovascular disease**

Based on three recent overviews of the evidence on the 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, though considerable uncertainties about whether it is an independent risk factor remain.[4, 27, 28]

3.2 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 only used 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. This includes conservative options such as weight loss, avoidance of alcohol or sedative medication, improved sleep hygiene and use of a lateral sleeping position. 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]

3.3 Description of technology under assessment

3.3.1 CPAP

CPAP devices are small, electric pumps which 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 disease[33] 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 are 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 which 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 amongst those accepting treatment of over 70%,[38] and 80%[39, 40] after one year have been reported, though lower rates have also been reported. Reasons for discontinuation primarily relate to physical discomfort, nasal dryness and congestion, difficulty adapting to the pressure, dislodgment during sleep, and the social consequences of using the unit. Serious side effects 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 auto-titrating and bi-level CPAP which aim to vary the pressure depending on need during the night and therefore reduce the pressure required and associated side effects. Lower treatment pressures have been reported with autotitrating compared to fixed CAP but no clinically important changes in adherence or other outcomes have been found, [37, 42] though one systematic review concluded that auto-CPAP may be of benefit in certain sub-groups, as yet undefined.[37] Similarly, there was no evidence of increased adherence with humidified CPAP though a need for further research has been noted.[37] Variations to 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.

3.3.2 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. Chilcott *et al* (2000)[44] highlighted concerns about (i) the haphazard and sporadic provision of CPAP devices throughout the UK and (ii) the potential scale of long-term costs related to provision of new devices and maintenance of an expanding pool of CPAP devices. On the first point, the authors suggested that there is a great deal of variation across the Region (Trent) in the pattern and range of services that are available for

diagnosing and treating OSAHS and that this perpetuates inequity across the NHS. On the second point they provide the example that if 60 new CPAP devices are provided each year, 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 at £250 (no price year given) and estimated, at that time, the annual maintenance costs and patient follow-up cost amount at an additional £250 per year. The cost of an initial investigation ranges from £370 to £790 per person investigated. They estimated that initial year one costs of about £60,000 may rise to annual costs of £95,000 in year five and £115,000 in year ten.

3.3.3 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 though 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 mandible movement. [45] They can be custom-made or pre-fabricated. Other variations in design are available. Most side effects of treatment are reported to be minor and temporary, e.g. excessive salivation, though some are more significant, e.g. bite changes.[46] Due to the perception that the modest increases in pharyngeal patency achieveable with mandibular devices and the lack of high quality evidence available on their effectiveness, dental devices are currently only considered appropriate for use in mild to moderate OSAHS (where airway collapse is more easily reversed), or where patients do not wish to use CPAP.[47]

3.4 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 the clinical and 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 since then. A systematic review in 2003 identified 12 trials; CPAP was compared to oral placebo, conservative therapy such as lifestyle changes and sham CPAP (an identical device 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 ESS score of 2.94 points (95% CI: 1.61, 4.26) with CPAP

compared to control. There was evidence of variation in the treatment effect which remained unexplained by age, sex, BMI, location of study or mean hours of CPAP use. Variation by study baseline disease severity and methodological quality were not investigated. The MSLT and MWT were pooled together which would seem inappropriate based upon 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 to control in patients with mild to moderate OSAHS. There was also a statistically significant improvement in sleep latency on the MWT by 2.1 minutes (95% CI: 0.5, 3.7) with CPAP compared to 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 to 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, though there was evidence of statistical heterogeneity (variation in the treatment effect) across the trials. There was a statistically significant benefit with CPAP compared to 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. Whilst this is an appropriate approach, it does reduce the power of any sub-group 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 parallal 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 where 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 to placebo devices that were similar devices placed in the mouth but did not protrude the mandible.[53] When parallel studies were pooled there was a statistically significant improvement with dental devices compared to control devices of 2.09 points on the ESS, though there was high statistical heterogeneity. Crossover trials also showed a statistically significant benefit of 1.81 points on the ESS. An earlier systematic review reported a statistically significant improvement on the AHI but reported contradictory results from trials on subjective sleepiness (ESS).[45]

4 Definition of decision problem

4.1 Decision problem

Untreated OSAHS is associated with increased daytime sleepiness, impairment of cognitive function and a reduction in quality of life. Due 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 life long condition which may be a risk factor for hypertension, myocardial infarction and stroke. Due to 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 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 and cost-effectiveness of CPAP is required. The main focus of interest is how CPAP compares to 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 sub-groups of people for whom this CPAP is particularly appropriate, should be investigated.

4.2 Overall aims and objectives of assessment

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.

5 Assessment of Clinical Effectiveness

5.1 Methods for Reviewing Clinical Effectiveness

5.1.1 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 11.1.

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

Further databases were searched to identify primary studies:

MEDLINE (1966-November week 3 2006) (OVID)
MEDLINE In-Process & Other Non-Indexed Citations (November 28 2006) (OVID)
EMBASE (1980-2006 week 47) (OVID)
Cochrane Central Register of Controlled Trials (Cochrane Library 2006, issue 4) (www.thecochranelibrary.com)
CINAHL (1982-November week 3 2006) (OVID)
Science Citation Index (1900-November 25 2006) (Web of Knowledge)
ISI Proceedings Science & Technology (1990-November 25 2006) (Web of Knowledge)
Zetoc Conferences (1993-November 29 2006) (http://zetoc.mimas.ac.uk/)

SIGLE (1980-2005/03) (SilverPlatter)

Index to Theses (1716-October 16 2006) (http://www.theses.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/)

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 which 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 (vol 2005 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 & 2006 http://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) http://www.brit-thoracic.org.uk/

Thoracic Society of Australia and New Zealand annual scientific meetings 2005 & 2006 http://www.thoracic.org.au/

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

5.1.2 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 were included in the review if they meet the following criteria.

5.1.2.1 Population

Studies of adults (16 years or older) with a diagnosis of predominantly obstructive sleep apnoea, confirmed by use of an appropriate tool (for example, a respiratory polysomnographic sleep study, analysed by an appropriately qualified respiratory physician, from which a standard severity criteria such as the apnoea/hypopnoea or arterial oxygen desaturation index has been derived) were included. Populations of any disease 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 differentiate OSAHS. Because of the complexities of differentiating the 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 had some patients with these co-morbid conditions were included.

5.1.2.2 Intervention and comparators

Studies of fixed CPAP or autotitrating CPAP therapy were eligible for inclusion provided the treatment was of at least one week duration. For the purposes of this review fixed and autotitrating CPAP were treated as the same intervention: studies comparing the two tecnologies 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 where it was stated sham CPAP and did not exclude studies based on the specific the sub-therapeutic pressure used.

5.1.2.3 Outcomes

The following outcomes were included:

Primary outcomes

- subjective sleepiness as assessed by the Epworth Sleepiness Scale (ESS)
- objective sleepiness as assessed by Maintenance of Wakefulness Test (MWT), Osler test, Multiple Sleep Latency 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 nightime 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), though it was thought unlikely that such data would be found in RCTs
- Quality of life, where it was measured using a standardised scale
- Mood, anxiety and depression, where it was 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.

5.1.2.4 Study design

Randomised controlled trials 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.

5.1.3 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 for 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 Revman and into a standard form in Word. Data extracted included patient characteristics (age, sex, severity of OSAHS, body mass index), 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 endpoint data were reported in the trials, except for blood pressure where a mixture of change and endpoint data were reported. Where both endpoint and change data were reported, preference was given to endpoint data for all outcomes except blood pressure where 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 endpoint data in some situations as they have two sources of measurement error (at baseline and follow-up).[54] However, unlike endpoint values, use of change scores removes a component of between person variability.[54] Whether the between –person variation is increased or reduced by using an endpoint 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 it was available as this outcome was being used in the economic model and change in blood pressure was preferred to endpoint for use in this model. All outcomes were continuous data and the mean difference between CPAP and comparator was calculated for each outcome.

Paired data were extracted from crossover trials where available. If the standard deviation or standard error from a paired analysis was not reported, the standard error was imputed from the t-statistic, the p-value or the confidence interval from a paired analysis.[52] For one crossover study it was necessary

to impute the standard error 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 there were a few instances, where there had been evidence of a carryover effect into the second period, and the authors reported only data from the first sequence of the crossover trial and these data were treated as data from parallel trial. This is not ideal data but, where this was the only data available it was used in the review.

Due 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 where 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 were extracted.

5.1.4 Quality assessment

Study quality was assessed based on criteria from CRD Report No 4 and additional criteria were used to assess crossover trials (see 5.2.1.2). 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.

5.1.5 Data analysis

Where sufficient data were available, they were pooled in quantitative syntheses using a random effects model. Studies comparing CPAP to placebo or best supportive/usual care were pooled separately from studies comparing CPAP to dental devices. Where data sets included both study designs, parallel and crossover trials were pooled together.[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 method in Revman was used. To transform the parallel data for entry into the generic inverse variance facility the standard error for the mean difference was calculated from the 95% confidence interval. This was calculated using the formula SE = (upper CI- lower CI)/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 sub-group analysis, since clinically important variations in the magnitude of treatment effects are likely in different severity groups. The sub-groups specified in advance were as follows.

- Population sub-groups:
    - Baseline disease severity, as classified using the AHI or the desaturation rate using the mean baseline score for each study: mild (AHI 5-14/hr or oxygen desaturation rate 5-10/hr), moderate (AHI 15-30/hr or oxygen desaturation rate 10-30/hr) and severe (AHI >30/h or oxygen desaturation rate >30/hr)
    - Baseline symptom severity, as classified using the mean baseline ESS score for each study: mild (0-9 points), moderate (10 to 15 points) and severe (16-24 points).
- Comparator sub-groups:
    - Sham CPAP, oral placebo and best supportive care.
- Study design sub-groups:
    - Parallel and crossover.
    - Endpoint 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.

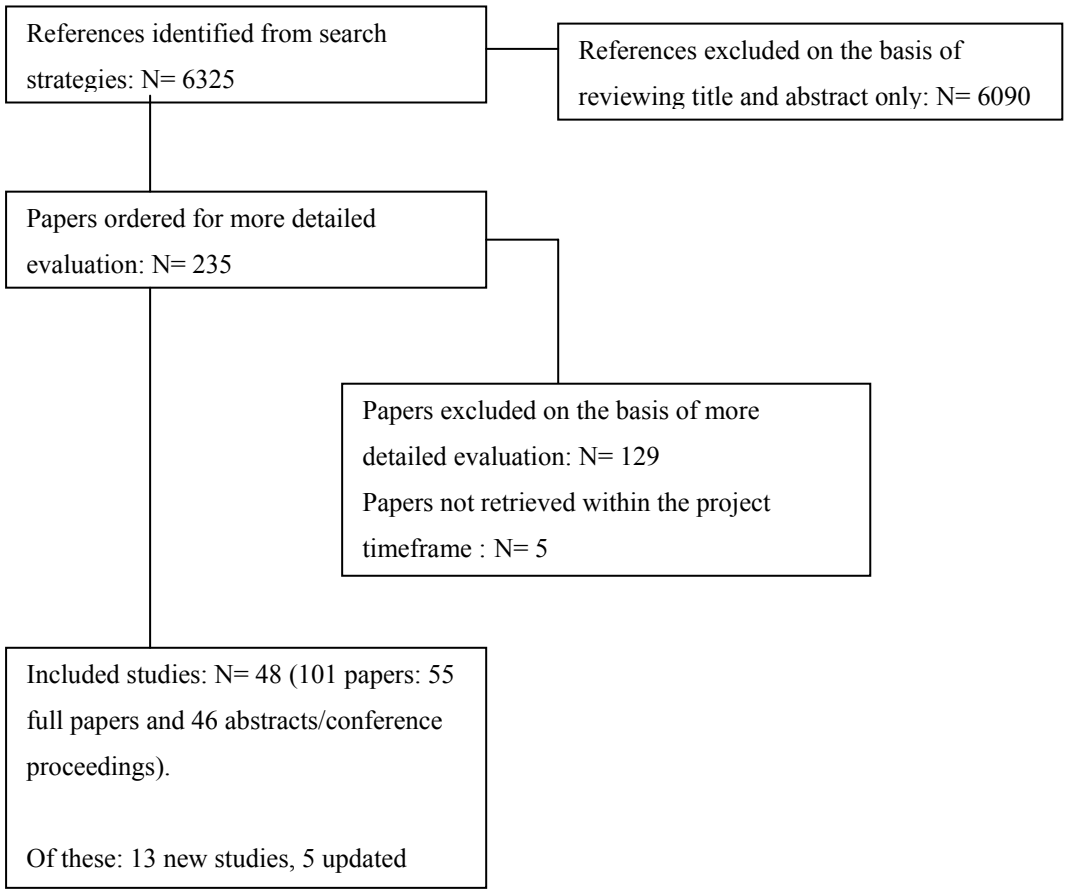
Where no new data were identified for specific outcomes since the review by Giles *et al* [50] we reported the analysis based on the data sets from that review, though we report the pooling from a random effects model, combining crossover and parallel designs, as per our protocol rather than a fixed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

5.2 Results of Review of Clinical Effectiveness

5.2.1 Quantity and quality of research available

The searches identified 6325 potentially relevant references (see Figure 5.1). On the basis of screening titles and abstracts, 235 full papers were ordered for further assessment. Inclusion screeing of full papers identified forty-eight individual relevant studies. Eighteen of these were new studies or provided additional data since the review by Giles *et al* [50] Four were available at the time of the review by 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]

Figure 5.1 Study selection



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 were excluded, that had been included in the review by Giles *et al* because they focused on participants with CNS dysfunction or heart failure and these populations were not considered in the current review.[74-76] Detailes of the included studies and their

related papers are provided in Appendix 11.5. For the purpose of simplicity the main papers from individual studies are referred to in the main body of the report though data from more than one paper may have been used.

5.2.1.1 Study characteristics

The characteristics of the included studies are summarised in Table 5.1. This table focuses on the study characteristics which were used for the sub-group 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 11.5

Intervention and comparators

Forty six of the 48 included studies used fixed pressure CPAP. The remaining two studies used auto-titrating pressure,[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 to sham CPAP (18 studies);[56, 58, 62-68, 73, 77, 79, 83-88] oral placebo (9 studies);[78, 82, 89-95] conservative/usual care (8 studies);[59, 69, 70, 96-100] dental devices (12 studies);[70, 72, 80-82, 101-107] and posture related devices (3 studies).[60, 61, 108]

Where sham CPAP was used as placebo, the sub-therapeutic pressure ranged from 0 to 4cm H_20. Where reported, the majority of studies (n=12) used a pressure of 2 cm H_20 or less; two used a pressure between 3 and 4 cm H_20.[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 nonadjustable 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 to some form of device to control sleeping position used: a backpack with soft ball inside to prevent supine position while sleeping;[108] a shoulder-head elevation pillow to maintain an upright position (60 degrees) while sleeping;[60] and a cervicomandibular collar to retain the head in a natural position and prevent the jaw 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/m^2) and 30 were of an obese population (BMI 30.1-40 kg/m^2); the highest mean BMI at baseline was 40.1 kg/m^2. [88] Two studies were of patients who were being treated for another primary disease: Type 2 diabetes[67] and headache symptoms.[98] Two studies specifically recruited patients with hypertension. [65, 68]

Table 5.1 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 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), the majority of studies (n=26) investigated a population with severe OSAHS, 15 with moderate disease, and 3 with mild. 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 was 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 where the comparator was postural therapy. This was also the dominant study design for trials comparing dental devices to CPAP. Parallel trials were the dominant design used in trials comparing CPAP to sham CPAP or conservative/usual.

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

Table 5.1 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 versus sham CPAP					
Parallel trials					
*Arias† 2006[63]	23	AHI ≥10 and ESS ≥10	Severe 44.1 (29.3)	NR	12
Barbè 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 2003[109]	60	AHI ≥5 and ESS ≥10	Severe I 62.5 (17.8) C65 (26.7)	Moderate I 14.4 (2.5) C14.1 (3.2)	9
*Campos-Rodriguez 2006[65]	72	AHI ≥10 and hypertension	Severe I 58.3 (24.6) C59.5 (21.7)	Moderate I 15 (3.9) C 13.6 (3.6)	4
‡Dimsdale 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
**Henke 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
*Hui 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

Study details	Number randomised N	Target population	Disease severity AHI Mean (SD)	Severity of sleepiness ESS Mean (SD)	Treatment duration (weeks)
Jenkinson 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)§ dips/hr >4% SaO_2 C 28.5 (10.7-68.7)	Severe I Median 16 (10.7-21.7) § C17 (10-23)	4
‡Norman 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 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/hr >4% SaO_2 C 35.9 (19.6)	Severe I 16.3 (3.3) C 16 (3.1)	4
*Spicuzza 2006[66]	25	moderate to severe OSAHS	Severe I 55.3 (11.9) C 59.2 (17.3)	NR	4
*West 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/hr >4% SaO_2 C 39.1 (24.8)	Moderate I 14.7 (3.5) C 13.6 (3.5)	12
Crossover trials					
*Arias 2005[56]	27	Men with AHI ≥10 and ESS ≥10	Severe 44 (27.5)	NR	12
*Coughlin 2007[62]	35	RDI > 15 and ESS ≥10 or two other symptoms	Severe RDI 39.7 (13.8)	Moderate 13.8 (4.9)	6
*Cross 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 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

Study details	Number randomised N	Target population	Disease severity AHI Mean (SD)	Severity of sleepiness ESS Mean (SD)	Treatment duration (weeks)
*Robinson 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/hr >4% SaO_2	Mild Median 5.3 (IQR 3.0-7.0)	4
CPAP versus oral placebo					
Crossover trials					
Barnes 2002[89]	42	AHI 5-30 and symptoms of OSAHS	Mild 12.9 (6.3)	Moderate 11.2 (5)	8
Barnes 2004[82]	114	AHI 5-30	Moderate 21.3 (13.6)	Moderate 10.7 (6.5)	12
Engleman 1994[90]	35	AHI ≥5 and at least two symptoms of OSAHS	Moderate Median 28 (range 7-129)	NR	4
Engleman 1996[91]	16	AHI ≥5 and at least two symptoms of OSAHS	Severe 49 (32.5)	NR	3
Engleman 1997[92]	18	AHI 5-14.9 and at least two symptoms of OSAHS	Mild 11 (4)	Moderate 14 (4)	4
Engleman 1998[93]	23	AHI ≥15 and at least two symptoms of obstructive sleep apnoea	Severe 43 (37)	Moderate 12 (4)	4
Engleman 1999[78]	37	AHI 5-14.9 and at least two symptoms of OSAHS including day time sleepiness (ESS ≥8 or reported sleepiness whilst driving)	Mild 10 (3)	Moderate 13 (3)	4
Faccenda 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 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
CPAP versus conservative/usual care					
Parallel trials					
Ballester 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

Study details	Number randomised N	Target population	Disease severity AHI Mean (SD)	Severity of sleepiness ESS Mean (SD)	Treatment duration (weeks)
Chakravorty 2002[97]	71	AHI >15	Severe I 55 (28.7) C35 (19.1)	Severe I 16 (5.6) C 14 (4.2)	12
*Drager 2006[69] Abstract	16	AHI>30, normotensive	Severe I 54 (8) C 65 (13)	NR	12
*Lam 2006[70]	101	AHI 5-40 or with 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 2005[110] Abstract	23	Primary headache symptoms and AHI ≥5			4
Lojander 1996[99]	44	Diagnosis of OSAHSand BMI < 40kgm^2	Moderate	NR	52
Monasterio 2001[100]	142	AHI 10-30 and absence of severe daytime sleepiness	Moderate I 20 (6) C 21 (6)	Moderate I12.1 (4.9) C13.2 (4.3)	24
‡Redline 1998[59]	111	RDI 5-30 and absence of "pathologic 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 versus posture related device					
Crossover trials					
Jokic 1999[108]	14	AHI <15 in the lateral position and AHI in the supine sleep position at least two times that in the lateral position.	Severe (supine) 63.8 (148.9) Mild (lateral) 4.9 (SE 4.1)	Moderate 13 (SD 1.3)	2
‡Skinner 2004[60]	14	AHI 10-60 and daytime symptoms of obstructive sleep apnoea	Moderate 27 (12)	Moderate 11.9 (4.6)	4
‡Skinner 2004[61]	10	AHI 10-60 and mild to moderate OSAHS	Moderate 29.4 (13.4)	Moderate 13.2 (SD 4.9)	4
CPAP versus dental devices					
Parallel trials					
††Fleetham 1998[101]	101	AHI>10	Severe I 37.6 (22.8) C38.7 (22.2)	Moderate I 12.8 (4.1) C11.1 (4.9)	12

Study details	Number randomised N	Target population	Disease severity AHI Mean (SD)	Severity of sleepiness ESS Mean (SD)	Treatment duration (weeks)
*Hoekema 2006 [102]	103	Adults with a diagnosis of OSAHS	NR	NR	8
*Lam 2006[70]	101	AHI 5-40 or with 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
Crossover trials					
Barnes 2004[82]	114	AHI 5-30	Moderate 21.3 (13.6)	Moderate 10.7 (6.5)	12
*Cibele 2006[72] Abstract	13	AHI ≥20	Severe 45.5 (SD 28)	Moderate 10.6 (SD 4)	4
Ferguson 1996[81]	27	AHI 15-50	Moderate 24.5 (8.8)	NR	16
Engleman 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 1997[80]	24	AHI 15-55	Moderate 26.8 (11.9)	Moderate I 10.3 (3.1) C 11.0 (3.8)	16
L' Estrange 1999[104] Abstract	15	AHI >50	Severe 63.7 (10	Moderate 17.2 (3.8)	8
††Olson 2002[50]	24	AHI >15 or AI>5 or AHI >5 and AI >15	NR	NR	6
Randerath 2002[105]	20	AHI 5-30 and clinical symptoms of OSAHS	Moderate 17.5 (7.7)	NR	6
Tan 2002[106]	24	AHI <50	Moderate 22.2 (9.6)	Moderate 13.4 (4.6)	8

* Additional data since the review by Giles *et al*; † data reported for first arm of crossover only ;‡ New data due to different inclusion criteria; § 5th-95th centile; [1] ** partial crossover, first arm data extracted only; †† unpublished data obtained from the systematic review by Giles *et al*; I Intervention (CPAP); C Comparator

5.2.1.2 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 analysis?
6.	Were appropriate methods used to account for missing data in the intention to treat 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)

Full details of the quality assessment are presented in Appendix 11.3. 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 eighteen 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 eleven studies used sham CPAP as a comparator. It was unclear in the remaining studies using sham CPAP whether participants were CPAP naïve. Intention-to-treat (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 twenty-six crossover studies included in the review, nineteen 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.

5.2.2 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.

5.2.2.1 Epworth Sleepiness Scale

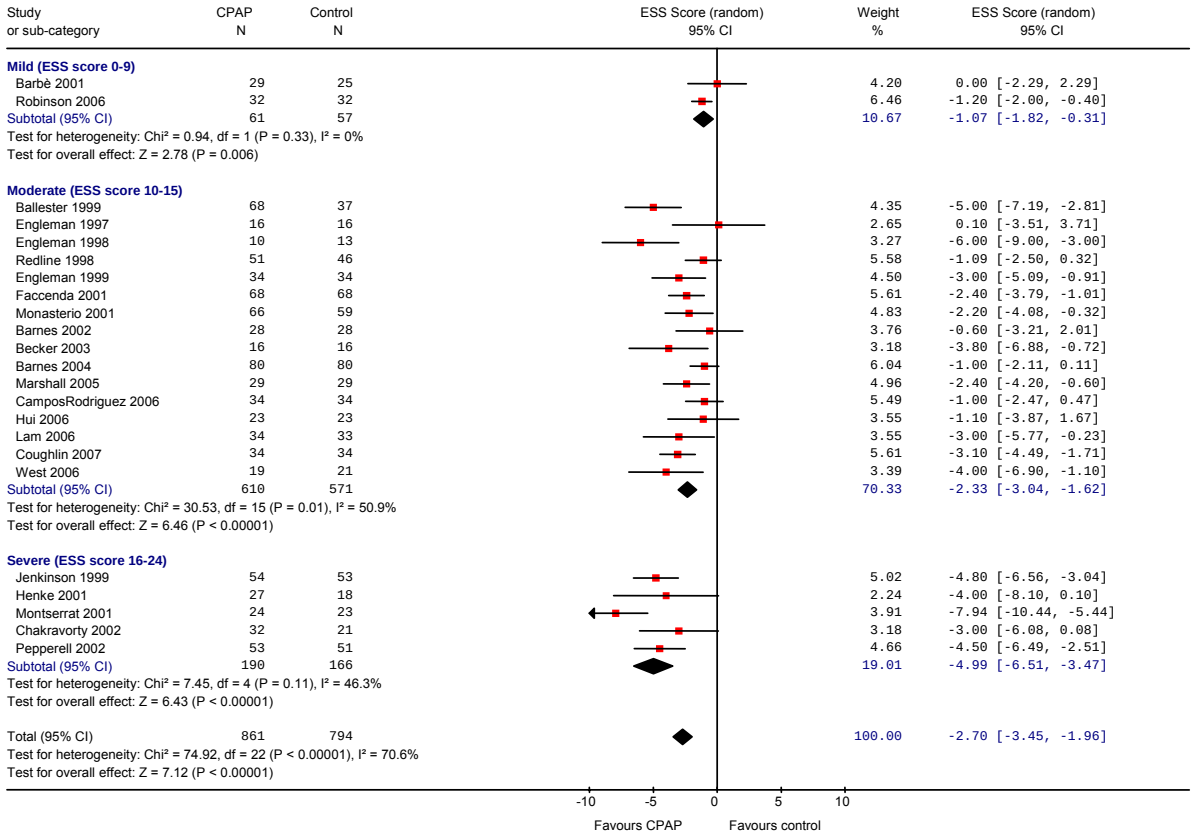
CPAP versus placebo or conservative/usual care

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 to control for daytime sleepiness as measured by the ESS (MD -2.7, 95% CI: -3.5, -2.0). However, heterogeneity was high (I^2 = 71%) and this treatment effect is unlikely to be generalisable. The heterogeneity was investigated using sub-group analysis.

- **Clinical sub-group analyses**

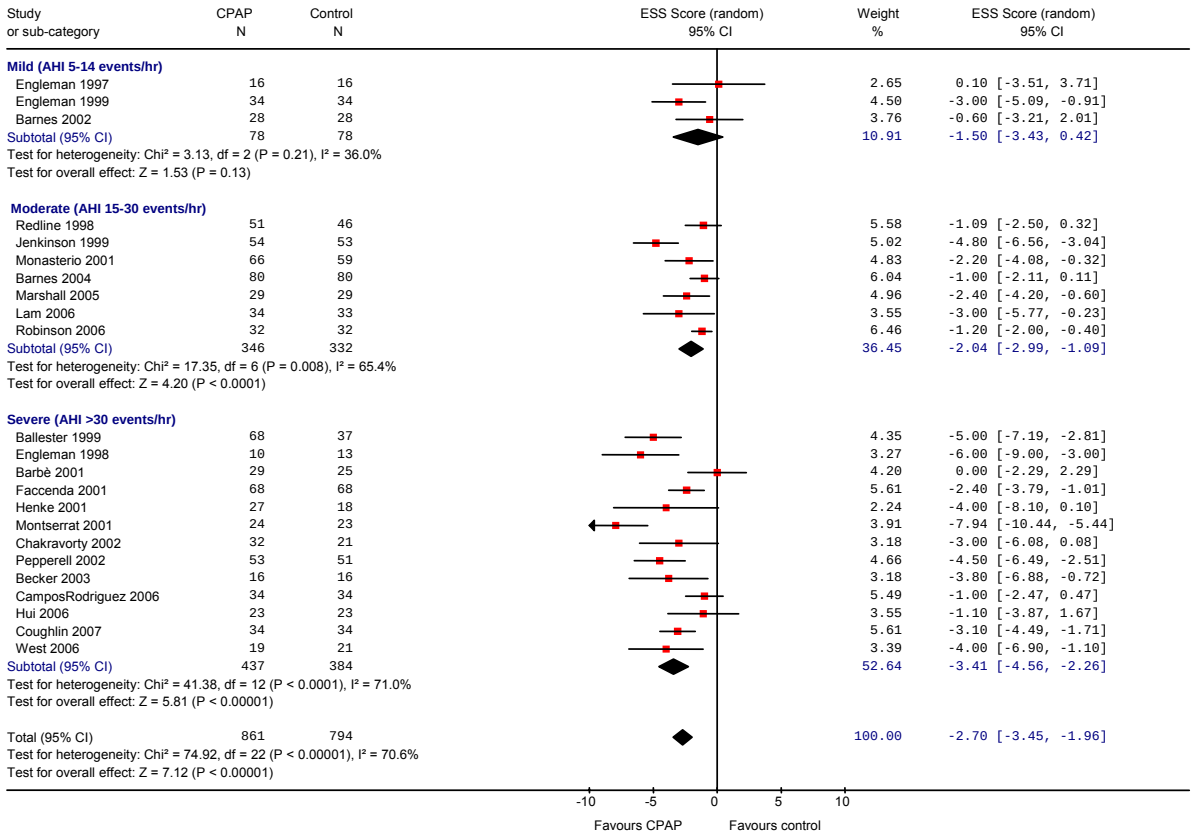
When studies were grouped by severity of daytime sleepiness at baseline (mild, moderate or severe, as defined by the ESS), heterogeneity was reduced. Although there was still evidence of moderate heterogeneity within the sub-groups, with the exception of two studies, the direction of the effect was consistently in favour of CPAP. (see Figure 5.2). There was a statistically significant improvement in symptoms of daytime sleepiness with CPAP treatment compared to placebo or usual care for all levels of disease severity. The improvement was greatest in trials where baseline sleepiness was severe (MD -5.0, 95% CI: -6.5, -3.5) and was consecutively smaller with moderate (MD -2.3, 95% CI: -3.0, -1.6) and mild severity (MD -1.1, 95% CI: -1.8, -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.

Table 5.2 Epworth Sleepiness Scale (CPAP versus placebo/usual care), stratified by severity of sleepiness at baseline (ESS)



When studies were grouped by disease severity (AHI) at baseline there was statistically significant improvement in daytime sleepiness with CPAP compared to placebo or usual care in trials of severe and moderate disease populations but not mild disease (Figure 5.3). As with the sub-group 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 sub-group analyses of trials of severe (I^2 = 71%) and moderate (I^2 = 65%) disease. Only three trials were available for the analysis of mild disease and there was low statistical heterogeneity.

Figure 5.2 Epworth Sleepiness Scale (CPAP versus placebo/usual care), stratified by disease severity at baseline (AHI or oxygen desaturation dip rate)



- **Other sub-group analyses**

The variation in treatment effect with study design (parallel and crossover trial), type of data (endpoint and change scores) and comparator (sham CPAP, oral placebo and conservative/usual care) was also investigated. Each sub-group 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 sub-groups investigated and the treatment effects in the sub-groups were consistent with each other i.e. the 95% confidence intervals overlapped (see Appendix 11.4, Table 11.1).

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 stogether, the treatment effect was consistent with the treatment effect from the overall analysis (MD -3.5, 95% CI: -4.5, -2.5). There was no statistical heterogeneity ($I^2 = 0\%$).

Further sub-group 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 where subjective outcome measures such as ESS are being used. Participant blinding was possible only in the studies where a sham CPAP was used as the comparator. Effectively sham CPAP provides the best placebo. Therefore, further sub-group analysis was conducted on the subset of studies using sham or placebo CPAP. Studies comparing CPAP to 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 twelve studies of CPAP versus sham CPAP were grouped based on baseline ESS the findings were similar to the sub-group analysis of symptom severity conducted on the complete dataset (CPAP versus oral placebo, sham placebo and usual care). (see Appendix 11.4, Figure 11.1) The benefit of CPAP was largest in the trials where mean baseline sleepiness was severe (MD -5.4, 95% CI: -7.0, -3.7, I^2 = 46%) and was consecutively smaller in trials of moderate (MD -2.4, 95% CI: -3.4, -1.4, I^2 = 31%) and mild daytime sleepiness at baseline (MD -1.1, 95% CI: -1.8, -0.3, I^2 = 0%). Statistical heterogeneity within sub-groups was low to moderate.

Sensitivity analyses

The effect of removing individual trials from the meta-analyses where studies were sub-grouped by mean baseline severity of sleepiness was investigated. The removal of individual studies resulted in only small minor variations in the size of treatment effect in the severe and moderate subjective sleepiness at baseline sub-groups and the difference between CPAP and control remained statistically significant (see Appendix 11.4, Table 11.2).

Using a fixed effect model rather than a random effects model did not result in any substantive changes to the results (see Appendix 11.4, Table 11.1).

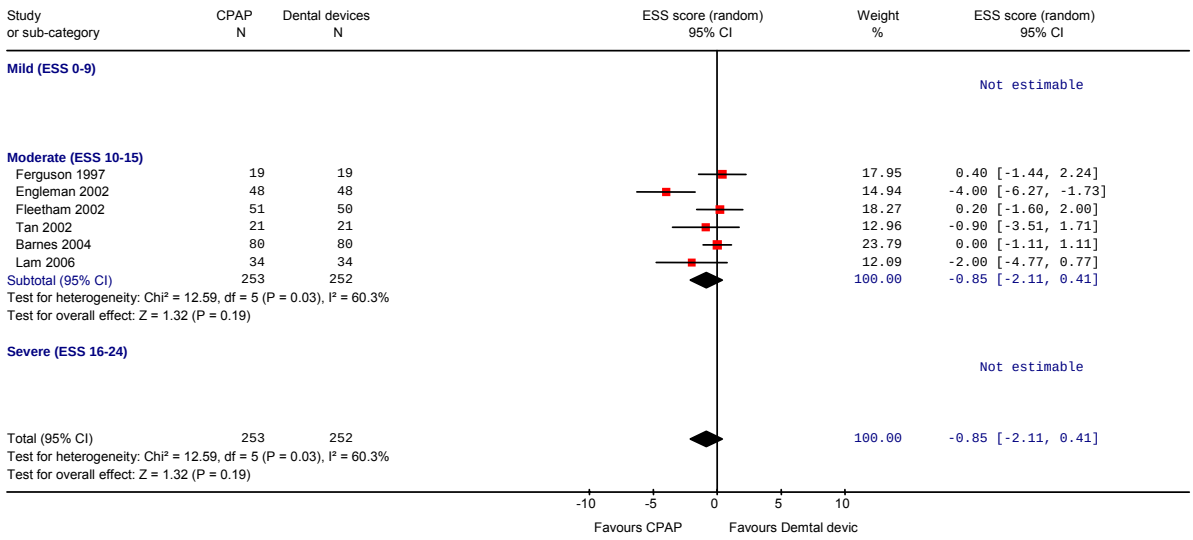
CPAP versus dental devices

Data were available for the ESS from six trials (n=337). All of these trials were of populations with moderate daytime sleepiness (ESS) at baseline. There was no statistically significant difference in the impact on day time sleepiness (ESS) between CPAP and dental devices (MD -0.9, 95% CI: -2.1, 0.4) (see Figure 5.4). There was evidence of moderate statistical heterogeneity (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 sub-group analyses**

When studies were sub-grouped on the basis of baseline disease severity (AHI), the findings were not substantially altered, though this analysis was limited by the small number of studies in the severe disease category and none in the mild group. There was no statistically significant difference between CPAP and dental devices in either severe or moderate disease sub-group (see Appendix 11.4, Table 11.3). The treatment effects in the severe and moderate disease severity sub-groups 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, -1.7) with CPAP compared to dental devices and the other trial reported no statistically significant difference (MD 0.4, 95%CI -1.6, 2.0).

Figure 5.3 Epworth Sleepiness Scale (CPAP versus dental devices), stratified by severity of sleepiness at baseline (ESS)



- **Other sub-group analyses**

The findings were similar within the sub-groups of crossover and parallel trials, though 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 sub-group (see Appendix 11.4, Table 11.3).

- **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 11.4, Table 11.4). 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 11.4, Table 11.3).

CPAP versus postural therapy

Data were available for the ESS from 3 small crossover trials (n=36); [60, 61, 108] the studies were not pooled for an overall treatment effect due to 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 back was two or more times the AHI during sleep in the lateral position): median difference -1.5 (95% CI: -2.9, 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 collar[61] (p=0.22 for difference in change) on the Scottish National Sleep Survey Questionnaire (SHS). Only overall baseline ESS scores were reported for the latter two studies so change scores and the corresponding mean difference could not be calculated.

5.2.2.2 Maintenance of Wakefulness Test

CPAP versus placebo or conservative/usual care

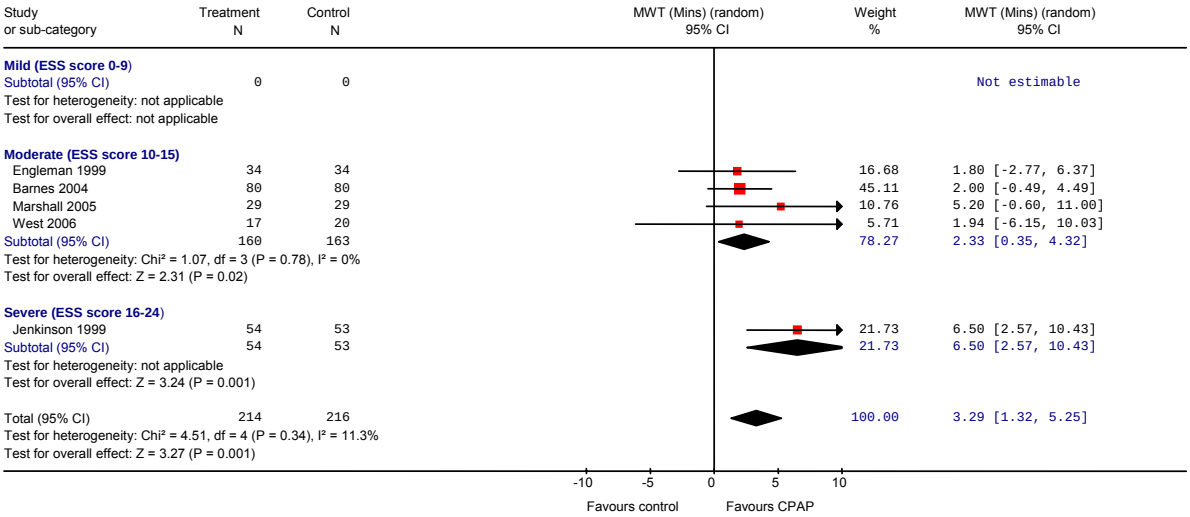
Outcome data were available from five studies (n=287) on the Maintenance of Wakefulness Test. One of these studies used the Osler test. [67] There was a benefit with CPAP compared to placebo/usual care in the length of time participants could stay awake in a setting conducive to sleep (MD 3.3 mins, 95% CI: 1.3, 5.3) and this was statistically significant (see Figure 5.5). Statistical heterogeneity was low (I^2 = 11%) and the treatment effect was consistently in favour of CPAP being beneficial.

- **Clinical sub-group analyses**

The sub-group 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 in the mild group. When studies were sub-grouped there was a statistically significant improvement with CPAP compared to control in the single severe study (MD 6.5 minutes, 95% CI: 2.6, 10.4) and the moderate sub-group (MD 2.3

minutes, 95% CI: 0.4, 4.3) (see Figure 5.5). The benefit was greatest in the study where symptoms were severe at baseline. The sub-group 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, though this analysis was limited by the small number of studies available (see Appendix 11.4, Table 11.5)

Figure 5.4 Maintenance of Wakefulness Test (CPAP versus placebo), stratified by severity of sleepiness at baseline (ESS)



- **Other sub-group analyses**

The variation in treatment effect with study design (parallel and crossover trial) was also investigated. In both sub-groups there was a statistically significant benefit with CPAP compared to control. The treatment effect from the pooled crossover trials was smaller than that from parallel trials, though the 95% confidence intervals overlapped (see Appendix 11.4, Table 11.5).

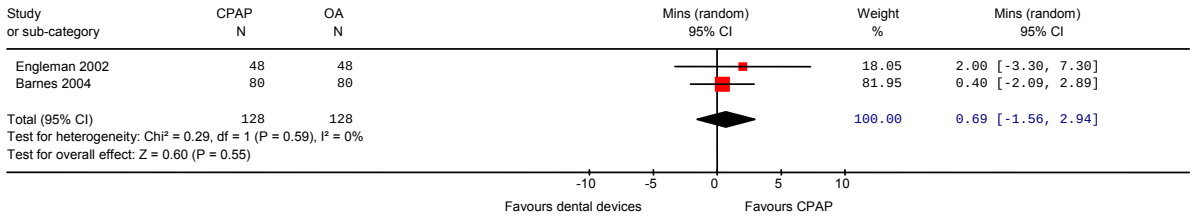
- **Sensitivity analyses**

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 though the effect size ranged from 2.3 to 4.4 (see Appendix 11.4, Table 11.6). Using a fixed effect rather than random effects model did not lead to any substantive changes to the results (see Appendix 11.4, Table 11.5).

CPAP versus dental devices

Data were available from two crossover trials (n=128) on the Maintenance of Wakefulness Test (see Figure 5.6). 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, 2.9). The studies reported consistent findings.

Figure 5.5 Maintenance of Wakefulness Test (CPAP versus dental devices)



CPAP versus postural therapy

Data were available for the MWT from one small crossover trial[108] (n=13). There was no statistically significant difference between CPAP and postural therapy in the length of time participants could stay awake, mean difference 1.7 minutes (95% CI: -1.9, 5.3; p=0.32).

5.2.2.3 Multiple Sleep Latency Test

CPAP versus placebo or conservative/usual care

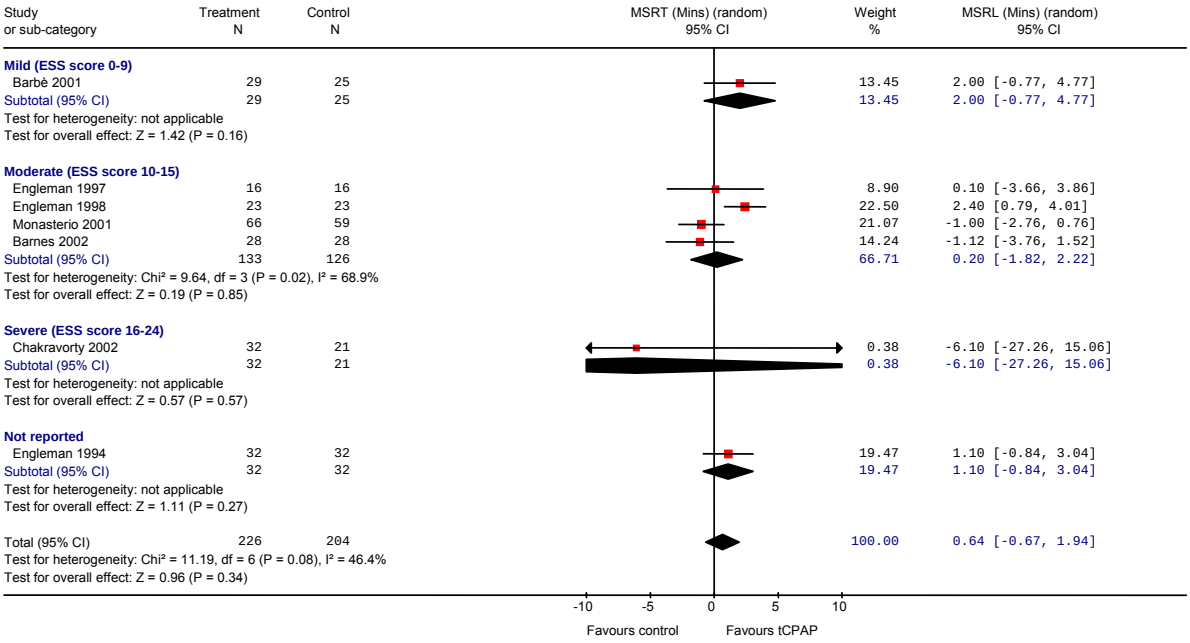
Outcome data were available from seven trials on the Multiple Sleep Latency test (n=331). There was no statistically significant difference between CPAP and placebo/usual care in the length of time it took participants to fall asleep in surroundings conducive to sleep (MD 0.6 minutes, -0.7, 1.9). There was evidence of moderate heterogeneity (I^2 = 46%). (see Figure 5.7).

Clinical sub-group analyses

The sub-group 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 one study could not be classified. (see Figure 5.7). 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, 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 sub-group (MD 0.2, 95% CI: -1.8, 2.2) nor in the single

trial of mild symptom severity (MD 2.0, 95% CI: -0.8, 4.8). When studies were sub-grouped by baseline disease severity (AHI) there was a statistically significant benefit with CPAP compared to 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 mild or moderate severity (see Appendix 11.4, Table 11.7).

Figure 5.6 Multiple Sleep Latency Test (CPAP versus placebo), stratified by severity of sleepiness at baseline (ESS)



- **Other sub-group 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 sub-group. (see Appendix 11.4, Table 11.7).

- **Sensitivity analyses**

The effect of removing individual trials from the meta-analysis was investigated. When the Monasterio trial 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 0.0 to 0.9 minutes when the individual studies were removed (see Appendix 11.4, Table 11.8). Using a fixed effect rather than random effects model did not lead to any substantive changes to the results (see Appendix 11.4, Table 11.7).

CPAP versus dental devices

No data were available for the MSLT.

CPAP versus postural therapy

No data were available for the MSLT.

5.2.2.4 Summary of sleepiness outcomes

- CPAP compared to 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 to control; the effect is probably different in 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 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 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 sub-grouped 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 sub-groups needs to be considered with that in mind.

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

Objective sleepiness was assessed using the MWT and MSLT. 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 to control. The average reduction in sleep

latency with CPAP compared to 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, though this analysis was limited by only one study of a severe symptom severity population and none of a mild population. The benefit with CPAP compared compared to control was robust across the methodological sub-group analysis (trial design) and sensitivity analyses investigating the influence of individual trials and using 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 to 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 is probably different in different groups of people. The average effect was a reduction in sleepiness of less than one ESS point (0.9) with CPAP compared to 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 taking in generalising this to all populations. The finding of no statistically significant difference between CPAP and dental devices was robust across sub-group analysis by disease severity (AHI) and trial design and sensitivity analyses investigating the influence of individual trials and using 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.

5.2.2.5 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 24hr blood pressure is given below and the full data are reported in Appendix 11.4.

Fifteen studies reported outcome data for daytime blood pressure (see Table 5.2); 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.[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 MAP, SBP and DBP;[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, anti-hypertensive medication remained unchanged throughout the studies.

Table 5.3 Summary of blood pressure data reported in included studies

				Ambulatory blood pressure monitoring (ABPM)									Conventional	
Study details	**Baseline daytime BP Mean (SD)**	**% (n) patients hypertensive at baseline**	**How BP was measured**	**Daytime MAP**	**Daytime SBP**	**Daytime DBP**	**Night MAP**	**Night SBP**	**Night DBP**	**24hr MAP**	**24hr SBP**	**24 hr DBP**	**Morning MAP**	**Evening MAP**
CPAP versus sham CPAP														
Arias[56]	SBP 127 (9) DBP 79 (5)		24hr ABPM using oscillometric method. Every 30mins 8am-11pm and every 60mins 11pm-8am. Patients asked to go to be no later than 11pm. (Endpoint data)		√	√		√	√					
Arias[63]	SBP 127 (9) DBP 79 (5)		24hr ABPM using oscillometric method. (Endpoint data)		√	√		√	√					
Barbè[83]	**CPAP** SBP 130 (11) DBP 82 (5) **Control** SBP 127 (10) DBP 80 (10)		24hr ABPM. At least 60 data points were taken for each participant. Daytime was 8 am to 11pm. (Endpoint data)		√	√		√	√		√	√		
Becker[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/or90mm/Hg BP medication unchanged	ABPM measured over 20 hrs using one minute recordings. Night BP was calculated for the hours in bed and on treatment and daytime BP for the remaining 12 hrs. (Change and endpoint data)	√	√	√	√	√	√	√	√			
Campos-Rodriguez[65]	**CPAP** MAP 101 (11) **Control** MAP 99 (10)	100% (>140/90mmHg in 3 independent measurements) BP medication unchanged	24hr ABPM using 30 min recordings. (Change and endpoint)	√			√			√	√	√		
Coughlin[62]		79% (n=27) (resting BP of 140/90mmHg)	Waking BP measured between 8am and 11am in a supine position after a 5 minute rest. It was recorded as the mean of three measurements taken at one minute intervals										√ MAP SBP	

				Ambulatory blood pressure monitoring (ABPM)									Conventional	
Study details	**Baseline daytime BP Mean (SD)**	**% (n) patients hypertensive at baseline**	**How BP was measured**	**Daytime MAP**	**Daytime SBP**	**Daytime DBP**	**Night MAP**	**Night SBP**	**Night DBP**	**24hr MAP**	**24hr SBP**	**24 hr DBP**	**Morning MAP**	**Evening MAP**
			using a automatic oscillometric digital BP monitor. (Endpoint data)										DBP	
Hui[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	24hr ABPM as outpatients during normal activities. BP was measured every 30 minutes for 48hrs and the second 24hrs of data were used. Patients recorded the the time at which they went to bed and woke up to identify the sleep and wake periods. (Change and endpoint data)	√	√	√	√	√	√	√	√	√		
Pepperell[87]	**CPAP** MAP 104 (10) **Control** MAP 104 (11)	19% (n=22) taking medication for hypertension	24hr ABPM measured during normal daily activities (except driving). Patients kept a diary and pressed the event monitor to identify sleep and wake periods. (Change data)	√			√			√	√	√		
Robinson[68]	**CPAP** MAP 106 (14) **Control** MAP 109 (13)	100% (BP >140/90 on 24hr ABPM or taking hypertensive drugs) Medication unchanged	24hr ABPM measured during normal daily activities (except driving). Patients kept a diary and pressed the event monitor to identify sleep and wake periods. (Change and endpoint data)	√			√			√	√	√		
CPAP versus oral placebo														
Barnes [89]	SBP 132 (11) DBP 84 (8)	25% (n=7) (24hr SBP>140 or DBP >90)	24hr ABPM measured every 20mins during daytime and every 60mins overnight (Change data)		√	√		√	√		√	√		
Barnes[82]	NR	15% (n=14) (SBP >140 and/or DBP >90)	24hr ABPM measured every 20mins during daytime and every 60mins overnight (Endpoint data)						√		√	√		
Engleman[91]	NR	38% (n=5) (defined as SBP>134 and DBP>84) Medication unchanged	24hr ABPM measured at 30 minute intervals during which patients conducted normal day-to-day activities in the community. (Endpoint data)	√	√	√	√	√	√					
Faccenda[94]	NR	NR	24 hr ABPM measured every 30mins over 48hrs during which patients went about their							√	√	√		

				Ambulatory blood pressure monitoring (ABPM)									Conventional	
Study details	**Baseline daytime BP Mean (SD)**	**% (n) patients hypertensive at baseline**	**How BP was measured**	**Daytime MAP**	**Daytime SBP**	**Daytime DBP**	**Night MAP**	**Night SBP**	**Night DBP**	**24hr MAP**	**24hr SBP**	**24 hr DBP**	**Morning MAP**	**Evening MAP**
			normal daily activities and these were recorded in a diary. The first 24hrs of data were discarded. (Endpoint data)											
CPAP versus conservative/usual care														
Lam[70]	**CPAP** SBP 128 (13) DBP 77 (11) **CT** SBP 126 (20) DBP 74 (14)	19% (n=19) Medication unchanged	Evening (8-9pm) and morning (8-9am) BP recorded during admission to the sleep clinic. The average of three readings taken at one minute intervals was used. (Endpoint data)										√ SBP DBP	√ SBP DBP
Monasterio[100]	**CPAP** SBP 126 (17) DBP 81 (12) **CT** SBP 132 (17) DBP 84 (11)	NS	Office daytime arterial blood pressure was recorded. (Endpoint data)										√ SBP DBP	
CPAP versus dental devices														
Barnes[82]	NR		See above						√		√	√		
Lam[70]	**CPAP** See above **Dental device** SBP 127 (15) DBP 76 (12)		See above										√	√

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 to placebo/usual care (MD -2.1 mmHg, 95% CI: -4.3, 0.0) and this was statistically significant (Figure 5.8). There was moderate statistical heterogeneity (I^2 = 59%).

- **Clinical sub-group 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 5.8); only one trial each of severe and moderate baseline sleepiness were 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, -2.0) and the difference between CPAP and control was statistically significant (see Figure 5.7). The difference between CPAP and control was not statistically significant for the moderate sub-group (MD -3.4 mmHg, 95% CI: -7.9, 1.2); the one trial of mild disease severity also reported no statistically significant difference bewteen CPAP and control (MD 1.1 mmHg, 95% CI: -2.9, 5.1) (see Figure 5.8). 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 11.4, Table 11.9).

- **Other sub-group analyses**

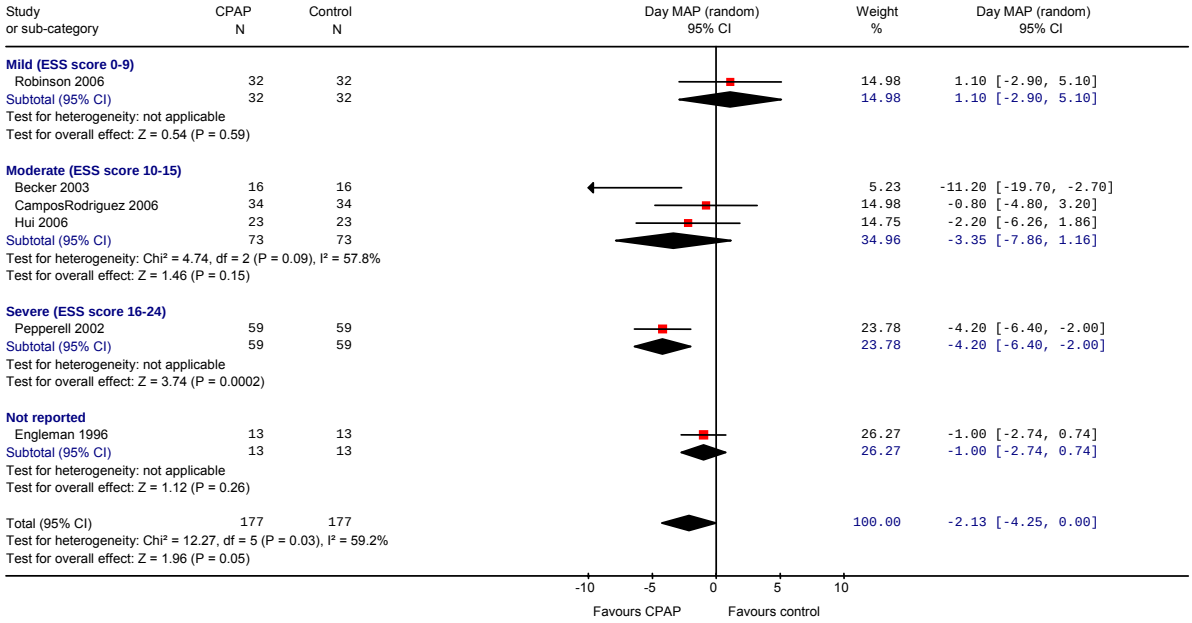
Studies were sub-grouped based on whether they were crossover or parallel and whether endpoint or change data were used. This analysis was limited by four of the six trials being parallel trials using change data (see Appendix 11.4, Table 11.9). For the sub-group of parallel trials using change from baseline data there was a statistically significant improvement with CPAP compared to control. For the other two sub-groups 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 11.4, Table 11.9).

- **Sensitivity analyses**

When studies were individually removed from the analysis the treatment effect ranged from -1.4 mmHg, to -2.7 mmHg and the treatment effect remained statistically significant in only

one instance (see Appendix 11.4, Table 11.10). There was no substantial change in the MAP results using a fixed effect model (see Appendix 11.4, Table 11.9).

Figure 5.7 Daytime mean arterial pressure using ABPM (CPAP versus placbo/usual care), stratified by severity of sleepiness at baseline (ESS)



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 though there was a small decrease in SBP in favour of CPAP (MD -1.1 mmHg, 95% CI: -3.4, 1.2) (see Figure 5.9). There was no evidence of statistical heterogeneity. Similarly, was no statistically significant difference between CPAP and control for DBP though there was a small decrease in favour of CPAP (MD -1.2 mmHg, 95% CI: -2.9, 0.5); heterogeneity was low (I^2 = 29%) (see Figure 5.10).

- **Clinical sub-group 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 symptoms 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] classified as mild disease severity (AHI) the studies were all classified as severe disease populations. When the single mild disease severity (AHI) study was removed from the

analyses for SBP and DBP, the difference between CPAP and control remained not statistically significant. (see Appendix 11.4, Table 11.11 and 11.12)

Figure 5.8 Daytime systolic BP using ABPM (CPAP versus placebo/usual care)

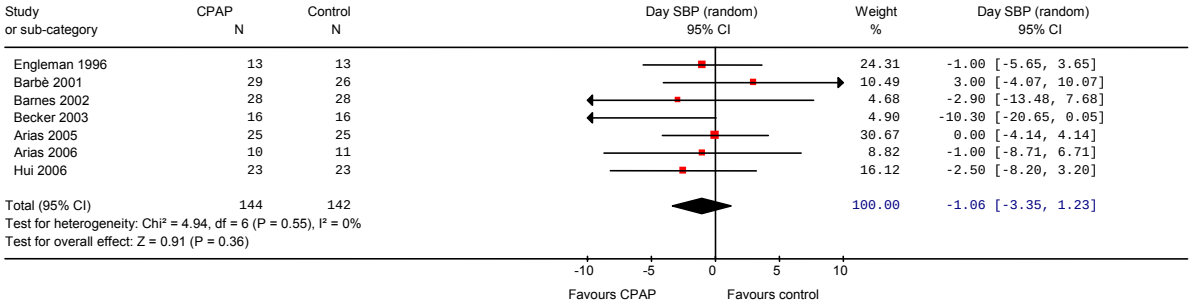
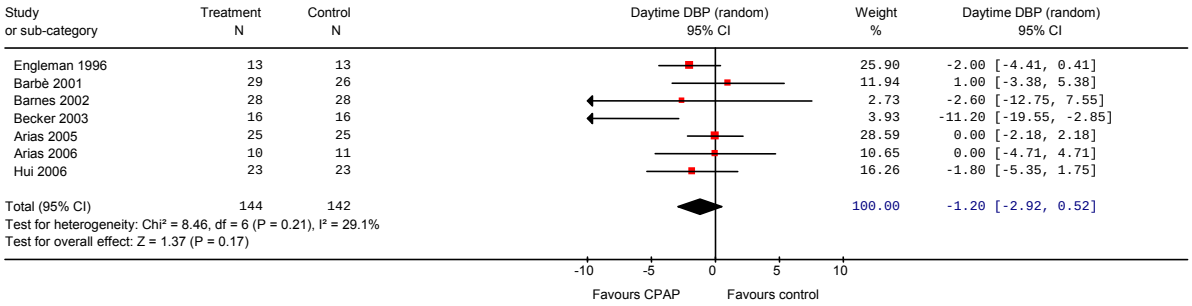


Figure 5.9 Daytime diastolic BP using ABPM (CPAP versus placebo/usual care)



- **Other sub-group analyses**

The treatment effects in the crossover and parallel sub-groups and endpoint data and change data sub-groups were consistent with each other i.e. the 95% confidence intervals overlapped. The SBP treatment effect ranged from +1.2 for parallel trials using endpoint data to -5.2 for parallel trials using change from baseline data though the difference between CPAP and control and was not statistically significant in any of the sub-groups (see Appendix 11.4, Table 11.11). The DBP treatment effect ranged from +0.5 for parallel trials using endpoint data to -5.7 for parallel trials using change from baseline data though the difference between CPAP and control and was not statistically significant in any of the sub-groups. (see Appendix 11.4, Table 11.12). These analyses are limited by the small number of studies in each of the sub-groups.

- **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 11.4, Table 11.11 and 11.12).

The standard error (SE) for the mean difference in systolic and diastolic blood pressure for Arias 2005[56] was imputed based on an estimated within-person correlation of 0.5. The meta analyses were rerun using a SE based on an assumed within-person correlation of 0.1 and 0.9. For systolic blood pressure this altered the treatment effect slightly but the finding of no statistically significant difference between CPAP and control did not change: assuming a within patient correlation of 0.1 gave a SE of 2.75 for the study and the overall pooled treatment effect was -1.2 mmHg (95% CI: -3.7, 1.2); assuming a correlation of 0.9 gave a SE of 1.18 for the study and the overall pooled estimate was -0.6 mmHg (95% CI: -2.4, 1.1). Similarly, for diastolic blood pressure 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, 0.5); assuming a correlation of 0.9 gave a SE of 0.53 and the overall treatment effect was -1.1 mmHg (95% CI: -2.7, 0.6).

Conventional clinic blood pressure

Three studies (n=226) used conventional or clinic daytime blood pressure: one study reported waking BP recorded as the mean of three measurements taken at one minute intervals between 8 -11am;[62] one study used a similar method to record morning (8-9am) and evening (8-9pm) BP. [70] 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 in daytime SBP (MD -6.62mmHg, 95% CI: -9.48, -3.76) and DBP (MD -3.47mmHg, 95% CI: -6.27, -0.68) with CPAP compared to placebo/usual care and these were both statistically significant (see Figure 5.11 and 5.12). Statistical heterogeneity was low (I^2 = 0% and 33% for SBP and DBP respectively).

Figure 5.10 Daytime conventional systolic BP (CPAP versus placebo/usual care)

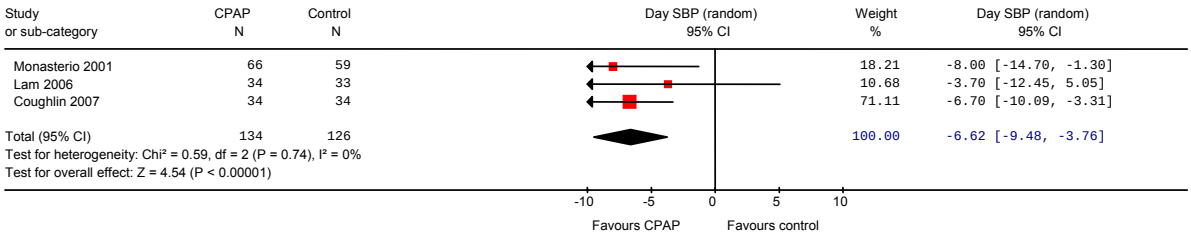
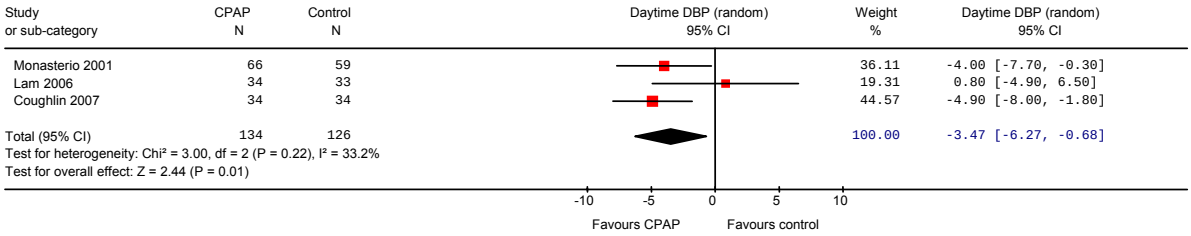


Figure 5.11 Daytime conventional diastolic BP (CPAP versus placebo/usual care)



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 5.2).[70] This study (a parallel trial, n=68) found no statistically significant difference between CPAP and dental device: morning SBP (MD -2.9 mmHg, 95% CI: -11.0, 5.2) and evening SBP (MD -4.9 mmHg, 95% CI: -14.8, 5.0); morning DBP (MD -1.6 mmHg, 95% CI: -7.4, 4.2) and evening DBP (MD -1.9 mmHg, 95% CI: -7.6, 3.8).

5.2.2.6 Night-time and 24hr 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 to placebo/usual care (MD -3.0 mmHg, 95% CI: -4.7, -1.4) and this was statistically significant. There was no statistical heterogeneity. The pooled treatment effects estimated by crossover and parallel trials and endpoint and change data separately were similar (see Appendix 11.4, Figure 11.2).

Data on SBP and DBP were available from seven trials (n=220).[64, 109] [56, 63, 83, 89] There was no statistically significant difference between CPAP and control for night-time SBP (MD -2.9 mmHg, 95% CI: -5.8, 0.1) or DBP (MD -1.3 mmHg, 95% CI: -3.2, 0.7). (see Appendix 11.4, Figure 11.3 and 11.4).

Data on 24hr blood pressure was 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 to oral placebo in 24hr DBP (MD -1.5 mmHg, 95% CI: -2.9, -0.1); there was no statistically significant difference in 24hr SBP (MD -1.3 mmHg, 95% CI: -3.3, 0.7); or 24hr MAP (MD -1.0 mmHg, 95% CI: -2.6, 0.6).

CPAP versus dental devices

One study reported 24hr 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 24hr systolic (MD 0.6 mmHg, 95% CI: -2.5, 3.7) or diastolic (MD 0.4 mmHg, 95% CI: -1.7, 2.5) blood pressure.

5.2.2.7 Summary of blood pressure outcomes

Data were available from 15 trials. Studies using 24 hour ambulatory blood pressure monitoring (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 to control; the size of the effect is probably differenct in 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 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 is probably different in 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 to an increase of 1.2 mmHg to a compared to 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 to an increase of 0.5 mmHg compared to 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 BP showed a large and statistically significant improvement in SBP and DBP with CPAP compared to control.

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

- CPAP versus dental devices

Only one study was available which 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 which did not report day and night blood pressure separately reported no statistically significant difference in 24hr SBP and DBP between the two interventions.

5.2.2.8 Health-Related Quality of Life

The most commonly used quality of life measures were the Functional Outcomes of Sleep (FOSQ) questionnaire, SF-36 and the Nottingham Health Profile (NHP) (see Table 5.3). The majority of studies where quality of life was assessed were of populations with moderate symptom severity (ESS) at baseline.

Table 5.4 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 Apnea Quality of Life Index		2[67, 70]
SF-36 (subscales)	3[78, 79, 89]	3[70, 77, 86]
SF-36 (Physical- mental component summary or total score)	1[82]	2[83, 86]
CPAP versus dental devices		
FOSQ	2[82, 103]	
Golombok Rust Inventory of Sexual Satisfaction		1[102a]
SAQLI		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 is published in Hoekema 2006[111]

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 to control on any of the subscales of the SF-36 though for two of the scales (vitality and physical role) there was a trend towards improvement with CPAP (see Table 5.4 below for the overall effect and Appendix 11.4, Figure 11.5 for forest plots). However, the pooled estimate is 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, Figure 11.5).

The treatment effects in the crossover and parallel sub-groups were consistent with each other i.e. the 95% confidence intervals overlapped (see Appendix 11.4, Figure 11.5). For bodily pain, general health and physical function there was a statistically significant benefit with CPAP compared to control for the parallel trial sub-group but not the crossover sub-group. This may be driven by two of the parallel trials being of populations with severe baseline

symptoms. There was no statistically significant difference between CPAP and control for the physical and mental component summary scores (2 trials, one of mild and one of severe symptoms (ESS) or the total score (1 trial, moderate symptom severity) (see Appendix 11.4, Figure 11.5)

Table 5.5 SF-36 subscales (CPAP versus placebo/usual care)

SF-36 Subscale (6 trials)	Mean difference (95% CI)	Statistical heterogeneity (I^2)
Bodily pain	4.3 (-0.9, 9.5)	48%
Emotional role	-0.4 (-12.3, 11.5)	72%
General health	3.2 (-0.4, 6.7)	0%
Mental health	2.2 (-2.2, 6.7)	52%
Physical function	2.6 (-0.6, 5.9)	8%
Physical role	6.9 (-3.8, 17.5)	63%
Social function	1.9 (-4.4, 8.1)	57%
Vitality	7.3 (-0.3, 14.9)	77%

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 to control for the activity level and social outcome subscales of the FOSQ (see Table 5.5 below for the overall effect and Appendix 11.4, Figure 11.6 for the 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 to control for the parallel trial of severe symptom severity population but not for the sub-group 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 symtpm severity (see Appendix 11.4, Figure 11.6).

Table 5.6 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, 0.3)	70%
Intimacy and sexual activity (n=4)	0.3 (-0.4, 0.9)	0%
Social outcome (n=4)	0.2 (0.0, 0.4)	0%
Vigilance (n=4)	0.2 (-0.1, 0.5)	76%
Total score (n=6)	0.4 (-0.2, 0.9)	51%

Nottingham Health Profile (NHP)

Data from the NHP was 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 unclassified [90] There was a statistically significant benefit with CPAP compared to placebo/usual care on the NHP Part 2 (MD -1.7, 95% CI: -2.9, -0.5) (see Appendix 11.4, Figure 11.7). There was no statistical heterogeneity. Monasterio *et al*[100] did not specify which part of the NHP they used but from the data presented 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, 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

Data were available on the SAQLI from two parallel trials, of moderate symptom severity populations. One study (n=67) reported all the subscales[70] and the overall score and one reported the overall score only (n=41).[67] There was a statistically significant improvement with CPAP compared to conservative treatment on the daily functioning, emotional and symptoms subscales but not for the social interaction subscale. (See Appendix 11.4, Figure 11.8). For the total score (A-D subscales) one study showed a significant benefit with CPAP compared to conservative treatment and one showed no significant difference between CPAP and sham CPAP.(See Appendix 11.4, Figure 11.8) When change data were used instead of endpoint data from the latter study 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 Euroqol thermometer (0-100) (MD 2.0, 95% CI: -8.1, 12.1). The Euroqol derived utility was CPAP 0.77 (SD 0.18) for CPAP versus 0.77 (SD 0.09) for conservative treatment. There was a .04 utility gain in the CPAP group and no change in the conservative treatment group, though 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 to 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, 0.5). These two studies had contradictory findings: one showed a statistically significant benefit with CPAP compared to dental devices and one found no difference between the two treatments (see Appendix 11.4, Figure 11.9).

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. [70] Unpublished data were available from Giles *et al* for two studies for a summed score, [101, 107] though it was unclear whether this was for subscales A-D or A-E therefore these studies were pooled separately. Based on the summed score for the latter two studies there was no difference between CPAP and dental devices (see Appendix 11.4, Figure 11.11). For the summed score 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 A-E for this study, CPAP no longer showed a benefit over dental devices (see Appendix 11.4, Figure 11.11).

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 11.4, Figure 11.12) reported a benefit with CPAP compared to dental device 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 to dental device on the bodily pain subscale of SF-36 but not on any of the other subscales (see Appendix 11.4, Figure 11.13). [70]

Golombok Rust Inventory of Sexual Satisfaction (GRISS)

This outcome was reported in two related papers [111] [102] The included male participants (n=38), who were in a heterosexual relationship, 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 11.4, Figure 11.14).

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: a shoulder-head elevation pillow (SHEP),[60] and a cervicomandibular support collar (CMSC). [61]

Functional Outcomes of Sleep Questionnaire

No statistically significant difference was found when CPAP was compared with either SHEP (p=0.93 for difference in change) or CMSC (p=0.85 for difference in change). Only overall baseline 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 SHEP (p=0.74 for difference in change), or CMSC (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 SHEP (p=0.31 for difference in change), or CMSC (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.

5.2.2.9 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, 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 sub-group 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 to control for the parallel trials but not 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 Nottingham Health Profile Part 2, there was a statistically significant benefit with CPAP compared to control based on a pooling of four studies. The treatment effect is probably different in different groups of people. The average effect was a reduction of 1.7 points with CPAP compared to 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, though only a small number of studies were available. On the Functional Outcomes of Sleep Questionnaire (four trials), a disease specific measure, there was a statistically significant benefit with CPAP compared to 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 Sleep Apnoea Quality of Life Index total score; one reported a significant benefit with CPAP compared to 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 Funcunctional Outcomes of Sleep Questionnaire and two studies reporting the Sleep Apnoea Quality of Life Index were pooled.were pooled. Three studies reported the SF-36 but all used different scores and the findings were not consistent.

5.2.2.10 Psychological outcomes

There was very little new data available on psychological outcomes since the review by Giles *et al*. One additional publication was available which reported the Profile of Mood State from

a one week study by the Dimsdale group[58] and the Brief Symptom Inventory from a 2 week study by the same group.[73]

CPAP versus placebo/usual care

General Health Questionnaire-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, 1.4) though 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 11.4, Figure 11.15).

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, 0.5) or the depression (MD -0.9, 95% CI: -1.9, 0.1) subscales. There was moderate statistical heterogeneity in both analyses (45% and 62% respectively) (see Appendix 11.4, Figure 11.16 and 11.17).

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 11.4, Figure 11.18).

Profile of Mood State

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 11.4, Figure 11.19).

UMACL

Three studies reported the the energetic arousal score from the University of Wales Institute of Science and Technology Mood Adjective Checklist (UMACL) and these were pooled (all crossover, n=73). [92, 93, 112] There was a statistically significant benefit in favour of CPAP compared to placebo (MD 1.7, 95% CI: -0.0, 3.3) (see Appendix 11.4, Figure 11.20). There was no statistical heterogeneity in this analysis.

CPAP versus oral devices

Hospital Anxiety and Depression Scale

One study reported the Hospital Anxiety and Depression Scale (crossover, n=48).[103] There was no statistically significant difference between CPAP and oral devices for the anxiety or depression subscales(see Appendix 11.4, Figure 11.21 and 11.22).

5.2.2.11 Summary of psychological outcomes

- CPAP versus control

Data were available for three psychological outcome measures from more two or more studies. There was no statistically significant difference between CPAP and control on the General Health Questionnaire-28 or the Hospital Anxiety and Depression Scale. There was a statistically significant benefit in favour of CPAP compared to control on the energetic arousal score from the University of Wales Institute of Science and Tecnology Mood Adjective Checklist. 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 Hospital Anxiety and Depression Scale.

5.2.2.12 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 sub-group 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 of mild symptom severity. Based on mean baseline AHI, a measure of disease severity, the populations in seven studies were classified as severe,[58, 73, 83, 85, 93, 103, 108] seven as moderate[77, 79, 82, 90, 100, 102, 113] and three as mild disease.[78, 89, 92]

A total of twenty-eight different cognitive tests were used, examining several areas of cognition (administered either 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, I-Q decrement, memory and learning (see Table 5.12). Seventeen tests were used by two trials or less; 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 11.4, Table 11.14). Testing protocol issues include order of test presentation, which is particularly an issue with test batteries containing many different types of test, [115] and time of day where 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 can have a significant beneficial impact on test performance when tests are administered at on more than one occasion. Stimulant use, 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,[77, 78, 82, 85, 89, 90, 92, 102, 108] and four trials used alternate 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).[77-79, 85, 89, 90, 92, 100, 102, 108, 113, 116, 117] 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.[77-79, 90, 92, 93, 102, 108] 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, 102, 108] No study specifically looked at the effect of mood in relation to cognitive function, although one trial[82] stated that significant depression was present in 40% of the included participants. Level of baseline function, compared to 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. Due 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 11.4, Table 11.13. Where endpoint data was not reported change scores were used.

CPAP versus placebo or conservative/usual care

Simulated driving task

Seven studies used a simulated driving task.[77, 78, 83, 90, 92, 93, 100] Daytime sleepiness , based on ESS scores at baseline, varied between study populations; one study was classified as severe, [77] one mild [83] and four 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 5.12), or in the number of obstacles hit, MD -5.74 (95% CI: -14.75, 3.27) (Figure 5.13). There was no statistical heterogeneity (I^2=0%) for trials reporting the number of obstacles hit.

One parallel group trial [118] used a different simulated driving test, based on the work of Land (1995). 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 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 to sham CPAP, though not all were statistically significant; standard deviation of position on road (median difference -0.1, p=0.08), standard deviation 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 endpoint 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).

Figure 5.12 SteerClear (CPAP versus placebo/ususal care) percentage of obstacles hit

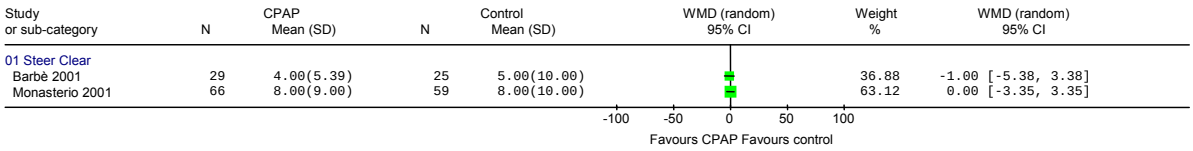
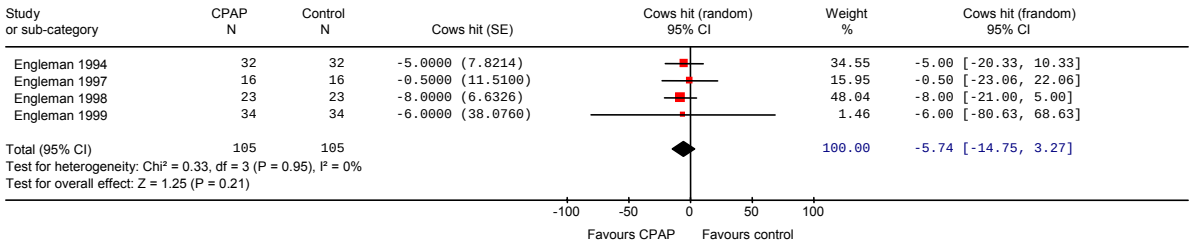


Figure 5.13 SteerClear (CPAP versus Placebo/usual care) number of obstacles hit



TrailMaking 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 (5 parallel, 3 crossover, n=260) reported on TMT part A[58, 73, 78, 83, 85, 89, 90, 100] and twelve (6 crossover, 6 parallel, n=406) reported on TMT part B. [58, 73, 78, 82, 83, 85, 89, 90, 92, 93, 100, 113]

TMT Part A

The severity of daytime sleepiness was classified as moderate in four studies,[73, 78, 89, 100] and one study each was classified as mild[83] and severe[85]; two studies did not report symptom severity.[58, 90] None of the studies showed a significant difference between CPAP and control

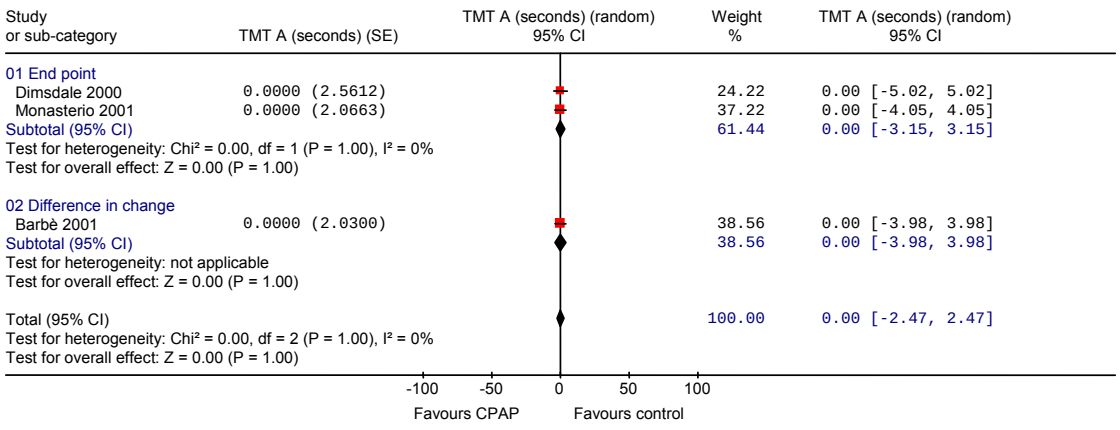
in the length of time it took to complete TMT(A) (see Table 5.7). None of the studies reported adequate allocation concealment, and it was unclear whether groups were similar at baseline in four of the included studies.[78, 89, 90, 100]

Table 5.7 Summary of TMT part A data reported in included studies

Study	CPAP	Control	MD	P value
Crossover	**Mean (SD)**	**Mean (SD)**		
Barnes, 2002 [89]	28.1 (NR)	27.6 (NR)	0.5	Not significant (precise p value not reported)
Engleman, 1994[90]	NR	NR	NR	Not significant (precise p value not reported)
Engleman, 1999[78]	26 (11)	29 (11)	-3	0.06
Parallel				
Barbe, 2001 [83]	47 (NR)	47 (NR)	0	p>0.2
Dimsdale, 2000 [58]	27.4 (NR)	27.4 (NR)	0	NR
Henke, 2001[85]	Only available in graph			Not significant (precise p value not reported)
Monasterio, 2001[100]	49 (19)	49 (20)	0	0.76
Norman, 2006 [73]	26.5 (NR)	21.7 (NR)	4.9	0.49 (relates to time x treatment interaction for 3-treatment groups)

Five trials (three crossover and two parallel) did not report sufficient data to calculate a variance. [73, 78, 85, 89, 90] Therefore only three of the eight trials reporting TMT A were used to generate a pooled estimate of treatment effect and are displayed on the forest plot below (Figure 5.14). 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, 2.5). There was no statistical heterogeneity (I2=0%). Given that only a proportion of the available studies could be pooled, caution needs to be taken in interpreting the pooled effect.

Figure 5.14 Trailmaking test Part A (CPAP versus placebo/usual care), stratified by type of data



TMT Part B

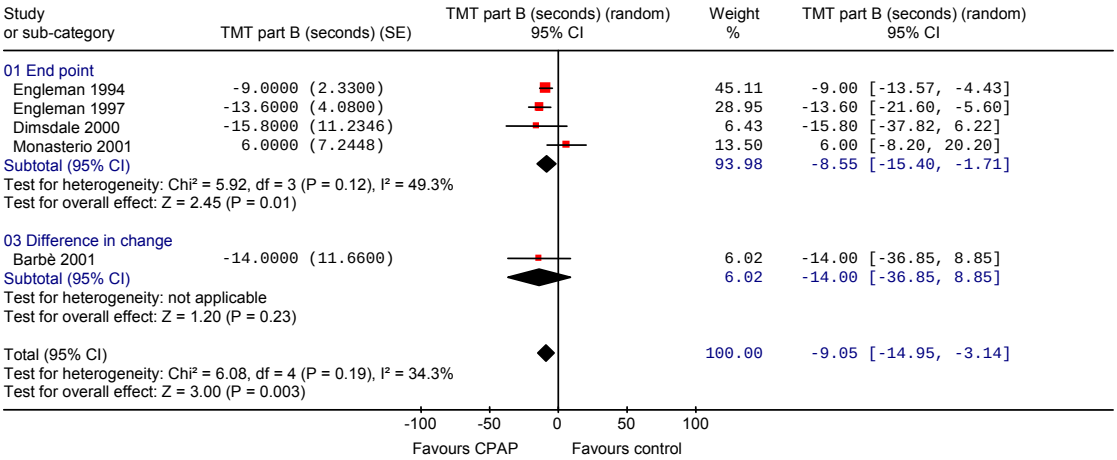
Where reported, the populations in the majority of trials were classified as having moderate baseline daytime sleepiness,[73, 78, 82, 89, 92, 93, 100] and one study each as having mild[83] and severe[85] daytime sleepiness. One trial reported a significant difference in favour of CPAP compared to oral placebo in the length of time taken to complete the task, no statistically significant between group differences were found in the other trials (see Table 5.8). Half of the studies did not report adequate allocation concealment, and it is unclear if trials had sufficient power to detect a treatment effect.

Table 5.8 Summary of TMT part B data reported in included studies

Study	**CPAP**	**Control**	**MD**	**P value**
Crossover	**Mean (SD)**	**Mean (SD)**		
Barnes, 2002[89]	60.1 (NR)	65.2 (NR)	-5.1	Not significant (p value not reported)
Barnes, 2004[82]	73.3 (29.5)	74.2 (32.2)	-0.9	Not significant (p value not reported)
Engleman, 1994 [90]	66 (28.3)	76 (28.3)	-10	0.02
Engleman, 1997 [92]	64.1 (22)	77.7 (36.8)	-13.6	0.02
Engleman, 1998 [93]	69 (32)	68 (32)	1	Not significant (p value not reported)
Engleman, 1999 [78]	63 (33)	65 (27)	-2	Not significant (p value not reported)
Parallel				
Barbe, 2001 [83]	96 (32.3)	110 (50)	-14	0.1
Dimsdale, 2000 [58]	71.2 (31.8)	87 (34.8)	-15.8	Not significant (p value not reported)
Henke, 2001 [85]	Only available in graph			Not significant (p value not reported)
Lojander , 1999 [113]	130, median	75, median		NR
Monasterio, 2001 [100]	106 (42)	100 (39)	6	0.15 (difference in change based on median values)

Seven trials did not report sufficient data or used different scales, therefore only data from two crossover[90, 93] and three parallel[58, 83, 100] trials were pooled (n=328) for TMT(B) (see Figure 5.15). There was a statistically significant benefit with CPAP compared to control for time (seconds) taken to complete the TMT(B) (MD -9.1, 95% CI: -14.9, -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.

Figure 5.15 Trailmaking test Part B (CPAP versus placebo/usual care), stratified by type of data



WAIS digit symbol substitution test (DSST)

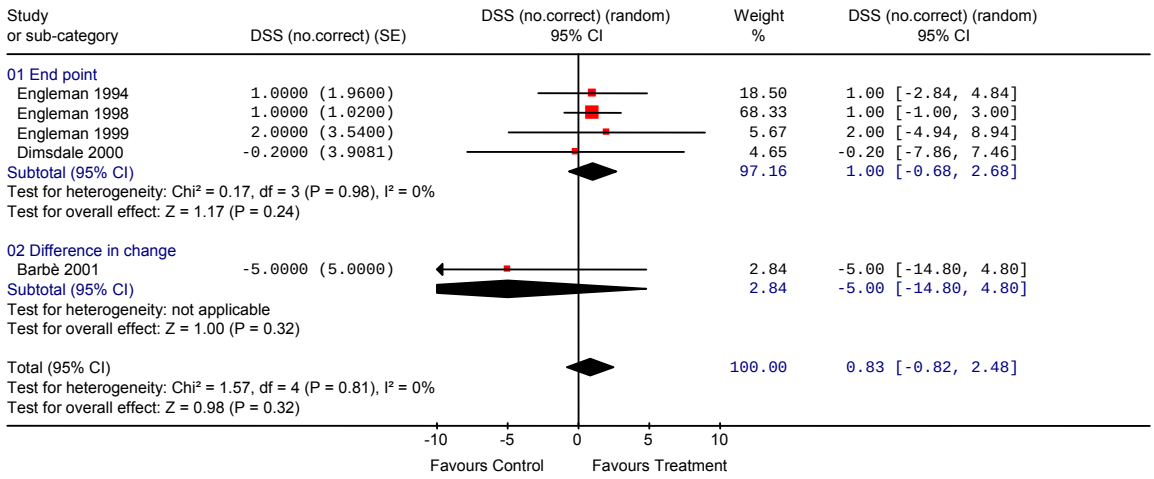
Ten studies used the DSST, a test of complex attention (5 parallel and 5 crossover , n=488).[58, 73, 78, 82, 83, 85, 89, 90, 93, 100] In this test of attention and processing, respondents are given a code table displaying the correspondence between pairs of digits (from 1 to 9) and symbols, and then 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 were classified as moderate[73, 78, 82, 89, 93, 100] and one trial each were classified as having mild[83] and severe[85] daytime sleepiness. Two trials found a significant benefit of CPAP compared to control in the number of correct responses,[78, 90] and 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 (see Table 5.9). Adequate allocation concealment was not reported in any of the trials.

Four studies did not provide sufficient data to calculate a variance and one trial used a different scale, therefore only five trials (3 crossover trials and 2 parallel, n=170) were pooled (Figure 5.16);[58, 78, 83, 90, 93] no statistically significant benefit with CPAP was found for CPAP compared to control in terms of the number of correct responses (MD 0.2, 95% CI: -0.6, 1.0). There was no statistical heterogeneity (I^2 = 0%)

Table 5.9 Summary of WAIS DSS data reported in included studies

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

Figure 5.16 WAIS digit symbol substitution test (CPAP versus placebo/usual care), stratified by type of data



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 trials were classified as moderate[78, 90, 92, 93, 100] and one trial as mild.[83] One crossover trial[78] 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 (see Table 5.10). None of the studies reported adequate allocation concealment, and one study reported a significant treatment by period interaction for the PASAT2[90] indicating a potential carry-over effect of treatment.

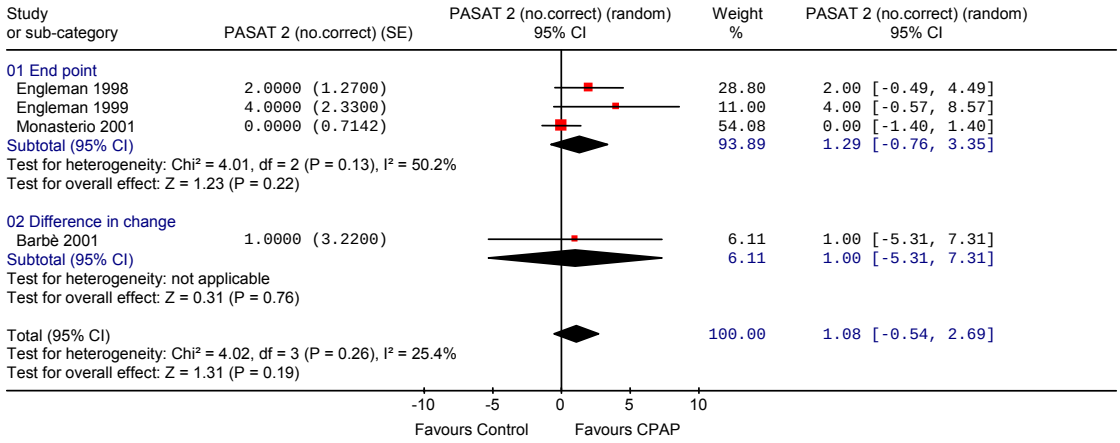
Table 5.10 Summary of PASAT data reported in included studies

Study	**CPAP**	**Control**	**MD**	**P value**
Crossover	**Mean (SD)**	**Mean (SD)**		
Barnes, 2004 [82]	PASAT1.2: 2.9 (0.9) PASAT2.4: 3.8 (1.8)	3.4 (0.9) 3.7 (0.9)	-0.5 0.1	Not significant (precise p-value not reported)
Engleman, 1994 [90]	NR	NR	NR	Not significant (precise p-value not reported)
Engleman, 1997 [92]	PASAT2: 37.8 (13.2)	35.3 (11.2)	2.5	Not significant (precise p-value not reported)
Engleman, 1998 [93]	PASAT2: 37 (11)	35 (11)	2	Not significant (precise p-value not reported)
Engleman, 1999 [78]	PASAT2: 40 (11)	36 (14)	4	0.02
Parallel				
Barbe, 2001 [83]	PASAT1: 15 (5.4) PASAT2: 16 (5.4) PASAT3: 12 (5.4) PASAT4: 5 (5.4)	15 (5) 15 (5) 12 (5) 5 (5)	0 1 0 0	>0.20 (difference in change) 0.04 0.09 >0.20
Monasterio, 2001 [100]	PASAT1: 5 (4) PASAT2: 12(4) PASAT3: 15 (4) PASAT4: 14 (4)	5 (3) 12 (4) 15 (4) 16 (4)	0 0 0 -2	0.32 (based on data for median values) 0.12 0.20 0.20

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 5.17). No statistically significant benefit with

CPAP compared to control for number of correct responses made was found (MD 2.30, 95% CI: 0.24, 4.37); statistical heterogeneity was low (I^2=25%).

Figure 5.17 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 5.11).

One small crossover study (n=28)[89] reported a significant improvement in the number of correct words in the CPAP group compared to oral placebo. 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.

Table 5.11 Summary of data for verbal fluency tests reported in included studies

Study	**CPAP**	**Control**	**MD**	**P value**
Crossover	**Mean (SD)**	**Mean (SD)**		
Barnes, 2002[89]	38.7 (NR) COWAT: No. correct	36 (NR)	2.7	0.02 (difference in change)
Barnes, 2004 [82]	46.5 (10.7) COWAT	46.3 (8.9)	0.2	NR

Study	CPAP	Control	MD	P value
Crossover	**Mean (SD)**	**Mean (SD)**		
Engleman, 1994 [90]	NR COWAT	NR	NR	Not significant (precise p-value not reported)
Engleman, 1997 [92]	38.5 (14) COWAT: No. correct	39.2(12.4)	-0.7	Not significant (precise p-value not reported)
Engleman, 1998 [93]	41 (12) COWAT: No. correct	42 (11)	-1	Not significant (precise p-value not reported)
Parallel				
Dimsdale, 2000 [58]	44.5 (12.1) No. correct	37.3(12.8)	7.2	NR
Henke, 2001 [85]	NR COWAT	NR	NR	Not significant (precise p-value not reported)
Monasterio, 2001 [100]	69 (27) Percentile	70 (29)	-1	0.53 (based on data for median values)
Norman, 2006 [73]	40.9 (NR) Total score	45.5 (NR)	-4.6	0.15 (relates to time x treatment interaction from a 3-arm trial)

Digit Vigilance Test

Two parallel group trials used the digit vigilance test (DVT), which is a measure of sustained attention and psychomotor speed, using a rapid visual tracking task (see Table 5.12).[58, 73] Only one trial reported baseline ESS[73], 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 task, but not errors made, in a two week study (n=31) comparing CPAP with supplemental oxygen, and placebo.[73] A one week, study (n=36) found a significant difference between CPAP and sham CPAP in the number of errors made;[58] however, after controlling for pre-treatment differences no significant difference between groups was found. A summary of the results are presented in Table 5.12.

Table 5.12 Summary of digit vigilance test data reported in the included studies

Study	CPAP	Control	MD	P value
Parallel	**Mean (SD)**	**Mean (SD)**		
Dimsdale 2000 [58]	Time: 6.9 (1.3) Errors: 10.1 (11.6)	Time: 6.6 (1.6) Errors: 12.3 (12.4)	0.3 -2.2	NR 0.49
Norman 2006 [73]	Time: 312.3 (NR) Errors: 7.2 (NR)	Time: 303.1 (NR) Errors: 10.6 (NR)	9.2 -3.4	0.02 (relates to time x treatment interaction from a 3-arm trial) 0.08 (relates to time x treatment interaction from a 3-arm trial)

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 and baseline comparisons were not always reported, intention to treat analysis was seldom conducted. Results for these studies are presented in Appendix 11.4, Table 11.13.

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 trial,[103] disease severity was also reported as moderate in the same trials. There were no statistically significant differences between treatment groups on any of the cognitive tests assessed (see Appendix 11.4, Table 11.13). None of these trials reported appropriate allocation concealment, and only one trial [82] reported adequate randomisation methods and used intention to treat analysis.

CPAP 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 11.4, Table 11.13). It is unclear whether performance differences at baseline existed, or whether the study was appropriately powered to detect an effect.

Table 5.13: List of cognitive tests reported by individual studies

Cognitive test	Barbe 2001[83]	Barnes 2002[89]	Barnes 2004[82]	Cibele 2006[72]	Dimsdale 2000[58]	Engleman 1994[90]	Engleman 1997[92]	Engleman 1998[93]	Engleman 1999[78]	Engleman 2002[103]	Henke 2001[85]	Hoekema 2006[102]	Jenkinson 1999[77]	Jokic 1999[108]	Lojander 1999[113]	Marshall 2005[79]	Monasterio 2001[100]	Norman 2006[73]
Tests of attention																		
CET														√				
DO					√													
DVT					√													√
PVT		√	√	√												√		
RT (8-C)							√	√										
RVIP							√	√										
STROOP		√	√		√													√
TMT	√	√	√		√		√	√	√	√	√			√	√		√	√
PASAT	√		√			√	√	√	√	√							√	
BW															√			
STEER CLEAR	√					√	√	√	√	√	√[c]						√	
Other driving tests												√	√					
Tests of verbal fluency																		
COWAT		√	√			√[a]	√[a]	√[a]			√							
VFT					√												√	√
Tests of memory																		
BVM																		√

BVRT							√	√							√			
CT														√				
HVL																		√
WMS	√	√(s)												√	√		√(s)	
WPMR		√																
MDT															√			
Tests of motor performance																		
PP														√				
FTT															√			
Tests of construction																		
CFD															√			
Copying															√			
CFT												√[b, c]						
Neurocognitive test batteries																		
WAIS	√(s)	√(s)	√(s)		√(s)	√(s)	√(s)	√(s)	√(s)	√(s)	√(s) [c]				√(s)		√(s)	√(s)
IQ-decrement																		
						√	√	√		√								

s: indicates that subscales were used; a: Borkowski's Controlled Oral Word Association Test; b: Medical college of Georgia Complex Figure Recall test; c: indicates that results presented in graph format only; FTT: CET: Continuous Endurance Test; DO: Digit Ordering; DVT: Digit Vigilance Test; PVT: Psychomotor Vigilance Test; RT-8: Eight Choice Reaction Time test; RVIP: Rapid Visual Information Processing task; TMT: Trail-making test; PASAT: Paced Auditory Serial Addition Task; BW: Bourdon-Wiersma test; COWAT: Controlled Oral Word Association Test; VFT: verbal fluency test; BVM: Brief Verbal Memory test; BVRT: Benton visual retention task; CT: Consonant Triagram; HVL: Hopkins Verbal Learning test; WMS: Wechsler Memory Scale; WPMR: Word Paired Memory Recall; MDT: memory distractor task; PP: Purdue Pegboard test; Finger tapping test; CFD: Clock-face drawing task; CFT: Complex figure test; WAIS: Wechsler Adult Intelligence Scales.

5.2.2.13 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 to placebo/usual care and the effect size ranged from -9.2 (95% CI: -18.3, -0.1) to -60 (95% CI: -72.1, -47.5) (see Appendix 11.4, Figure 11.23).

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 to dental devices (MD -8.4, 95% CI: -10.5, -6.3) (see Appendix 11.4, Figure 11.25). Statistical heterogeneity was low to moderate (I^2 = 40%).

CPAP versus postural therapy

Data were available for the AHI from 3 small crossover trials (n=36). [60, 61, 108] There was a statistically significant benefit with CPAP on the AHI compared to postural therapy (SHEP, mean difference 15.5, p= 0.008; CMSC, mean difference in change 16.8 , p=0.001; backpack with soft ball inside, mean difference 6.1, 95% CI: 2, 10.2, p=0.007).

5.2.2.14 Adverse effects

Reporting of adverse effects was patchy across studies. Reported adverse effects with CPAP were mainly related to discomfort with the equipment (for example machine noise, a feeling of pressure and mask discomfort); dry mouth; and stuffy or runny nose (see Table 5.14). Reported adverse effects with use of dental devices were mainly related to excess salivation, tooth and temporomandibular joint discomfort.

Table 5.14 Adverse effects

Side-effect		Study	CPAP n/N	Control n/N	Dental device n/N
Mask discomfort or other problems with		Engleman 1999	8/34	0/34	-
mask/headgear		Lojander 1996	2/13	0/20	-
Machine noise		Lam 2006	8/34	-	0/34
Sleep disturbance		Engleman 1999	8/34	0/34	-
		Engleman 2002	16/48	-	12/48
		Lojander 1996	1/13	0/20	-
Difficulty falling asleep with prescribed pressure		Engleman 1999	1/34	0/34	-
Feeling of pressure		Lam 2006	11/34	-	0/34
Pressure (on face)		Randerath 2002	8/19	-	2/19
Pressure(in mouth)		Randerath 2002	0/19	-	2/19
Early awakening		Engleman 1999	1/34	0/34	-
Residual sleepiness		Engleman 1999	0/34	3/34	-
Dry throat/nose/mouth		Engleman 1999	4/34	0/34	-
		Engleman 2002	5/48	-	0/48
		Lojander 1996	2/13	0/20	-
		Lam 2006	16/34	-	11/34
Rhinorrhea		Lojander 1996	7/13	0/20	-
Skin irritation or abrasion		Redline 1998	2/51	0/46	
		Lam 2006	7/34	-	0/34
Minor nosebleeds (related to nasal spray)		Redline 1998	1/51	2/46	-
Use of antibiotics during intervention period		Redline 1998	7/51	2/46	-
Excess salivation		Engleman 2002	0/48	-	9/48
		Lam 2006	0/34	-	19/34
Tooth discomfort		Lam 2006	0/34		11/34
Tooth damage		Engleman 2002	0/48		3/48
Temporomandibular joint discomfort		Engleman 2002	0/48		33/48
		Lam 2006	0/34		13/34
		Randerath 2002	0/19		8/19
Removal of appliance during sleep		Engleman 2002	7/48		19/48
Leakage		Engleman 2002	11/48		0/48
Stuffy nose		Engleman 2002	8/48		0/48
Inconvenience		Engleman 2002	6/48		0/48
Side-effect severity	None	Ferguson 1996	11/25		10/21
		Ferguson 1997	10/20		7/20
	Mild	Ferguson 1996	1/25		9/21
		Ferguson 1997	4/20		9/20
	Moderate	Ferguson 1996	5/25		5/21
		Ferguson 1997	3/20		4/20
	Severe	Ferguson 1996	4/25		1/21
		Ferguson 1997	3/20		1/20

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 SHEP, mean difference -0.8, p=0.16. However, there were significantly fewer self-reported adverse events with a cervicomandibular support collar than with CPAP, mean difference in change 4.2, p=0.01. Type of adverse event and indication of perceived severity were not reported in either study.

6 Assessment of cost-effectiveness evidence

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

(i) 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 submission [120] to the National Institute for Health and Clinical Excellence (NICE) (Section 6.1).

(ii) The systematic review (i) was used to inform the development of an economic model to evaluate the cost-effectiveness of CPAP for the treatment of OSAHS (Section 6.2).

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 Cost-effectiveness review methods

A systematic review of cost-effectiveness studies was undertaken to compare CPAP to other interventions routinely used for the treatment of OSAHS in the 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 (Section 5) 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 11.1.3).

- 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 http://www.nice.org.uk/.(see Appendix 11.6 for economic evaluation data extraction table and Table 6.27 for economic evaluation quality assessment table).

6.1.2 Cost-effectiveness review results

The above searches identified four full economic evaluations for inclusion in the cost-effectiveness review of published studies.[122] [123] [44] [124] One manufacturer (ResMed) submitted a full cost-effectiveness study to NICE.[120] Two manufacturers, comprising Fisher Paykel Ltd[125] 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 followed by an overall summary of the cost-effectiveness evidence base.

6.1.2.1 Review of Manufacturers' submissions

ResMed Model[120]

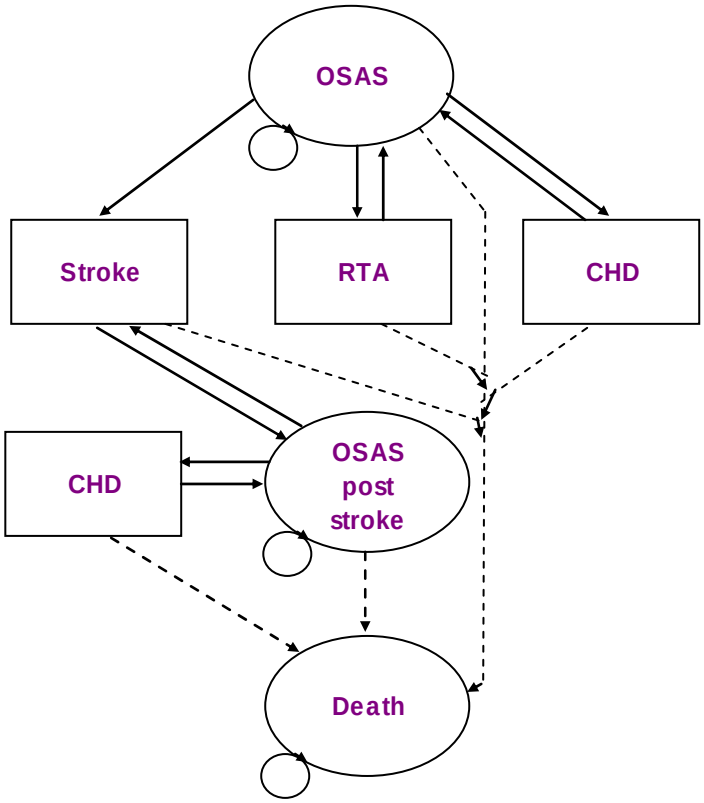
Overview: ResMed performed a cost-utility analysis comparing CPAP using fixed pressure and CPAP using auto-titrated pressure (APAP) with a 'do nothing' alternative for the treatment of patients with severe OSAHS.[120] The hypothetical patient population depicted by the model consisted of 55 year old patients with severe OSAHS as defined by an AHI

exceeding 30 and daytime sleepiness represented by a score of 12 on the Epworth Sleepiness Scale (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 which ever visit takes place first. For each year in the model patients can remain event-free in the severe OSAHS state, can have a non-fatal or fatal stroke, cardiovascular events (CVE, e.g. MI) or a road traffic accident (RTA) as illustrated in Figure 6.1. In each subsequent year patients who have had a non-fatal or fatal CVE or a RTA can have a stroke, CVE or a RTA. Patients, however, who have a stroke, can no longer drive and are, therefore, not at subsequent risk of a RTA.

Figure 6.1 Structure of ResMed Model

(adaptation of Figure 6.1, P9 in ResMed submission)



The primary measure of cost-effectiveness was incremental cost per quality-adjusted life-years (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, 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 CVE and RTA 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 three months post initiation of CPAP in order to generate 'do nothing' and nCPAP utility values, respectively. The EQ-5D instrument (EuroQoL Group 1990[127]) 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,* 1996).[128] No information was obtained on the HRQoL of OSAHS patients with stroke and 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 6.1 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.

Table 6.1 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

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 to the treated patients for reasons other than chance, thus undermining the internal validity of the study results. Results were extrapolated from 12 to 14 years. No method of extrapolation was reported. The authors justified the use of a 14 year time horizon since 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 to 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 a RTA, ResMed took the average risk increase of a RTA in patients with OSAHS based on two studies. One study assessed RTA in patients with OSAHS before and after treatment with CPAP (George *et al*).[131] Patients were followed-up for at least three 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 a 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 controls. Using data from the Department of Transport data [133] and assuming all OSAHS patients were drivers of a licensed motor vehicle, ResMed estimated that the risk of a 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 CPAP (fixed). 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 six studies which followed patient compliance for at least one year.[134] [39] [135] [40] [136] They took the average compliance across the studies, the follow-up time for which varied between two and seven years. For patients who continued their use of the device for at least one year, it was assumed that there would be no further loss to compliance, based on expert clinical opinion. For CPAP (auto) it was estimated that compliance would be 84%. The increase in compliance with CPAP (auto) compared to CPAP (fixed) 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 6.2 and 6.3 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 6.4). Confidence intervals were calculated based on the resource use estimates provided by clinical experts.

Table 6.2 ResMed estimates of healthcare resource use

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

Table 6.3 ResMed unit costs

Resource	Cost	Source
Myocardial infarction episode	£1,694.51	Department of Health, 2005
Home-based cardiac rehabilitation for the first year following an MI	£3,702.49	Taylor *et al*, 2006
Stroke episode	£1,667.23	Department of Health, 2005
Annual cost of stroke rehabilitation	£0	Not included?
Initial outpatient visit with specialist	£115.00	Department of Health, 2005
Follow-up outpatient visit with specialist	£108.00	Department of Health, 2005
Initial sleep study	£115.35	Department of Health, 2005
Follow-up sleep study	£107.87	Department of Health, 2005
Specialist nurse visit (for 30 minute appointment)	£34.00	Department of Health, 2005
Technician visit (for 30 minutes appointment)	£9.50	Department of Health, 2005
Fatal car accident	£5,688.23	Department of Transport, 2004
Serious/slight car accident	£12,019.89	Department of Transport, 2004
CPAP S8 Escape	£280.00	ResMed
APAP S8 AutoSet Spirit	£410.00	ResMed
HumidAire H3i (Humidifier)	£150.00	ResMed
Ultra Mirage II Nasal (Mask)	£80.00	ResMed
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

NB the nightly cost of using an Embletta X10 (portable diagnostic device) is based on an acquisition cost of £6,690, a shelf-life of 5 years and the device being used 4 nights a week for 50 weeks a year.

Table 6.4 ResMed annual cost associated with CPAP

YEAR 1	**CPAP (fixed)**	**CPAP (auto)**
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	0
Dose titration study (inpatient)	4.31	0
Consultant visit during titration phase	43.2	0
Specialist nurse visit during titration phase	38.08	0
Technician visit during titration phase	90.25	0
CPAP machine	280	410
Mask	80	80
Humidifier	57	57
Sundries	100	100
Follow-up visit within 3 months of starting CPAP	81	81
Follow-up visit 4 to 6 months of starting CPAP	81	81
YEAR 1 TOTAL	1087.72	1039.54
YEARS 2 to 7 & 9 to 14		
Follow-up outpatient visit	37.25	37.25
Replacement mask	80	80
Sundries	100	100
TOTAL FOR EACH YEAR (2 to 7 & 9 to 14)	217.25	217.25
YEAR 8		
Follow-up outpatient visit	37.25	37.25
Replacement CPAP machine	280	410
Replacement mask	80	80
Replacement humidifier	57	57
Sundries	100	100
YEAR 8 TOTAL	554.25	684.25

Model validity: 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 standard deviation, 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 standard deviation 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 a RTA was modelled as a normal distribution with mean=2.6, standard deviation=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 number 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.

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 sub-groups 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 of treatment with CPAP compared to no treatment are provided in Table 6.5. Based on the Markov model, differences in health gain between patients receiving CPAP and patients who are untreated becomes apparent after two to three years of treatment.

Table 6.5 ResMed probabilities of expected outcomes at 14 years

Outcome	**Probability after 14 years**		
Survival	No treatment	CPAP (fixed)	CPAP (auto)
CVE	0.57 (0.55 to 0.66)	0.74 (0.69 to 0.80)	0.78 (0.73 to 0.81)
Stroke	0.35 (0.20 to 0.53)	0.16 (0.08 to 0.26)	0.14 (0.07 to 0.25)
RTA	0.39 (0.23 to 0.60)	0.17 (0.08 to 0.29)	0.15 (0.07 to 0.28)
Event-free survival	0.30 (0.15 to 0.47)	0.63 (0.52 to 0.73)	0.68 (0.56 to 0.74)
QALYs	7.22 (6.85 to 7.62)	8.19 (7.79 to 8.69)	8.32 (7.97 to 8.81)

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)). The secondary cost driver in untreated patients was the cost associated with managing RTA (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).

Key results of the cost-effectiveness model are shown in Table 6.6. 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. CPAP was associated with lower costs and higher effects than no treatment). However, at one year, the cost per QALY for CPAP is expected to exceed £20,000. After two 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 to no treatment and CPAP (auto) was compared to no treatment. Based on this indirect analysis, the authors found that CPAP (auto) dominated CPAP (fixed).

Table 6.6 Key ResMed Model results at end of 14 years

Model result	CPAP (fixed)	CPAP (auto)	No treatment
Base case			
Cost per QALY gained compared to no treatment	-£1,620 95% CI -£4,123 to £259	-£1,845 95% CI -£3,936 to £37	-
Cost per life year gained compared to no treatment	-£9,215 95% CI -£19,824 to -£22,224	-£9,845 95% CI -£18,530 to £218	-
Cost per event-free life year gained	-£4,813 95% CI -£10,195 to £1,158	-£5,441 95% CI -£10,005 to £135	-
Secondary analysis			
Cost per QALY gained compared to no treatment when clinical outcomes relating to cardiovascular and cerebrovascular outcomes are excluded	£2,311 95% CI £483 to £3,254	£2,173 95% CI £460 to £2,912	-
Cost per QALY gained compared to no treatment when clinical outcomes relating to cardiovascular and cerebrovascular and RTA are excluded	£4,551 95% CI £2,259 to £6,597	£4,219 95% C £2,124 to £5,799	-
Expected alive	74%	78%	57%
Increase probability of survival compared to no treatment	26%	32%	-
Expected survival event-free	63%	68%	30%
Increase probability of event-free survival compared to no treatment	100%	113%	-
Reduction in relative risk of having a cardiovascular event compared to no treatment	55%	60%	-
Reduction in relative risk of having a stroke compared to no treatment	57%	63%	-
Reduction in relative risk of having a RTA compared to no treatment	36%	41%	-
Expected cost (NHS perspective) per patient	£9,086 95% CI £6,851 to £11,117	£8,622 95% CI £6,712 to £10,947	£10,645 95% CI £7,912 to £14,177
Reduction in NHS management costs compared to no treatment	15% (£1,559)	19% (£2,023)	-

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 a RTA, utility for treated and untreated OSAHS, cost of managing a non-fatal RTA and the cost of managing stroke rehabilitation.

Table 6.7 ResMed Model results of deterministic sensitivity analysis at end of 14 years

Model results that are sensitive to input values		
Scenario	*Base case value*	*Effect*
Time to start of treatment 4.8 months to 12.0 months	8.4	Relative cost-utility changes marginally but CPAP (fixed) and CPAP (auto) remain dominant vs. no treatment
Compliance rate with CPAP (fixed) ranges 0.5 to 1.0	0.79	Relative cost-utility of CPAP (fixed) ranges form £703 to -£2,543. 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) ranges 0.7 to 1.0	0.79	Relative cost-utility of CPAP (auto) ranges form -£1,574 to -£2,564. Relative cost-utility of CPAP (fixed) remains unchanged
Risk of cardiovascular / cerebrovascular events among treated and untreated patients ranges 50% below and 75% above the base case value	1.0	As risk increases, relative cost-utility of CPAP (fixed) ranges from £24 to -£2,843, CPAP (auto) ranges from -£218 to -£2,999. If risk falls to 60% below the base case value, CPAP (fixed) ceases to be dominant
Ratio of cardiovascular events to stroke among untreated OSAHS patients 1:4 to 1:0	0.47: 0.53	As the ratio increases, the relative cost-utility of CPAP (fixed) ranges from --£404 to -£3,534 and for CPAP (auto) ranges from -£870 to £3,374.
Risk of untreated OSAHS patients having an RTA 1.0 to 5.0 above background rate	2.6	As risk increases, relative cost-utility of CPAP (fixed) ranges from -£498 to --£3,107, CPAP (auto) ranges from --£812 to £3,244.
Utility for untreated OSAHS 0.5 to 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 0.5 to 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 patient 0.5 to 0.9	0.590	As utility increases, relative cost-utility of CPAP (fixed) ranges from -£1,532 to -£2,020, CPAP (auto) ranges from -£1,751 to -£2,262
Utility of non-fatal stroke in treated OSAHS patient 0.5 to 0.9	0.649	As utility increases, relative cost-utility of CPAP (fixed) ranges from -£1,694 to -£1,510, CPAP (auto) ranges from --£1,914 to £1,739
Utility of non-fatal cardiovascular event in untreated OSAHS patient 0.5 to 0.9	0.664	As utility increases, relative cost-utility of CPAP (fixed) ranges from -£1,565 to -£1,708, CPAP (auto) ranges from -£1,787 to £1,936
Utility of non-fatal cardiovascular event in treated OSAHS patient 0.5 to 0.9	0.730	As utility increases, relative cost-utility of CPAP (fixed) ranges from -£1,646 to -£1,602, CPAP (auto) ranges from -£1,858 to £1,835
Utility of non-fatal RTA in untreated OSAHS patient 0.5 to 0.9	0.701	As utility increases, relative cost-utility of CPAP (fixed) ranges from -£1,573 to -£1,901, CPAP (auto) ranges from -£1,792 to £1,901
Utility of non-fatal RTA in treated OSAHS patient 0.5 to 0.9	0.771	As utility increases, relative cost-utility of CPAP (fixed) ranges from -£1,649 to -£1,607, CPAP (auto) ranges from -£1,876 to £1,831
NHS cost of cardiac rehabilitation in the first year following a non-fatal cardiovascular event ranges from £1,851 to £7,404	£3,702	As the cost increases the relative cost-utility of CPAP (fixed) ranges from -£1,445 to -£1,970 and that of CPAP (auto) from -£1,677 to -£2,180
Annual NHS cost of stroke rehabilitation following non-fatal stroke ranges from £5,070 to £20,280	£10,140	As the cost increases the relative cost-utility of CPAP (fixed) ranges from -£287 to -£4,286 and that of CPAP (auto) from -£456 to £4,623
NHS cost of managing a non-fatal RTA ranges from £6,000 to £22,000	£12,020	As the cost increases the relative cost-utility of CPAP (fixed) ranges from -£1,113 to -£2,461 and that of CPAP (auto) from -£1,384 to -£2,609
Model results that are not sensitive to input values		
Scenario	*Base case value*	*Effect*
% of OSAHS patients who are male ranges from 0.5 to 1.0	0.70	Relative effect unchanged
Probability of having a home diagnostic sleep study 0.5 to 1.0	0.75	Relative effect unchanged
Probability of having a home titration study 0.5 to 1.0	0.99	Relative effect unchanged
Probability of switching (fixed) to (auto) CPAP in the 2nd year 0 to 0.1	0.06	Relative effect unchanged
Probability of a clinician visit within 3 months after starting treatment 0.5 to 1.0	0.75	Relative effect unchanged
Probability of an annual visit with a consultant ranges from 0.0 to 0.5	0.13	Relative effect unchanged. Relative cost-utility of CPAP (fixed) and CPAP (auto) changes marginally
Probability of an annual visit with a specialist nurse ranges from 0.4 to 1.0	0.61	Relative effect unchanged
Initial NHS cost of managing an episode of cardiovascular event ranges from £1,000 to £2,500	£1,695	Relative effect unchanged. Relative cost-utility of CPAP (fixed) and CPAP (auto) changes marginally
Initial NHS cost of managing an episode of stroke ranges from £1,000 to £2,500	£1,667	Relative effect unchanged. Relative cost-utility of CPAP (fixed) and CPAP (auto) changes marginally
NHS cost of managing fatal RTA ranges from £2,000 to £8,000	£5,688	Relative effect unchanged
Annual discount rate 0% to 6%	3.5%	Relative effect unchanged. Relative cost-utility of CPAP (fixed) and CPAP (auto) changes marginally

The results of the univariate sensitivity analyses are reported in Table 6.7. No rationale was provided for the ranges over which input values were varied.

Cost-effectiveness acceptability curves (CEAC) 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 when compared to a 'do nothing' option than when CPAP (fixed) is compared to a 'do nothing' option at a willingness to pay threshold of less than £5,000 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 to 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 Section 5 demonstrates, a considerable RCT-based literature exists which examines the efficacy and effectiveness of CPAP compared to 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 Section 5.

Choice of comparators**:** ResMed did not include the full range of comparators that are discussed in Section 5. 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 to a 'do-nothing' alternative, the comparative benefit of CPAP is increased, as compared, for example, to dental devices. ResMed briefly describe 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 life time horizon. ResMed used a 14 year time horizon for analytical convenience. It was assumed that the device life of CPAP was seven 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 the 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 larger 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 and are not summarised here since they did not contain a full cost-effectiveness analyses.[125, 126]

6.1.2.2 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 old who were newly diagnosed with moderate to severe OSAHS, classified as having an AHI of 15 or more events per hour. The analysis was undertaken from the U.S. third party payer perspective and the societal perspective.

The authors developed a Markov model with a five year time horizon. Each Markov cycle lasted one 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 RTA. 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 via 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 by age-group and sex. These were adjusted for the impact of CPAP on RTA 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 U.S. The probabilities of RTA were stratified by the relevant patient groups. A RTA could result in a fatality, property damage only, or was injury-related. The injury-related RTA 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 a RTA, the severity of injury was estimated as 85.6%, 10.5%, 3.3%, 0.4% and 0.2% for severity levels one through to five. RTA survivors in level five MAIS state were assumed to be unable to drive again and therefore were confined to a tunnel state in the model.

Table 6.8 Studies with rates of RTA with and without CPAP therapy used in the Ayas *et al* model

Source	Country	No patients	Mean AHI	Mean age	Definition of crash	Rates of RTA	
						CPAP	No CPAP
George	Canada	210	54	52	From provincial insurance database	CPAP	No CPAP
Findley	US	50	37	56	State DMV (injury or property damage>$500)	0.06/y	0.18/y
Krieger	France	547	59.8	56.6	Self report	0/y	0.07/y
Engleman	Scotland	215	47	53	Self report (major incidents)	0.0256/y	0.084/y
Horstmann	Switzerland	85	NA	NA	Self report	0.001/16,000km driven	0.005/16,000km driven
Suratt & Findley	US	22	NA	NA	NS	2.7/1,000,000km driven	10.6/1,000,000km driven
Cassel	Germany	59	38.9	49	Self report	0.023/y	0.30/y
Yamamoto	Japan	39	55.7	48	Self report	0.14/100,000km	0.8/100,000km

The effect of CPAP on RTA was based on a random-effects meta-analysis of eight observational studies in which actual RTA were observed in patients pre and post initiation of CPAP.[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 RTA 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, as compared to 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 one year. The FCI weights were applied using similar methods to Graham *et al*.[143]

The transition probability to death was estimated by taking the yearly, sex-specific probability of a RTA death to the rate of death due to natural causes, based on U.S. 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 two and year five, 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 five years.

For the analysis undertaken from a societal perspective, productivity losses associated with RTA were also included such as losses in household and market productivity and associated workplace costs were calculated using the human capital approach. Also non-medical costs including legal costs and insurance administration costs were included. Societal costs of RTA 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. Also 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 three month period but did not benefit from the device over the period.

Summary of cost-effectiveness: From a third party payer perspective, CPAP was more costly and more effective than no CPAP and the ICER was $3,354 per QALY (95% CI, $1,062 per QALY to $9,715 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 $6,114). Based on the probabilistic sensitivity analysis, if the value of society's willingness to pay for a QALY is $50,000, 100% of the 1,000 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; that is, it was associated with lower costs and greater effects compared to 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 of the ICER, resulting in a more than ten-fold higher ICER when comparing the third party payer perspective to 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 five-fold.

Comments on Ayas: 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 three month post CPAP utility estimate used for the CPAP arm. As revealed by the systematic review (Section 5), there is a considerable amount of other data 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 larger than the reduction with CPAP indicated by the weight of evidence incorporated in the systematic review in Section 5.

The impact of CPAP on RTAs were based on eight before and after studies, pre and post CPAP. Another influence which 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 a RTA, thereby falsely inflating rates prior to using CPAP. The authors undertook a sensitivity analysis, using the odds ratio of the lower of the confidence interval, which gave an ICER of around $3,530 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 (nasal CPAP) 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 of 30 or more events per hour and an ESS of greater than 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 five years and over the lifetime. Each Markov cycle lasted one 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, non-fatal CHD or death. During the cycle, patients could experience a temporary event: a stroke, CHD or a 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 as compared to 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 3.6mm Hg 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 6.9).

Table 6.9 Probability values used in the Mar *et al* model

Probabilities (relative risks)	Untreated OSAS patients	nCPAP OSAS patients
CHD	1.185	1
Stroke	1.353	1
Car accident	8.1	1
Death after stroke	1.1	1.1
Death after CHD	1.1	1.1

Utility values were obtained as described on P98 (see summary of effectiveness review for the ResMed submission).

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 the 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 five years. Data relating to the last 5,000 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 Euros 7,861 per QALY over a five year time horizon and Euros 4,938 per QALY for the life time horizon.

Based on the univariate-way and multivariate sensitivity analyses, ICER estimates were robust to many assumptions associated with the parameter estimates chosen and remained in the region of Euro 5,000 to Euro 10,000. The only case where the ICER was found to exceed Euros 20,000 per QALY was for a worst case scenario analysis in which the authors used the lower limit of the confidence interval obtained from the patient preference utility survey and a five 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. Besides this, they presented disaggregated incremental effectiveness data (for CVE risk, RTAs and utility effect) and disaggregated incremental cost information, both for a 50 year old male using nCPAP for a five year and lifespan time horizon. They 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 five 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 of more than 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: 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* study[122], considerable amounts 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 for the impact of a 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 Report [44]

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 (nasal CPAP) 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 it by comparing the results to 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 one year are reported in Table 6.10.

Table 6.10 Gain in QALYs at one year in the Chilcott *et al* report

	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

Summary of resource utilisation and cost data: The cost analysis was undertaken from the health care perspective. As for the Mar *et al* analysis[123], the Trent report considered the costs of investigation, diagnosis and treatment of OSAHS and maintenance and medical follow-up costs. Unlike 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 five 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 6.11. The results were extrapolated up to five years duration assuming that the benefits of accrued in the trial period were maintained.

Table 6.11 Baseline cost per QALY gained in the Chilcott *et al* report

Time horizon	Cost per QALY gained
One month	£99,000
One year	£8,300
Two years	£5,200
Five years	£3,200

Several univariate sensitivity analyses were undertaken comprising: the impact of the analytical time horizon, costs of investigation for nCPAP, long-term costs of maintenance, follow-up and other healthcare resource usage, the long-term impact of gross annual healthcare costs, the potential impact of improved mortality from use of nCPAP treatment, the impact of uncertainty in morbidity benefits from nCPAP therapy and the discount rate. All estimates of cost-effectiveness over one year were less than £16,000 per QALY gained.

The authors suggested that the cost-effectiveness of dental devices compared to no treatment was likely to be similar or worse than the cost-effectiveness of nCPAP therapy compared to 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 to dental devices. The implied differences in costs, 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* two weeks' duration;[146, 147] Jenkinson *et al* four

weeks' duration [77]). 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 to 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 nCPAP, pre-treatment, full health and immediate death. To assess the reliability of the results patients completed the exercise on two occasions 2 to 3 weeks apart. The mean utility score for the pre-treatment health state was 0.63 (+/-0.29) and the mean utility score for the nCPAP treatment health state was 0.87 (+/-0.17). The intra class 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 perspective. Costs included the cost of supplies, 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 $2,348 (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 amortization of capital costs over seven 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 $9,792 per QALY gained by nCPAP was calculated as well as a low estimate of CAN $3,397 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: As all the patients were currently receiving nCPAP therapy, their valuation of the pre-treatment health state was done retrospectively. As such 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 is 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.

6.1.2.3 Discussion of manufacturers' submissions and published cost-effectiveness studies

Of the studies reviewed, none compared all therapies identified in the NICE scope: that is, none compared CPAP versus 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 (ResMed[120] and Chilcott *et al*[44]) examined the treatment of OSAHS in the UK NHS context, the others focussing on the U.S.,[122] Spanish[123] and Canadian[124] health care systems.

The existing cost-effectiveness studies had several limitations which 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.

6.2 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 impacts of the different therapies. Several sources of evidence were used to inform the analysis. The model was developed based on the methodological guidance for the NICE Reference Case (http://www.nice.org) as reported in Table 6.12. The development of the model was informed by research in the published literature including the clinical effectiveness systematic review reported in Section 5, 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 (termed the York economic model from now on), is described in two parts. First, the methods used to perform the economic analysis are described, comprising 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. Second, the results of the base-case analysis are presented and the role of parameter uncertainty is investigated through probabilistic sensitivity analysis.

Table 6.12 Summary of NICE Reference Case

Element of health technology assessment	Reference case
Defining the decision problem	The 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, for example, time trade-off, standard gamble (not rating scale)
Source of preference data	Representative sample of the public
Discount rate	An 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

6.2.1 Methods of York economic model

6.2.1.1 Overview

A cost-utility analysis was undertaken which compared CPAP to use of dental devices and conservative management: 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, for example 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 (Section 5), it was necessary to estimate the relationships between clinical endpoints and QALYs using other data. Three clinical endpoints 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 endpoint (see Section 5). The second clinical endpoint was differential treatment effect on blood pressure which was reported in trials, and this was related to CVE risks and hence to QALYs in the model. The third endpoint was differences in the risk of RTA which was based on non-randomised evidence and 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, 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 (for example, the apnoea/hypopnoea 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 to 58 years old (see Section 5)) 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 old.
- Sub-group analyses were undertaken by gender, OSAHS severity (as measured by ESS) and other relevant baseline patient characteristics.

Secondary analysis

- Scenario analyses were 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 diastolic blood pressure (DBP) and MacMahon *et al* (1990)[145]
    - APAP machine with 5 year life span and humidifier
    - Treatment effects from BRMA (APBM only)
    - Treatment effects from BRMA (APBM and office measurements)
- Sub-group analyses
    - For a cohort aged (35 and 65)
- Other relevant modelling assumptions
- Uncertainty and value of information analysis

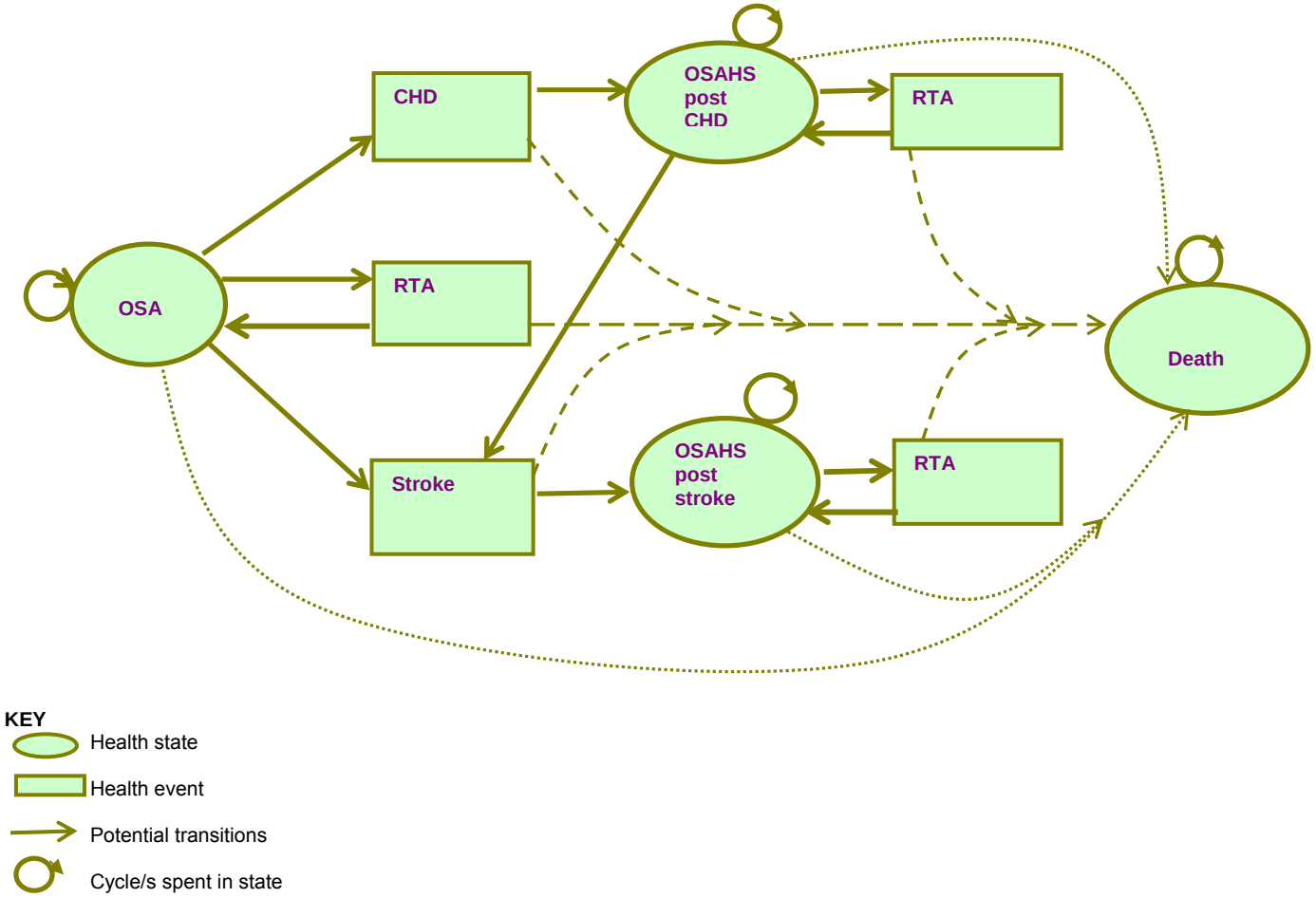
The York economic model is fully probabilistic and the results from the model are presented probabilistically to reflect the implications of parameter uncertainty on decision uncertainty.

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 to the potential costs of additional research to indicate whether there is value in further research to reduce the decision uncertainty.

6.2.1.2 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 11.8). The structure of the model is shown in Figure 6.2. The model characterises the patient's prognosis over their lifetime in terms of four health states: that is (i) OSAHS, (ii) OSAHS post coronary heart disease (CHD), (iii) OSAHS post stroke and (iv) 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 Section 5, 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, a patient 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 which incorporates the increased mortality and morbidity associated with having had a first CHD event. They could then remain in this state until death, experience a RTA or have a stroke from which they may become disabled.

Figure 6.2 York economic model structure



Alternatively, from the initial OSAHS health state they could experience a stroke. 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 a RTA. In contrast, if they become disabled post stroke, it is assumed they are no longer able to drive and therefore have 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, whether directly or as a result of a RTA. The model does not separately record CHD events following a stroke.

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

6.2.1.3 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 the clinical effectiveness section (Section 5) as well as relevant evidence from non-randomised trials, modelling studies, analyses of administrative databases and expert clinical opinion. Also, individual patient data from three trials.[87 144, 151] were obtained through 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: (i) HRQoL studies, utilities and QALYs; (ii) literature linking CVE, particularly stroke and CHD, to OSAHS; and (iii) literature linking RTAs to OSAHS. The search strategies are presented in Appendix 11.1.3.

Utility estimation for inclusion in the York economic model

As reviewed in Section 5, the evidence base on the effectiveness of CPAP in OSAHS consists of a number of randomised trials of assorted designs (cross-over 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 treatment effects in terms of a reduction in the number of CVE, nor 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 Section 5 highlighted the measures used to describe the efficacy of treatments for OSAHS in randomised controlled trials, 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*, 1998).[97] Therefore an additional literature search was undertaken and this identified four other papers which contained potentially relevant HRQoL/utility data for inclusion in the model.

Table 6.13 Summary of studies reporting utility data

AUTHORS	METHOD	STUDY DESIGN	UTILITY VALUES (MEAN (SD))	SOURCE OF VALUES
Tousignant *et al* (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 *et al* 1997[152]	EQ-5D	Before and after study. Patients completed EQ-5D before commencing treatment with nCPAP and 5 weeks later	Baseline EQ-5Dindex = 0.79 (0.21) Post treatment EQ-5Dindex =0.84(0.25)	Patients attending sleep clinic for nCPAP therapy (N=108)
Chakrovarty *et al* 2002[97]	EQ-5D, SG	RCT comparing 3 months treatment with CPAP to 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: compete cure or failure leading to a worst health state/death	*CPAP group:* SG pre-treat=0.32 (0.17) SG post treat=0.55 (0.26) EQ-5Dindex pre treat=0.73 (0.18) EQ-5Dindex post treat=0.77 (0.18) *Lifestyle group*: SG pre-treat=0.31 (0.13) SG post treat=0.35 (0.12) EQ-5Dindex pre treat=0.77 (0.12) EQ-5Dindex post treat=0.77 (0.09)	Patients referred to hospital sleep clinic (N=71)
Mar *et al* 2003[123]	EQ-5D	Before and after study. Patients completed EQ-5D pre-treatment and after using nCPAP for 3 months	Baseline EQ-5Dindex=0.74 Post treat EQ-5Dindex= 0.81	Patients referred to sleep unit (N=46)

SG = standard gamble

Table 6.13 reports key information on the four studies (see Appendix 11.7 for more details). Jenkinson *et al* [152] and Chakrovarty *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, Chakrovarty *et al*[97] reported pre-treatment ESS of 16 (SD 6) and a post-treatment score of 8 (SD 6). In the lifestyle arm, Chakrovarty *et al*[97] reported 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 to placebo and 6 studies comparing CPAP to 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* based on UK public preferences.[153] The EQ-5D data were used to calculate utility based on general UK population tariff values.[128] The three datasets were then used to develop prediction models to estimate the relationship between ESS and: i) utility values based on SF-6D and ii) 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 to 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 6.3). However, typically, EQ-5D scores do not follow a normal distribution, and as expected the EQ-5D scores in the dataset formed a distribution skewed to the left, with a large number of observations clustered at a score of 1. Figure 6.3 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 SF-6D.

Table 6.14 Predicting utility scores from ESS for use in York economic model

Utility	Coefficient	Standard error	P-value	95% confidence interval	
OLS model for utility based on SF-6D (n=294)					
ESS	-.0095213	.0013849	0.000	-.0122512	-.0067915
Baseline ESS	.0050331	.0011942	0.000	.0026791	.0073871
Baseline utility	.5588972	.0534972	0.000	.4534455	.6643489
Constant	.8067555	.0115013	0.000	.7840845	.8294265
OLS model for utility from EQ-5D (n=94)					
ESS	-.0096984	.003947	0.016	-.0175364	-.0018604
Baseline ESS	.0029526	.0033693	0.383	-.0037382	.0096435
Baseline utility	.6287684	.1346153	0.000	.3614492	.8960877
Constant	.8925207	.0286109	0.000	.8357052	.9493363

The results of the regression analyses are shown in Tables 6.14 and 6.15. The models indicate that an increase of one 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 sub-group effect.

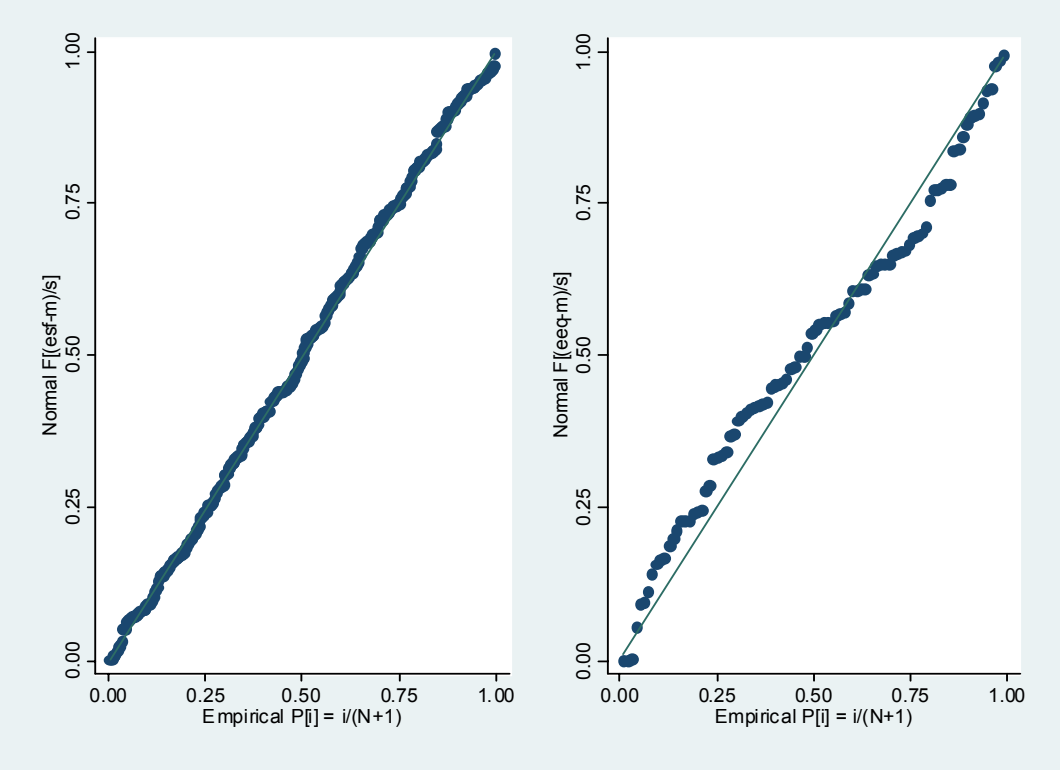
The Cholesky decomposition of the covariance matrix from the regressions was employed to characterise the uncertainty around the estimated coefficients and to reflect the correlation between coefficients in the probabilistic sensitivity analysis.[150] The baseline utility for the hypothetical patient population was predicted from the specified baseline ESS score. Changes in ESS associated with treatment were converted to changes in utility (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* and are reported in Table 6.15.[155] 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 a RTA was based on EQ-5D measures from the Health Outcomes Data Repository (HODaR).[156] HODaR recorded EQ-5D data for individuals six weeks after their inpatient episode (at Cardiff hospital, UK) for injuries experienced from a RTA. Data were extracted for all patients who had a traffic accident as a motorcycle rider, an occupant of a three-wheel motor vehicle, a car occupant or an occupant of a pick-up truck or a van (V20 to V59, ICD10 codes). Results were found for 56 patients. A gamma distribution was used to characterise the uncertainty around the utility decrements associated with clinical events.

Figure 6.3 Standardised normal plot of residuals for use in York economic model



Equations based on SF-6D (left) and EQ-5D (right)

Table 6.15 Utility scores for use in the York economic model

Utility	Mean	SD	Source
OSAHS untreated (baseline)	Baseline ESS * -0.01 + 0.89[T]		Estimated from prediction equation (see Table 6.14)
OSAHS treated with CPAP (change from baseline)	$MD\_ESS_{CPAP\_CM}$ * -0.01		Estimated from prediction equation (see Table 6.14)
OSAHS treated with dental devices (change from baseline)	$MD\_ESS_{DD\_CM}$ * -0.01		Estimated from prediction equation (see Table 6.14)
Stroke (absolute decrement)	-0.0524	0.0002	Sullivan and Ghushchyan [155]
CHD (absolute decrement)	-0.0635	0.0001	Sullivan and Ghushchyan [155]
RTA (absolute utility)	0.62	0.27	HODaR[156]
Age decrement (per year)	-0.0007	0	Sullivan and Ghushchyan [155]

[T]When using equation based on EQ-5D; MD_ESS = mean difference in ESS

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 Section 5 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 Figure 5.2 in Section 5). These analyses cannot be interpreted as sub-group 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 sub-group analyses 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 needs 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 CVE. Published risk equations predict the risk of CHD and stroke[157] over a range of 4 to 12 years as a function of either systolic or diastolic blood pressure (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 mean arterial pressure (MAP). The risk equations were estimated separately for men and women using the baseline characteristics of the hypothetical patient population shown in Table 6.16, 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 body mass index (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.

Table 6.16 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
10 year probability of stroke event	3.4% (male); 3.7% (female)
10 year probability of death from CVD	3.8% (male); 3.6% (female)
10 year probability of CHD	19.7% (male); 19.2% (female)
10 year probability of death from CHD	3.9% (male); 3.7% (female)

ECG-LVH = Electrocardiographic Left Ventricular Hypertrophy

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 to 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 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 a 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 to usual care is estimated to be relatively low using the Framingham risk equations (RR~=0.98 for mean reduction in SBP of 1.06 mm Hg). 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 CVD events. Random fluctuations in blood pressure may cause the relationship between blood pressure and incidence of CVD events 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 linear in reduction of DBP. They estimate that a 7.5mm Hg 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 to usual care is estimated to be higher based on the MacMahon *et al* analysis in comparison to the Framingham risk equations (RR = 0.96 for CHD and RR= 0.94 for stroke given a mean reduction in DBP of 1.20 mm Hg).

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 bivariate random effects meta-analysis (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, 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 11.8.

The results of the BRMA are shown in Table 6.17. The estimate for the mean change in ESS is similar to that reported in Section 5. This is not surprising given the relatively small number of data points that inform this estimate. However, the estimate for the mean change in BP differs somewhat to that reported in Section 5. 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 ambulatory blood pressure monitoring (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 Section 5 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 to that recorded by an office 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 6.17.

Table 6.17 Results of a bivariate random effects meta-analysis for mean difference in ESS and mean difference in SBP (CPAP versus conservative management)

	ESS, CPAP vs CM mean difference (SD)	**SBP, CPAP vs CM** mean difference (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)

No trials reported change in daytime SBP based on ABPM for the comparison of CPAP to 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 to placebo would be equal to the ratio of the observed treatment effects on ESS. The mean difference in ESS for CPAP versus conservative management ($MD\_ESS_{CPAP\_CM}$) and for CPAP versus dental devices ($MD\_ESS_{CPAP\_DD}$) were reported in Section 5. 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 to conservative management was therefore calculated as $MD\_SBP_{DD\_CM} = MD\_SBP_{CPAP\_CM}*(MD\_ESS_{DD\_CM}/MD\_ESS_{CPAP\_CM})$.

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 Section 5 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 6.8). Only one additional study was found (Barbe *et al*[162]). Since this study reported a relative risk rather than an odds ratio (as in the Ayas paper[122]), 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 6.18. Note that although the relative risk reduction of experiencing a RTA with CPAP treatment is large, the absolute baseline risk is very low.

Table 6.18 Meta-analysis to calculate the RTA rates with CPAP compared to without CPAP

	Odds ratio	Variance
Ayas et al, 2006[122] (based on 8 studies)	0.15	0.00094
Barbe et al, 2007[162] (single study)	0.33	0.02075
Pooled data *Ayas*[122] *and Barbe*[162]	0.17	0.00098

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 to 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 a RTA. For the base-case analysis the proportion of first strokes that were disabling was estimated to be 30.9% based on the ESPS-2 Second European Stroke Prevention Study.[163] Note that the base-case analysis applies to patients that hold a driving license. For OSAHS sufferers who do not drive the appropriate analysis is one in which the risk of RTA is excluded.

In summary, Table 6.19 shows the treatment effects used to populate the York economic model.

Table 6.19 Treatment effects used to populate York economic model

	CPAP vs CM mean (SD)	CPAP vs DD mean (SD)	DD vs CM mean (SD)
ESS (mean difference)			
Overall*	-2.7 (0.38)	-0.85 (0.64)	-1.85†
Mild baseline severity (ESS)	-1.07 (0.39)	n/a	
Moderate	-2.33 (0.36)	-0.85 (0.64)	-1.48†
Severe	-4.99 (0.76)	n/a	
Blood pressure (mean difference)			
SBP*	-1.06 (1.17)		-0.73†
DBP	-1.20 (0.88)		-0.82†
RTA (odds ratio)*	0.17 (0.001)		0.25†

* base case analysis; †derived parameter

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. As such, 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 one year after initiation of treatment, and that compliance was steady after a period of four years with 68% of patients continuing treatment. The percentage of patients compliant at two and three years after treatment initiation was read from the survival curve (74% and 73%) and these data were then used to model the rate of discontinuation from years one to four in the model. Patients discontinuing treatment were assumed immediately to return 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 6.20 reports the parameters associated with CHD, stroke and RTAs.

Table 6.20 Parameters associated with CHD, stroke, RTAs and death from other causes used in the York economic model†

Parameter	Mean	95% CI	Source
Stroke			
Relative risk of death following stroke	2.3	2.0 to 2.7	Dennis *et al*[164]
CHD			
Relative risk of death following CHD	3.2	2.67 to 3.83	Rosengren[165]
RTA			
Rate of non-fatal RTA for male license holders	0.0089	*	DoT, Highways economic note[133]
Rate of non-fatal RTA for female license holders	0.0082	*	DoT, Highways economic note[133]
Rate of fatal RTA for male license holders	0.00014	*	DoT, Highways economic note[133]
Rate of fatal RTA for female license holders	0.000060	*	DoT, Highways economic note[133]

† 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.
* Estimates based on population (rather than sample) data, therefore no uncertainty expressed.

The mortality rate for individuals who have not experienced CHD or stroke (by age and sex) was taken from UK life tables of the Government Actuary Department http://www.gad.gov.uk. For each age band, the all-cause hazard was reduced by the proportion of people dying of CVD or IHD causes to get the hazard of death for non-CVD or non-IHD causes using methods developed by Chiang (1968). 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 3.2 [165] and 2.3,[164] respectively, were employed. These relative risks were applied to the non-cardiovasular/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 healthcare and PSS related to OSAHS. Costs were reported in prices relating to 2005 and any 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 healthcare resources comprising any healthcare 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 against CPAP for OSAHS in the UK.

Table 6.21: Costs and resource use associated with treatments for OSAHS included in the York economic model

Parameters		Costs, £ (2006) Mean (SD)	Probability Mean (SD)	#	Source
CPAP INITIAL COSTS					
Outp. visit	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**			
Titration	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 times CPAP/APAP used for dose titration			163	
	Total cost of in-home titration	**2.34**			
	Probability of inpatient titration		0.01		Assume if not home titration must be inpatient titration (1-0.99)
	Unit cost sleep study follow up	107.87			NHS Reference cost 2006
	Total cost of inpatient titration	**1.08**			
	Probability of seeing a specialist nurse for titration		1		Assumption
	Unit cost of 30 minute appt with specialist nurse	34			NHS Reference cost 2006
	Total cost of specialist nurse involved in titration	**34**			
	Probability of seeing a consultant for titration		0.4		ResMed survey of clinicians
	Total cost of titration by consultant	**43.1**			
	Total cost of 30 min appt with technician	**9.5**			
TOTAL INITIAL CPAP COSTS (First year)		**164.64**			
TOTAL INITIAL APAP COSTS (First year)†		**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 (i.e. 6.33)
	Annual equivalent cost of CPAP mask	80			ResMed
	Annual sundries	15			Clinical opinion
	Annual follow-up	79			Clinical expert referring to NHS tariff
TOTAL CPAP ONGOING COSTS (Yearly)		**218.24**			44.24+80+15+79
	APAP machine	410			ResMed
	Humidifer	150			ResMed
	Estimated device life of APAP and humidifier			5	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)†		359			100+100+80+79
DENTAL DEVICECOSTS					

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 cost a consultant appointment
CONSERVATIVE MANAGEMENT COST			
One-off consultation with a GP	21		PSSRU 2006[166]

NB some figures are approximate as reported to limited number of decimal places

[†]Applied in sensitivity analysis

The cost of CPAP, dental devices and conservative management used in the York economic model are shown in Table 6.21. 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 seven years (which was the device life used by ResMed and confirmed by a clinical expert) and that a dental device lasts for two years (based on clinical opinion). The costs of the devices were expressed as equivalent annual costs[121] 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 which 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 (http://www.ic.nhs.uk/). Twelve units of dental activity (UDA) are applied to Band 3.[167] It is not known what the national average reimbursement rate for a UDA (Personal communication with the Department of Health: the value of UDAs vary because of a number of factors, including the contract values negotiated locally by 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). Therefore, the value of a UDA was obtained from published material (Bath & North East Somerset Primary Care Trust http://www.banes-pct.nhs.uk/documents/Board_Papers/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 an 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 in which the patient may receive advice on posture, dietary habits and lifestyle. A unit cost of a GP appointment was obtained from the PSSRU Unit costs of health and social care report.[166]

The unit costs associated with stroke, CHD and RTAs are reported in Table 6.22. Published references were used to estimate these parameters. The uncertainty around the costs was characterised by gamma distributions where mean costs and standard deviation were presented, and by normal distributions where the costs were based on coefficients from a regression analyses. The Department of Transport information regarding the costs of RTAs were presented as point estimates. In order to characterise the uncertainty around these estimates it was assumed that the standard deviation would be equal to that reported by HODaR (Currie *et al* (2005)[156]) for the hospital cost associated with non-fatal RTAs (mean £2,437, SD £1,643).

Table 6.22: Mean costs associated with CHD, stroke and RTAs used in the York economic model

Parameter	Costs(£) Mean	SD	Source
CHD & stroke			
Cost of fatal CVE	3,021	367	Briggs *et al*, 2007[168]
Acute cost of CHD	9,997	428	Briggs *et al*, 2007[168]
Ongoing cost of CHD	751	117	Briggs *et al*, 2007[168]
Acute cost of stroke	9,067	294	Bravo *et al*, 2007[169]
Ongoing cost of stroke	2,392	2,82	Bravo *et al*, 2007[169]
RTA			
Cost RTA all injury	2,700	1,643	DoT, Highways economic note[133]
Cost of fatal RTA	5,450	1,643	DoT, Highways economic note[133]

6.2.2 Results of York economic model

6.2.1.4 Base-case analysis

The base-case analysis is based on a hypothetical cohort of men aged 50 years old with the baseline cardiovascular risk factors described in Table 6.23. In this cohort CPAP was associated with both higher costs and higher QALYs in comparison to treatment with dental devices or conservative management. The incremental cost-effectiveness of CPAP compared to dental devices is estimated to be £4,000 per QALY. CPAP might therefore be considered cost-effective at a cost-effectiveness threshold per QALY of £20,000.

Table 6.23: Base case results from York economic model comparing costs and QALYs of conservative management, dental devices and CPAP

Base-case: male, aged 50	Conservative management	Dental device	CPAP
Treatment costs	£21	£1,726	£2,465
RTA costs	£2,201	£1,138	£904
CVE costs	£5,918	£5,932	£5,931
TOTAL COSTS	£8,140	£8,797	£9,301
TOTAL QALYs	11.93	12.26	12.39
ICER		**£2,000**	**£3,899**
Probability 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*

Similar results were obtained for a hypothetical cohort of women aged 50, as shown in Table 6.24.

Table 6.24: Results from York economic model comparing costs and QALYs of conservative management, dental devices and CPAP in females aged 50

Female, aged 50	Conservative management	Dental device	CPAP
Treatment costs	£21	£1,824	£2,608
RTA costs	£2,139	£1,108	£878
CVE costs	£5,840	£5,829	£5,820
TOTAL COSTS	£7,999	£8,762	£9,306
TOTAL QALYs	12.71	13.02	13.15
ICER		**£2,432**	**£4,335**
Probability 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*

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 and the results are shown in Table 6.25. Note that the trials comparing CPAP to 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 6.25 (i.e. these cost-effectiveness results by severity only include treatment effects on ESS). It can be seen that cost-effectiveness varies according to severity, with CPAP most cost-effective (lower ICER) in severe 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 sub-group with mild disease was estimated to be £20,585.

Table 6.25: Results from the York economic model for sub-groups grouped according to baseline severity of OSAHS as measured by ESS

Mild OSAHS, male aged 50 (mean baseline ESS=7)	**Conservative management**	**Dental device***	**CPAP**
Total cost	£21	NA	£2,726
Total QALYs	14.56	NA	14.69
ICER			**£20,585**
Probability cost-effective for threshold:			
£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)	**Conservative management**	**Dental device**	**CPAP**
Total cost	£21	£1,906	£2,726
Total QALYs	13.51	13.70	13.80
ICER		**ED**	**£9,391**
Probability cost-effective for threshold:			
£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 50 (mean baseline ESS=16)	**Conservative management**	**Dental device***	**CPAP**
Total cost	£21	NA	£2,726
Total QALYs	13.01	NA	13.62
ICER			**£4,413**
Probability cost-effective for threshold:			
£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
* note that all of the trials comparing CPAP to dental devices were classified as moderate OSAHS based on average baseline ESS
NA = not applicable
NB: Only differential treatment effects on ESS are included

6.2.1.5 Secondary analysis

There are a number of uncertainties over several of the modelling assumptions, and results are shown as a set of sub-group and scenario analyses in Table 6.26. 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 largest effect on the CPAP ICER comes from the applying the highest feasible acquisition cost for the treatment by including the costs of an APAP machine and a humidifier.

Table 6.26: Results from the York economic model for a range of scenario and sub-group analyses

	Male			Female		
Scenario	**CM**	**DD**	**CPAP**	**CM**	**DD**	**CPAP**
Sub-group analysis: cohort aged 35						
Cost	£8,521	£9,356	£10,034	£8,177	£9,155	£9,868
QALY	15.55	15.99	16.15	16.21	16.60	16.76
ICER		£1,894	£4,143		£2,477	£4,454
Sub-group analysis: cohort aged 65						
Cost	£5,969	£6,398	£6,728	£5,159	£5,709	£6,078
QALY	7.95	8.17	8.26	8.89	9.12	9.21
ICER		£1,866	£2,960		£2,426	£3,944
Scenario analysis: Change in ESS linked to SF-6D utility score rather than EQ-5D						
Cost	£8,129	£8,781	£9,295	£8,003	£8,761	£9,307
QALY	10.66	10.95	11.06	11.35	11.62	11.74
ICER		£2,258	£4,451		£2,748	£4,669
Scenario analysis: Relative risk reduction for CVE based on DBP and MacMahon et al[145]						
Cost	£8,133	£8,734	£9,207	£7,949	£8,656	£9,189
QALY	11.92	12.28	12.42	12.70	13.04	13.19
ICER		£1,678	£3,330		£2,040	£3,756
Scenario analysis: Exclude CVE events from model						
Cost	£2,488	£3,171	£3,736	£2,389	£3,252	£3,894
QALY	13.41	13.77	13.90	14.48	14.82	14.96
ICER		£1,896	£4,184		£2,557	£4,732
Scenario analysis: Exclude CVE and RTA events from model						
Cost	£21	£1,906	£2,726	£21	£2,038	£2,920
QALY	13.69	13.92	14.02	14.69	14.93	15.04
ICER		ED	£8,098		ED	£8,113
Scenario analysis: APAP machine with 5 year life span and humidifier						
Cost	£8,150	£8,816	£10,939	£7,979	£8,741	£11,036
QALY	11.92	12.25	12.38	12.70	13.01	13.14
ICER		£2,017	£16,362		£2,408	£18,356
Scenario analysis: Treatment effects from BRMA (APBM only)						
Cost	£8,132	£8,799	£9,283	£7,973	£8,737	£9,275
QALY	11.93	12.26	12.40	12.69	13.01	13.14
ICER		£2,003	£3,678		£2,412	£4,093
Scenario analysis: Treatment effects from BRMA (APBM and office measurements)						
Cost	£8,139	£8,771	£9,237	£7,989	£8,728	£9,222
QALY	11.92	12.27	12.42	12.70	13.04	13.19
ICER		£1,787	£3,097		£2,170	£3,249

CM = conservative management; DD = dental device; ED = extended dominance; BRMA = bivariate random effects meta-analysis; APBM = ambulatory blood pressure measurement

6.2.1.6 1.2.2.3 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 five years and incidence of OSAHS of 0.1% in the UK population aged between 16 and 65 (39m) gives an effective population of 0.18m (http://www.statistics.gov.uk/cci/nugget.asp?ID=949). This corresponds to a population EVPI of £33m (male). When CVE and RTA events were excluded from the model, the population EVPI rises to approximately £51m (based on per episode EVPI of £277 in men).

Table 6.27: Economic Evaluation Quality Assessment

REFERENCE NUMBER	Ayas[122]	Mar[123]	ResMed[120]	Trent[44]
COST EFFECTIVENESS				
Study question				
Were costs & effects examined	√	√	√	√
Alternatives compared	√	√	√	√
Viewpoint/s clearly stated	√	√	√	√
Selection of alternatives				
All relevant alternatives compared	√	√	√	√
For the alternatives compared were all clearly described	√	√	√	√
Rationale for choosing the alternative programmes compared is stated	√	√	√	√
Form of evaluation				
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 source of effectiveness estimates used are stated	√	√	√	√
Effectiveness data from RCT or review of RCTs	X	X	x	x
Potential biases identified	√	√	x	√
Details of method of synthesis or meta-analysis of estimates are given	√	√	√	√
Costs				
All the important & relevant resource use included	√	√	√	√
All the important & relevant resource use measured accurately	√	√	√	√
Appropriate unit costs estimated	√	√	√	√
Unit costs reported separately from resource use data	√	√	√	√
If productivity costs were included, were they treated separately from other costs	√	NA	x	x
The year & country to which unit costs apply is stated with appropriate adjustments for inflation &/or currency conversion	√	√	√	x
Benefit measurement & valuation				
The primary outcome measure for the economic evaluation is clearly stated	√	√	√	√
Methods to value health states & other benefits are stated	√	√	√	√

Details of the individuals from whom valuations were obtained are given	√	√	√	√
Decision modelling				
Details of any model used are given	√	√	√	NU
The choice of model used & the key input parameters on which it is based are adequately detailed & justified	√	√	√	NU
All model outputs described adequately	√	√	√	NU
Discounting				
Discount rate used for both costs & 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 & confidence intervals are given for stochastic data	NA	NA	NA	NA
Uncertainty around cost-effectiveness estimates expressed	NA	NA	NA	NA
Sensitivity analysis used to assess uncertainty in non-stochastic variables and analytic methods	NA	NA	NA	NA
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 & appropriate?	√	X	x	NU
Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs) & 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	√	√	√	√
Applicable to the UK setting	X	X	√	√

Key: √=Yes, X=No, NA=Not Applicable, NU = Not Undertaken, P=Partial, U=Uncertain

7 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. 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.

8 Discussion

8.1 Statement of principal findings

8.1.1 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 severity at baseline was classified based on AHI, most included studies were classified as being of severely symptomatic 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 four 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 sub-grouped based on mean severity of daytime symptoms at baseline, but not when sub-grouping 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 mainly targeted at controlling its symptoms and consequences such as 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 ESS.

There was clear evidence of a benefit with CPAP compared to 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 sub-group 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, though there was some evidence of a beneficial impact on quality of life and daytime mean arterial blood pressure

(MAP). The identified studies comparing CPAP to 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 were available and there was some inconsistency in the findings making it difficult to draw firm conclusions. 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 road traffic accidents 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 such as driving and employment performance. In this review, sleepiness was quantified as subjective daytime sleepiness as measured by the ESS and objective sleepiness 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 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. This estimated mean difference 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 sub-grouped 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, -3.5), and was smaller with moderate (MD -2.3 points, 95% CI -3.0, -1.6) and mild symptoms (MD -1.1 points, 95% CI -1.8, -0.3). These were all statistically significant. It is not surprising to find a smaller benefit in the studies of populations who 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 sub-groups, 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 to 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: 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 real-life situations where the ability to resist sleep while driving or carrying out a daily activity is important rather than how quickly a person can fall asleep, when instructed to do so, as on 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 one point (0.9) in favour of CPAP compared to dental devices, but might be anywhere between an increase in sleepiness of 0.4 points with CPAP to 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 to 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 to dental devices and postural therapy. Assessment of the comparative clinical effectiveness of CPAP and dental devices or postural therapy is limited by the volume 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 was 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 ambulatory blood pressure monitoring (ABPM), there was a statistically significant benefit with CPAP compared to placebo/usual care in daytime mean arterial pressure (MAP). Based on the random effects pooling used, the size of the effect is probably different in 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 though there was small a decrease on both measures in favour of CPAP (MD -1.1mmHg, 95% CI -3.4, 1.2 and MD -1.2mmHg, 95% CI -2.9, 0.5 respectively). It should be noted that not all the trials in the analysis of MAP were the same as those in the SDP 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 sub-group 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 SDP with CPAP compared to control. Given the evidence that a person's actual blood pressure is more accurately reflected by the repeated measurements of ABPM than 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 though 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, though 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 to 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 to control on the SF 36 bodily pain, general health and physical function subscales in the parallel trial sub-group; this may have been driven by two trials of severely symptomatic populations.

Quality of life data regarding CPAP compared to dental devices (all moderate symptom severity) were inconsistent: on the FOSQ one study showed a statistically significant benefit with CPAP compared to 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 to 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. Sub-group 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 to 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 to 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 to normative performance. The findings were contradictory from trials for individual cognitive tests with some showing a benefit with CPAP and others not.

8.1.2 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 the former dominated the latter. There are a number of methodological weaknesses associated with the RedMed analysis including:

- The results of a before and after study[123] were used to examine the impact of no treatment compared to CPAP on health related quality of life (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 to 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 life-time 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 £1,500 to £3,000. 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, cardiovascular events and road traffic accidents.
- 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 to 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 sub-set of studies; and it used trial evidence on changes in blood pressure following intervention to estimate differences in the rates of cardiovascular events over time.

The York model found that, on average, CPAP was associated with higher costs and benefits compared to 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 £3,899 for men and £4,335 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 Section 5 only included trials where CPAP was a comparator. As a consequence, trials comparing dental devices to 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* (2004) 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 £4,413 (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 under-estimate.

A series of other sub-group 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 compared to men; this may be due to the fact that women have a lower baseline risk of CVD and RTA giving less potential for QALY gains. They also typically have a longer life expectancy, resulting in higher treatment costs compared to 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 co-morbidity 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 RTA. The inclusion of CVE 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 RTA were lower with CPAP in comparison to 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 RTA or fatal CVE with CPAP was that more patients remained alive and at risk of non-fatal CVE, partially off-setting any savings from a reduced risk of events overall. Omitting the impact of CVD had little effect in the study results. Even when incorporating the larger relative risk reduction for CVE implied by the MacMahon study the reduction in blood pressure associated with CPAP contributed little to the estimation of its cost-effectiveness. When the impact of CVD and RTA was omitted, the incremental cost of CPAP compared to usual care increased, but the ICER remained low at £8,098. 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 five years. This indicated that the upper bound for the value of further research was between £33m-£50m. 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 one 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 was found of 0.005 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 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, for example, in terms of its affects on usual activities or anxiety and depression. This analysis suggests 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 healthcare. 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.

8.2 Strengths and limitations of the assessment

8.2.1 Clinical effectiveness

While there is clear and robust evidence of a benefit with CPAP compared to 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 sub-group analyses make clinical sense. However, the sub-group 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 sub-group 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 sub-group 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 where 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 where sham CPAP was used as the comparator; effectively it provides the best placebo in this field. When only studies using a sham CPAP comparator were sub-grouped by baseline symptom severity (ESS) the findings were similar to those using the complete dataset sub-grouped by baseline symptom severity (ESS): there was a statistically significant benefit with CPAP compared to sham CPAP for each of the three sub-groups and the treatment effect was largest for the severe symptom sub-group 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 to control on the ESS and MWT is consistent with previous systematic reviews.[48 50] A previous sub-group analysis reported a more pronounced effect of CPAP in participants with moderate and severe symptoms at baseline, though 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 primary outcome.[174] A small but statistically significant decrease in 24 hour MAP of 1.7mmHg was reported (MD -1.7 mmHg, 95%CI -2.7, -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, -0.2) compared to 2.1 mmHg (MD -2.1, 95%CI -4.3, 0.0) in the current review). Unlike the current review, there was a significant improvement with CPAP compared to placebo for SBP (-2.3mmHg (95% CI -4.3, -0.2) compared -1.1mmHg (95% CI -3.4, 1.2) in the current review); and DBP (-2.9mmHg (95% CI -4.4, -0.4) compared to -1.2mmHg (95% CI -2.9, 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 where 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.

8.2.2 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 expected value of perfect information (EVPI). The analysis suggests that CPAP is cost-effective

compared to dental devices and conservative management assuming a cost-effectiveness threshold of £20,000 with one exception: 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. As such 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 contained predominantly patients receiving CPAP. To ameliorate 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 RTA 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 BP, this outcome is infrequently reported, and the trials are too short in length to directly measure impact on CVE, and so estimated changes in CVE rates are inferred from other published risk equations.

8.3 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 where cognitive impairment and cerebrovascular disease are more prevalent and the OSAHS may be complicated.

- There is evidence of a benefit with CPAP on MAP though 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 BP 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 to CPAP in mild and severe disease populations is unclear.
- 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 Section 5, 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 BP or RTA by baseline OSAHS severity, these effects have been removed entirely from this analysis.

8.4 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 where there has been an adequate diagnostic assessment. In view of the diagnostic complexity of sleep apnoea, adequate diagnostic assessment should include a multi-channel sleep study reported by an appropriately trained physician (such as a consultant respiratory physician). The detailed consideration of what would constitute an appropriate multi-channel sleep study and the associated cost implications were outside the remit of this technology appraisal.

9 Conclusions

9.1 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, though 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 compared to 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.

9.2 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.
- Further investigation of the effect of CPAP on hypertension and what 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 which are adequately powered to identify changes in cardiovascular events 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 where cardiovascular comorbidity complicates assessment) and women would be beneficial.

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11 Appendices

11.1 Literature search strategies

11.1.1 Searches for systematic reviews and guidelines

Cochrane Database of Systematic Reviews (Cochrane Library 2006, issue 3) (www.thecochranelibrary.com)

Searched 17/10/06. The 53 records retrieved were scanned to remove references to infants and children and 11 records were downloaded.

1. MeSH descriptor Sleep Apnea Syndromes explode all trees
2. apnea or apnoea
3. hypopnea or hypopnoea
4. hypoapnea or hypoapnoea
5. "sahs" or "shs" or "osas" or "osa"
6. (#1 OR #2 OR #3 OR #4 OR #5)
7. MeSH descriptor Positive-Pressure Respiration explode all trees
8. cpap or apap or ncpap or autocpap or auto-cpap
9. positive near3 airway near3 pressure
10. (#7 OR #8 OR #9)
11. (#6 AND #10)

Database of Abstracts of Reviews of Effects (CRD administration database)

Searched 17/10/06. 66 records were retrieved.

1. s apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea
2. s sahs or shs or osas or osa
3. s s1 or s2
4. s cpap or apap or ncpap or autocpap
5. s positive(3w)airway(3w)pressure
6. s s4 or s5
7. s s3 and s6

Health Technology Assessment Database (CRD administration database)

Searched 17/10/06. 8 records were retrieved.

1. s apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea
2. s sahs or shs or osas or osa
3. s s1 or s2

4. s cpap or apap or ncpap or autocpap
5. s positive(3w)airway(3w)pressure
6. s s4 or s5
7. s s3 and s6

National Research Register (2006, issue 3)

(http://www.update-software.com/National/). Searched 17/10/06. 77 records were retrieved.

1. SLEEP APNEA SYNDROMES explode all trees (MeSH)
2. (apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea)
3. (sahs or shs or osas or osa)
4. (#1 or #2 or #3)
5. POSITIVE-PRESSURE RESPIRATION explode all trees (MeSH)
6. (cpap or apap or ncpap or autocpap)
7. (positive near airway near pressure)
8. (#5 or #6 or #7)
9. (#4 and #8)

Scottish Intercollegiate Guidelines Network

(http://www.sign.ac.uk). Searched 17/10/06. The website was scanned and 1 record was retrieved.

National Guideline Clearinghouse

(http://www.guideline.gov/). Searched 17/10/06. The following search terms were used. The results were scanned and 7 records were retrieved.

apnea
apnoea
hypopnea
hypopnoea
hypoapnea
hypoapnoea
sahs
shs
osas
osa

Health Services/Technology Assessment Text (HSTAT)

(http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat). Searched 17/10/06. The following search terms were used. The results were scanned and 1 record was retrieved.

apnea
apnoea
hypopnea
hypopnoea
hypoapnea
hypoapnoea

Turning Research into Practice Database (Trip)

(http://www.tripdatabase.com/). Searched 17/10/06. The following search terms were used. The results were scanned and 2 records were retrieved.

cpap or apap or ncpap or autocpap
apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea

Health Evidence Bulletins Wales

(http://hebw.cf.ac.uk/index.html). Searched 17/10/06. The website was scanned and 0 records were retrieved.

Clinical Evidence

(http://www.clinicalevidence.com). Searched 17/10/06. Chapters were scanned online and 8 records were retrieved.

National Library for Health Guidelines Finder

(http://www.library.nhs.uk/guidelinesfinder/). Searched 20/10/06. 1 record was retrieved.

apnea or apnoea
hypopnoea or hypopnea
hypoapnea or hypoapnoea

11.1.2 Searches for trials

MEDLINE (1966-November week 3 2006) (OVID)

Searched 29/11/06. 2346 records were retrieved

1. exp sleep apnea syndromes/
2. (apnea or apnoea).ti,ab.
3. (hypopnea or hypopnoea).ti,ab.
4. (hypoapnea or hypoapnoea).ti,ab.
5. sleep disordered breathing.ti,ab.
6. (sleep adj2 respirat$ disorder$).ti,ab.

7. sahs.ti,ab.
8. shs.ti,ab.
9. osa.ti,ab.
10. osas.ti,ab.
11. osahs.ti,ab.
12. or/1-11
13. exp positive-pressure respiration/
14. (positive adj3 airway adj3 pressure).ti,ab.
15. (cpap or ncpap or apap or bipap).ti,ab.
16. (c pap or bi pap or nc pap).ti,ab.
17. autocpap.ti,ab.
18. or/13-16
19. 12 and 18

MEDLINE In-Process & Other Non-Indexed Citations (November 28. 2006) (OVID)

Searched 29/11/06. 113 records were retrieved

1. (apnea or apnoea).ti,ab.
2. (hypopnea or hypopnoea).ti,ab.
3. (hypoapnea or hypoapnoea).ti,ab.
4. sleep disordered breathing.ti,ab.
5. (sleep adj2 respirat$ disorder$).ti,ab.
6. sahs.ti,ab.
7. shs.ti,ab.
8. osa.ti,ab.
9. osas.ti,ab.
10. osahs.ti,ab.
11. or/1-10
12. (positive adj3 airway adj3 pressure).ti,ab.
13. (cpap or ncpap or apap or bipap).ti,ab.
14. (c pap or bi pap or nc pap).ti,ab.
15. autocpap.ti,ab.
16. or/12-15
17. 11 and 16

EMBASE (1980-2006 week 47) (OVID)

Searched 29/11/06. 2744 records were retrieved.

1. Sleep Apnea Syndrome/

2. (apnea or apnoea).ti,ab.
3. (hypopnoea or hypopnea).ti,ab.
4. (hypoapnea or hypoapnoea).ti,ab.
5. Sleep Disordered Breathing/
6. sleep disordered breathing.ti,ab.
7. (sleep adj2 respirat$ disorder$).ti,ab.
8. sahs.ti,ab.
9. shs.ti,ab.
10. osa.ti,ab.
11. osas.ti,ab.
12. osahs.ti,ab.
13. or/1-12
14. positive end expiratory pressure/
15. (positive adj3 airway adj3 pressure).ti,ab.
16. (cpap or ncpap or apap or bipap).ti,ab.
17. (c pap or bi pap or nc pap).ti,ab.
18. autocpap.ti,ab.
19. or/14-18
20. 13 and 19

Cochrane Central Register of Controlled Trials (Cochrane Library 2006, issue 4)

(www.thecochranelibrary.com). Searched 29/11/06. 461 records were retrieved.

1. MeSH descriptor Sleep Apnea Syndromes explode all trees
2. apnea or apnoea
3. hypopnea or hypopnoea
4. hypoapnea or hypoapnoea
5. "sleep disordered breathing"
6. sleep near2 respirat* disorder*
7. sahs or shs or osa or osas or osahs
8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
9. MeSH descriptor Positive-Pressure Respiration explode all trees
10. positive near3 airway near3 pressure
11. cpap or ncpap or apap or bipap
12. c-pap or bi-pap or nc-pap
13. autocpap
14. (#9 OR #10 OR #11 OR #12 OR #13)
15. (#8 AND #14)

CINAHL (1982-November week 3 2006) (OVID)

Searched 29/11/06. 419 records were retrieved.

1. exp Sleep Apnea Syndromes/
2. (apnea or apnoea).ti,ab.
3. (hypopnea or hypopnoea).ti,ab.
4. (hypoapnea or hypoapnoea).ti,ab.
5. sleep disordered breathing.ti,ab.
6. (sleep adj2 respirat$ disorder$).ti,ab.
7. sahs.ti,ab.
8. shs.ti,ab.
9. osa.ti,ab.
10. osas.ti,ab.
11. osahs.ti,ab.
12. or/1-11
13. exp Positive Pressure Ventilation/
14. (positive adj3 airway adj3 pressure).ti,ab.
15. (cpap or ncpap or apap or bipap).ti,ab.
16. (c pap or bi pap or nc pap).ti,ab.
17. autocpap.ti,ab.
18. or/13-17
19. 12 and 18

Science Citation Index (1900-November 25 2006) (Web of Knowledge)

Searched 29/11/06. 2745 records were retrieved.

1. TS=(apnea or apnoea)
2. TS=(hypopnea or hypopnoea)
3. TS=(hypoapnea or hypoapnoea)
4. TS="sleep disordered breathing"
5. TS=(sahs or shs or osa or osas or osahs)
6. #1 or #2 or #3 or #4 or #5
7. TS=(positive same airway same pressure)
8. TS=(cpap or ncpap or apap or bipap)
9. TS=("c pap" or "nc pap" or "bi pap")
10. TS=autocpap
11. #7 or #8 or #9 or #10
12. #6 and #11

ISI Proceedings Science & Technology (1990-November 25 2006) (Web of Knowledge)

Searched 29/11/06. 407 records were retrieved.

1. TS=(apnea or apnoea)
2. TS=(hypopnea or hypopnoea)
3. TS=(hypoapnea or hypoapnoea)
4. TS="sleep disordered breathing"
5. TS=(sahs or shs or osa or osas or osahs)
6. #1 or #2 or #3 or #4 or #5
7. TS=(positive same airway same pressure)
8. TS=(cpap or ncpap or apap or bipap)
9. TS=("c pap" or "nc pap" or "bi pap")
10. TS=autocpap
11. #7 or #8 or #9 or #10
12. #6 and #11

Zetoc Conferences (1993-November 29 2006)

(http://zetoc.mimas.ac.uk/). Searched 29/11/06. 113 records were retrieved.

conference: autocpap

conference: bi pap

conference: c pap

conference: nc pap

conference: bipap

conference: apap

conference: ncpap

conference: cpap

conference: positive airway pressure

The records retrieved from this search in Zetoc were loaded into an endnote library and duplicates were removed. The following search was then carried out within that endnote library:

apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea

sleep or sahs or shs or osa or osas or osahs

SIGLE (1980-2005/03) (SilverPlatter)

Searched 29/11/06. 3 records were retrieved.

1. (apnea or apnoea) in ti,ab
2. (hypopnea or hypopnoea) in ti,ab

3. (hypoapnea or hypoapnoea) in ti,ab
4. sleep disordered breathing in ti,ab
5. (sleep near2 respirat* disorder*) in ti,ab
6. (sahs or shs or osa or osas or osahs) in ti,ab
7. #1 or #2 or #3 or #4 or #5 or #6
8. (positive near3 airway near3 pressure) in ti,ab
9. (cpap or ncpap or apap or bipap) in ti,ab
10. (c pap or bi pap or nc pap) in ti,ab
11. autocpap in ti,ab
12. #8 or #9 or #10 or #11
13. #7 and #12

Index to Theses (1716-October 16 2006)

(http://www.theses.com/). Searched 29/11/06. 14 records were retrieved.

1. (apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea or sleep) and (cpap or ncpap or apap or bipap or c pap or bi pap or nc pap or autocpap)
2. (apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea or sleep)and (positive airway pressure)
3. (sahs or shs or osa or osas or osahs) and (cpap or ncpap or apap or bipap or c pap or bi pap or nc pap or autocpap)
4. (sahs or shs or osa or osas or osahs) and (positive airway pressure)

NHS Economic Evaluation Database (NHS EED) (CRD internal administration system)

Searched 01/12/06. 24 records were retrieved.

1. s apnea or apnoea
2. s hypopnea or hypopnoea
3. s hypoapnea or hypoapnoea
4. s sleep(w)disordered(w)breathing
5. s sleep(2w)respirat$(w)disorder$
6. s sahs or shs or osa or osas or osahs
7. s s1 or s2 or s3 or s4 or s5 or s6
8. s positive(3w)airway(3w)pressure
9. s cpap or ncpap or apap or bipap
10. s c(w)pap or bi(w)pap or nc(w)pap
11. s autocpap
12. s s8 or s9 or s10 or s11
13. s s7 and s12

Health Economic Evaluations Database (HEED) (1995-November 2006) (CD-ROM)

Searched 01/12/06. 17 records were retrieved.

1. ax=apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea
2. ax=sleep and disorder*
3. ax=sahs or shs or osa or osas or osahs
4. cs=1 or 2 or 3
5. ax=positive and airway and pressure
6. ax=cpap or ncpap or apap or bipap or pap or autocpap
7. cs=5 or 6
8. cs=4 and 7

EconLit (1969-2006/10) (SilverPlatter)

Searched 01/12/06. 0 records were retrieved.

1. (apnea or apnoea) in ti,ab
2. (hypopnea or hypopnoea) in ti,ab
3. (hypoapnea or hypoapnoea) in ti,ab
4. sleep disordered breathing in ti,ab
5. (sleep near2 respirat* disorder*) in ti,ab
6. (sahs or shs or osa or osas or osahs) in ti,ab
7. #1 or #2 or #3 or #4 or #5 or #6
8. (positive near3 airway near3 pressure) in ti,ab
9. (cpap or ncpap or apap or bipap) in ti,ab
10. (c pap or bi pap or nc pap) in ti,ab
11. autocpap in ti,ab
12. #8 or #9 or #10 or #11
13. #7 and #12

EconPapers (http://econpapers.repec.org/)

Searched 01/12/06. The search results were scanned and 0 records were retrieved.

apnea

apnoea

hypopnea

hypopnoea

hypoapnea

hypoapnoea

sleep and disorder*

11.1.3 Cost-effectiveness searches

The following databases were searched for economic evaluations of sleep apnoea.

NHS Economic Evaluation Database (NHS EED) (CRD internal administration system)

Searched 13/1/07. 42 records were retrieved.

S sleep(w)apn$

S apn$

S hypoapn$

S sleep(w)disordered(w)breathing

S sleep(2w)respirat$(2w)disorder$

S sahs or shs or osa or osas or soahs

S s1 or s2 or s3 or s4 or s5 or s6

Health Technology Assessment Database (CRD administration database)

Searched 13/1/07. 8 records were retrieved.

S sleep(w)apn$

S apn$

S hypoapn$

S sleep(w)disordered(w)breathing

S sleep(2w)respirat$(2w)disorder$

S sahs or shs or osa or osas or soahs

S s1 or s2 or s3 or s4 or s5 or s6

S econ$ or cost$

S s7 and s8

Health Economic Evaluations Database (HEED) (1995-January 2007) (CD-ROM)

Searched 13/1/07. 70 records were retrieved.

Apn* or hypoapn*

'Sleep disordered' within 3

sahs or shs or osa or osas or soahs

IDEAS http:\\ideas.repec.org

Searched 13/1/07. 0 records were retrieved.

Apnoea or apnea or hypoapnoea or hypoapnea

MEDLINE (1950 to Jan 10 2007) (OVID)

Searched 13/1/07. 494 records were retrieved.

1 exp sleep apnea syndromes/ (12843)

2 (apnea or apnoea).ti,ab. (17402)

3 (hypopnea or hypopnoea or hypoapnea or hypoapnoea).ti,ab. (2515)

4 sleep disordered breathing.ti,ab. (1603)

5 (sleep adj2 respirat$ disorder$).ti,ab. (154)

6 (sahs or shs or osa or osas or osahs).ti,ab. (4375)

7 or/1-6 (21688)

8 economics/ (24617)

9 exp "costs and cost analysis"/ (125794)

10 economic value of life/ (4779)

11 economics, medical/ (6672)

12 economics,nursing/ (3725)

13 (econom$ or cost or costs or costly or costing or prices or pricing or pharmacoeconomic$).ti,ab. (239906)

14 (expenditure$ not energy).ti,ab. (10278)

15 (value adj3 money).ti,ab. (472)

16 budget$.ti,ab. (10745)

17 or/8-16 (337377)

18 7 and 17 (521)

19 (letter or editorial or historical-article).pt. (1006834)

20 18 not 19 (504)

21 animals/ not (humans/ and animals/) (3010245)

22 20 not 21 (494)

EMBASE (1980-2007 week 1) (OVID)

Searched 13/1/07. 569 records were retrieved.

1 sleep apnea syndrome/ (11977)

2 (apnea or apnoea).ti,ab. (15034)

3 (hypopnoea or hypopnea or hypoapnea or hypoapnoea).ti,ab. (2219)

4 sleep disordered breathing/ (484)

5 sleep disordered breathing.ti,ab. (1555)

6 (sleep adj2 respirat$ disorder$).ti,ab. (100)

7 (sahs or shs or osa or osas or osahs).ti,ab. (3866)

8 or/1-7 (19042)
9 health economics/ (8941)
10 exp economic evaluation/ (84200)
11 exp health care cost/ (85556)
12 exp pharmacoeconomics/ (44276)
13 (econom$ or cost or costs or costly or costing or prices or pricing or pharmacoeconomic$).ti,ab. (189706)
14 (expenditure$ not energy).ti,ab. (8248)
15 (value adj3 money).ti,ab. (376)
16 budget$.ti,ab. (7647)
17 or/9-16 (280800)
18 8 and 17 (655)
19 (letter or editorial or note).pt. (712099)
20 18 not 19 (586)
21 ((energy or oxygen) adj3 (cost or expenditure$)).ti,ab. (10286)
22 (metabolic adj3 cost$).ti,ab. (502)
23 exp animal/ or exp animal experiment/ (1206737)
24 (rat or rats or mouse or mice or hamster$ or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (1857239)
25 or/21-24 (2100839)
26 20 not 25 (569)

11.1.4 Searches to inform the model

All searches were conducted in Ovid Medline.

Traffic accidents and cardiovascular events

The following strategy was used to identify literature linking traffic accidents and cardiovascular events (particularly stroke and coronary heart disease) to sleep apnoea.

MEDLINE (In-Process & Other Non-Indexed Citations and MEDLINE 1950 to Present). Searched 15/1/07

1 Accidents, Traffic/
2 road accidents.ti,ab.
3 traffic accidents.ti,ab.
4 (stroke or strokes).ti,ab.
5 (chd or cardiovascular disease).ti,ab.
6 exp heart diseases/ or exp vascular diseases/

7 exp Cerebrovascular Accident/
8 or/1-7
9 exp sleep apnea syndromes/
10 8 and 9
11 ep.fs.
12 10 and 11
13 limit 12 to yr="1990 - 2007"

The results of set 13 were scanned for epidemiological records and sets of selected records were downloaded

Quality of life studies

The following strategy was used to identify quality of life studies/utilities studies in Medline.

MEDLINE (In-Process & Other Non-Indexed Citations and MEDLINE 1950 to Present). Searched 8/7/07.

1 exp sleep apnea syndromes/
2 (apnea or apnoea).ti,ab.
3 (hypopnea or hypopnoea).ti,ab.
4 (hypoapnea or hypoapnoea).ti,ab.
5 sleep disordered breathing.ti,ab.
6 (sleep adj2 respirat$ disorder$).ti,ab.
7 (sahs or shs or osa or osas or osahs).ti,ab.
8 or/1-7
9 quality of life/
10 (quality adj2 life).ti,ab.
11 utility.ti,ab.
12 utilities.ti,ab.
13 standard gamble.ti,ab.
14 tto.ti,ab.
15 (time tradeoff or time trade off).ti,ab.
16 (eq or euroqol).ti,ab.
17 osa 18.ti,ab.
18 sf 36.ti,ab.
19 sgrq.ti,ab.
20 respiratory questionnaire.ti,ab.
21 practical sleep scale.ti,ab.
22 sleep scale.ti,ab.
23 scopa.ti,ab.

24 objective daytime sleepiness.ti,ab.
25 oxford sleep resistance.ti,ab.
26 osler test.ti,ab.
27 stai.ti,ab.
28 emotional control scale.ti,ab.
29 cecs.ti,ab.
30 life orientation test.ti,ab.
31 satisfaction with life scale.ti,ab.
32 swls.ti,ab.
33 calgary sleep apnea quality.ti,ab.
34 (functional outcomes adj2 sleep).ti,ab.
35 osa patient oriented severity.ti,ab.
36 osa18.ti,ab.
37 cohen$ pediatric osa.ti,ab.
38 (comment or letter or editorial).pt.
39 or/9-37
40 8 and 39
41 40 not 38
42 limit 41 to yr="2000 - 2007"
43 limit 42 to english language (491)

491 records were downloaded (set 43) and assessed for relevance.

Rates of road accidents

Searches for recent studies on rates of road accidents were undertaken using the strategy described by Ayas NT and colleagues in their meta-analysis of all studies that examined MVC rates in patients with OSAH before and after CPAP.[122] Ayas and colleagues' reported their search as follows: "A comprehensive search of MEDLINE (1966 to March 2005) using Ovid was conducted using the following exploded MESH terms: *sleep apnea syndromes* AND *positive pressure respiration* OR *continuous positive airway pressure* AND *automobile driving* OR *accident*."

This search was rerun in Ovid Medline (1950 to 2007 March week 1) and included searches of in process citations. The search results were limited to those added to Medline since February 2005 to ensure no records were missed. The correct MeSH term ACCIDENTS was used rather than the term ACCIDENT noted by Ayas and colleagues, on the assumption that this was a transcription error in their paper.

8 new records were identified.

1 exp sleep apnea syndromes/
2 exp positive pressure respiration/
3 exp continuous positive airway pressure/
4 1 and (2 or 3)
5 exp automobile driving/
6 exp accidents/
7 5 or 6
8 4 and 7
9 200503$.ep.
10 (200504$ or 200505$ or 200506$ or 200507$ or 200508$ or 200509$ or 20051$).ep.
11 (2006$ or 2007$).ep.
12 (200503$ or 200504$ or 200505$ or 200506$ or 200507$ or 200508$ or 200509$ or 20051$).ed.
13 (2006$ or 2007$).ed.
14 or/9-13
15 8 and 14 (8)

Search for data on life expectancy for individuals who have suffered a stroke

Ovid Medline (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>) was searched on 27 April 2007 for a known paper on post-stroke life expectancy by Dennis and Burn.[164] Once identified, the 'Find similar' option was selected and also the citing papers option to identify similar records. After assessing those references for relevance a series of searches was undertaken and the results in set 5, 11, 12, 15, 17, 22 and 24 were assessed to identify further relevant studies.

1 dennis $.au. and stroke.ti. (130)
2 burn $.au. (1073)
3 1 and 2 (6)
4 find similar to Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. (76)
5 find similar to Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. (76)
6 from 5 keep 2-3,5-6 (4)
7 *cerebrovascular disorders/ (27223)
8 *survival rate/ (335)
9 7 and 8 (0)
10 stroke$1.ti. (30599)
11 8 and 10 (2)

12 (7 or 10) and survival rate/ (634)
13 from 12 keep 4,8,14,17,33,44,81,109,132-134,148,159 (13)
14 *cerebrovascular accident/ (16575)
15 8 and 14 (2)
16 14 and survival rate/ (386)
17 16 not 13 (375)
18 cerebrovascular accident/ (22109)
19 survival rate/ (77068)
20 survival analysis/ (59922)
21 exp great britain/ (220221)
22 18 and (19 or 20) and 21 (48)
23 stroke register.ti,ab. (162)
24 23 and 21 (33)

Google was searched (27/4/07) using the following search terms.

Life expectancy stroke

Stroke life expectancy

Life tables stroke

11.2 Excluded studies

Study	Reason(s) for exclusion				
	Appropriate intervention[a]	**Relevant comparator[b]**	**Appropriate study design[c]**	**Appropriate participants[d]**	**Appropriate outcome measures[e]**
1992[175]	No	No	No	No	No
1997[176]	No	No	No	Yes	No
2002[177]	No	Yes	No	Yes	Yes
Abe 2005[178]	No	No	No	Yes	No
Adlakha 2006[179]	No	No	No	Yes	No
Ahmed 2005[180]	Yes	No	No	Yes	Yes
Akashiba 1993[181]	No	No	No	Yes	Yes
Almirall 2005[182]	Yes	No	No	Yes	Yes
Anonymous 2003[183]	No	No	No	No	No
Antic 2006[184]	Yes	No	No	Yes	Yes
Ayas 2006[185]	No	No	No	No	No
Babar 2003[186]	No	No	No	No	No
Badia 1997[187]	Yes	Yes	Unclear	Yes	Yes
Bakshi 2005[188]	No	No	No	Yes	No
Barry 1999[189]	No	No	No	No	No
Becker 1989[190]	No	No	No	Yes	No
Becker 1995[191]	No	No	No	Yes	No
Beecroft 2003[192]	Yes	No	No	Yes	Yes
Berka 2006[193]	No	No	No	Yes	Yes
Bloch 2006[194]	No	No	No	No	No
Bradley 1990[195]	No	No	No	No	No
Braghiroli 1998[196]	No	No	No	No	No
Buechner 2001[197]	No	No	No	Yes	Yes
Buttner 2004[198]	Yes	No	No	Yes	Yes
Castronovo 2003[199]	Yes	No	No	Yes	Yes
Chakravorty 1998[200]	Yes	No	No	Yes	Yes
Chasens 2003[201]	Yes	No	No	Yes	Yes
Chazan 2004[202]	Yes	No	No	Yes	No
Chrysostomakis 2004[203]	No	No	No	Yes	No
Ciftci 2005[204]	Yes	No	No	No	Yes
Clark 1996[149]	Yes	Yes	No	Yes	Yes
Deegan 1995[205]	No	No	No	No	No
Dhillon 2003[206]	Yes	No	No	Yes	Yes
Donadio 2006[207]	Yes	Yes	No	Yes	Yes
Dorkova 2006[208]	No	No	No	Yes	Yes
Douglas 1998[209]	No	No	No	No	No
Douglas 2004[210]	No	No	No	No	No

Drummond 2005[211]	Yes	Yes	Yes	No	Yes
Engleman 1993[212]	Yes	Yes	No	Yes	Yes
Engleman 2002[213]	No	No	No	No	No
Fairbairn 2006[214]	Yes	Yes	No	Yes	Yes
Ficker 1997[215]	No	No	Yes	Yes	Yes
Ficker 2002[216]	Yes	No	Yes	Yes	Yes
Fitzpatrick 2005[217]	No	Yes	Yes	No	No
Flemons 1998[218]	Yes	Yes	Yes	Yes	Yes
Fletcher 2000[219]	No	No	No	No	No
Gagnadoux 2006[220]	No	No	No	No	No
Golish 2000[221]	No	No	No	No	No
Goncalves 2005[222]	Yes	No	No	Yes	Yes
Gotsopoulos 2002[223]	No	No	Yes	Yes	Yes
Grimm 2000[224]	Yes	No	No	No	Yes
Hahn 2003[225]	No	No	No	Yes	Yes
Hermida 2003[226]	Yes	Yes	No	Yes	Yes
Hermida 2003[227]	Yes	Yes	No	Yes	Yes
Hermida 2004[228]	Yes	Yes	No	Yes	Yes
Hernandez 1999[229]	Yes	Yes	Yes	Yes	No
Hetzel 1994[230]	Yes	No	No	Yes	Yes
Hira 1998[231]	Yes	Yes	No	Yes	Yes
Hirshkowitz 2005[232]	No	No	No	No	No
Hla 2002[233]	Yes	No	No	No	Yes
Hoster 1995[234]	No	No	Yes	Yes	No
Huang 2001[235]	No	No	Unclear	No	Yes
Iellamo 2006[236]	No	No	No	No	No
Itzhaki 2006[237]	Yes	No	No	Yes	Yes
Jenkinson 2001[144]	Yes	Yes	Yes	No	Yes
Juhasz 1997[238]	No	No	Yes	Yes	No
Kajaste 2004[239]	Yes	Yes	Yes	Yes	Yes
Kaleth 2003[240]	Yes	No	No	Yes	No
Kaleth 2005[241]	Yes	No	Yes	Yes	No
Karacan 1995[242]	No	No	No	Yes	Yes
Kiely 1999[243]	Yes	No	No	Yes	Yes
Konermann 1995[244]	Yes	No	No	Yes	Yes
Krieger 1986[245]	No	No	No	No	Yes
Lafond 2005[246]	Yes	No	No	Yes	Yes
Lafond 2007[247]	No	No	Yes	Yes	Yes
Lewis 2002[248]	Yes	No	No	Yes	Yes
Li 2004[249]	Yes	Unclear	Yes	No	Yes
Litvin 2006[250]	No	No	No	Yes	No
Logan 2003[251]	Yes	No	No	Yes	Yes

Mador 2005[252]	Yes	No	Yes	Yes	Yes
Malow 2005[253]	Yes	Yes	Yes	Yes	No
Marrone 1990[254]	No	No	No	Yes	No
Marshall 2004[255]	Yes	No	No	Yes	Yes
Mayer 1993[256]	No	No	Yes	Yes	Yes
McArdle 2001[257]	Yes	Yes	Yes	Yes	No
McEvoy 1984[258]	Yes	No	No	Yes	Yes
McFadyen 2001[259]	Yes	Yes	No	Yes	Yes
McNab 2006[260]	No	No	No	Yes	Yes
Morrish 2004[261]	No	No	No	Yes	No
Mulgrew 2007[262]	Yes	No	Yes	Yes	Yes
Nagasaka 1997[263]	No	Yes	No	Yes	No
Newsom-Davis 2001[264]	No	No	No	No	Yes
Nooman 1998[265]	No	No	No	Yes	Yes
Pepin 2006[266]	Yes	Yes	Unclear	Yes	No
Phillips 1990[267]	Yes	No	Unclear	Yes	Yes
Poluektov 1994[268]	No	No	No	No	No
Risk 2004[269]	No	No	No	Yes	Yes
Rosenthal 2003[270]	Yes	No	No	Yes	Yes
Rosenthal 2006[271]	No	No	No	Yes	Yes
Sakakibara 2005[272]	No	No	No	No	No
Sanders 1998[273]	No	No	No	No	No
Sanders 2001[274]	No	No	No	No	No
Sanner 2000[275]	Yes	Yes	No	Yes	Yes
Sanner 2003[276]	Yes	No	No	Yes	Yes
Schutte-Rodin 2006[277]	No	No	No	No	No
Seiler 1998[278]	Yes	No	Yes	Yes	Yes
Shadan 2006[279]	Yes	No	No	Yes	No
Shimizu 2003[280]	Yes	No	No	Yes	No
Skomro 2003[281]	Yes	No	No	No	Yes
Smith 2005[282]	Yes	No	No	Yes	Yes
Stammnitz 1993[283]	No	No	No	Yes	Yes
Stoohs 1993[284]	Yes	No	No	Yes	No
Suhner 2003[285]	Yes	No	No	Yes	Yes
Veale 2003[286]	Yes	No	No	Yes	Yes
Verbraecken 2002[287]	Yes	Unclear	No	No	No
Voronin 2002[288]	No	Yes	No	No	Yes
Weaver 2004[289]	Yes	Yes	Yes	Yes	No
Weisfogel 2003[290]	Yes	No	No	No	Yes
Weissenberg 1994[291]	No	No	No	Yes	Yes
Westbrook 1990[292]	No	No	No	No	No
Westbrook 2004[293]	Yes	No	No	Yes	Yes

Wiest 1998[294]	No	No	No	No	No
Woodson 2003[295]	Yes	No	Yes	Yes	Yes
Woodson 2003[296]	Yes	No	Yes	Yes	Yes
Worsnop 1994[297]	Yes	Yes	Yes	No	Yes
Yen 1997[298]	Yes	No	No	Yes	No
Zimmerman 2005[299]	Yes	No	No	Yes	Yes

a. Does the study look at CPAP/APAP devices, and does the intervention last ≥ than 1 week?
b. Does the study have relevant comparators (placebo/sham treatment/no treatment or oral devices)?
c. Is the study a randomised controlled trial (RCT)?
d. Does the study include participants with OSAHS, ≥ 16 years old, that do not specifically relate to a population with either brain disease, heart failure or chronic airways disease?
e. Does the study look at subjective daytime sleepiness, objective daytime sleepiness, subjective health status, blood pressure, AHI, oxygen desaturation > 4%, driver simulation tests or other psychometric assessments

11.3 Quality assessment

	Was the method used to assign participants to treatment groups or the sequence of treatments really random?	Was treatment allocation concealed?	Were the groups similar at baseline in terms of ESS and AHI?	If not, were adjustments made for differences baseline	Did the analysis include an intention to treat analysis?	Were appropriate methods used to account for missing data in the intention to treat analysis?	What proportion of participants was lost to follow-up for the primary outcomes?	Was the study described as blind or double blind?	Who was blinded?	*Studies using sham CPAP as comparator*	Was the study parallel design?	Were the participants CPAP naïve?	*Crossover trials*	Was an appropriate analysis using paired data performed?	Was there a treatment by period interaction?
Arias 2005[56]	?	?	?	X	X	NA	7.4%	√	Participants	√	X	√	√	√	X
Arias 2006[63]	√	?	?	NA	X		8.7%	√	Participants	√	X	√	√	X	?
Ballester 1999 [96]	?	?	√	NA	?	NA	NR	X	NA	NA	√	?	X	NA	NA
Barbe 2001 [83]	√	?	√	NA	X(1 not included)	NA	1.8%	√	Participants. Psychologist administered tests	√	√	?	X	NA	NA
Barnes 2002 [82]	√	X	?	NA	√	√	23%	X	Staff administering psychometric tests	NA	X	?	√	√	X
Barnes 2004 [89]	√	X	?	NA	X (14 not included)	NA	33.30%	X	Staff administering psychometric tests	NA	X	?	√	√	√ (ESS)
Becker 2003 [109]	?	√	√	NA	X (28 not included)	NA	46.60%	X	NA	√	√	?	X	NA	NA
Campos-Rodriguez et al 2006[65]	?	X	√	NA	X (4 not included)	NA	5.6%	√	Participants, outcome assessor and nurse following CPAP monitors	√	√	√	X	NA	NA
Chakrovarty 2002[97]	?	?	?[e]	NA	X (18 not included)	NA	25.40%	X	NA	NA	√	?	X	NA	NA
Cibele 2006 [72]	?	?	?	NA	?	NA	?	√	?	NA	X	?	√	?	?

Coughlin et al 2007[62]	√	√	?	NA	X (1 not included)	NA	2.3%	√	Participants and investigators	√	X	√	√	√	X
Cross 2005[88]	?	?	?	NA	?	NA	NR	√	Participants and outcome assessors	√	X	?	√	?	?
Dimsdale 2000[58]	√	X[g]	√ (RDI)	NA	X	NA	?	√	Participants and investigators (not involved with CPAP titration)	√	√	√	X	NA	NA
Drager 2006[69]	?	?	?	?	?	?	?	√	Outcome assessors	NA	√	?	X	NA	NA
Engleman 2002[103]	?	?	?	NA	X (3 not included)	NA	5.8%	√	Staff scoring sleep data	NA	X	?	√	√	?
Engleman 1999[78]	?	?	?	NA	X (3 not included and 2 additional for PASAT)	NA	8.1%	X		NA	X	?	√	√	X
Engleman 1998[93]	?	?	?	NA	X (1 not included)	NA	4.3%[b]	√		NA	X	?	√	√	√ (ESS)[d]
Engleman 1997[92]	?	?	?	NA	X (2 not included)	NA	11.1%	X		NA	X	?	√	√	√ (MSLT)
Engleman 1996[91]	?	?	?	NA	X (3 not included)	NA	18.8%	X	NA	NA	X	?	√	√	?
Engleman 1994[90]	?	?	?	NA	X (3 not included)	NA	8.6%	X	NA	NA	X	?	√	√	√ (PASAT 2)[d]
Faccenda 2001[94]	√	?	?	NA	X (3 not included)	NA	4.20%	X	NA	NA	X	?	√	√	
Ferguson 1996[81]	?	?	√ (AHI)	NA	X (2 not included)	NA	7.40%	X	NA	NA	X	?	√	√	X
Ferguson 1997[80]	?	?	√	NA	X (4 not included)	NA	16.7%	X	NA	NA	X	?	√	√	X
Fleetham 1998[50]	?	?	√	NA	?	?	?	X	NA	NA	√	?	A	NA	NA
Henke 2001[85]	?	?	√	NA	X (10 not included)	NA	22.2%[c]	√	Participants, Staff who had contact with participants	√	Partial cross-over	?	X	NA	NA
Hoekema 2006[102]	√	?	√	NA	√	?	None reported	NA	NA	NA	√	NA	X	NA	NA
Hui 2006[64]	√	?	√	NA	X (10 not included)	NA	17.9%	√	Participants and	√	√	√	X	NA	NA

									outcome assessors						
Jenkinson 1999[77]	√	√	√	NA	?	NA	5.60%	√	Patients and staff scoring and administering	√	√	√	X	NA	NA
Jokik 1999[108]	?	?	?	NA	X (1 not included)	NA	0%	√	Staff scoring sleep data and administering psychometric tests	NA	X	?	√	Yes	?
Lam 2006[70]	√	?	√	NA	X (10 not included)	NA	9.9%	X	NA	NA	√	?	X	NA	NA
L'Estrange 1999[104]	?	?	NA	?	?	NA	40%	X	NA	NA	X	?	√	?	?
Lim 2005[110]	?	?	√	NA	?	NA	?	X	NA	NA	√	?	X	NA	NA
Lojander 1996[99]	?	?	√	NA	X (5 not included, 4 not analysed as per protocol)	NA	33.30%	X	NA	NA	√	?	X	NA	NA
Marshall 2005[79]	√	X	?	NA	X (2 not included)	NA	6.4%	√	Participants Investigator collecting daytime data	√	X	√	√	√	X
McArdle 2001[95]	√	√	?	NA	?	NA	4.30%	X	NA	NA	X	?	√	√	X
Monasterio 2001[100]	√	?	√	NA	X (17 not included)	NA	12%	√	Staff who did data entry and analysis	NA	√	?	X	NA	NA
Montserrat 2001[86]	√	?	√ (AHI)	NA	X (2 not included)	NA	4.30%	√	Patients and interviewers	√	√	?	X	NA	NA
Norman 2006[73]	√	X[g]	√ CPAP had higher baseline SBP than control	√	X	NA	?	√	Participants and investigators (not involved with CPAP titration)	√	√	√	X	NA	NA

Olson 2002[107]	?	?	?	?	?	?	?	X	NA	X	Partial crossover	√	√	?	?
Pepperell 2002[87]	?	√	√	NA	√	√	11.9%	√	Patients and investigators	√	√	?	X	NA	NA
Randerath 2002[105]	?	?	√ (AHI)	NA	?	NA	NR	X	NA	NA	X	?	√	X	?
Redline 1998[59]	√	?	√ (ESS)	NA	X (14 not included)	NA	12.6%	NA	NA	NA	√	?	X	NA	NA
Robinson 2006[68]	?	X[g]	?	?	?	NA	8.6%	√	Participants and outcome assessors	√	X	?	√	√	X
Skinner 2004a[60]	?	?	?	NA	X (1 not included)	NA	7.1%	X	NA	NA	X	√	√	√	?
Skinner 2004b[61]	?	Un-clear	Unclear	NA	√	NA	0%	X	NA	NA	X	√	√	√	X
Spicuzza 2006[66]	?	?	√ (AHI not assessed)	NA	?	?	NR	?	Participants and clinical staff in contact with them	√	√	√	X	NA	NA
Tan 2002[106]	?	?	?	NA	√ (3 not included)	?	12.50%	X	NA	√	X	?	√	√	X
West 2006[67]	√	?	√	NA	X (1 participant received a defective machine delivering minimal pressure; data were included in sham CPAP group)	NA	4.8%	√	Participants and investigators	√	√	√	X	NA	NA

[b] The one patient who dropped out was replaced by the next available recruit; [c] Six dropped out and 4 completed the study but were dropped from the analysis as the polysomnogram was conducted at the incorrect time [d] an unpaired comparison of first treatment assessment period was conducted based on the evidence of carryover for this variable; [e] AHI seemed higher in CPAP group though both fell into the severe category, ESS was similar; [f] partial crossover, only data from parallel phase used; [G] although pre-sealed, opaque envelopes used, they were not sequentially numbered.

√ yes, meets criteria; X no, does not meet criteria; ? unclear whether meets criteria

11.4 Clinical effectiveness – additional tables

Table 11.1 Sub-group analysis for the Epworth Sleepiness Scale (CPAP versus placebo/usual care)

	Number of trials	**Random effects Mean difference (95% CI)**	**Fixed effect Mean difference (95% CI)**	**Statistical heterogeneity (I^2)**
Baseline ESS				
Mild (0-9)	2		-1.1 (-1.8, -0.3)	0%
Moderate (10-15)	16	-2.3 (-3.0, -1.6)	-2.1 (-2.6, -1.7)	51%
Severe (16-24)	5	-5.0 (-6.5, -3.5)	-5.0 (-6.1, -4.0)	46%
Baseline AHI				
Mild (AHI 5-14)	3	-1.5 (-3.4, 0.4)		36%
Moderate (AHI 15-30)	7	-2.0 (-3.0, -1.1)		65%
Severe (AHI >30)	13	-3.4, (-4.6, -2.3)		71%
Study design				
Crossover	7	-2.0 (-4.5, -1.7)		36%
Parallel	13	-3.5 (-4.8, -2.3)		73%
Change data	3 (2 parallel and one crossover)	-1.5 (-2.6, -0.4)		
Comparator				
Sham CPAP	12	-3.0 (-4.2, -1.9)		36%
Oral placebo	6	-2.1 (-3.5, -0.8)		63%
Conservative/usual care	5	-2.7 (-4.1, -1.3)		56%

Figure 11.1 Epworth Sleepiness Scale (CPAP versus sham CPAP) stratified by severity of sleepiness at baseline (ESS)

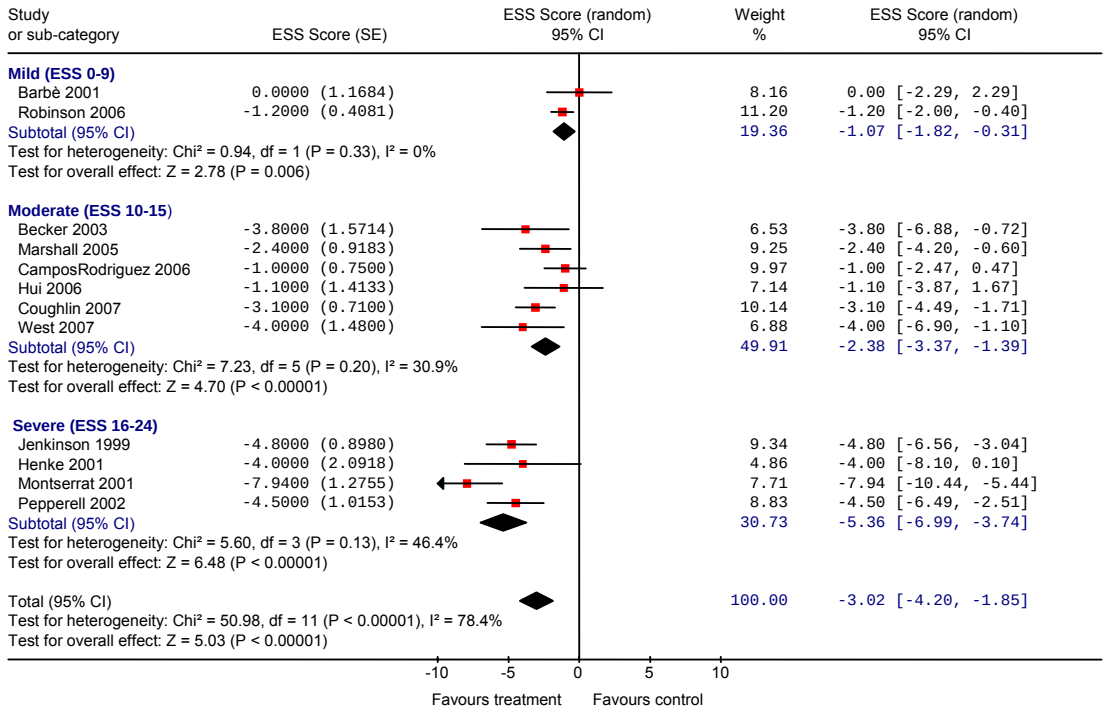


Table 11.2 Removal of individual studies from the Epworth Sleepiness Scale meta-analysis (CPAP versus placebo/usual care)

Baseline symptom severity		**Overall treatment effect Mean difference (95% CI)**	**Statistical heterogeneity (I^2)**
Mild (ESS 0-9)			
	Barbe 2001	0.0 (-2.3, 2.3)	
	Robinson 2006	-1.2 (-2.0, -0.4)	
Moderate (ESS 10-15)			
Study removed	Ballester 1999	-2.1 (-2.8, -1.5)	41%
	Engleman 1997	-2.4 (-3.1, -1.7)	52%
	Engleman 1998	-2.2 (-2.8, -1.5)	42%
	Redline 1998	-2.5 (-3.2, -1.7)	50%
	Engleman 1999	-2.3 (-3.0, -1.6)	53%
	Faccenda 2001	-2.3 (-3.1, -1.6)	54%
	Monasterio 2001	-2.4 (-3.1, -1.6)	54%
	Barnes 2002	-2.4 (-3.2, -1.7)	52%
	Becker 2003	-2.3 (-3.0, -1.6)	52%
	Barnes 2004	-2.5 (-3.2, -1.8)	46%

Baseline symptom severity		**Overall treatment effect**	**Statistical heterogeneity (I^2)**
		Mean difference (95% CI)	
	Marshall 2005	-2.3 (-3.1, -1.6)	54%
	Campos-R 2006	-2.5 (-3.2, -1.7)	50%
	Hui 2006	-2.4 (-3.1, -1.7)	53%
	Lam 2006	-2.3 (-3.0, -1.6)	54%
	Coughlin 2007	-2.3 (-3.0, -1.5)	51%
	West 2007	-2.3 (-3.0, -1.5)	52%
Severe (ESS 14-24)			
Study removed	Jenkinson 1999	-5.0 (-7.2, -2.8)	59%
	Henke 2001	-5.1 (-6.9, -3.4)	58%
	Montserrat 2001	-4.4 (-5.5, -3.2)	0%
	Chakravorty 2002	-5.4 (-7.0, -3.7)	46%
	Pepperell 2002	-5.1 (-7.2, -3.0)	58%

Table 11.3 Sub-group analysis for the Epworth Sleepiness Scale (CPAP versus dental devices)

	Number of trials	**Random effects Mean difference (95% CI)**	**Fixed effect Mean difference (95% CI)**	**Statistical heterogeneity (I^2)**
Baseline ESS				
Mild (0-9)				
Moderate (10-15)	6	-0.9 (-2.1, 0.4)	-0.5 (-1.3, 0.2)	0%
Severe (16-24)				
Baseline AHI				
Mild (AHI 5-14)	0			
Moderate (AHI 15-30)	4	-0.2 (-1.1, 0.7)		0%
Severe (AHI >30)	2	-1.8 (-6.0, 2.3)		88%
Study design				
Crossover	4	-1.0 (-1.1, 0.7)		72%
Parallel	2	-0.6 (-2.7, 1.5)		41%

Table 11.4 Removal of individual studies from the Epworth Sleepiness Scale meta-analysis (CPAP versus dental devices)

Baseline symptom severity		**Overall treatment effect**	**Statistical heterogeneity (I^2)**
		Mean difference (95% CI)	
Moderate (ESS 10-15)			
Study removed	Ferguson 1997	-1.2 (-2.7, 0.4)	65%
	Engleman 2002	-0.1 (-0.9, 0.6)	0%
	Tan 2002	-0.9 (-2.3, 0.6)	68%
	Barnes 2004	-1.2 (-2.8, 0.5)	64%
	Fleetham 2002	-1.1 (-2.7, 0.4)	66%
	Lam 2006	-0.7 (-2.1, 0.7)	65%

Table 11.5 Sub-group analysis for Maintenance of Wakefulness Test (CPAP versus placebo/usual care)

	Number of trials	Random effects Mean difference (95% CI)	Fixed effect Mean difference (95% CI)	Statistical heterogeneity (I^2)
Baseline ESS				
Mild (0-9)	0			
Moderate 10-15)	4	2.3 (0.4, 4.3)	2.3 (0.4, 4.3)	0%
Severe (16-24)	1	6.5 (2.6, 10.4)	6.5 (2.6, 10.4)	
Overall effect		3.3 (1.3, 5.3)	3.2 (1.4, 5.0)	11.3%
Baseline AHI				
Mild (AHI 5-14)	1	1.8 (-2.8, 6.4)		
Moderate (AHI 15-30)	3	4.1 (01.0, 7.3)		50%
Severe (AHI >30)	1	1.9 (-6.2, 10.0)		
Study design				
Crossover	3	2.4 (0.3, 4.4)		0%
Parallel	2	5.6 (2.1, 9.2)		0%

Table 11.6 Removal of individual studies from the Maintenance of Wakefulness Test meta-analysis (CPAP versus placebo/usual care)

		Overall treatment effect Mean difference (95% CI)	Statistical heterogeneity (I^2)
Study removed	Engleman 1999	3.8 (1.2, 6.3)	27%
	Barnes 2004	4.4 (1.9, 6.9)	0%
	Marshall 2005	3.1 (0.8, 5.5)	25%
	West 2007	3.5 (1.1, 5.9)	32%
	Jenkinson 1999	2.3 (0.4, 4.3)	0%

Table 11.7 Sub-group analysis for Multiple Sleep Latency Test (CPAP versus placebo/usual care)

	Number of trials	Random effects Mean difference (95% CI)	Fixed effect Mean difference (95% CI)	Statistical heterogeneity (I^2)
Baseline ESS				
Mild (0-9)	1	2.0 (-0.8, 4.8)		
Moderate 10-15)	4	0.2 (-1.8, 2.2)		69%
Severe (16-24)	1	-6.1 (-27.3, 15.1)		
Not reported	1	1.1 (-0.8, 3.0)		
Overall effect		0.6 (-0.7, 1.9)	0.8 (-0.1, 1.6)	46%
Baseline AHI				
Mild (AHI 5-14)	2	-0.7 (-2.9, 1.4)		0%
Moderate (AHI 15-30)	2	0.0 (-2.1, 2.1)		60%
Severe (AHI >30)	3	2.3 (0.9, 3.7)		0%
Study design				
Crossover	4	1.0 (-0.6, 2.5)		45%
Parallel	3	0.2 (-2.4, 2.7)		43%

Table 11.8 Removal of individual studies from the Multiple Sleep Latency Test meta-analysis (CPAP versus placebo/usual care)

		Overall treatment effect	
		Mean difference (95% CI)	**Statistical heterogeneity (I^2)**
Study removed	Barbe 2001	0.4 (-1.1, 1.9)	52%
	Engleman 1997	0.7 (-0.8, 2.1)	55%
	Engleman 1998	0.0 (-1.0, 1.2)	9%
	Monasterio 2001	1.2 (0.0, 2.4)	19%
	Barnes 2002	0.9 (-0.4, 2.3)	45%
	Chakrovarty 2002	0.7 (-0.7, 2.0)	54%
	Engleman 1994	0.5 (-1.2, 2.2)	55%

Table 11.9 Sub-group analysis for daytime mean arterial pressure (CPAP versus placebo/usual care)

	Number of trials	**Random effects Mean difference (95% CI)**	**Fixed effect Mean difference (95% CI)**	**Statistical heterogeneity (I^2)**
Baseline ESS				
Mild (0-9)	1	1.1 (-2.9, 5.1)		
Moderate 10-15)	3	-3.4 (-7.9, 1.2)		58%
Severe (16-24)	1	-4.2 (-6.4, -2.0)		
Not reported	1	-1.0 (-2.7, 0.7)		
Overall effect		-2.1 (-4.3, 0.0)	-2.00 (-3.16, -0.83)	59%
Baseline AHI				
Mild (AHI 5-14)				
Moderate (AHI 15-30)	1	1.1 (-2.9, 5.1)		
Severe (AHI >30)	5	-2.7 (-4.9, -0.4)		59%
Study design				
Crossover (endpoint)	1	-1.0 (-2.7, 0.7)		
Parallel (endpoint)	0			
Crossover (change)	1	1.1 (-2.9, 5.1)		
Parallel (change)	4	-3.5 (-6.2, -0.7)		48%

Table 11.10 Removal of individual studies for the daytime mean arterial pressure (CPAP versus placebo/usual care)

		Overall treatment effect Mean difference (95% CI)	**Statistical heterogeneity (I^2)**
Study removed	Robinson 2006	-2.7 (-4.9, -0.4)	59%
	Becker 2003	-1.7 (-3.5, 0.1)	48%
	Campos-Rodriguez	-2.4 (-4.9, 0.1)	66%
	Hui 2006	-2.2 (-4.7, 0.4)	67%
	Pepperell 2002	-1.4 (-3.6, 0.8)	42%
	Engleman 1996	-2.6 (-5.4, 0.3)	60%

Table 11.11 Sub-group analysis for daytime systolic BP (CPAP versus placebo/usual care)

	Number of trials	Random effects Mean difference (95% CI)	Fixed effect Mean difference (95% CI)	Statistical heterogeneity (I^2)
Baseline AHI				
Mild (AHI 5-14)	1	-2.9 (-13.5, 7.7)		
Moderate (AHI 15-30)	0			
Severe (AHI >30)	6	-1.0 (-3.3, 1.4)		0%
Overall effect	7	-1.1 (-3.4, 1.2)	-1.1 (-3.4, 1.2)	0%
Study design				
Crossover (endpoint)	2	-0.4 (-3.5, 2.7)		0%
Parallel (endpoint)	2	1.2 (-4.0, 6.4)		0%
Crossover (change)	1	-2.9 (-13.5, 7.7)		
Parallel (change)	2	-5.2 (-12.4, 2.1)		

Table 11.12 Sub-group analysis for daytime diastolic BP (CPAP versus placebo/usual care)

	Number of trials	Random effects Mean difference (95% CI)	Fixed effect Mean difference (95% CI)	Statistical heterogeneity (I^2)
Baseline AHI				
Mild (AHI 5-14)	1	-2.6 (-12.8, 7.6)		
Moderate (AHI 15-30)	0			
Severe (AHI >30)	6	-1.2 (-3.1, 0.7)		40%
Overall effect	7	-1.2 (-2.9, 0.5)	-0.06 (-2.37, 0.25)	29%
Study design				
Crossover (endpoint)	2	-0.9 (-2.9, 1.0)		31%
Parallel (endpoint)	2	0.5 (-2.7, 3.7)		0%
Crossover (change)	1	-2.6 (-12.8, 7.6)		
Parallel (change)	2	-5.7 (-14.8, 3.4)		76%

Figure 11.2 Night-time mean blood pressure (CPAP versus placebo/usual care)

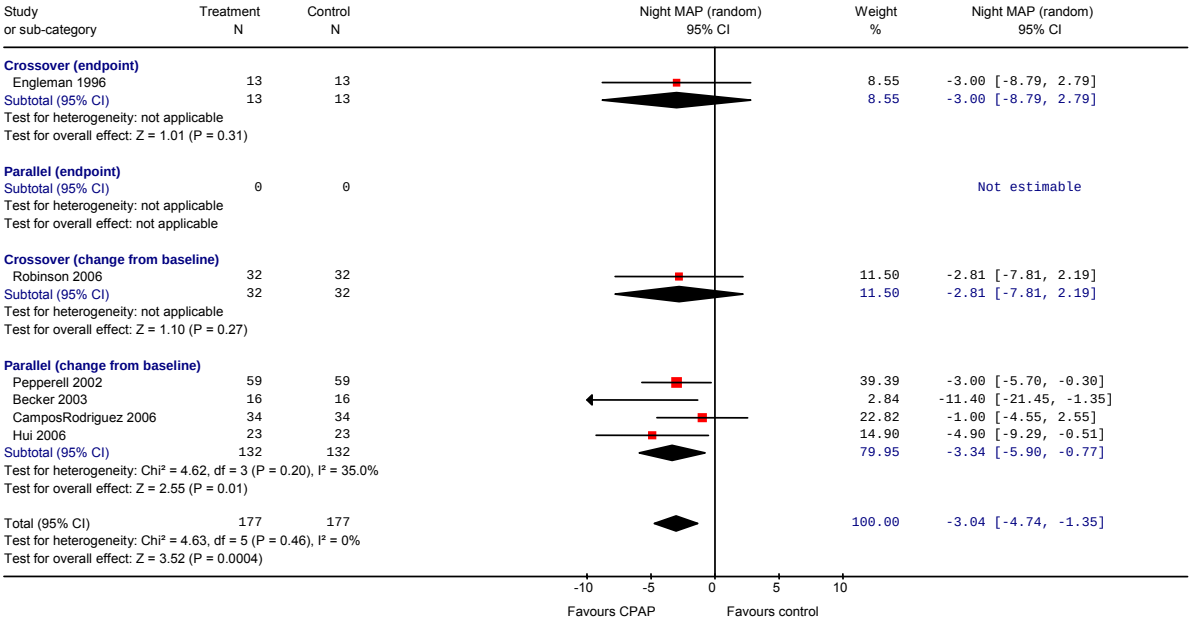


Figure 11.3 Night-time systolic blood pressure (CPAP versus placebo/usual care)

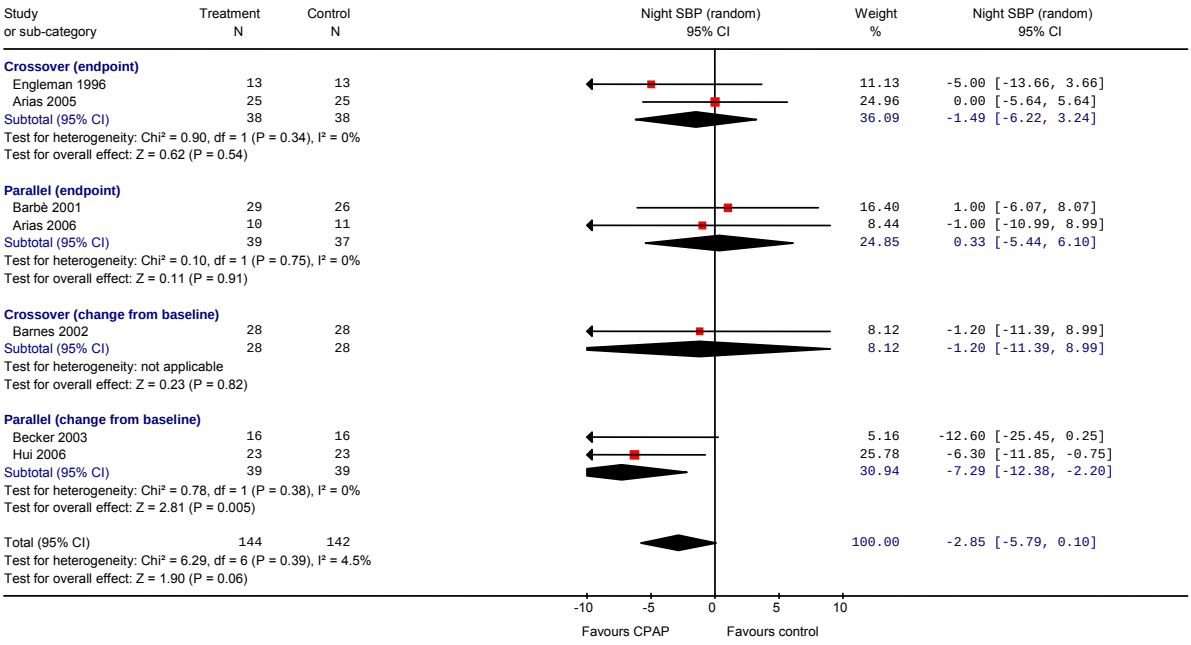


Figure 11.4 Night-time diastolic blood pressure (CPAP versus placebo/usual care)

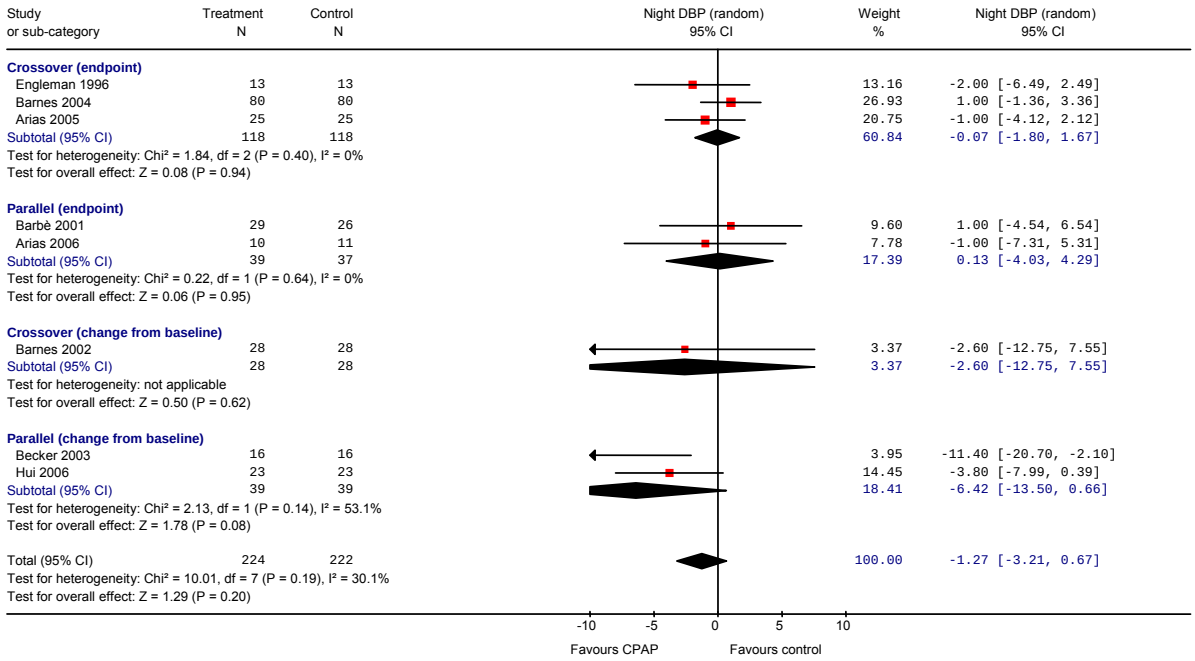
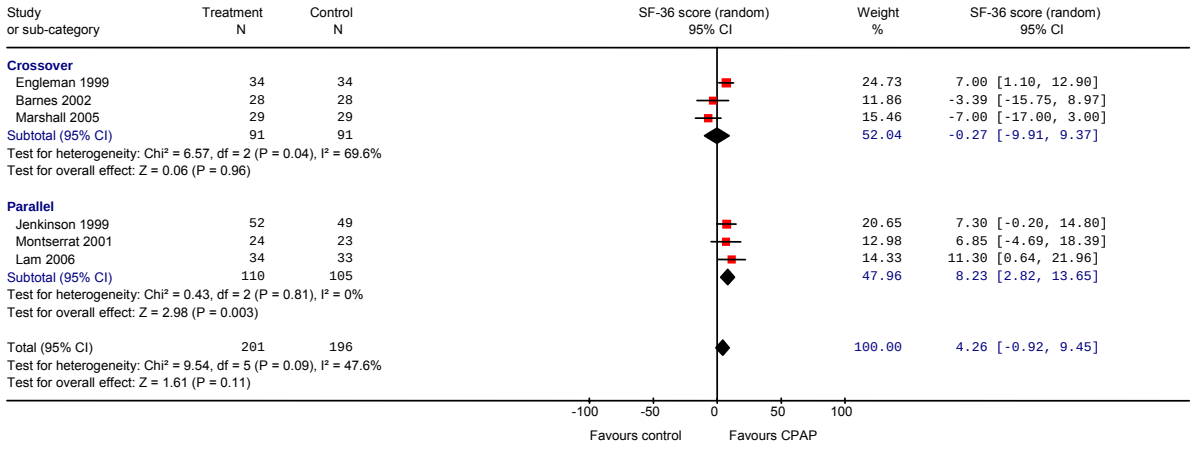
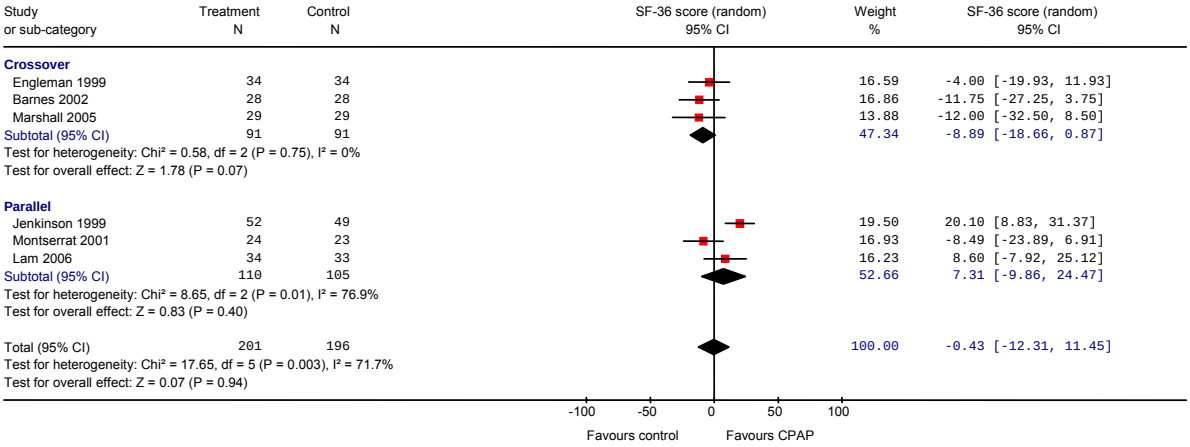


Figure 11.5 SF 36 subscales (CPAP versus placebo/usual care)

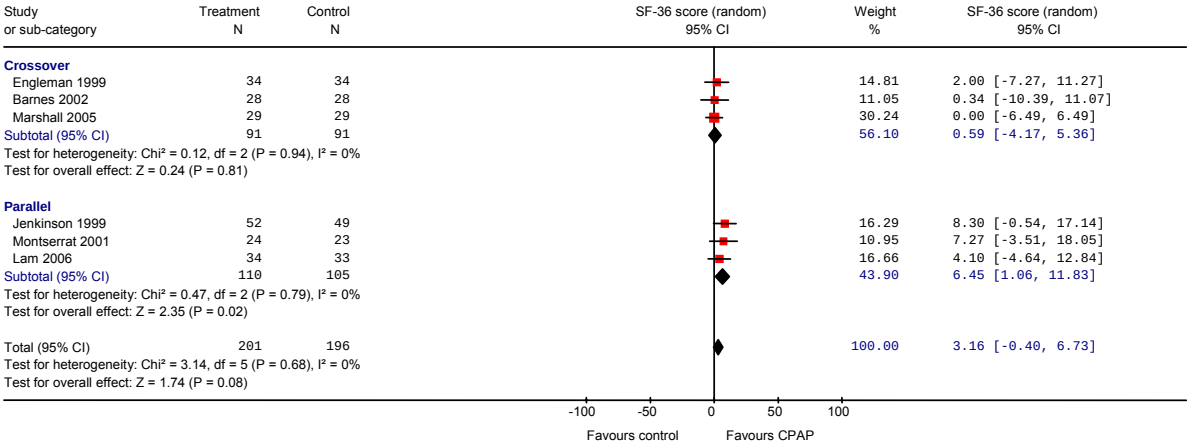
Bodily pain



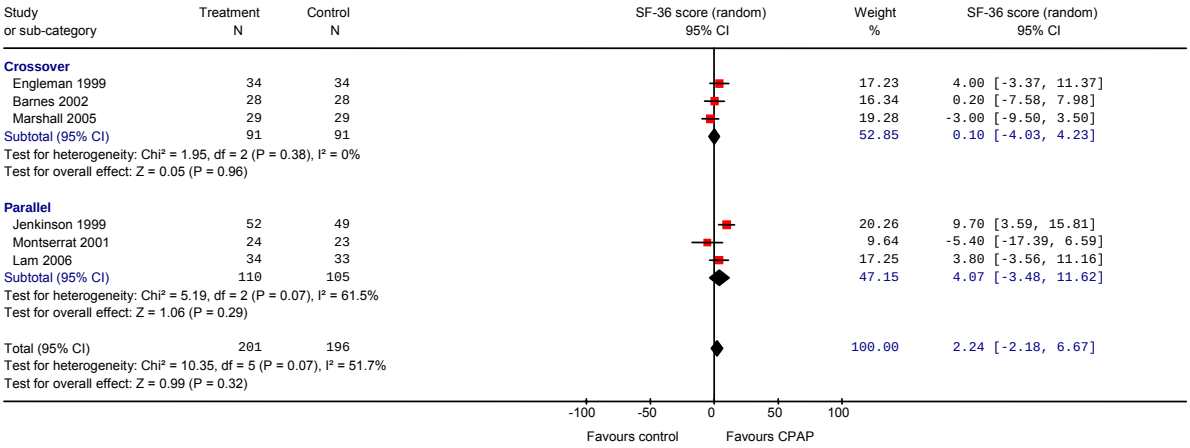
Emotional role



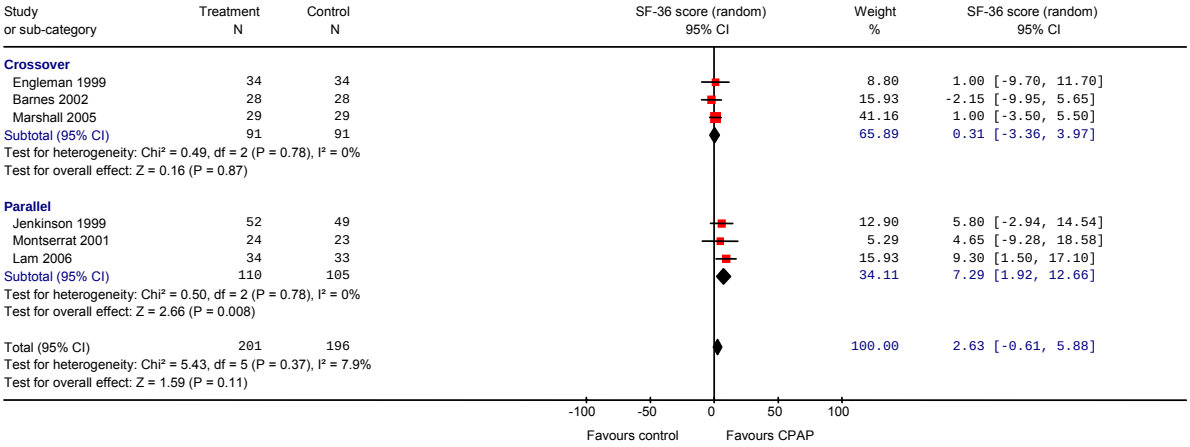
General health



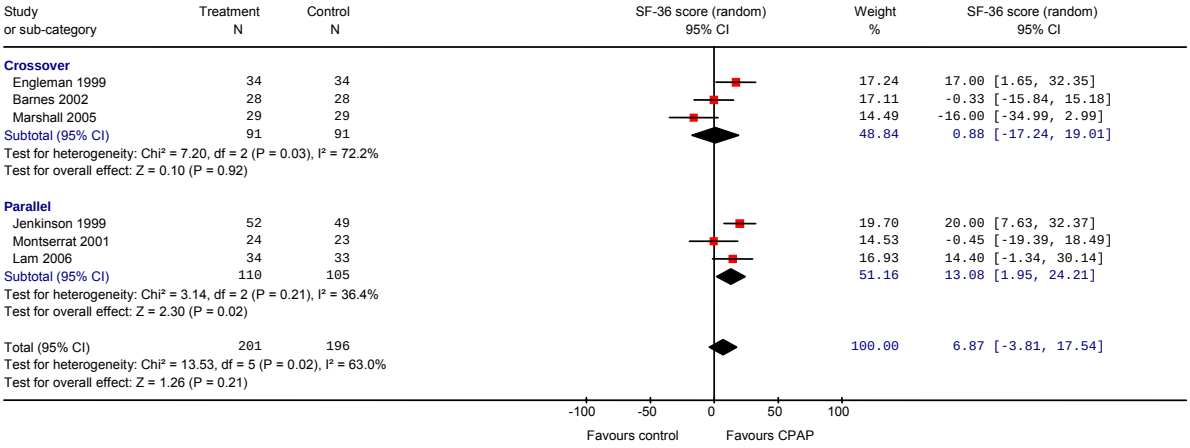
Mental health



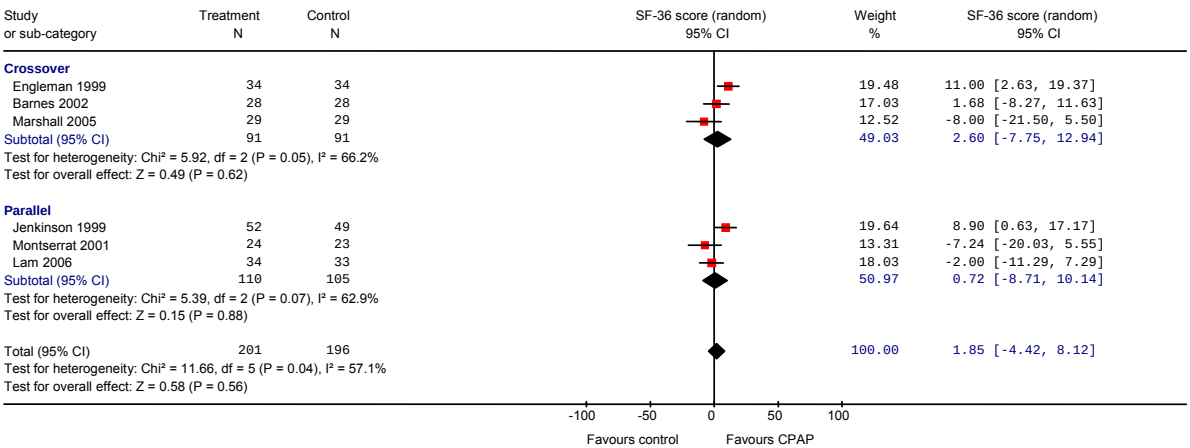
Physical function



Physical role

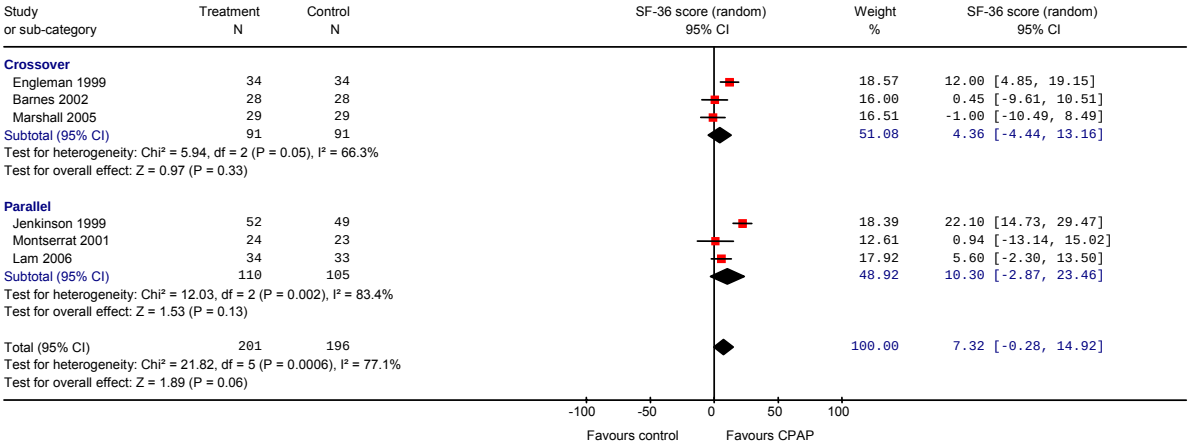


Social function

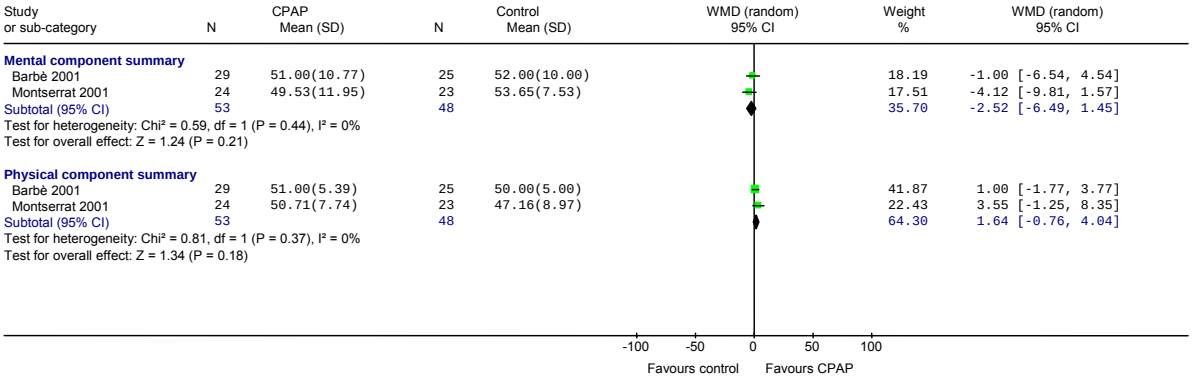


:

Vitality



SF-36 Summary Component Scores



SF-36 total score

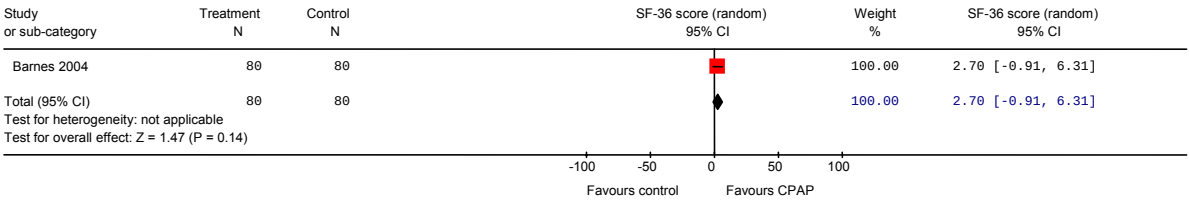
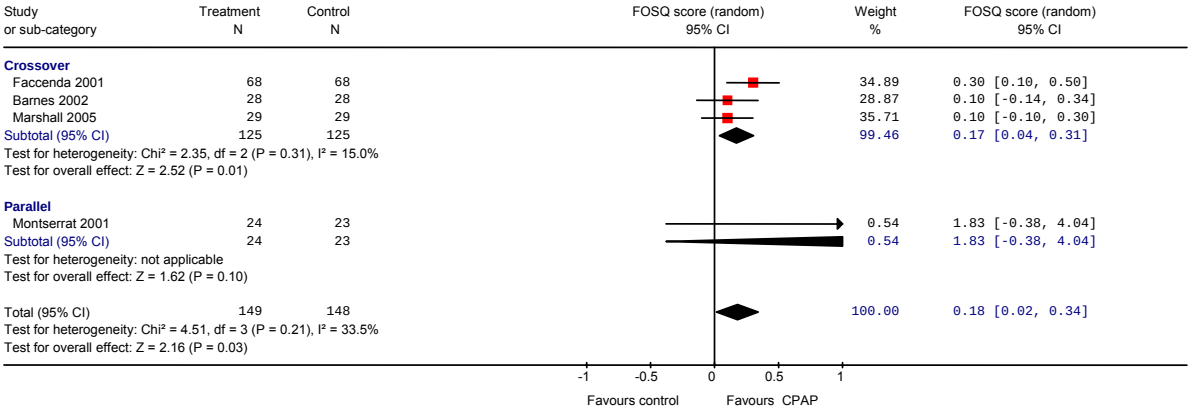
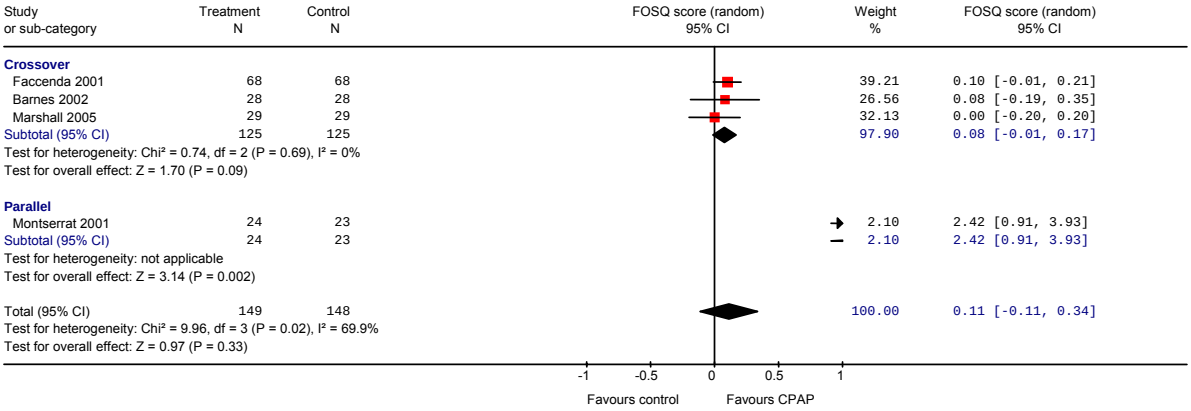


Figure 11.6 Functional Outcomes of Sleep Questionnaire (FOSQ) subscales (CPAP versus control)

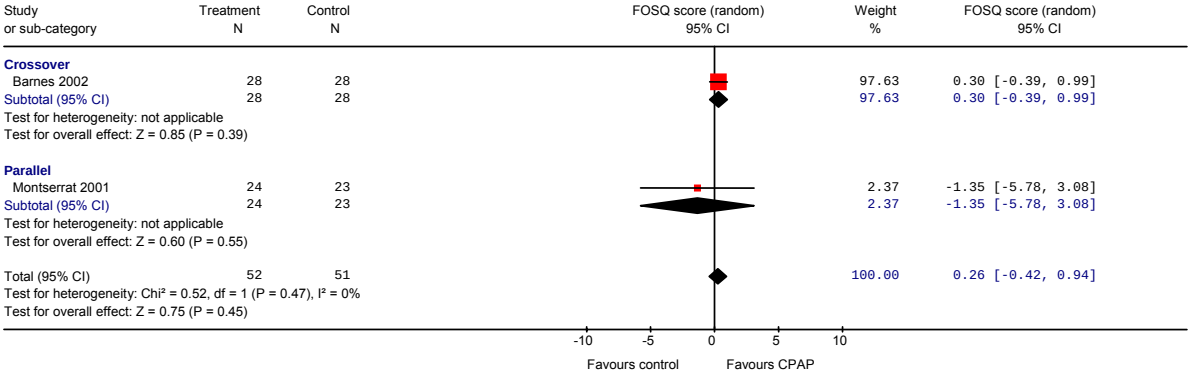
FOSQ Activity level



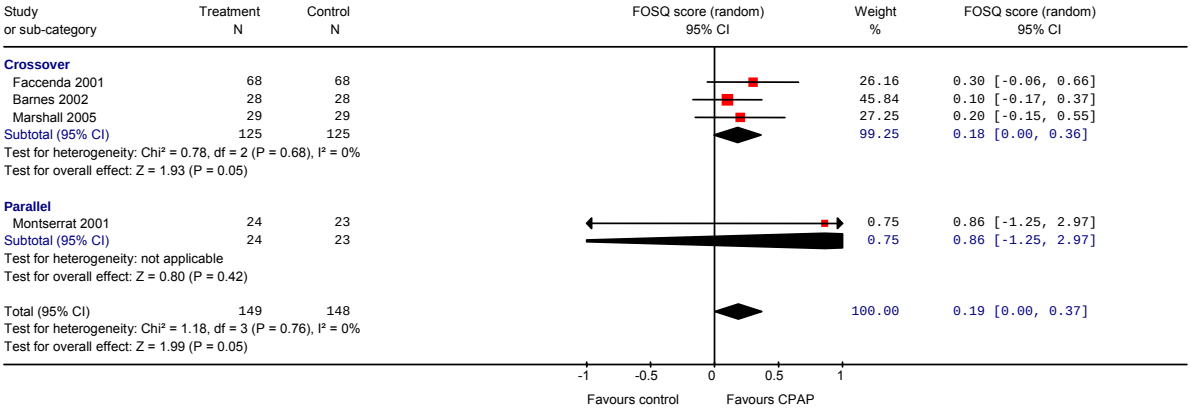
FOSQ General productivity



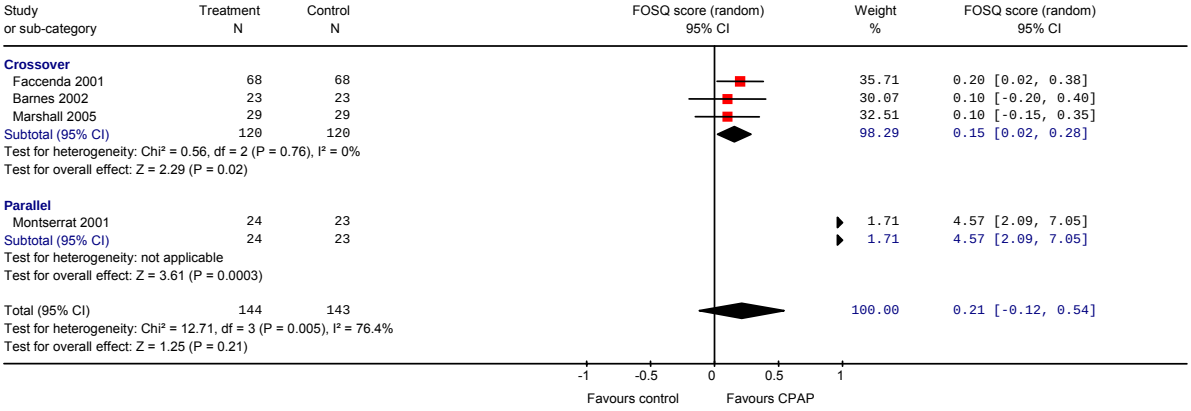
FOSQ Intimacy and sexual activity



FOSQ Social outcome



FOSQ Vigilance



FOSQ Total score

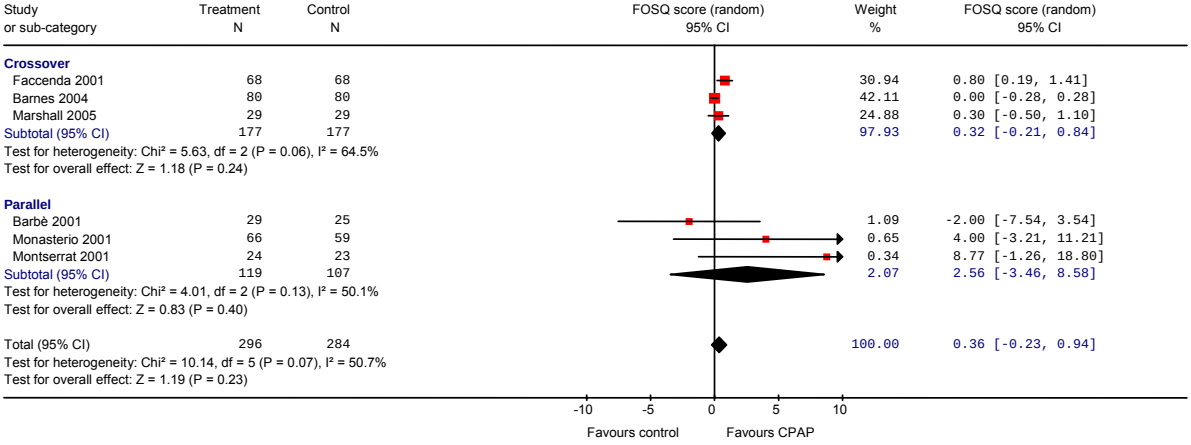


Figure 11.7 Nottingham Health Profile (Part 2) (CPAP versus placebo/usual care)

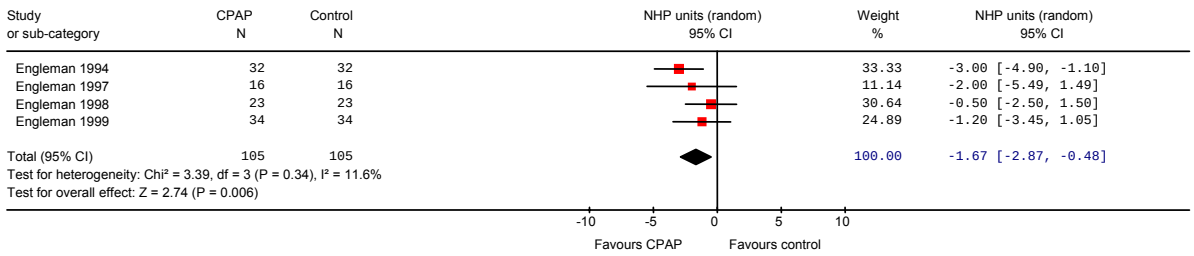


Figure 11.8 Sleep Apnoea Quality of Life Index (CPAP versus placebo/usual care)

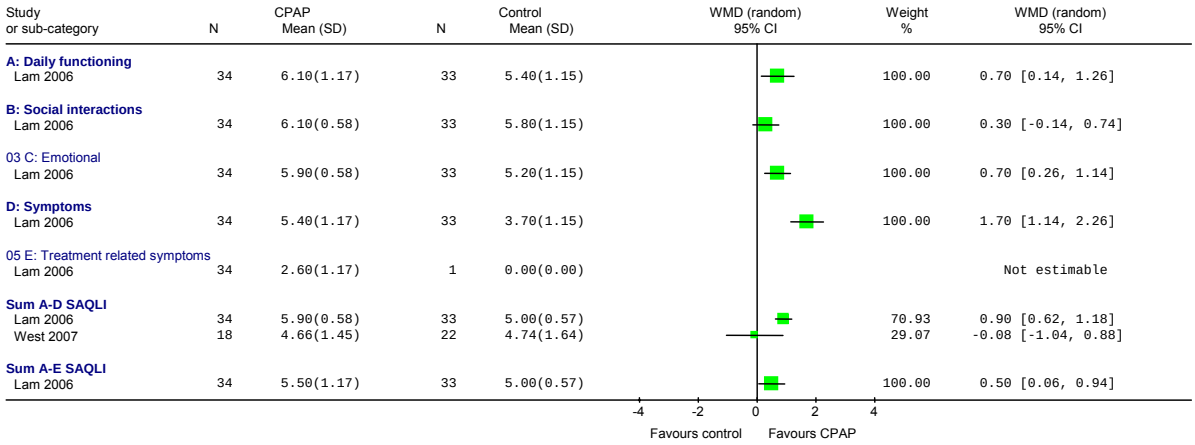


Figure 11.9 Functional Outcomes of Sleep Questionnaire (CPAP versus dental devices)

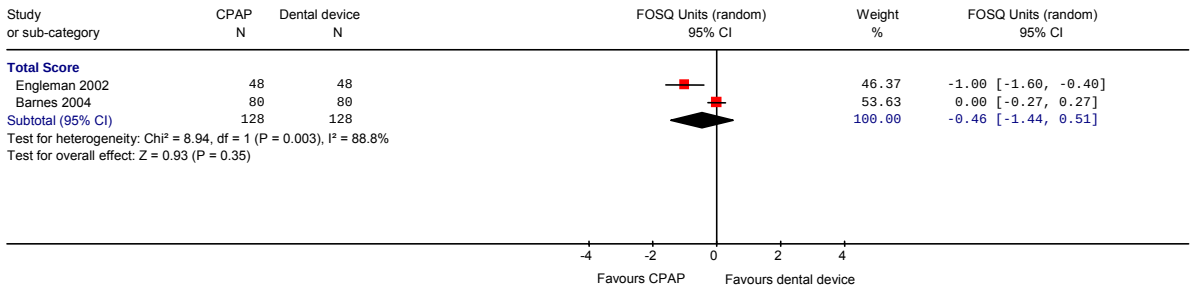


Figure 11.10 SAQLI -summed score (CPAP versus dental device)

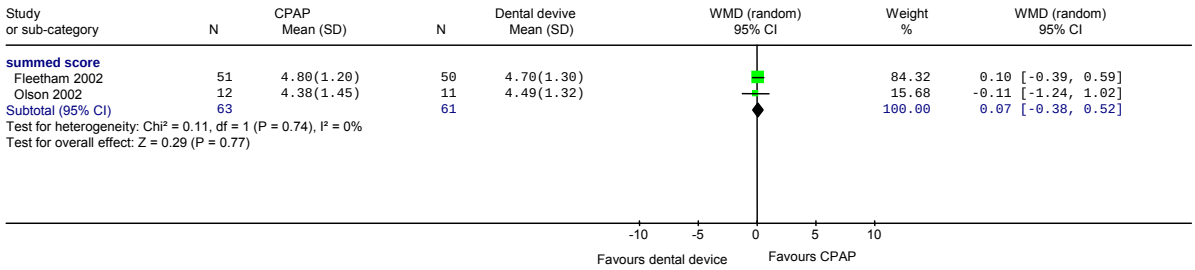


Figure 11.11 SAQLI – subscales and summed scores A-D and A-E (CPAP versus dental devices)

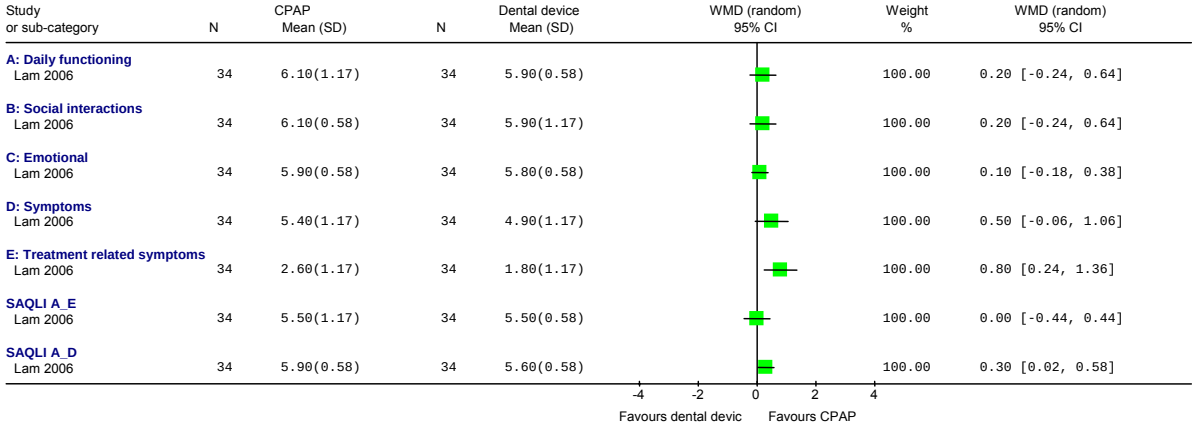


Figure 11.12 SF-36 Summary and total scores (CPAP versus dental devices)

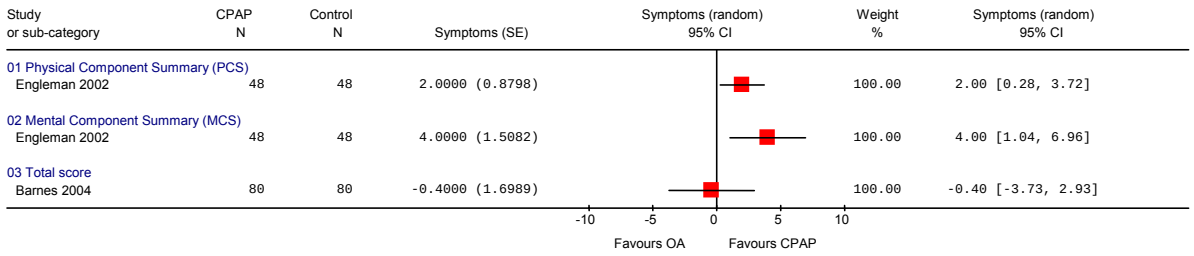


Figure 11.13 SF-36 subscales (CPAP versus dental devices)

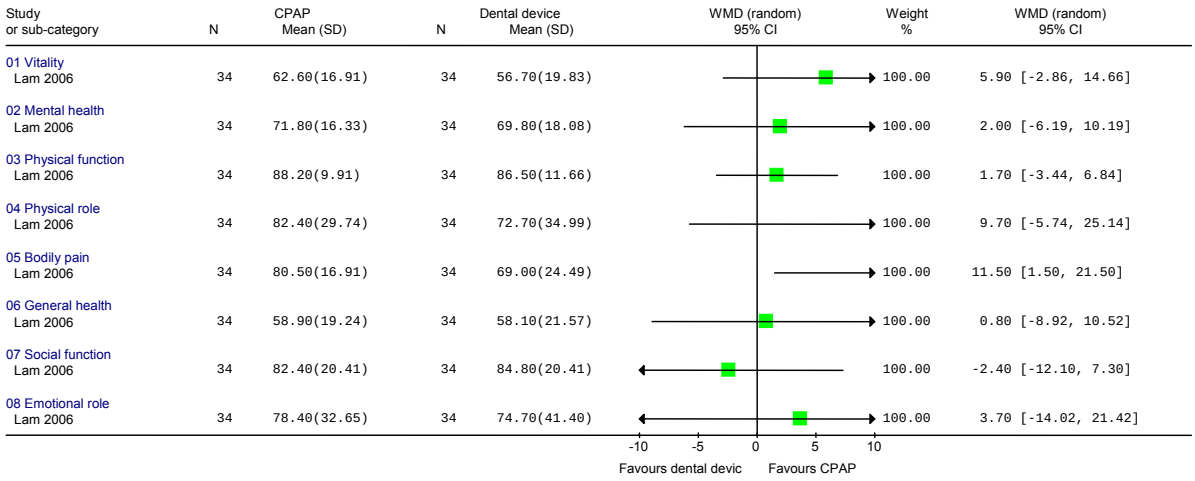


Figure 11.14 GRISS (CPAP versus dental device)

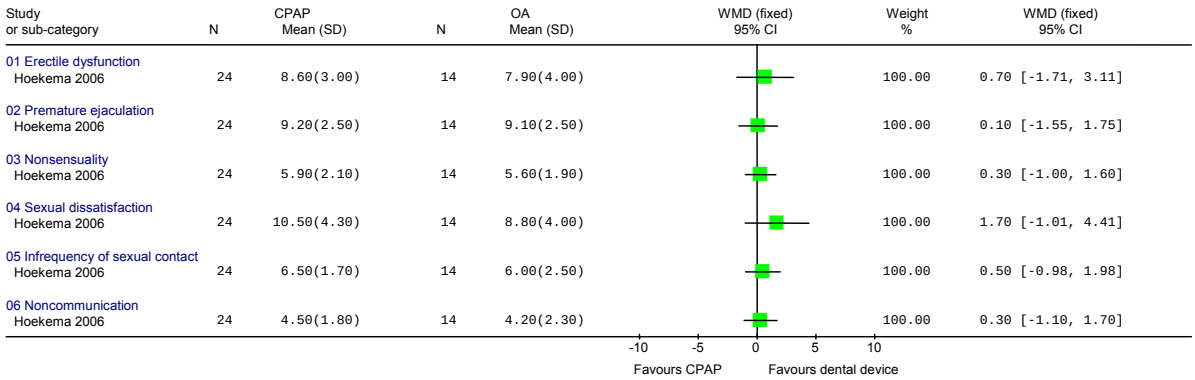


Figure 11.15 General Health Questionnaire-28 (CPAP versus placebo)

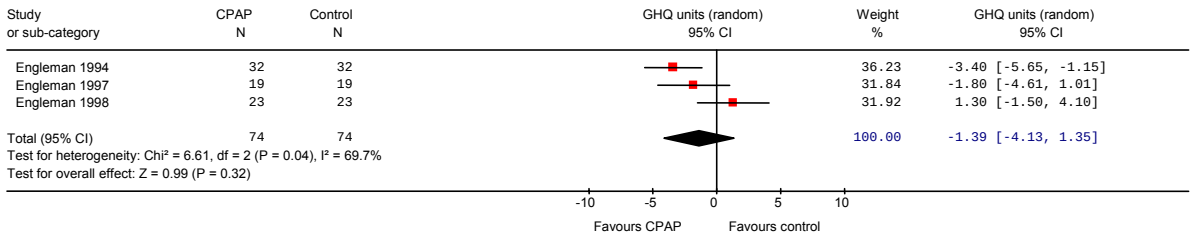


Figure 11.16 Hospital Anxiety and Depression scale – Anxiety (CPAP versus placebo)

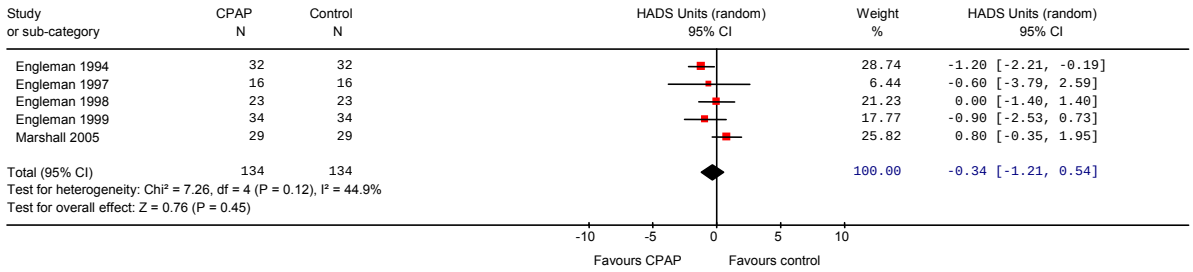


Figure 11.17 Hospital Anxiety and Depression scale – Depression (CPAP versus placebo)

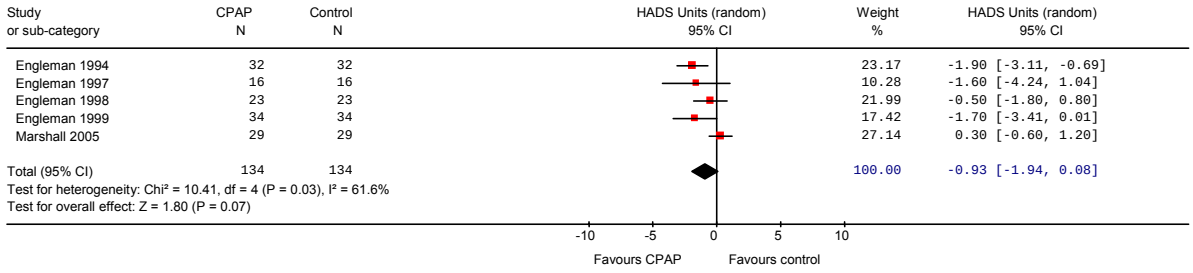


Figure 11.18 Brief Symptom Inventory (CPAP versus placebo)

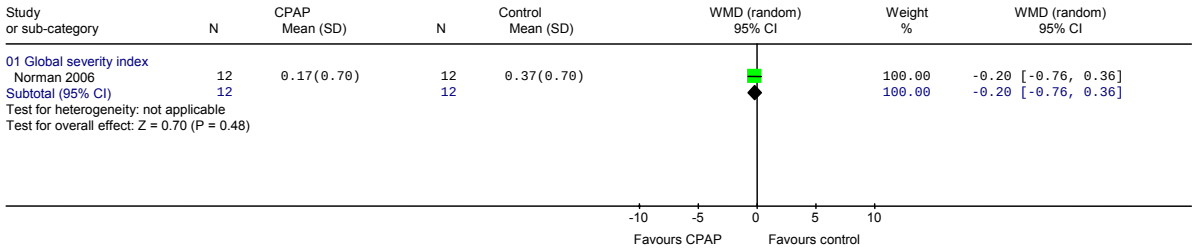


Figure 11.19 Profile of Mood State (CPAP versus placebo)

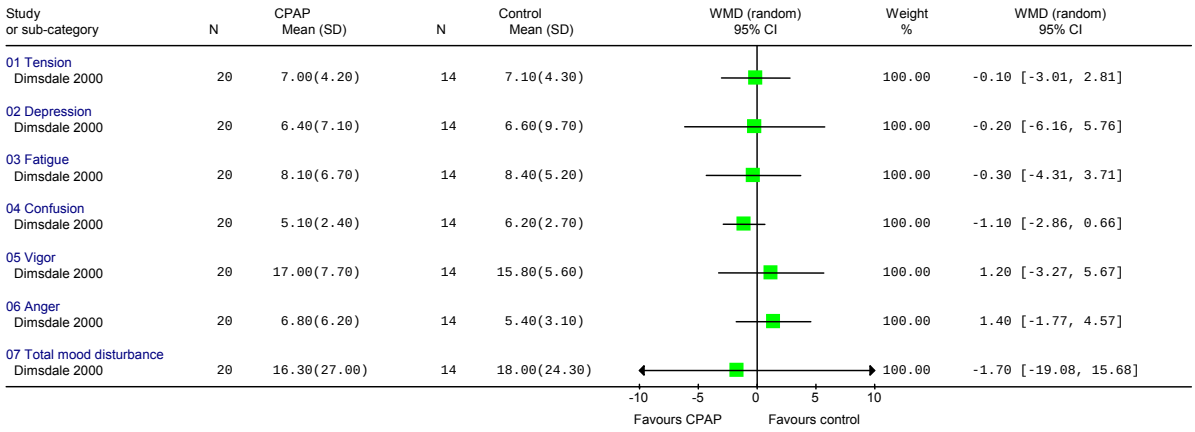


Figure 11.20 UMACL – Energetic arousal score (CPAP versus control)

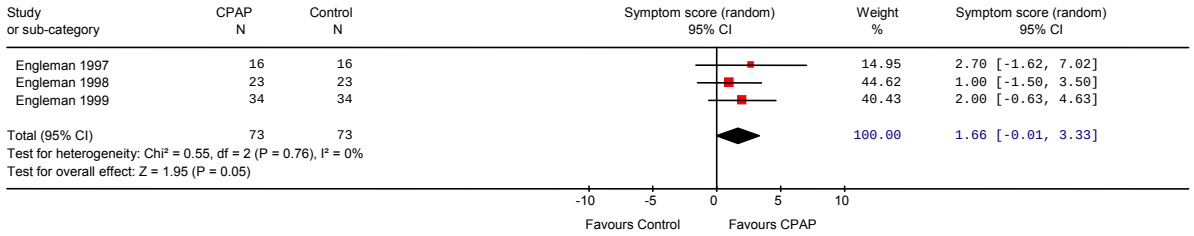


Figure 11.21 Hospital Anxiety and Depression Scale – Anxiety (CPAP versus dental device)

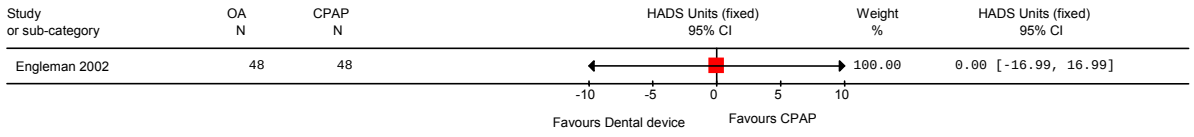


Figure 11.22 Hospital Anxiety and Depression Scale – Depression (CPAP versus dental device)

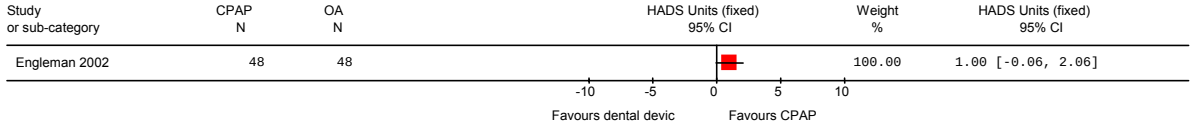


Table 11.13 Summary of neurocognitive outcomes for individual studies

Test / Study	Baseline	Follow-up 1	Follow-up 2
Benton Visual Retention Test (direction of improvement +): Visuospatial memory test composed of 10 geometric designs, each design is exposed for 10 seconds, after which time the subject is required to reproduce the design from memory.			
Crossover trials			
Engleman 1994[90]	CPAP: NR, OP: NR Both: NR	Data not reported because there was no statistically significant difference between CPAP and oral placebo.	
Engleman 1997[92]	CPAP: NR, OP: NR Both: NR	CPAP: 7.3 (SE 0.6), OP: 7.3 (SE 0.6) MD (SD): 0, P value: ns	
Engleman 1998[93]	CPAP:NR OP: NR Both: 7.3 (SD 2.3), n=23	CPAP: 7.7 (SD 1.5), OP: 7.7 (SD 1.7) MD (SD): 0, P value: ns	
Parallel trials			
Lojander 1999[113]*	*Correct* CPAP: 8.5 (6-10), n=10, CM: 7 (3-10), n=17 *Errors* CPAP: 2 (0-9), n=10, CM: 5 (0-9), n=17 *Delayed* CPAP: 4 (4-4), n=10, CM: 4 (1-4), n=17	*Correct* CPAP: 8.5, n=10, CM: 7, n=16 MD (SD): , P value:ns *Errors* CPAP: 3, n=10, CM: 5, n=17 MD (SD): , P value:ns *Delayed* CPAP: 4, n=10, CM: 4, n=17 MD (SD): , P value:ns	*Correct* CPAP: 9.5, n=9, CM: 5, n=12 MD (SD):, P value:ns *Errors* CPAP: 1, n=10, CM: 5, n=17 MD (SD): , P value:ns *Delayed* CPAP: 4, n=10, CM: 4, n=17 MD (SD): , P value:ns
Brief Visuospatial Memory (Direction of improvement +): the respondent is briefly shown a number of geometric figures presented on a single page and asked to reproduce as many figures as possible in their correct location. After a delay which includes primarily verbal activities, the task is repeated. The respondent is then asked to identify, from 12 figures, which were included in the six geometric figures originally presented. An optional copy trial may be administered.			
Parallel trials			
Norman 1996[73]	*BVM-TR* CPAP: 26.4, n=17 Sham CPAP: 26.1, n=14 *BVM-DL* CPAP: 10.8, n=17 Sham CPAP: 10.5, n=14	*BVM-TR* CPAP: 29.7, n=17 Sham CPAP: 25.7 (SE 0.6) MD (SD): P value: 0.143 *BVM-DL* CPAP: 10.7, n=17 Sham CPAP: 9.4, n=14 MD (SD): P value: 0.138 NB. P value based on treatment x time interaction (3 treatment arms)	
Bourdon-Wiersma test (Direction of improvement +, except 'errors'): After scanning a series of rows of groups of black dots, respondents are asked to strike out all groups of four dots.			
Parallel trials			
Lojander 1999[113]*	*Marked* CPAP: 128 (56 to160), n=10 CM: 120 (62 to 400), n=17 *Errors* CPAP: 11 (1 to 18), n=10	*Marked* CPAP: 118, n=10, CM: 111, n=16 MD (SD): P value: ns *Errors* CPAP: 12, n=10, CM: 4, n=16	*Marked* CPAP: 103, n=9 CM: 116, n=12 MD (SD): P value: ns *Errors*

	CM: 4 (0 to 44), n=17	MD (SD): P value:	CPAP: 12, n=9 CM: 4, n=12 MD (SD):, P value: ns
Concentration Endurance Test (Direction of improvement +, except errors): This test of sustained attention and visual scanning consists of 14 lines with 47 characters in each line (each character consists of a letter, 'd' or 'p' marked with one, two, three or four small dashes). The respondent is required to scan the lines and cross out all occurrences of the letter 'd' with two dashes while ignoring all other characters.			
Crossover trials			
Jokic 1999[108]	*Total score* Both: 482.3 (SD 38.6), n=13 *% Errors* Both: 7.4 (SD 3.1), n=13	*Total score* CPAP: 532.3 (SD 73.5), CM: 530 (SD 55.6) MD (SD): 2.3, P value: 2.36 *% Errors* CPAP: 4.4 (SD 5.4) CM: 4.5 (SD 6.4) MD (SD): -0.1, P value: 2.82	
Clock Face Drawing (direction of improvement -): Respondents are asked to draw the face of a clock and then add in a specified time.			
Parallel Trials			
Lojander 1999[113]*	CPAP: 1 (1 to 3), n=10 CM: 1 (1 to 3), n=17	CPAP: 1, n=10 , CM: 1, n=16 MD (SD): P value: ns (change)	CPAP: 1, n=9 , CM: 2, n=12 MD (SD): P value: ns (change)
Copying (direction of improvement -): Respondents are asked to reproduce a set of designs.			
Parallel trials			
Lojander 1999[113]*	CPAP: 1 (1 to 3), n=10 CM: 2 (1 to 4)	CPAP: 1, CM: 2 MD (SD): P value: ns	CPAP: 1, CM: 2 MD (SD): P value: ns
Complex Figure Test (Direction of improvement +): Subject is required to make a pen/paper copy of a complex figure			
Parallel trials			
Henke 2001 [85]	CPAP: Not reported Sham CPAP: Not reported	Data presented in graph only. No statistically significant difference between groups at follow-up.	
Consonant Trigram (Direction of improvement +): Distractor task – Respondents are asked to count backwards from a given number on hearing/seeing the stimulus item. When signalled to stop counting respondents are asked to report or identify the stimulus item.			
Crossover trials			
Jokic 1999[108]	*3s delay* Both: 12.3 (SD 4.4) , n=13 *9s delay* Both: 9.8 (SD 2.5) , n=13 *18s delay* Both: 6.6 (SD 0.6) , n=13 *Total correct position* Both: 34.3 (SD 7), n=13 *Total correct sequence* Both: 38.9 (SD 9), n=13	*3s delay* CPAP: 13.2 (SD 1.5) CM other: 13.4 (SD 1.7) MD (SD): -0.2, P value: 1.86 *9s delay* CPAP: 10.5 (SD 1.5) CM other: 10.2 (SD 2.6) MD (SD): 0.3, P value: 1.94 *18s delay* CPAP: 8.0 (SD 3.6) CM other: 8.2 (SD 1.0) MD (SD): -0.2, P value: 2.34 *Total correct position* CPAP: 40.2 (SD 10.6) CM other: 41.5 (SD 11.6) MD (SD): -1.3, P value: 2.88	

		Total correct sequence CPAP: 37.1 (SD 8.0) CM other: 38.4 (SD 11.1) MD (SD): -1.3, P value: 0.77	
Controlled Oral Word Association Test (direction of improvement +): Three word naming trials; Respondents are asked to name words that begin with a specified set of letters in 60 seconds			
Crossover trials			
Barnes 2002[89]	CPAP: NR OP: NR Both: 35.3 (SD 10.7), n=28	*No. of words correct* CPAP: 38.7, OP: 36.0 MD (SD): 2.7, P value: 0.02 (difference in change)NB. After treatment x period interaction accounted for p=ns.	
Barnes 2004[82]	CPAP: NR Comparator: NR Both: 43.2 (SE 1.1), n=80	CPAP: 46.5 (SE 1.2) OA: 46.3 (SE 1.1) OP: 46.3 (SE 1.0) CPAP/OA MD (SD): 0.2 CPAP/OP MD (SD): 0.2 P value:ns	
Engleman 1994[90]	CPAP: NR OP: NR	Data not reported because there was no statistically significant difference between CPAP and oral placebo	
Engleman 1997[92]	CPAP: NR OP: NR n=16	*No. of words correct* CPAP: 38.5 (SE 3.5) OP: 39.2 (SE 3.1) MD (SD): -0.7, P value: ns	
Engleman 1998[93]	CPAP: NR OP: NR Both: 39 (SD 12), n=23	*No. of words correct* CPAP: 41 (SD 12) OP: 42 (SD 11) MD (SD): -1, P value: ns	
Parallel trials			
Henke 2001[85]	CPAP: NR Sham CPAP: NR	Data not reported. No statistically significant difference between groups at follow-up.	
Digit Ordering (Direction of improvement +): Respondents are asked to recall digit sequences in ascending order			
Parallel trials			
Dimsdale 2000[58]	*No. correct* CPAP: 87.8 (SE 1.9), n=20 Sham CPAP: 85.7 (SE 2.2), n=16 *No. items* CPAP: 4.3 (SE 0.7), n=20 Sham CPAP: 2.6 (SE 0.8), n=16	*No. correct* CPAP: 90.6 (SE 1.7), n=20 Sham CPAP: 86.1 (SE 2.0), n=16 MD (SD): 4.5, P value: ns *No. items* CPAP: 4.9 (SE 0.7), n=20 Sham CPAP: 2.7 (SE 0.8), n=16 MD (SD): 2.2 P value: ns	
Driving simulator test (Direction of improvement -): Respondents are asked to steer an image of a car bonnet down the centre of a winding road as accurately as possible using a standard computer game steering wheel.			
Crossover trials			
Engleman 1994[90] Steerclear	*Obstacles hit* CPAP: NR OP: NR	*Obstacles hit* CPAP: 76 (SE 5), OP: 81 (SE 6) MD (SD): -5, P value: 0.01	

	N= 32		
Engleman 1997[92] Steerclear	*Obstacles hit* CPAP: NR OP: NR n=16	*Obstacles hit* CPAP: 74.8 (SE 7.3) OP: 75.3 (SE 8.9) MD (SD): -0.5, P value: ns	
Engleman 1998[93] Steerclear	*Obstacles hit* CPAP: NR OP: NR Both: 100 (SD 63), n=22	*Obstacles hit* CPAP: 63 (SD 27), OP: 71 (SD 40) MD (SD): -8, P value: ns	
Engleman 1999[78] Steerclear	*Obstacles hit* CPAP: NR OP: NR Both: 295 (SD 183), n=34	*Obstacles hit* CPAP: 189 (SD 156), OP: 195 (SD 158) MD (SD): -6, P value: ns	
Engleman 2002[103] Steerclear	*Obstacles hit* CPAP: NR OA: NR n=48	*Obstacles hit* CPAP: 49 (SD 60), OA: 50 (SD 44) MD (SD): 1, P value: 0.266	
Parallel trials			
Barbe 2001[83] Steerclear	*Obstacles hit (%)* CPAP: 5 (SE 1), n= 29 Sham CPAP: 6 (SE 2), n=25	*Obstacles hit (%)* CPAP: 4 (SE 1), n=29 Sham CPAP: 5 (SE 2), n=25 MD (SD): -1, P value: >0.20 (difference in change)	
Hoekema 2006[102]***	*Lapses of attention (total)* CPAP: 10.0 (1 to 16.8), n= 10 OA: 5.0 (2 to 14), n=9 *Lapses of attention (0-5min)* CPAP: 0.0 (0 to 0), n= 10 OA: 0.0 (0 to 1), n=9 *Lapses of attention (6-10min)* CPAP: 0.0 (0 to 1), n= 10 OA: 0.0 (0 to 1), n=9 *Lapses of attention (11-15min)* CPAP:1 0.0 (0 to 2.5), n= 10 OA: 0.0 (0 to 5), n=9 *Lapses of attention (16-20min)* CPAP: 3.0 (0.8 to 7.8), n= 10 OA: 2.0 (0 to 5.5), n=9 *Lapses of attention (21-25min)* CPAP: 4.0 (0.0 to 8.5), n= 10 OA: 2.0 (0 to 4), n=9	*Lapses of attention (total)* CPAP: 0.5 (0 to 5.3), n= 10 OA: 0.0 (0 to 2), n=9 MD (SD):, P value: ns *Lapses of attention (0-5min)* CPAP: 0.0 (0 to 0), n= 10 OA: 0.0 (0 to 0.5), n=9 MD (SD): , P value: ns *Lapses of attention (6-10min)* CPAP: 0.0 (0 to 0.3), n= 10 OA: 0.0 (0 to 0), n=9 MD (SD): , P value: ns *Lapses of attention (11-15min)* CPAP: 0.0 (0 to 1), n= 10 OA: 0.0 (0 to 0), n=9 MD (SD): , P value: ns *Lapses of attention (16-20min)* CPAP: 0.0 (0 to 0.5), n= 10 OA: 0.0 (0 to 0.5), n=9 MD (SD): , P value: ns *Lapses of attention (21-25min)* CPAP: 0.0 (0.0 to 2.5), n= 10 OA: 0.0 (0 to 1), n=9 MD (SD): , P value: ns	
Jenkinson 1999**[77] Other DST	*SD position on road* CPAP:0.36 (0.15 to 1.12), n=26 Sham CPAP: 0.35 (0.15 to 1.17),	*SD position on road* CPAP: 0.21 (0.14 to 0.63), n=26 Sham CPAP: 0.30 (0.14 to 1.19), n=33	

	n=33 *SD deterioration (SD/hr)* CPAP: 0.18 (-1.14 to 30.3), n=26 Sham CPAP: 0.18 (-0.02 to 2.67), n=33 *Off-road events (no./hr)* CPAP: 17.8 (0.4 to 149), n=26 Sham CPAP: 34.8 (0.9 to 149)), n=33 *Length of drive (min)* CPAP: 24.8 (7.6 to 30), n=26 Sham CPAP: 27.6 (10.9 to 30), n=33 *Reaction time (seconds)* CPAP: 2.8 (1.8 to 4.9), n=26 Sham CPAP: 2.8 (1.7 to 5.5), n=33	MD (SD): -0.07, P value: 0.08 *SD deterioration (SD/hr)* CPAP: 0.06 (-1.02 to 0.40), n=26 Sham CPAP: 0.24 (-0.04 to 2.64), n=33 MD (SD): -0.18, P value: 0.007 *Off-road events (no./hr)* CPAP: 9 (0 to 76), n=26 Sham CPAP: 23 (0 to 150), n=33 MD (SD): -14, P value: 0.07 *Length of drive (min)* CPAP: 30 (17.6 to 30), n=26 Sham CPAP: 26.9 (9.1 to 30), n=33 MD (SD): 3.1, P value: 0.08 *Reaction time (seconds)* CPAP: 2.3 (1.5 to 3.5), n=26 Sham CPAP: 2.7 (1.6 to 4.0), n=33 MD (SD): -0.4, P value: 0.04	
Monasterio 2001[100] Steerclear	*Obstacles hit (%)* CPAP: 10 (SD 8), n=66 CM: 10 (SD 3), n=59	*Obstacles hit (%)* CPAP: 8 (SD 9), n=66 CM: 8 (SD 10), n=59 MD (SD): 0, P value: 0.88	
Digit Vigilance Test (direction of improvement -): Respondents are asked to find and cross out either 6s (standard administration) or 9s (alternate administration), which appear randomly within 59 rows of single digits. These 59 rows of digits are printed in red on the first stimulus page and in blue on the second.			
Parallel trials:			
Dimsdale 2000[58]	*Time* CPAP: 7.5 (SE 0.4), n=20 Sham CPAP: 6.4 (SE 0.4), n=16 *Errors* CPAP: 7.1 (SE 3.1), n=20 Sham CPAP: 18.3 (SE 3.7), n=16	*Time* CPAP: 6.9 (SE 0.3), n=20 Sham CPAP: 6.6 (SE 0.4), n=16 MD (SD): -0.3, P value: *Errors* CPAP: 10.1 (SE 2.6), n=20 Sham CPAP: 12.3 (SE 3.1), n=16 MD (SD): -2.2, P value: 0.035	
Norman 2006[73]	*Time (s)*[b] CPAP: 350.9, n=17 Sham CPAP: 326.4, n=14 *Errors* CPAP: 5.6, n=17 Sham CPAP: 14.1, n=14 *5.6*	*Time* CPAP: 312.3, n=17 Sham CPAP: 303.1, n=14 MD (SD): 9.2, P value: 0.02 *Errors* CPAP: 7.2, n=20 Sham CPAP: 10.6, n=16 MD (SD): -2.4, P value: 0.08 NB. P value based on treatment x time interaction (3 treatment arms)	
Finger tapping task (Direction of improvement +): Speed of finger tapping is measured for the index finger of the right and left hand separately; five times for a period of 10 seconds each.			
Parallel			
Lojander 1999[113]*	CPAP: 48 (42-55), n=10 CM other: 44 (34-55), n=17	CPAP: 48, n=10, CM other: 44, n=16 MD (SD): P value:	CPAP: 45, n=9 CM other: 43, n=12 MD (SD): P value:

IQ decrement (Direction of improvement +): NART score minus WAIS-R subtests			
Crossover			
Engleman 1994[90]	CPAP: NR, OP: NR n=32	CPAP: 4.0 (SE 2.1), OP: 7.2 (SE 2.0) MD (SD): -3.2, P value: 0.04	
Engleman 1997[92]	CPAP: NR, OP: NR n=16	CPAP: 7.0 (SE 3.1) OP: 5.3 (SE 3.5) MD (SD): 1.7, P value: ns	
Engleman 1998[93]	CPAP: NR, OP: NR Both: 6 (SD 12), n=23	CPAP: 3.0 (SD 11), OP: 4.0 (SD 11) MD (SD): -1, P value: ns	
Engleman 2002[103]	CPAP: NR, OA: NR n=34	CPAP: -1.0 (SD 14), OA: -2.0 (SD 14) MD (SD): 1, P value: 0.549	
Hopkins verbal learning task (Direction of improvement +): Respondents are asked to verbally repeat a list of words (immediately and after a delay) and to identify the words from the list from a verbal presentation (including both the target words and the distractors).			
Parallel trials			
Norman 2006[73]	*Immediate recall* CPAP: 24.7, n=17 OA: 26.3, n=14 *Delayed recall* CPAP: 8.9, n=17 OA: 9, 14	*Immediate recall* CPAP: 24.2, n=17 OA: 25.5, n=14 MD (SD): -1.3, P value: 0.486, P value: 0.679 (difference in change) *Delayed recall* CPAP: 8.8, n=17, OA: 8.3, n=14 MD (SD): 0.5 P value: 0.641, P value: 0.347 (difference in change) NB. P value based on treatment x time interaction (3 treatment arms)	
Memory Distractor Task (Direction of improvement -):			
Parallel trials			
Lojander 1999[113]*	CPAP: 3 (1 to 3), n=10 CM: 3 (1 to 5), n= 17	CPAP: 3 CM: 3 MD (SD):, P value:	CPAP: 3 CM: 3 MD (SD): , P value:
Paced Auditory Serial Addition Task (Direction of improvement +): A series of single digits are presented at a set rate, the respondents are asked to add the numbers in pairs, such that each number is added to the one that immediately precedes it.			
Crossover trials			
Barnes 2004[82]	*PASAT 1.2* CPAP: NR, Comparator: NR Both: 3.4 (SE 0.2), n=80 *PASAT 2.4* CPAP: NR, Comparator: NR Both: 4.2 (SE 0.2), n=80	*PASAT 1.2* CPAP: 2.9 (SE 0.1), OA: 2.6 (SE 0.03) OP: 3.4 (0.1) CPAP/OA MD (SD): 0.3 CPAP/OP MD (SD): -0.5 P value: ns *PASAT 2.4* CPAP: 3.8 (SE 0.2), OA: 3.7 (SE 0.1) OP: 3.7 (SE 0.1) CPAP/OA MD (SD): 0.1 CPAP/OP MD (SD): 0.1 P value: ns	
Engleman 1994[90]	*PASAT 2* CPAP: NR, OP: NR *PASAT 4*	There was an improvement with CPAP but also an order effect. Data were analysed from first assessment only and	

	CPAP: NR, OP: NR	no statistically significant difference between CPAP and placebo was found. Data not reported because there was no statistically significant difference between CPAP and oral placebo	
Engleman 1997[92]	*PASAT 2* CPAP: NR, OP: NR n=16	*PASAT 2* CPAP: 37.8 (SE 3.3), OP: 35.3 (SE 2.8) MD (SD): 2.5, P value: ns	
Engleman 1998[93]	*PASAT 2* CPAP: NR OP: NR Both: 31 (SD 8), n=23	*PASAT 2* CPAP: 37 (SD 11), OP: 35 (SD 11) MD (SD): 2, P value: ns	
Engleman 1999[78]	*PASAT 2* CPAP: NR, OP: NR Both: 31 (SD 12), n=32	*PASAT 2* CPAP: 40 (SD 11), OP: 36 (SD 14) MD (SD): 4, P value: 0.02	
Engleman 2002[103]	*PASAT 2* CPAP: NR, OA: NR Both: Not reported, n=48	*PASAT 2* CPAP: 40 (SD 11), OA: 39 (SD 10) MD (SD): 1, P value: 0.064	
Parallel trials			
Barbe 2001[83]	*PASAT 1* CPAP: 15 (SE 1), n=29 Sham CPAP: 14 (SE 1), n=25 *PASAT 2* CPAP: 14 (SE 1), n=29 Sham CPAP: 15 (SE 1), n=25 *PASAT 3* CPAP: 10 (SE 1), n=29 Sham CPAP: 11 (SE 1), n=25 *PASAT 4* CPAP: 5 (SE 1), n=29 Sham CPAP: 4 (SE 1), n=25	*PASAT 1* CPAP: 15 (SE 1), Sham CPAP: 15 (SE 1) MD (SD): 0, P value: >0.20 (difference in change) *PASAT 2* CPAP: 16 (SE 1), Sham CPAP: 15 (SE 1) MD (SD): 1, P value: 0.04 (difference in change) *PASAT 3* CPAP: 12 (SE 1), Sham CPAP: 12 (SE 1) MD (SD): 0, P value: 0.09 (difference in change) *PASAT 4* CPAP: 5 (SE 1), Sham CPAP: 5 (SE 1) MD (SD): 0, P value: >0.20 (difference in change)	
Monasterio 2001[100]	*PASAT 1* CPAP: 4 (SD 3), n=66 CM: 4 (SD 3), n=59 *PASAT 2* CPAP: 10 (SD 4), n=66 CM: 10 (SD 5), n=59 *PASAT 3* CPAP: 14 (SD 5), n=66 CM: 13 (SD 5), n=59 *PASAT 4* CPAP: 13 (SD 5), n=66 CM: 13 (SD 4), n=59	*PASAT 1* CPAP: 5 (SD 4), CM: 5 (SD 3) MD (SD): 0, P value: 0.32 *PASAT 2* CPAP: 12 (SD 4), CM: 12 (SD 4) MD (SD): 0, P value: 0.12 *PASAT 3* CPAP: 15 (SD 4), CM: 15 (SD 4) MD (SD): 0, P value: 0.20 *PASAT 4* CPAP: 14 (SD 4), CM: 16 (SD 4) MD (SD): -2, P value: 0.20	

		NB. Reduced version with 20 items for each condition. It is unclear whether the score is for number correct or percentage correct.	
Purdue Pegboard (Direction of improvement +): Test of manual dexterity. Following standard instructions the subject places pegs onto a pegboard.			
Crossover trials			
Jokic 1999[108]	*Dominant hand (no. correct)* CPAP: NR CM other: NR Both: 13 (SD 3.6), n=13 *Non-Dominant hand (no. correct)* CPAP: NR CM other: NR Both: 13 (SD 1.5), n=13 *Both hands (no. correct)* CPAP: NR CM other: NR Both: 10.8 (SD 1.5), n=13 *Right/left/both hands (no. correct)* CPAP: NR CM other: NR Both: 36.8 (SD 6.7), n=13 *Assembly* CPAP: NR CM other: NR Both: 34.6 (SD 5.7), n=13	*Dominant hand (no. correct)* CPAP: 15.3 (SD 1.7) CM other: 14.3 (SD 1.7) MD (SD): 1, P value: 0.25 *Non-Dominant hand (no. correct)* CPAP: 14.1(SD 2.3) CM other: 12.8 (SD 2.3) MD (SD): 1.3, P value: 0.16 *Both hands (no. correct)* CPAP: 11.1(SD 1.0) CM other: 11.5 (SD 1.0) MD (SD): -0.4 , P value:1.41 *Right/left/both hands (no. correct)* CPAP: 39.6 (SD 10.7) CM other: 38.6 (SD 4.9) MD (SD): 1, P value: 1.47 *Assembly* CPAP: 35.1(SD 7.6) CM other: 35.4 (SD 8.1) MD (SD): -0.3, P value: 2.05	
Psychomotor Vigilance Test (Direction of improvement -): test of sustained attention. Typically requires subject to respond as quickly as possible to a specific stimulus while maintaining accuracy (eg. pressing a button on seeing a dot/light on the computer screen).			
Crossover trials			
Barnes 2002 [89]	*Inverse of mean of slowest 10%* CPAP: NR, OP: NR Both: 2.7 (SE 0.5), n=28	*Inverse of mean of slowest 10%* CPAP: 2.6, OP: 2.6 MD (SD): 0 P value: ns (difference in change)	
Barnes 2004 [82]	*Inverse of mean of slowest 10%* CPAP: NR, Comparator: NR Both: 2.7 (SE 0.1), n=80 *Lapses (>500ms RT)* CPAP: NR, Comparator: NR Both: 2.5 (SE 0.3), n=80 *Errors* CPAP: NR, Comparator: NR Both: 7.4 (SE 0.8), n=80	*Inverse of mean of slowest 10%* CPAP: 2.7 (SE 0.1), OA: 2.7 (SE 0.1) OP: 2.6 (SE 0.1) CPAP/OA MD (SD): 0, CPAP/OP MD (SD):0.1 P value: ns *Lapses (>500ms RT)* CPAP: 2.1 (SE 0.2), OA: 2.2 (SE 0.2) OP: 2.7 (SE 0.3) CPAP/OA MD (SD): -0.1, CPAP/OP MD (SD): -0.6, P value (CPAP/OP): <0.05 *Errors* CPAP: 7.4 (SE 0.7), OA: 7.5 (SE 0.8) OP: 7.8 (SE 0.8) CPAP/OA MD (SD): -0.1, CPAP/OP	

		MD (SD): -0.4, P value: ns	
Cibele 2006[72]	Not reported	Not reported	
Marshall 2005[79]	*Mean RT(ms)* CPAP: NR, Sham CPAP: NR Both: 264 (SE 5), n=29 *Lapses (>500ms RT)* CPAP: NR, Sham CPAP: NR Both: 1.3 (SE 0.3), n=29 *Errors* CPAP: NR, Sham CPAP: NR Both: 2.8 (SE 0.5), n=29	*Mean RT(ms)* CPAP: 266 (SE 5) Sham CPAP: 259 (5) MD (SD): 7, P value: NR *Lapses (>500ms RT)* CPAP: 1.3 (SE 0.4) Sham CPAP: 1.0 (SE 0.4) MD (SD): 0.3, P value: NR *Errors* CPAP: 3.2 (SE 0.7), Sham CPAP: 3.3 (SE 0.7) MD (SD): -.01, P value: NR	
Reaction time, ms (Direction of improvement -)			
Crossover trials			
Engleman 1994[90]	CPAP: NR, OP: NR	Data not reported because there was no statistically significant difference between CPAP and oral placebo	
Engleman 1997[92]	CPAP: NR, OP: NR n=16	CPAP: 365 (SE 16), OP: 356 (SE 14) MD (SD): 9, P value: ns	
Engleman 1998[93]	CPAP: NR, OP: NR Both: 346 (SD 57), n=23	CPAP: 327 (SD 46), OP: 325 (SD 38) MD (SD): 2, P value: ns	
Rapid Visual Information Processing Task (Direction of improvement +): Single digits are presented in quick succession on a computer screen, and respondents are asked to identify (button press) target sequences of numbers.			
Crossover trials			
Engleman 1994[90]	CPAP: NR, OP: NR	Data not reported because there was no statistically significant difference between CPAP and oral placebo	
Engleman 1997[92]	CPAP: NR, OP: NR n=16	*No. Correct* CPAP: 36.9 (SE 3.2), OP: 34.8 (SE 3.2) MD (SD): 2.1, P value: ns	
Engleman 1998[93]	CPAP: NR, OP: NR Both: 28 (SD 10), n=23	*No. Correct* CPAP: 34 (SD 15), OP: 35 (SE 13) MD (SD): -1, P value: ns	
STROOP colour and word test (Direction of improvement +): Respondents are asked to name colour words printed in different colours, name the printed colours, or read a set of colour-words while naming colours of another set of colour-words.			
Crossover trials			
Barnes 2004[89]	CPAP: NR, Comparator: NR Both: 4.8 (SE 0.8), n=80	CPAP: 9.3 (SE 0.9), OA: 10.3 (SE 0.9) OP: 9.2 (SE 0.9) CPAP/OA MD (SD): -1 CPAP/OP MD (SD): 0.1 P value:ns	
Parallel trials			
Dimsdale 2000[58]	*Naming (no. correct)* CPAP: 73.6 (SE 2.5), n=20 Sham CPAP: 77.7 (SE 2.9), n=16 *Naming (errors)* CPAP: 0.3 (SE 0.2), n=20	*Naming (no. correct)* CPAP: 80.3 (SE 2.7), n=20 Sham CPAP: 82.2 (SE 3.2), n=16 MD (SD):1.9, P value:ns *Naming (errors)*	

	Sham CPAP: 0.2 (SE 0.2), n=16 *Reading (no. correct)* CPAP: 93.1 (SE 1.9), n=20 Sham CPAP: 92.4 (SE 2.2), n=16 *Reading (errors)* CPAP: 0.2 (SE 0.2), n=20 Sham CPAP: 0.2 (SE 0.2), n=16 *Inference (no. correct)* CPAP: 40 (SE 1.6), n=20 Sham CPAP: 38.5 (SE 1.9), n=16 *Inference (errors)* CPAP: 0.5 (SE 0.3), n=20 Sham CPAP: 0.4 (SE 0.3), n=16	CPAP: 0.1 (SE 0.1), n=20 Sham CPAP: 0.3 (SE 0.1), n=16 MD (SD):-0.2, P value:ns *Reading (no. correct)* CPAP: 95.6 (SE 2.0), n=20 Sham CPAP: 92.8 (SE 2.3), n=16 MD (SD):2.8, P value:ns *Reading (errors)* CPAP: 0.1 (SE 0.1), n=20 Sham CPAP: 0.01 (SE 0.1), n=16 MD (SD):0.19, P value:ns *Inference (no. correct)* CPAP: 44.2 (SE 1.8), n=20 Sham CPAP: 41 (SE 2.1), n=16 MD (SD):3.2, P value:ns *Inference (errors)* CPAP: 0.3 (SE 0.3), n=20 Sham CPAP: 0.8 (SE 0.3), n=16 MD (SD):-0.5, P value:ns	
Norman 2006[116]	*Colour* CPAP: 67.7, n=17 Sham CPAP:73.7, n=14 *Colour-word ratio* CPAP: 37.7, n=17 Sham CPAP: 37.9, n=14	*Colour* CPAP: 72.3, n=17 Sham CPAP:77.9, n=14 MD (SD):-5.6 , P value: 0.532 *Colour-word ratio* CPAP: 37.3, n=17 Sham CPAP:41.9, n=14 MD (SD): -4.6, P value: 0.061 NB. P value based on treatment x time interaction (3 treatment arms)	
Trail Making Test (Direction of improvement -): complex attention task in which respondents are asked to draw lines to connect consecutively numbered circles on one sheet (part A) and then connect the same number of consecutively numbered and lettered circles on another sheet by alternating between the two sequences (part B).			
Crossover trials			
Engleman 1994[90]	*Part A / Part B* CPAP: NR, OP: NR n=32	*Part A* Data not reported because there was no statistically significant difference between CPAP and oral placebo *Part B* CPAP: 66 (SE 5), OP: 76 (SE 5) MD (SD): -9, P value: 0.02	
Engleman 1997[92]	*Part B* CPAP: NR, OP: NR n=16	*Part B* CPAP: 64.1 (SE 5.5), OP: 77.7 (SE 9.2) MD (SD): -13.6, P value: 0.02	
Engleman 1998[93]	*Part B* CPAP: NR, OP: NR Both: 84 (SD 41), n=23	*Part B* CPAP: 69 (SD 32), OP: 68 (SD 32) MD (SD): 1, P value: ns	
Engleman 1999[78]	*Part A* CPAP: NR, OP: NR Both: 34 (SD 12), n=34 *Part B*	*Part A* CPAP: 26 (SD 11), OP: 29 (SD 11) MD (SD): -3, P value: 0.06 *Part B*	

	CPAP: NR, OP: NR Both: 76 (SD 36), n=34	CPAP: 63 (SD 33), OP: 65 (SD 27) MD (SD): -2, P value: ns	
Engleman 2002[103]	*Part B* CPAP: NR, OA: NR n=34	*Part B* CPAP: 59 (SD 21), OA: 64 (SD 28) MD (SD): -5, P value: 0.106	
Barnes 2002[89]	*Part A* CPAP: NR, OP: NR Both: 28.2 (SD 9), n=28 *Part B* CPAP: NR, OP: NR Both: 65.3 (SD 30.2), n=28	*Part A* CPAP: 28.1, OP: 27.6 MD (SD): 0.5, P value: ns *Part B* CPAP: 60.1, OP: 65.2 MD (SD): -5.1, P value: ns	
Barnes 2004[82]	*Part B* CPAP: NR, OA:NR, OP: NR All: 85.9 (SE 4.4), n=80	*Part B* CPAP: 73.3 (SE 3.3), OA: 76.0 (SE 3.7) OP: 74.2 (SE 3.6) CPAP/OA MD (SD): -2.7, CPAP/OP MD (SD): -0.9, P value: ns	
Jokic 1999[108]	*Part A* CPAP: NR, CM other: NR Both: 28.1 (SD 2.1), n=13 *Part B* CPAP: NR, CM other: NR Both: 73.8 (SE 34.7), n=13	*Part A* CPAP: 20.5 (SD 3.2), CM other: 21.9 (SD 7.9) MD (SD): -1.4, P value: 1.17 *Part B* CPAP: 56.5 (SD 7), CM other: 57.7 (SD 6.6) MD (SD): -1.2, P value: 2.18	
Parallel trials			
Barbe 2001[83]	*Part A (seconds)* CPAP: 49 (SE 4), n=29 Sham CPAP: 49 (SE 4), n=25 *Part B (seconds)* CPAP: 122 (SE 16), n=29 Sham CPAP: 108 (SE 11), n=25	*Part A (seconds)* CPAP: 47 (SE 3), n=29 Sham CPAP: 47 (SE 3), n=25 MD (SD):0, P value: >0.2 (difference in change) *Part B (seconds)* CPAP: 96 (SE 6), n=29 Sham CPAP: 110 (SE 10), n=25 MD (SD):-14, P value: 0.1 (difference in change)	
Dimsdale 2000[58]	*Part A* CPAP: 33.3 (SE 2.2), n=20 Sham CPAP: 32.4 (SE 2.7), n=16 *Part A(errors)* CPAP: 0.2 (SE 0.1), n=20 Sham CPAP: 0.1 (SE 0.1), n=16 *Part B* CPAP: 81.1 (SE 8), n=20 Sham CPAP: 88.3 (SE 9.8), n=16 *Part B(errors)* CPAP: 1.2 (SE 0.3), n=20 Sham CPAP: 0.8 (SE 0.4), n=16	*Part A* CPAP: 27.4 (SE 1.6), n=20 Sham CPAP: 27.4 (SE 2), n=16 MD (SD):0, P value:ns *Part A(errors)* CPAP: 0.03 (SE 0.1), n=20 Sham CPAP: 0.2 (SE 0.1), n=16 MD (SD):-0.17, P value:ns *Part B* CPAP: 71.2 (SE 7.1), n=20 Sham CPAP: 87 (SE 8.7), n=16 MD (SD):-14.5, P value:ns *Part B(errors)* CPAP: 0.5 (SE 0.2), n=20 Sham CPAP: 1.1 (SE 0.3), n=16	

		MD (SD):-0.6, P value:ns	
Henke 2001[85]		*Part A / Part B* Data presented as graph. No statistically significant difference between groups at follow-up.	
Lojander 1999[113]*	*Part B* CPAP: 111 (65 to 180), n=10 CM: 83 (50 to 290), n=17	*Part B* CPAP: 128 , CM: 82 MD (SD): P value:	*Part B* CPAP: 130, CM: 75 MD (SD): P value:
Monasterio 2001[100]	*Part A* CPAP: 56 (SD 26), n=66 CM: 54 (SD 18), n=59 *Part B* CPAP: 121 (SD 44), n=66 CM other: 125 (SD 47), n=59	*Part A(seconds)* CPAP: 49 (SD 19), n=66 CM: 49 (SD 20), n=59 MD (SD):0, P value: 0.76 *Part B(seconds)* CPAP: 106 (SD 42), n=66 CM: 100 (SD 39), n=59 MD (SD):6, P value: 0.15	
Norman 2006[73]	*Part A* CPAP: 32.4, n=17 Sham CPAP: 25.5, n=14 *Part B* CPAP: 70.8, n=17 Sham CPAP: 70.3, n=14	*Part A* CPAP: 26.5, n=17 Sham CPAP: 21.7, n=14, MD (SD):4.8 P value: 0.494 *Part B* CPAP: 63.4, n=17 Sham CPAP: 59.6, n=14 MD (SD):3.8, P value: 0.823 NB. P value based on treatment x time interaction (3 treatment arms)	
Verbal Fluency test (Direction of improvement +): word naming task			
Parallel trials			
Dimsdale 2000[58]	*No. Correct* CPAP: 40.6 (SE 2.9), n=20 Sham CPAP: 35.9 (SE 3.4), n=16 *Perseveration* CPAP: 1.1 (SE 0.4), n=20 Sham CPAP: 0.9 (SE 0.5), n=16 *Intrusions* CPAP: 0.2 (SE 0.1), n=20 Sham CPAP: 0.5 (SE 0.1), n=16 *Variations* CPAP: 0.5 (SE 0.3), n=20 Sham CPAP: 0.7 (SE 0.3), n=16	*No. Correct* CPAP: 44.5 (SE 2.7), n=20 Sham CPAP: 37.3 (SE 3.2), n=16 MD (SD):, P value: ns *Perseveration* CPAP: 0.8 (SE 0.3), n=20 Sham CPAP: 1.2 (SE 0.3), n=16 MD (SD):-0.4, P value: ns *Intrusions* CPAP: 0.1 (SE 0.1), n=20 Sham CPAP: 0.4 (SE 0.2), n=16 MD (SD):-0.3, P value: ns *Variations* CPAP: 0.6 (SE 0.2), n=20 Sham CPAP: 0.8 (SE 0.3), n=16 MD (SD):-0.2, P value: ns	
Monasterio 2001[100]	*Score: percentile* CPAP: 69 (SD 29), n=66 CM: 66 (SD 28), n=59	*Score: percentile* CPAP: 69 (SD 27), n=66 CM: 70 (SD 29), n=59 MD (SD):-1, P value: 0.53	
Norman 2006[73]	*Total score*	*Total score*	

	CPAP: 38.4, n=17 Sham CPAP: 42.3, n=14	CPAP: 40.9, n=17 Sham CPAP: 45.5, n=14 MD (SD):-4.6, P value: 0.149 NB. P value based on treatment x time interaction (3 treatment arms)	
Wechsler Adult Intelligence Scales: Neuropsychological test battery			
Crossover trials			
Barnes 2002[89]	*Digit symbol substitution task* CPAP: NR, OP: NR Both: 46.5 (SD 4.0), n=28	*Digit symbol substitution task* CPAP: 47.3, OP: 48.0 MD (SD): -0.7, P value: 0.07 (difference in change)	
Barnes 2004 [82]	*Digit symbol substitution task* CPAP: NR, OA: NR, OP: NR All: 46.4 (SE 0.4), n=80 *Digit backwards* CPAP: NR, OA: NR, OP: NR All: 4.4 (SE 0.1), n=80	*Digit symbol substitution task* CPAP: 47.3 (SE 0.4), OA: 47.5 (SE 0.4) OP: 46.8 (SE 0.4) CPAP/OA MD (SD): -0.2 CPAP/OP MD (SD): 0.5 P value: ns *Digit backwards* CPAP: 4.6 (SE 0.1), OA: 4.6 (SE 0.1) OP: 4.8 (SE 0.1) CPAP/OA MD (SD): 0 CPAP/OP MD (SD): -0.2 P value: ns	
Engleman 1994[90]	*Digit symbol substitution task* CPAP: NR, OP: NR n=32 *Block design* CPAP: NR, OP: NR n=32	*Digit symbol substitution task* CPAP: 52.0 (SE 2.0) OP: 51.0 (SE 2.0) MD (SD): 1, P value: 0.05 *Block design* Data not reported because there was no statistically significant difference between CPAP and oral placebo	
Engleman 1998[93]	*Digit symbol substitution task* CPAP: NR, OP: NR Both: 48.0 (SD 12.0), n=23 *Block design* CPAP: NR, OP: NR Both: 29.0 (SD 11.0), n=23	*Digit symbol substitution task* CPAP: 52.0 (SD 13.0), OP: 52.0 (SD 14.0) MD (SD): 0, P value: ns *Block design* CPAP: 33.0 (SD 9.0), OP: 31.0 (SD 8.0) MD (SD): 2, P value: ns	
Engleman 1999[78]	*Digit symbol substitution task* CPAP: NR, OP: NR Both: 54.0 (SD 12.0), n=34 *Block design* CPAP: NR , OP: NR Both: 29.0 (SD 10.0), n=34	*Digit symbol substitution task* CPAP: 59.0 (SD 12.0) OP: 57.0 (SD 14.0) MD (SD): 2, P value: 0.0004 *Block design* CPAP: 31.0 (SD 12.0) OP: 32.0 (SD 10.0) MD (SD): -1, P value: ns	
Parallel trials			
Barbe 2001[83]	*Digit symbols* CPAP: 42.0 (SE 2.0), n=29	*Digit symbols* CPAP: 43.0 (SE 3.0), n=29	

	OP: 44.0 (SE 4.0), n=25 *Block design* CPAP: 33.0 (SE 1.0), n=29 OP: 32.0 (SE 2.0), n=25 *Digit forward* CPAP: 9.0 (SE 0.3), n=29 OP: 10.0 (SE 0.4), n=25	OP: 47 (SE 4.0), n=25 MD (SD): -4, P value: >0.20 (difference in change) *Block design* CPAP: 34.0 (SE 1.0), n=29 OP: 33.0 (SED 2.0), n=25 MD (SD): 1, P value: >0.20 (difference in change *Digit forward* CPAP: 9.0 (SE 0.3), n= 29 OP: 10.0 (SE 1.0), n=25 MD (SD): -1, P value: >0.20 (difference in change)	
Dimsdale 2000[73]	*Digit symbols* CPAP: 51.3 (SE 2.3), n=20 Sham CPAP: 52.9 (SE 2.8), n=16 *Digit forward* CPAP: 8.1(SE 0.7), n=20 Sham CPAP: 8.6 (SE 0.8), n=16 *Digit forward + backward* CPAP: 14.7(SE 1.1), n=20 Sham CPAP: 14.7 (SE 1.2), n=16	*Digit symbols* CPAP: 53.2 (SE 2.5), n=20 Sham CPAP: 53.5 (SE 3.0), n=16 MD (SD): -0.3, P value: *Digit forward* CPAP: 8.6 (SE 0.6), n=20 Sham CPAP: 8.7 (SED 0.7), n=16 MD (SD): -0.1, P value: *Digit forward + backward* CPAP: 16.2 (SE 1.1), n= 20 Sham CPAP: 15.1 (SE 1.3), n=16 MD (SD): 1.1, P value:	
Henke 2001[85]	*Digit symbols* *Digit backwards*	Data presented as graphs. Rather than assess change scores a binary variable was created of improved or not improved and the two groups were compared based on this. No significant difference between groups.	
Lojander 1999[113]*	*Verbal intelligence quotient* CPAP: 121 (110 to 148), n=10 CM: 111 (91 to 140), n=17 *Performance quotient* CPAP: 115 (110 to 143), n=10 CM: 114 (84 to 147), n=17	*Verbal intelligence quotient* CPAP: 115, n=10 OP: 104, n=16 MD (SD): , P value: ns *Performance quotient* CPAP: 123, n=10 OP: 109, n=16 MD (SD): P value: ns	*Verbal intelligence quotient* CPAP: 114, n=9 OP: 105, n=12 MD (SD): , P value: ns *Performance quotient* CPAP: 106, n=9 OP: 109, n=12 MD (SD): P value: ns
Monasterio 2001[100]	*Digit symbols* CPAP: 9 (SD 3), n=66 CM: 9 (SD 3), n=59 *Block design* CPAP: 10 (SD 3), n=66 CM: 10 (SD 3), n=59 *Digit forward + backward* CPAP: 10 (SD 2), n=66 CM: 10 (SD 3), n=59	*Digit symbols (scaled score)* CPAP: 9.0 (SD 3.0), n=66 CM: 9.0 (SD 2.0), n=59 MD (SD): 0, P value: 0.97(difference in change) *Block design (Scaled score)* CPAP: 11.0 (SD 3.0), n=66 CM: 11.0 (SD 3.0), n=59 MD (SD): 0, P value: 0.82 (difference in change)	

		Digit forward + backward (scaled score: mean 10, SD 3) CPAP: 11.0 (SD 3.0), n=66 CM: 11.0 (SD 2.0), n=59 MD (SD): 0, P value: 0.56 (difference in change)	
Norman 2006[73]	*Digit symbols* CPAP: 65.8, n=17 Sham CPAP: 67.6, n=14 *Digit forward* CPAP: 18.6, n=17 Sham CPAP: 21.2, n=14 *Letter sequencing* CPAP: 11.0, n=17 Sham CPAP: 11.7, n=14 *Symbol search* CPAP: 31.8, n=17 Sham CPAP: 32.1, n=14	*Digit symbols (no. correct)* CPAP: 73.8, n=17, CM: 68.7, n=14 MD (SD): 5.1, P value: 0.256 *Digit forward (total score)* CPAP: 26.4, n=17, CM: 22.5, n=14 MD (SD): 3.9, P value: 0.378 *Letter sequencing* CPAP: 11.9, n=17, CM: 12.9, n=14 MD (SD): -1, P value: 0.827 *Symbol search (no. correct)* CPAP: 33.8, n=17, CM: 37.7, n=14 MD (SD): -3.9, P value: 0.614 NB. P value based on treatment x time interaction (3 treatment arms)	
Wechsler Memory Scale (Direction of improvement +): Battery of memory tests.			
Crossover trials			
Barnes 2002[89]	*Visual reproduction* CPAP: NR, OP: NR Both: 33.5 (SD 5.4), n=28	*Visual reproduction* CPAP: 34.7, OP: 35.1 MD (SD): -0.4, P value: ns	
Jokic 1999[108]	No baseline data N=13	*Visual reproduction* CPAP: 10.6 (SD 4.4), CM other: 10.3 (SD 2) MD (SD): 0.3, P value: 0.72 *Orientation* CPAP: 5.0 (SD 0), CM other: 5.0 (SD 0) MD (SD): 0, P value: 1 *Information* CPAP: 5.5 (SD 1.2), CM other: 5.9 (SD 0) MD (SD): -0.4, P value: 0.14 *Mental control* CPAP: 7.3 (SD 2.1), CM other: 7.4 (SD 1.2) MD (SD): -0.1, P value: 0.9 *Logical memory* CPAP: 11.4 (SD 3.3), CM other: 12.0 (SD 3.8) MD (SD): -0.6, P value: 0.42 *Associate learning* CPAP: 14. 8 (SD 1.0), CM other: 16.6 (SD 4.2) MD (SD): -1.8, P value: 0.06 *Digit forward* CPAP: 6.5 (SD 2.1), CM other: 6.5 (SD	

		1.5) MD (SD): 0, P value: 1 *Digit backwards* CPAP: 4.9 (SD 2.1), CM other: 5.0 (SD 1.7) MD (SD): -0.1, P value: 0.86 *Recall (logical memory)* CPAP: 9.0 (SD 5.0), CM other: 9.5 (SD 3.5) MD (SD): -0.5, P value: 0.52 *Recall (visual reproduction)* CPAP: 9.2 (SD 4.5), CM other: 9.9 (SD 2.1) MD (SD): -0.7, P value: 0.15 *Recall (associate learning)* CPAP: 6.1 (SD 3.1), CM other: 6.3 (SD 3.3) MD (SD): -0.2, P value: 0.54 *Memory Quotient* CPAP: 122.2 (SD 24.7), CM other: 122.8 (SD 20.2) MD (SD): -0.6, P value: 0.83	
Parallel trials			
Barbe 2001[83]	*Mental control* CPAP: 6.0 (SE 0.4), n=29 Sham CPAP: 6.0 (SE 1.0), n=25 *Verbal paired associate* CPAP: 14 (SE 1.0), n=29 Sham CPAP: 15 (SE 1.0), n=25	*Mental control* CPAP: 6.0 (SE 0.4), n=29 Sham CPAP: 7.0 (SE 0.4) MD (SD): -1, P value: >0.20 (difference in change) *Verbal paired associate* CPAP: 15.0 (SE 1.0), n=29 Sham CPAP: 15.0 (SE 1.0), n=25 MD (SD): 0, P value: >0.20 (difference in change)	
Lojander 1999[113]*	*Memory Quotient* CPAP: 128 (105 to 151), n=10 CM: 118 (99 to 150), n=17	CPAP: 129 n=10, CM: 115, n=16 MD (SD):, P value: ns	CPAP: 121 n=9, CM: 120, n=12 MD (SD): , P value: ns
Monasterio 2001[100]	No baseline data reported	*Mental control (percentile)* CPAP: 51.0 (SD 274), n=66 CM: 53.0 (SD 27.0), n=59 MD (SD): -2 , P value: 0.08 (difference in change) *Verbal paired associate (percentile)* CPAP: 41.0 (SD 30.0), n=66 CM: 43.0 (SD 32.0), n=59 MD (SD): -2, P value: 0.63 (difference in change) *Verbal paired associate (percentile)* CPAP: 61.0 (SD 24.0), n=66 CM: 63.0 (SD 25.0), n=59 MD (SD): -2, P value: 0.06 (difference in	

		change)	
Word Paired Memory Recall (Direction of improvement +): respondents were asked to learn a series word-pair associates, this was followed by a retention period, after which respondents were asked to recall target words.			
Crossover trials			
Barnes 2002[89]	CPAP: NR, OP: NR Both: 1.5 (SD 1.2), n=28	CPAP: 1.9, OP: 1.55 MD (SD): 0.35, P value: ns	

CPAP: Continuous Positive Airway Pressure; Sham CPAP: subtherapeutic CPAP; OP: Oral placebo; OA: Oral appliance; CM: conservative management. * Values presented are median (range); ** values presented are median (5^{th} -95^{th} percentile);***values are median (interquartile range)

Table 11.14 Test procedures for neurocognitive trials

Study	Time of day	Caffeine / medication	Test order	Environment	Special exclusion criteria	Test-retest
Barbe 2001[83]	None reported	Drug intake and alcohol consumption were assessed at each test period	None reported	None reported	Cognitive deterioration of any cause, illicit drugs or excessive alcohol use	None reported
Barnes 2002[89]	The NAB was administered 3 times during the day of the MSLT and a mean score was computed to account for time of day effects. Other NC tests were only administered during the first session.	None reported	None reported	None reported	Fluency of English language, no history of cerebrovascular disease, closed head injury associated with loss of consciousness greater than 15 mins, psychiatric illness, or drug or alcohol abuse.	Participants attended a familiarisation session 1 week prior to baseline assessment and performed an abbreviated version of the neurocognitive tests
Barnes 2004[82]	None reported	Clinically significant depression was present in 40 % of the OSAHS participants (as measured by BDI).	None reported	None reported	Fluency of English language, no history of cerebrovascular disease, closed head injury associated with loss of consciousness greater than 15 mins, psychiatric illness, or drug or alcohol abuse.	Participants attended a familiarisation session 1 week prior to baseline assessment and performed an abbreviated version of the neurocognitive tests.
Cibele 2006[72]	NR	NR	NR	NR	NR	NR
Dimsdale [117]	Tests were administered early afternoon.	None reported	None reported	None reported	No major illness, other than OSA, hypertension medication tapered before participation.	Alternate forms were used for word fluency test (considered to be most likely test to show a learning effect)
Engleman 1994[90]	Cognitive function was assessed in-	Participants were asked to avoid caffeine-	Tests were conducted on the last day of	None reported	None reported	Participants attended a familiarisation

Study	Time of day	Caffeine / medication	Test order	Environment	Special exclusion criteria	Test-retest
	between MSLT naps across the course of a day.	containing drinks before attending assessments and offered only decaffeinated drinks during the assessment day.	each treatment period and were administered in a standardised order at the same time of day.			session with the psychometric battery prior to baseline assessment. Alternative forms of two neurocognitive tests were used at follow-up assessment.
Engleman 1997[92]	Assessments were conducted across the day.	None reported	Tests were conducted on the last day of each treatment period and were administered in a standardised order.	None reported	Individuals with co-existing neurological disorders were excluded.	Participants attended a familiarisation session with the psychometric battery prior to baseline assessment. Alternative forms of two neurocognitive tests were used at follow-up assessment.
Engleman 1998[93]	None reported	None reported	Tests were administered in a standardised order.	None reported	Individuals with co-existing neurological disorders were excluded.	None reported
Engleman 1999[78]	Afternoon, during "post-lunch dip" in performance.	None reported	Tests were administered in a standardised order.	None reported	None reported	Participants attended a familiarisation session with the psychometric battery prior to baseline assessment.
Engleman 2002[103]	None reported	None reported	None reported	None reported	None reported	NR
Henke 2001[85]	Tests were administered between 2pm and 6 pm.	None reported	None reported	None reported	None reported	Participants attended a familiarisation session with the psychometric battery prior to baseline assessment. Four parallel test packets were administered on a randomised counterbalanced schedule.
Hoekema 2006[300]	Between noon and 2 pm.	Participants were instructed to refrain from stimulating products, such as caffeine, up to 3 hrs before testing and not to smoke 30 mins before	Test was administered at the same time of day in subsequent sessions.	Room conditions: light were dimmed, noise shut out, and room temperature was kept at 22C> the test was completed	Individuals without a driving licence, or involved with shift work or night-time work were excluded.	A practice session immediately prior to baseline assessment was provided.

Study	Time of day	Caffeine / medication	Test order	Environment	Special exclusion criteria	Test-retest
		testing.		in the absence of company.		
Jenkinson 1999[118]	3 30 minute drives (11.000, 12.00 and 14.00 hours)	None reported	The tests were performed at the same time of day on each occasion.	None reported	Individuals considered too mentally impaired to provide reliable informed consent were excluded.	An initial training drive was administered prior to the first drive on each day.
Jokic 1999[108]	Cognitive tests were administered after the third MSLT test, which was conducted 2 hrs after waking and given at 2 hr intervals.	Participants were asked to avoid caffeine-containing drinks before attending assessments and offered only decaffeinated drinks during the assessment day. A urine toxicology screen was performed on day 15 of each study limb for use of any drugs that might affect sleep quality or daytime function.	Each test was administered at the same time of day on each study limb. Order was balanced throughout study.	None reported	None reported	Participants attended a familiarisation session with the psychometric tests prior to baseline assessment.
Lojander 1995[113]	Tests were performed in the morning.	None reported	None reported	None reported	Individuals with other diseases and daytime hypoxemia were excluded.	None reported
Marshall 2005[79]	PVT was administered twice a day with a 1 minute practice session before each 10 minute data collection session at 14.30 and 16.30 on each of the four study days (beginning and end of each treatment period).	None reported	Testing procedures were time of day fixed.	None reported	Individuals who performed shift workers, with extreme somnolence requiring immediate treatment, had a chronic sleep restriction, taking sedatives, alcohol intake > 3 standard units/24 hrs or caffeine dependency were excluded.	None reported
Monasterio 2001[100]	Tests were administered at 9am.	None reported	Testing procedures were administered at the same time each session.	None reported	Individuals with hazardous jobs (drivers or those handling dangerous machinery), conditions that might affect cognition or QOL (severe neurological disease, psychiatric disease, severe chronic disease, or illiteracy)	None reported
Norman 2006 [116]	Tests were administered at 1pm.	None reported	None reported	None reported	Individuals were excluded if they had a history of heart, liver, renal disease, diabetes, psychosis, narcolepsy,	Employed alternate forms for tests.

Study	Time of day	Caffeine / medication	Test order	Environment	Special exclusion criteria	Test-retest
					current drug or alcohol abuse, severe asthma, or cerebrovascular disease, were pregnant, or were taking prescription medications except hypertensive medication. Those taking hypertensive underwent a 3 wk washout period before study entry.	

Figure 11.23 Apnoea-Hypopnoea Index (CPAP versus placebo/usual care)

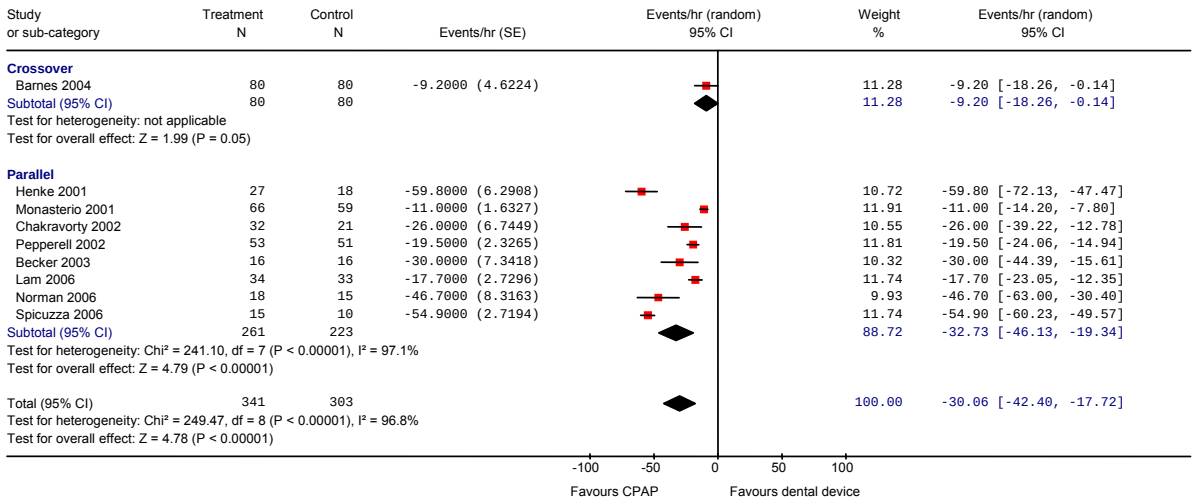
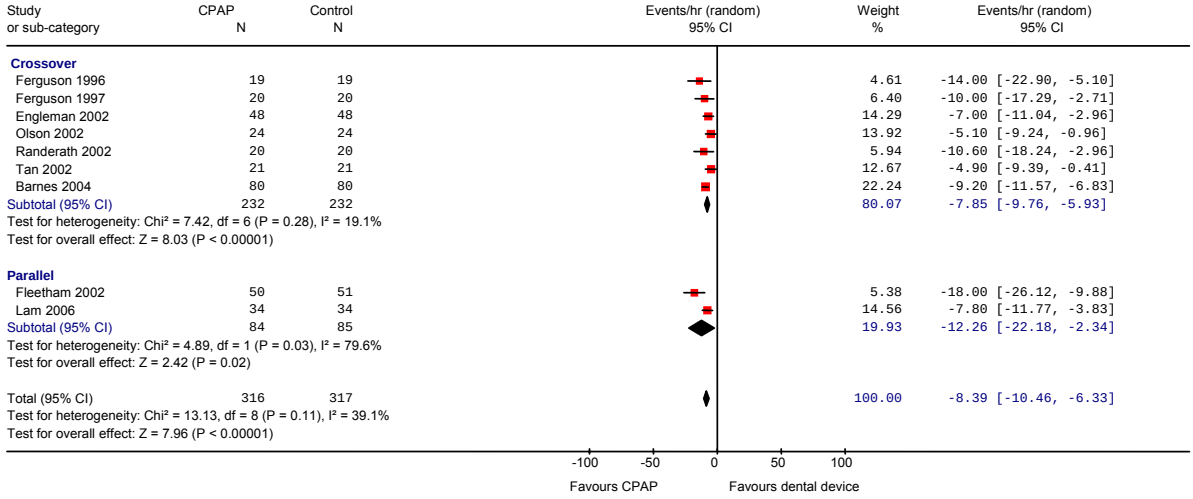


Figure 11.24 Apnoea-Hypopnoea Index (CPAP versus dental device)



11.5 Data extraction tables for clinical effectiveness trials

<table>
<tr><th>Study details</th><th>Intervention</th><th>Participants</th></tr>
<tr>
<td>Arias 2005 [56]
Related papers [301, Arias, 2005 Arias, 2005 #1425, #1428, 302-304]

Country Spain

Design Crossover study.

Duration 2 x 12 weeks (no washout period).

Inclusion criteria Men with OSAHS.

Exclusion criteria Obstructive or restrictive lung disease demonstrated on pulmonary function testing, current use of cardioactive medication, cardiac rhythmn disturbances, hypertension or 24 hr mean blood pressure of 135 and/or 85 mmHg or more, left ventricular ejection fraction <50%, ischemic or</td>
<td>CPAP (following a full night titration using an automated pressure setting device to set the pressure)

Comparator Sham nasal CPAP.</td>
<td>Number randomised Total: 27 (baseline data for BP is presented for completers (n=25))

Number of withdrawals Total: 2 CPAP: 2 Comparator: 0

Reasons for withdrawals Participants were not included in analysis due to insufficient use of CPAP.

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>52 (SD 13) yrs</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n= 27</td><td></td><td></td></tr>
<tr><td>AHI</td><td>29.0 (SD 26.9)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>BMI</td><td>30.5 (SD 4.0) Kg/m^2</td><td></td><td></td></tr>
<tr><td>Blood pressure (mmHg):
Daytime SBP
Daytime DBP
Nightime SBP
Nightime DBP</td><td>
127 (SD 9)
79 (SD 5)
118 (SD 11)
71 (SD 7)</td><td></td><td></td></tr>
</table>
Additional information 24hr blood pressure (BP), urinary catecholamines, heart rate, and ecocerdiographic parameters. Outcomes were assessed at study entry and after first treatment period and</td>
</tr>
</table>

<table>
<tr><td>valvular heart disease, hypertrophic restrictive or infiltrative cardiomyopathy, pericardial disease or stroke, diabetes mellitus, morbid obesity, daytime hypoxemia or hypercapnia.</td><td></td><td>after second treatment period. BP was measured every 30 minutes from 8am to 11pm and every 60 minutes from 11pm to 8am using a cuff.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Arias 2006 [63]

Country Spain

Design Crossover trial (outcome data appeared to be from the first sequence and data were treated as parallel data)

Duration 2 X 12 weeks (no washout period).

Inclusion criteria Individuals with OSA (AHI >9 and ESS>9), and in whom pulmonary artery systolic pressure (PASP) could be estimated.

Exclusion criteria Obstructive or restrictive lung disease demonstrated on pulmonary function test, connective tissue or chronic thrombo-</td><td>CPAP (following a full night titration using an automated pressure setting device to set the pressure)
Adherence to treatment: 6.2 hrs/night (SD 1.1).

Comparator Sham CPAP.
Adherence to treatment: 5.8 hrs/night (SD 1.4).</td><td>Number randomised Total: 23 CPAP: NR Comparator: NR

Number of withdrawals Total: 2 CPAP: NR Comparator: NR

Reasons for withdrawals 2 participants not included in the analyses due to insufficient (< 3.5 hr/night) CPAP use.

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>51 (SD 13) yrs</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=22
Female n=1</td><td></td><td></td></tr>
<tr><td>AHI</td><td>44.1 (SD 29.3)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>BMI</td><td>30.9 (SD 4) Kg/m^2</td><td></td><td></td></tr>
<tr><td>Blood pressure (mmHg):
Daytime SBP
Daytime DBP
Nightime SBP
Nightime DBP</td><td>

127 (SD 10)
79 (SD 5)
118 (SD 12)
71 (SD 7)</td><td></td><td></td></tr>
</table></td></tr>
</table>

<table>
<tr><td>embolic diseases, current cardioactive medication, cardiac rhythm disturbances, known hypertension or 24hr mean BP of 135 and/or 85 mmHg or more, left ventricular ejection fraction <50%, iscaemic or valvular heart disease, cardiomyopathy, pericardial disease or stroke, diabetes, morbid obesity, day-time hypoxaemia or hypercapnia, history of cocaine or antidepressant drug use.</td><td></td><td>Additional information 24hr BP, heart rate, ecocardiographic parameters, urinary catecholamines and levels of pulmonary artery pressure were assessed at study entry and after each 12 week treatment period. Ambulatory BP monitoring was performed using an oscillometric method.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Ballester 1999 [96]

Setting Spain

Design Parallel

Duration 12 weeks

Notes Two patients randomised to CPAP group for every one randomised to control group, 9 patients excluded.

Inclusion criteria
Men and women with severe symptoms and AHI >15 or mild to</td><td>CPAP CPAP (following full-night titration using an automated pressure setting device) and conservative treatment

Adherence (hrs/nt): 5.2 (+/-2). Adequate compliance (defined as >4.5 hrs/night) was achieved in 73% of participants.

Comparator Conservative treatment (postural advice, avoid sedatives and alcohol, lose weight)</td><td>Number randomised Total: n=105 CPAP: n=68 Comparator: n=37

Number of withdrawals Total:Unclear CPAP: n=0 Comparator: Not reported

Reasons for withdrawals No record of dropouts recorded for control group.

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>53 (SD 10) yrs</td><td>53 (SE 1.3)</td><td>54 (SE 1.5)</td></tr>
<tr><td>Sex</td><td>Male n= 92
Female n= 13</td><td>Male n= 60
Female n= 8</td><td>Male n= 32
Female n= 5</td></tr>
<tr><td>AHI</td><td>56 (SD 20)</td><td>55 (SE 2.7)</td><td>58 (SE 3)</td></tr>
<tr><td>ESS</td><td>12 (SD5)</td><td>12.1 (SE 0.6)</td><td>11.4 (SE 1)</td></tr>
<tr><td>BMI</td><td>32 (SD 6) kg/m^2</td><td>32 (SE 0.6)</td><td>34 (SE 1.2)</td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td>-</td><td>-</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>moderate symptoms and AHI>10.</td><td></td><td>
<table>
<tr><td>Sleep Questionnaire</td><td></td><td>23.2 (SE 0.8)</td><td>21.0 (SE 1.2)</td></tr>
<tr><td>Associated symptoms</td><td></td><td>43.4 (SE 0.8)</td><td>41.8 (SE 1.1)</td></tr>
<tr><td>Daytime function</td><td></td><td>33.9 (SE 1.3)</td><td>32.3 (SE 1.7)</td></tr>
<tr><td>NHP:
Emotional reactions
Sleep
Physical
Social isolation
Pain
Energy</td><td></td><td>
28.4 (SE 3.3)
30.1 (SE 3.3)
24.2 (SE 2.6)
14.2 (SE 2.3)
20.5 (SE 3.3)
34.3 (SE 4.7)</td><td>
29.4 (SE 5.0)
23.1 (SE 3.8)
25.0 (SE 3.6)
13.2 (SE 3.0)
20.6 (SE 4.0)
23.2 (SE 4.6)</td></tr>
</table>
</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Barbè 2001[83]

Setting Spain

Design Parallel

Duration 6 weeks

Inclusion criteria Men and women with an AHI >30, an ESS of 10 or less and had no or mild symptoms of daytime sleepiness. Participants with severe cardiac disease were excluded.</td><td>CPAP (following full-night titration)
Adherence to treatment: 5hrs/night.

Comparator Sham CPAP (no pressure added) following mock titration.
Adherence was not reported for the control group. However, treatment adherence was reported to be similar in both groups.</td><td>Number randomised Total: 55 CPAP: 29 Comparator: 26

Number of withdrawals Total: 1 CPAP: 0 Comparator: 1

Reasons for withdrawals Loss to follow-up due to change in residence.

Baseline characteristics (baseline data is presented for completers, n=54)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td></td><td>54 (SD 2) yrs</td><td>52 (SD 2) yrs</td></tr>
<tr><td>Sex</td><td>Male n=49
Female n=5</td><td>Male n=26
Female n=3</td><td>Male n=23
Female n=2</td></tr>
<tr><td>AHI</td><td></td><td>54 (SD 3)</td><td>57 (SD 4)</td></tr>
<tr><td>ESS</td><td></td><td>7 (SE 0.4)</td><td>7 (SE 0.4)</td></tr>
<tr><td>BMI</td><td></td><td>29 (SD1) kg/m^2</td><td>29 (SD 0.4) kg/m^2</td></tr>
<tr><td>Blood pressure:</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

		24 hr systolic: 126 (SE 2) / 123 (SE 2) diurnal systolic: 130 (SE 2) / 127 (SE 2) nocturnal systolic: 118 (SE 2) / 118 (SE 3) 24 hr diastolic: 79 (SE 1) / 77 (SE 2) diurnal diastolic: 82 (SE 1) / 80 (SE 2) nocturnal diastolic: 73 (SE 1) / 73 (SE 2) SF-36: PCS score: 49 (SE 1) / 48 (SE 1) MCS score: 51 (SE 2) / 50 (SE 2) FOSQ: 102 (SE 3) / 107 (SE 3) MSLT, min: 12 (SE 1) / 10 (SE 1) **Additional information** Outcomes: ESS, FOSQ, BP, AHI, MSLT, SF-36, and cognitive function (see Table 11.13).
Study details	**Intervention**	**Participants**
Barnes 2002 [89] **Setting** Australia **Design** Crossover **Duration** Two periods of 8 weeks. No washout period. **Inclusion criteria** Mean and women with an AHI of 5-30 with symptoms of sleep disordered breathing.	**CPAP** Adherence (hrs/nt): 3.53 (n=23) **Comparator** Oral placebo (lactose tablet)	**Number randomised** Total: n=42 **Number of withdrawals** Total: n=14 CPAP: Not reported Comparator: Not reported **Reasons for withdrawals:** Work commitments (n=6), intolerance of CPAP (n=5), unrelated surgery (n=1), subsequent diagnosis of periodic limb movement syndrome (n=1), and loss of interest (n=1) **Baseline characteristics** Age: Total 45.5 (SD 10.7) Sex: Total Male: n=35, Female: n=7

<table>
<tr>
<td>Participants excluded who suffered from excessive daytime sleepiness requiring urgent treatment.</td>
<td></td>
<td>
<table>
<tr><td>AHI</td><td>12.9 (SD 4.24)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>11.2 (SD 5)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>30.2 (SD 4.8)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>MSLT, min</td><td>12.5 (SD 4.8)</td><td></td><td></td></tr>
<tr><td>Symptom questionnaire:
Sleepiness
Sleep fragmentation
Personality change
Morning confusion
Total score</td><td>
26.3 (SD 9.4)
21.9 (SD 9.5)
8.6 (SD 6.1)
6.4 (SD 5.3)
63.2 (SD 21.7)</td><td></td><td></td></tr>
<tr><td>FOSQ:
General productivity
Social outcome
Activity level
Vigilance
Intimate relationships
Total score</td><td>
3.3 (SD 0.6)
3.2 (SD 1.0)
3.1 (SD 0.6)
3.0 (SD 0.7)
3.0 (SD 1.3)
0.8 (SD 0.1)</td><td></td><td></td></tr>
</table>

7 participants were hypertensive at study entry (defined as BP >140mmHg, or a mean 24-hr diastolic BP >90mmHg).

Additional information Outcomes: ESS, FOSQ, AHI, MSLT, symptoms, and cognitive function (see Table 11.13).</td>
</tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Barnes 2004 [82]

Setting Australia</td><td>CPAP Treatment adherence (machine usage): 3.6 hrs/nt (+/- 0.3) and 4.2 nights/per week (+/- 0.3).</td><td>Number randomised Total: Unclear, at least 99 randomised.

Number of withdrawals Total: 30 CPAP: 8 MAS: 14 Oral: 8</td></tr>
</table>

Design Three-way crossover trial.

Duration 3 x 12 weeks (two-week washout period between each treatment).

Notes Authors report that 80 participants completed all three treatment arms.

Inclusion criteria Patients with mild to moderate OSA.

Comparator

1. Mandibular advancement splint (MAS). Mean mandibular advancement was 10.3mm (range 1 to 13mm). MAS was advanced weekly during a wash-in period as tolerated by the participant until the maximum confortable protrusion was reached. The screw was sealed. Treatment adherence (self-reported): 5.5 hrs/nt (+/- 0.3) and 5.3 nights/per week (+/- 0.3)
2. Placebo (dummy pill). Treatment adherence (pill count): tablets taken for 94.3% (+/- 1.2) treatment nights.

Reasons for withdrawals CPAP: time commitments (n=5), relocated (n=1), intolerant to CPAP (n=1), illness (n=1).
MAS: teeth unsuitable for MAS (n=5), time commitments (n=2), did not tolerate MAS (n=2), unrelated illness (n=1), lost weight and felt better (n=1), lost to follow-up (n=1).
Placebo: time commitments (n=6), wanted CPAP treatment (n=1), illness (n=1).

Baseline characteristics

	Total	CPAP	Comparator
Age	47 (SE 0.9) yrs		
Sex	Male n=64 Females n=16		
AHI	21.3 (SE 1.3)		
ESS	10.7 (SE 0.4)		
BMI	31.1 (SE 0.5)		
Blood pressure: 24 hr Systolic BP 24 hr Diastolic BP Night diastolic	 126.5 (SE 1.0) 76.3 (SE 0.8) 69.4 (SE 1.3)		
FOSQ, mean score	3.1 (SE 0.1)		
SASQ	64.7 (SE 1.7)		
POMS – total mood disorder	15.5 (SE 2.0)		
BDI	9.2 (SE 0.5)		
SF 36	69.4 (SE 1.3)		

16 participants were hypertensive (defined as: >140 and/or BP diastolic >90)

<table>
<tr><td></td><td></td><td>Additional information Outcomes were measured at baseline and at the end of each intervention period: ESS, FOSQ, ODI 4%, AHI, MWT, SF-36, and cognitive function (see Table 11.13).</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Becker 2003 [84, 109]
Related papers[84, 305]

Setting Germany

Design Parallel placebo controlled trial

Duration 9 weeks.

Notes A maximum of 4 patients per week could be included in the study. If more than one patient was eligible on one day, the patient with the most pronounced sleep apnoea was invited to participate first.

Inclusion criteria Men and women with OSA (AHI greater than 5 and excessive daytime sleepiness).

Exclusion criteria Predominantly central sleep apnoea, respiratory failure, heart failure, myocardial infarction 3 months before the study, relevant cardiac arrhythmia, and</td><td>CPAP (following overnight manual titration)
Adherence (hrs/nt): 5.5 (SD 2.0)

Comparator Sham CPAP (Pressure 3 or 4 cm H_20). Adherence (hrs/nt): 5.4 (SD 2.2)</td><td>Number randomised Total: 60 CPAP: 30 Comparator: 30

Number of withdrawals Total: 28 CPAP: 14 Comparator: 14

Reasons for withdrawals CPAP: refused to continue n=3, technical fault with BP device n=6, antihypertensive medication change n=3, other =2.
Comparator: refused to continue n=2, technical fault with BP device n=5, antihypertensive medication change n=4, other =3.

Baseline characteristics (presented for completers only)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age (yrs)</td><td></td><td>54.4 (SD 8.9)</td><td>52.3 (SD 8.4)</td></tr>
<tr><td>Sex</td><td>Male n=29
Female n=3</td><td>Male n=15
Female n=1</td><td>Male n=14
Female n=2</td></tr>
<tr><td>AHI</td><td></td><td>62.5 (SD 17.8)</td><td>65.0 (SD 26.7)</td></tr>
<tr><td>ESS</td><td></td><td>14.4 (SD 2.5)</td><td>14.1 (SD 3.2)</td></tr>
<tr><td>BMI ($Kg/m^{2)}$</td><td></td><td>33.3 (SD 5.1)</td><td>33.5 (SD 6.0)</td></tr>
<tr><td>Blood pressure (mmHg):
24 hr BP
24 hr SBP
24 hr DBP
Daytime BP
Daytime SBP
Daytime DBP</td><td></td><td>

100.4 (SD 15.9)
135.9 (SD 17.5)
83.4 (SD 15.9)
103.6 (SD 16.1)
140.1 (SD 17.6)
86.4 (SD 16.1)</td><td>

99.5 (SD 12.3)
136.2 (SD 13.1)
81.1 (SD 12.3)
103.5 (SD 12.1)
141.0 (SD 13.8)
85.4 (SD 12.3)</td></tr>
</table></td></tr>
</table>

<table>
<tr>
<td>professional driver.</td>
<td></td>
<td>
<table>
<tr><td>Nighttime BP</td><td></td><td>96.2 (SD 17.6)</td><td>93.6 (SD 15.2)</td></tr>
<tr><td>Nighttime SBP</td><td></td><td>129.9 (SD 20.0)</td><td>129.2 (SD 16.9)</td></tr>
<tr><td>Nighttime DBP</td><td></td><td>79.1 (SD 17.0)</td><td>75.4 (SD 15.2)</td></tr>
</table>

8/16 in CPAP group hypertensive. 13/16 in control group hypertensive.

Additional information The outcomes that were measured at baseline and at 9 weeks: Daytime mean arterial pressure, night-time mean arterial pressure, ESS, AHI, REM%, Min SaO2. BP was measured using a cuff (recording time was limited to 20hrs). During the diagnostic period. participants spent an 7.2 hrs in bed; nighttime BP was calculated for this time period. Daytime BP was recorded for the remaining 12 hrs.</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Campos-Rodriguez 2006 [65]

Setting Spain.

Design Parallel group trial.

Duration 4 weeks.

Inclusion criteria Adults with OSAHS and hypertension (defined as >140/90mmHg in 3 independent measurements.

Exclusion criteria Greater than 30% central sleep apnoea, respiratory failure, heart failure, ischeamic heart disease, cardiac arrythmia, neoplastic</td>
<td>CPAP (following a full-night titration) Adherence not reported.

Comparator
Sham CPAP (pressure <2cm H_20) (following a mock titration night)</td>
<td>Number randomised Total: 72 CPAP: 36 Comparator: 36

Number of withdrawals Total: 4 CPAP: 2 Comparator: 2

Reasons for withdrawals CPAP: one participant changed treatment, and one did not attend follow-up. Comparator: one did not tolerate placebo and one changed antihypertensive treatment.

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age, yrs</td><td></td><td>55.3 (SD 9.6)</td><td>58.0 (SD 7.0)</td></tr>
<tr><td>Sex</td><td>Male n=41
Female n=27</td><td>NR</td><td>NR</td></tr>
<tr><td>AHI</td><td></td><td>58.3 (SD 24.6)</td><td>59.5 (SD 21.7)</td></tr>
<tr><td>ESS</td><td></td><td>15.0 (SD 3.9)</td><td>13.6 (SD 3.6)</td></tr>
<tr><td>BMI</td><td></td><td>35.7 (SD 5.6)</td><td>33.8 (SD 6.3)</td></tr>
<tr><td>Blood pressure:</td><td></td><td></td><td></td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>or systemic diseases, patients with secondary hypertension, or professional driver. Participants were also excluded if their antihypertensive medication was changed during the course of the trial.</td>
<td></td>
<td>
<table>
<tr><td>24 hr BP</td><td></td><td>97.7 (SD 10.7)</td><td>96.2 (SD 10.1)</td></tr>
<tr><td>24 hr systolic BP</td><td></td><td>131.9 (SD13.5)</td><td>130.4 (SD 15.9)</td></tr>
<tr><td>24 hr diastolic BP</td><td></td><td>78.4 (SD 10.3)</td><td>77.6 (SD 8.7)</td></tr>
<tr><td>Daytime BP</td><td></td><td>100.8 (SD 10.7)</td><td>98.9 (SD 10.0)</td></tr>
<tr><td>Night-time BP</td><td></td><td>94.6 (SD 11.1)</td><td>93.5 (SD11.4)</td></tr>
</table>

Additional information ESS, AHI, and 24hr BP. Participants were assessed at trial entry and after 4 weeks of treatment. BP was measured using cuff inflation every 30 minutes for 24hrs. All participants were naive to CPAP treatment.
</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Chakravorty 2002 [97]
Related paper [306]
Setting UK

Design Parallel group trial.

Duration 12 weeks

Inclusion criteria Participants with AHI >/= 15.</td>
<td>CPAP (following home-based titration using an automated pressure setting device) Adherence to treatment not reported.

Comparator Conservative management (verbal advice, leaflet listing strategies for sleep hygiene, quitting smoking, reducing alcohol consumption, and controlling stress was provided, verbal and written advice on ideal body weight, weight reduction and exercise).</td>
<td>
Number randomised Total: 71 CPAP: 37 Comparator: 34

Number of withdrawals Total: 18 CPAP: 5 Comparator: 13

Reasons for withdrawals CPAP: failed to tolerate CPAP n=4, subsequently underwent surgery n=1 Comparator: excluded due to health reasons n=5, preferred surgery n=2, withdrew other n=6

Baseline characteristics (based on completers only)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>50 (SD 11)</td><td>49 (SD 11)</td><td>52 (SD 9.6)</td></tr>
<tr><td>Sex</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>AHI</td><td>49 (SD 28)</td><td>55 (SD 28.7)</td><td>35 (SD 19.1)</td></tr>
<tr><td>ESS</td><td>14 (SD 5)</td><td>16 (SD 5.6)</td><td>14 (SD 4.2)</td></tr>
<tr><td>BMI</td><td>37 (SD 12)</td><td>40 (SD 14.5)</td><td>32.3 (SD 5.5)</td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td>-</td><td>-</td></tr>
<tr><td>Euroqol (0-100)</td><td></td><td>59 (SD 19.8)</td><td>68 (SD 16.8)</td></tr>
<tr><td>Ueq*</td><td></td><td>0.73 (SD 0.18)</td><td>0.77 (SD 0.12)</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td>
<table>
<tr><td>Usg**</td><td></td><td>0.32 (SD 0.17)</td><td>0.31(SD 0.13)</td></tr>
</table>
*Standard gamble utility, **Euroqol derived utility

Additional information Outcomes included: ESS, AHI, quality of life, and utility.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Cibele 2006 [72]
Setting Brazil

Design Crossover trial.

Duration 1 month OA or OA placebo and then 1 month nCPAP (1 week washout period between OA devices and CPAP treatment).

Notes Conference abstract - insufficient outcome data available.

Inclusion criteria Adults with moderate to severe OSA (AHI≥20).</td><td>CPAP Adherence to treatment not reported.

Comparator Oral appliance (repositioning mandibular appliance with progressive adjustment) or placebo oral appliance (splint at lower arch).</td><td>Number randomised Total: 13

Number of withdrawals: The authors do not report any losses to follow-up.

Reasons for withdrawals NA

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age, yrs</td><td>44 (SD 8)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=12</td><td></td><td></td></tr>
<tr><td>AHI</td><td>45.5 (SD 28)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>10.6 (SD 4)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>27.4 (SD 5)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
</table>
Additional information Outcomes include: ESS, SF-36, PVT (attention test) (see Table 11.13), and oxidative stress. Outcomes were assessed before treatment and at each treatment phase.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Coughlin 2007[62]
Related papers[307]

Setting UK</td><td>CPAP (Following titration in sleep laboratory using automated pressure setting device)
Adherence (machine running time): CPAP 3.9 hrs/night (range 0-7.4).</td><td>Number randomised Total: 35

Number of withdrawals Total: 1 CPAP: 1 Comparator: 0

Reasons for withdrawals One participant withdrew during the first treatment period (CPAP limb) for</td></tr>
</table>

<table>
<tr>
<td>Design Crossover trial.

Duration 2 x 6 weeks (no washout period).

Notes Participants spent significantly more each night on the therapeutic CPAP machine than sham CPAP machine (p<0.01).

No evidence of a carryover effect for any outcome variable.

Inclusion criteria Untreated male patients with OSAHS.

Exclusion criteria Any abnormality identified on baseline ECG, or if there was evidence of diabetes, renal liver or cardiac disease, or if participants had symptoms of peripheral neuropathy or waking blood pressure ≥180/110, or a level of blood pressure requiring treatment.</td>
<td>Comparator Sham CPAP (pressure <1cm H_20).
Adherence (machine running time): sham CPAP 2.6 hrs/night (range 0-7.5).</td>
<td>personal reasons.

Baseline characteristics (based on 34 participants)

<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age, yrs</td><td>49.0 (SD8.3)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=34</td><td></td><td></td></tr>
<tr><td>RDI</td><td>39.7 (SD 13.8)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>13.8 (SD 4.9)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>36.1 (SD 7.6)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>NR</td><td></td><td></td></tr>
</table>

27 participants (79%) were hypertensive (resting blood pressure of 140/90mmHg).

Additional information
Outcomes included: ESS, waking BP, fasting glucose, Baroreceptor sensitivity, fasting insulin, cholesterol, and incidence of metabolic syndrome. Outcomes were assessed at baseline and after each intervention period. Waking BP was measured from 8am to 11am in a supine position after a 5 minute rest. It was recorded as the mean of three measurements taken at one minute intervals.</td>
</tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Cross 2005[308]
Related paper[88]</td><td>CPAP Treatment adherence: CPAP 5.5 hrs/night (1.2).</td><td>Number randomised Total: 31

Number of withdrawals Total: Not reported CPAP: Not reported Comparator: Not reported</td></tr>
</table>

<table>
<tr>
<td>Setting UK

Design Crossover trial.

Duration 2 x 6 weeks (washout period not reported).

Notes Conference abstract.

Inclusion criteria Adults with severe OSA (two major symptoms of OSAHS, >20 of 4% nocturnal desaturation/hr)</td>
<td>Comparator Sham CPAP. Treatment adherence: 3.3 hrs/night (2.2).</td>
<td>Reasons for withdrawals

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age, yrs</td><td>51 (SD 5)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=30</td><td></td><td></td></tr>
<tr><td>AHI</td><td>63 (SD 26)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>BMI</td><td>40.1 (SD 8.4)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not reported</td><td></td><td></td></tr>
</table>
Additional information Outcomes include: bilateral forearm blood flow (measured using venous occlusion plethysomograhy with unilateral intrabrachial infusions).</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Dimsdale 2000[58]
Related papers[117, 309-314]

Setting USA

Design Parallel group trial.

Duration 1 week.

Notes Patients were treatment naive.

Inclusion criteria Adults (between 30-65yrs), within 100-170% of ideal weight, and RDI >15.</td>
<td>CPAP (following manual overnight titration)
Compliance was reported to >5hrs per night.

Comparator Sham CPAP (pressure: 2cm H_20) (following mock titration)
Adherence was reported to be >5hrs per night.</td>
<td>Number randomised Unclear: 39 participants completed the study, but related papers indicate that a greater number of participants may have originally been randomised (n ranges from 38-48)

CPAP: n= 21 Comparator: n= 18

Number of withdrawals The authors do not report any withdrawals for BP or QOL outcomes. The papers report that POMS had 34 participants (CPAP n=20)

Reasons for withdrawals Not reported

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td></td><td>47.7yrs (SD 8.1)</td><td>48.9yrs (SD 9.9)</td></tr>
</table>
</td>
</tr>
</table>

Exclusion criteria Major ongoing illness other than sleep apnoea and hypertension (>140/90mmHg but <180/110mmHg).

Sex		Male n=15 Female n=6	Male n=16 Female n=2
AHI	Not assessed	-	-
ESS	Not assessed	-	-
BMI		32.7 (SD 4.9)	28.5 (SD 5.0)
Blood pressure mmHg: Mean screening systolic BP Mean screening diastolic BP		 128 (SD 15) 82 (SD 8)	 123 (SD 12) 78 (SD 9)
RDI		53.6 (SD 23.2)	41.7 (SD 25.6)
POMS: Tension Depression Fatigue Confusion Vigour Anger Total mood disturbance		 10.9 (SD 7.1) 12.5 (SD 15.1) 13.3 (SD 8.2) 7.6 (SD 5.0) 15.3 (SD 7.7) 14.3 (SD 11.9) 43.2 (SD 48.5)	 9.9 (SD 5.5) 12.7 (SD 10.1) 11.6 (SD 6.6) 8.3 (SD 3.5) 15.3 (4.7) 9.2 (SD 6.5) 36.5 (SD 28.4)

10 participants were hypertensive (CPAP 6, sham CPAP 4). Participants receiving antihypertensive medication had their medication tapered and their BP status confirmed after a 3-week washout.

Additional information Outcomes included BP and RDI. Participants wore ambulatory BP monitor for a 24 hour period on three occasions: before randomisation, after 1 day of treatment, and after 1 week of treatment. BP was taken every 15 minutes 6am to 10pm and every 30 minutes 10pm to 6am. Related papers report QOL (MOS) (Profant #216), mood (POMS) (Yu #486), and cognitive outcomes (Bardwell

<table>
<tr><td></td><td></td><td>#396) (see Table 11.13); assessed before treatment and after 1 week of treatment.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Drager 2006[69]

Setting Brazil

Design Parallel group trial.

Duration 12 weeks

Notes Conference abstract - insufficient outcome data available.

Inclusion criteria Normotensive participants with OSA.</td><td>CPAP Adherence to treatment not reported.

Comparator Usual care.</td><td>Number randomised Total: 16 CPAP: NR Comparator: NR

Number of withdrawals Total: No reported dropouts

Reasons for withdrawals NA

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td></td><td>45 (SE 3)</td><td>47 (SE 4)</td></tr>
<tr><td>Sex</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>AHI</td><td></td><td>54 (SE 8)</td><td>65 (SE 13)</td></tr>
<tr><td>ESS</td><td>Not assessed</td><td>-</td><td>-</td></tr>
<tr><td>BMI</td><td></td><td>31 (SE 1)</td><td>30 (SE 1)</td></tr>
<tr><td>Blood pressure (mmHg):
Mean Systolic BP</td><td></td><td>118 (SE 4)</td><td>125 (SE 5)</td></tr>
</table>
Additional information Outcomes included BP, carotid-femeral pulse wave velocity, cholesterol level, and heart rate. Participants were assessed at baseline and after 3 months.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Engleman 1994[90]

Setting UK

Design Crossover trial.</td><td>CPAP (following overnight titration) Adherence (hrs/nt): 3.7

Comparator Oral placebo (inactive ranitidine).</td><td>Number randomised Total: 35

Number of withdrawals Total: 3 CPAP: Not reported Comparator: Not reported

Reasons for withdrawals Pressure at work (n=1), relocation (n=1), reluctance to use CPAP (n=1).</td></tr>
</table>

<table>
<tr>
<td>Duration 2 x 2 weeks (no washout period)

Notes Significant learning effect on some outcome measures, especially cognitive tests.

Inclusion criteria Men and women with AHI ≥5 and at least two symptoms of obstructive sleep apnoea. Included consecutive patients referred for investigation of OSA.

Exclusion criteria No co-existing disorder causing excessive sleepiness, and lived within 50 miles of the laboratory.</td>
<td></td>
<td>Baseline characteristics (based on completers only)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age, yrs</td><td>49 (SE 1.5)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=26
Female n=6</td><td></td><td></td></tr>
<tr><td>AHI (median)</td><td>28</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>BMI</td><td>33 (1.6)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
</table>
Additional information These outcomes were measured on the last day of each treatment period: MSLT, cognitive function (National Adult Reading Test, Weschler Adult Intelligence Scale, Trailmaking A and B, Steer Clear, Rapid Visual Information Processing Test, Paced Auditory Serial Addition Test, Borkowski Test, Benton Revised Visual Retention Test) (see Table 11.13), In-house symptom score, Hospital Anxiety and Depression Score, General Health Questionnaire, Nottingham Health Profile, Energetic arousal score, Compliance, Patient preference.</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Engleman 1996[91]

Setting UK

Design Crossover trial.

Duration 2 x 4 weeks (no washout period)

Inclusion criteria Men and women</td>
<td>CPAP Adherence (hrs/nt): 4.3 hrs (SE 0.6).

Comparator Oral placebo (inactive ranitidine).</td>
<td>Number randomised Total: 16

Number of withdrawals Total: 3 CPAP: Not reported Comparator: Not reported

Reasons for withdrawals Equipment unavailability (n=1), poor ambulatory BP (n=1), and non-attendance (n=1).

Baseline characteristics (completers only, n=13)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>with AHI ≥5 and at least two symptoms of obstructive sleep apnoea.</td>
<td></td>
<td>
<table>
<tr><td>Age, years</td><td>51 (SE 3)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=11
Female n=2</td><td></td><td></td></tr>
<tr><td>AHI</td><td>49 (SE 9)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>BMI</td><td>36 (SE 2.6)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not reported</td><td></td><td></td></tr>
</table>

5 participants were classified as hypertensive (24 hr BP >134 and diastolic BP >84 mm Hg), 4 participants were taking antihypertensive medication; medication did not change throughout trial period.

Additional information Outcome was 24 hour ambulatory blood pressure. BP was recorded every 30mins for a 24 hr period with a cuff.</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Engleman 1997[92]

Setting UK

Design Crossover trial.

Duration 2 x 4 weeks (no washout period)

Notes No tests reported for differential carryover for period or washout effect.

Ten patients refused to participate in study.</td>
<td>CPAP (following titration study)
Treatment adherence (machine useage): 3.2 hrs/nt (SE 0.7)

Comparator Oral placebo (inactive ranitidine)</td>
<td>Number randomised Total: 18

Number of withdrawals Total: 2 CPAP: 2 Comparator: 0

Reasons for withdrawals Relocated (n=1), intolerant of noise from CPAP unit and declined to complete treatment limb (n=1).

Baseline characteristics (based on completers)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>52 (SE 2)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Males n=12
Females n=4</td><td></td><td></td></tr>
<tr><td>AHI</td><td>11 (SE 1)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>14 (SE 1)</td><td></td><td></td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><td>Inclusion criteria Patients with mild sleep apnoea (5-14.9 AHI) and at least two symptoms of obstructive sleep apnoea.</td><td></td><td><table><tr><td>BMI</td><td>29.8 (SE 1.8)</td><td></td><td></td></tr><tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr></table>
Additional information Outcomes were measured on the last day of each treatment: MSLT, cognitive function (National Adult Reading Test, Weschler Adult Intelligence Scale, Trailmaking A and B, Steer Clear, Rapid Visual Information Processing Test, Paced Auditory Serial Addition Test, Borkowski Test, Benton Revised Visual Retention Test) (see Table 11.13), In-house symptom score, Hospital Anxiety and Depression Score, General Health Questionnaire, Nottingham Health Profile Energetic arousal score, Compliance, patient preference.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Engleman 1998[93]

Setting UK

Design Crossover trial.

Duration
2 x 4 weeks (no washout period).

Inclusion criteria Patients with AHI of at least 15, and two or more symptoms of sleep disorder breathing.

Exclusion criteria Individuals with lung disease, neurological disorders, co-existing sleep disorder, or who lived more than 50 miles from the Scottish National Sleep Centre were</td><td>CPAP (following overnight titration)
Adherence (hrs/nt): 3.2

Comparator Oral placebo.</td><td>Number randomised Total: 23

Number of withdrawals Total: 1 CPAP: 1 Comparator: 0

Reasons for withdrawals Myocardial infarction during CPAP limb. Participant position refilled by next available recruit.

Baseline characteristics<table><tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr><tr><td>Age</td><td>47 (SD 12)</td><td></td><td></td></tr><tr><td>Sex</td><td>Males n=21
Females n=2</td><td></td><td></td></tr><tr><td>AHI</td><td>43 (SD 37)</td><td></td><td></td></tr><tr><td>ESS</td><td>12.0 (SD 4)</td><td></td><td></td></tr><tr><td>BMI</td><td>BMI 30 (SD 7).</td><td></td><td></td></tr><tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr><tr><td>UMACL, energetic</td><td>21 (SD 5)</td><td></td><td></td></tr></table></td></tr>
</table>

<table>
<tr>
<td>excluded.</td>
<td></td>
<td>
<table>
<tr><td>arousal score</td><td></td><td></td><td></td></tr>
<tr><td>Symptom score, total</td><td>5.1 (SD 1.5)</td><td></td><td></td></tr>
<tr><td>HADS
Anxiety
Depression</td><td>
8.3 (SD 4.4)
5.7 (SD 4.4)</td><td></td><td></td></tr>
<tr><td>GHQ-28</td><td>6.6 (SD 6.5)</td><td></td><td></td></tr>
<tr><td>NHP pt2</td><td>8.0 (SD 5.0)</td><td></td><td></td></tr>
</table>

Additional information Outcomes were measured on the last day of each treatment: ESS, AHI, NHP, MSLT, HADS, GHQ-28, UMACL, cognitive function (see Table 11.13), Preference.</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Engleman 1999[78]

Setting UK

Design Crossover trial.

Duration 2 x 4 weeks (no washout period)

Inclusion criteria New outpatient attendees with at least two symptoms of OSA including sleepiness (Epworth score 8 or more) and mild sleep apnoea (AHI 5-14.9 per hour).</td>
<td>CPAP (following overnight titration)
Heated humidified nasal CPAP
Treatment adherence (machine usage): 3.2 (hrs/nt) (SD 2.4).

Comparator Oral placebo.</td>
<td>Number randomised Total: 37

Number of withdrawals Total: 3 CPAP: Not reported Comparator: Not reported

Reasons for withdrawals Unwilling to persist with CPAP treatment (n=1), failed to attend final assessment (n=1), travel to centre too demanding (final CPAP limb) (n=1).

Baseline characteristics (based on completers only)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age, years</td><td>44 (SD 8)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n= 21
Female n=13</td><td></td><td></td></tr>
<tr><td>AHI</td><td>10 (SD 3)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>13 (SD 3)</td><td></td><td></td></tr>
<tr><td>BMI, kg/m^2</td><td>BMI 30 (SD 5)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
</table>
</td>
</tr>
</table>

		Symptoms, total score	22 (SD 6)		
		UMACL, energetic arousal score	18 (SD 5)		
		HADS: Anxiety Depression	 9.0 (SD 4.2) 7.4 (SD 4.1)		
		NHP pt 2	10.5 (SD 4.8)		
		SF-36: Health transition Physical function Role –physical Role – emotional Bodily pain Mental health Social function General health Vitality	 3.1 (SD 0.6) 75 (SD 27) 58 (SD 36) 62 (SD 38) 68 (SD 31) 64 (SD 19) 60 (SD 27) 68 (SD 21) 33 (SD 19)		
		Additional information Outcomes included MWT, ESS, UMACL, symptom questionnaire, HADS, NHP part2, SF-36, WAIS-R, cognitive function (see Table 11.13).			
Study details	**Intervention**	**Participants**			
Engleman 2002[103] Related papers[112, 315] **Setting** UK **Design** Crossover trial.	**CPAP** (following all night titration) Adherence (hrs/nt): 6.1 (+/- 1.9) **Comparator** Oral appliance (OA). Participants were randomised to receive one of two oral devices 1. two mouthguards providing complete occlusal coverage	**Number randomised** Total: 51 **Number of withdrawals** Total: 3 CPAP: 2 Comparator: 1 **Reasons for withdrawals** Uncontactable (first CPAP limb) (n=1), unable to spare time due to starting a new job (during first CPA and first OA limb)			

<table>
<tr>
<td>Duration 2 x 8 weeks (no washout period)

Inclusion criteria Patients between 18-70 years with AHI of 5 or more and two symptoms of sleep apnoea/hypopnoea syndrome.

Exclusion criteria Individuals with fewer than 4 teeth remaining in either arch, co-existing narcolepsy, or periodic limb movement of more than 10 per/hr, major medical illness, shift work, or living more than 50 miles away from Edinburgh.</td>
<td>contructed by an ethylenemethylacrylate/polystryne material and the two units were sealed in protrusion 2. manufactured from less flexible 1MEDL dual laminate material, without occlusal coverage.
Both were individually fitted to produce 80% of maximal comfortable mandibular protrusion, with 2-4mm of inter-dental clearance

Adherence (hrs/nt): 5.6 (+/- 2.0)</td>
<td>Baseline characteristics (n=48)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>46 (SD 9)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n= 36
Female n=12</td><td></td><td></td></tr>
<tr><td>AHI</td><td>31(SD 26)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>14 (SD 4)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>Not reported</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
</table>
Additional information Outcomes were measured on the last day of each treatment: SF-36, ESS, MWT, HADS, AHI, FOSQ, PASAT, cognitive function (see Table 11.13), preference.</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Faccenda 2001[94]}
Related papers[316, 317]}

Setting UK

Design Crossover trial.

Duration 2 x 4 weeks (no washout period)

Inclusion criteria Patients that exhibit two symptoms of sleep apnoea/hypopnoea syndrome and an</td>
<td>CPAP (following full night titration using an automated pressure setting device)
Adherence (hrs/nt): 3.3 (range 0 to 8.1)

Comparator Oral placebo. Treatment adherence (capsule counting): a median of 0 tablets (95th percentile, 1.4 tablets) were missed over the one month period.</td>
<td>Number randomised Total: 71

Number of withdrawals Total: 3 CPAP: 2 Comparator: 1

Reasons for withdrawals Not reported

Baseline characteristics (n=68)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age, yrs</td><td>50 (29-72)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=55
Female n=13</td><td></td><td></td></tr>
<tr><td>AHI</td><td>35 (15-129)</td><td></td><td></td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>AHI of 15 or greater.

Individuals taking hypotensive medication were excluded.</td>
<td></td>
<td>
<table>
<tr><td>ESS</td><td>15 (6-24)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>30 (21-53)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not reported</td><td></td><td></td></tr>
</table>
Data presented as median (range) unless otherwise stated

Additional information Outcomes were measured on the last day of each 1 month period treatment: ESS; AHI; BP. BP was measured via arm cuff, programmed to record every 30mins for 48 hr period. Data for second 24 hr period used (6pm-6pm).</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Ferguson 1996[81]648}

Setting Canada

Design Crossover trial.

Duration 2 x 16 weeks. Washout period: 2 weeks.

Notes Patients randomised after 2 week wash-in period. Unclear about patient preference - only provided results for 7 patients who were treatment successes with both treatments. No evidence of carryover effect between treatment periods.

Inclusion criteria Patients with mild to moderate sleep apnoea and at least</td>
<td>CPAP (following over night titration)
The use of a humidifier was optional, but encouraged. Intranasal corticosteroids and/or anticholinergic medications to relieve nasal symptoms caused by CPAP use were used.

Treatment adherence (% night treatment used): 10 patients used CPAP 100%, 4 patients used CPAP> 75%, 3 patients used CPAP 25-75%, 4 patients used CPAP < 25 %.
% night treatment used: 9 patients used CPAP 100%, 5 patients used CPAP > 75%, 3 patients used CPAP 25-75%, 4 patients used CPAP < 25 %.

Comparator Oral appliance. OA was</td>
<td>Number randomised Total: 26

Number of withdrawals Total: 1 CPAP: 0 Comparator: 1

Reasons for withdrawals Relocated (n=1).

Baseline characteristics (n=27, based on number recruited for washout period before randomisation)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>46.2 (SD 10.9)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=24
Female n=3</td><td></td><td></td></tr>
<tr><td>AHI</td><td>24.5 (SD 8.8)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>BMI</td><td>30.4 (SD 4.8)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
</table>
Additional information Outcomes measured at end of each 4 month period: sleep variables, symptom questionnaire, patient preference, side effects.</td>
</tr>
</table>

<table>
<tr><td>ten teeth in each of the mandibular and maxillary arches.</td><td>constructed to position the mandible 3mm posterior to the position of maximal acceptable advance and with a 7mm opening between the upper and lower incisors. Material was added to increase the vertical dimension of the appliance in a few participants. Oral device was constructed was constructed of an acrylic polymer.

Treatment adherence (% night treatment used): 15 patients used OA 100%, 9 patients used OA > 75%, 1 patient used OA 25-75% % night treatment used: 12 patients used OA 100%, 8 patients used OA > 75%, 4 patients used OA 25-75%, 1 patient used OA < 25 %.</td><td></td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Ferguson 1997[80] #607}

Setting Canada

Design Crossover trial.

Duration 2 x 16 weeks. Washout period: 2 weeks.

Notes Patients randomised after 2 week wash-in period. No evidence of carryover effect.</td><td>CPAP Participants used a variety of different airway access devices based on their own preference. The use of a cold flow-by humidifier was optional but encouraged. Intranasal corticosteroids and/or anticholinergic medications were used to relieve nasal symptoms.

Comparator Oral appliance. The amount of mandibular advancement was initially set at 70% of maximal mandibular advancement. The amount of mandibular</td><td>Number randomised Total: 24 (baseline data for ESS is presented for completers n=20)

Number of withdrawals Total: 4 CPAP: not reported Comparator: not reported

Reasons for withdrawals Refused follow-up assessments (n=1), refused to cross-over from oral appliance to CPAP (n=3).

Baseline character
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>44 (SD 11)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=19</td><td></td><td></td></tr>
</table></td></tr>
</table>

<table>
<tr>
<td>Inclusion criteria Patients with symptomatic mild to moderate sleep apnoea (AHI 15-55), and at least 10 teeth in each of the mandibular and maxillary arches.</td>
<td>advancement was increased over the treatment period by a mean of 1.8mm (SD 1.2) until snoring stopped and symptoms improved, or until participants could not tolerate further advancement.</td>
<td>
<table>
<tr><td></td><td>Female n=5</td><td></td><td></td></tr>
<tr><td>AHI</td><td>27 (SD 12)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not reported</td><td>11 (SD 3.8)</td><td>10.3 (SD 3.1)</td></tr>
<tr><td>BMI</td><td>32 (SD 8)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
</table>
Additional information Outcomes were measured at the end of each treatment period: sleep variables, symptom questionnaire, patient preference, side effects.
</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Fleetham 2002[50] (unpublished data from Giles et al., 2006)
Related papers[101, 119, 218]

Setting Canada

Design Parallel group trial.

Duration 12 weeks.

Inclusion criteria AHI > 10.</td>
<td>CPAP Treatment adherence: Not reported

Comparator Adjustable oral appliance.</td>
<td>Number randomised Total: 101 CPAP: NR Comparator: NR

Number of withdrawals Total: NR

Reasons for withdrawals

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td></td><td>49.0 +/-9.4</td><td>6.2 +/-11.3</td></tr>
<tr><td>Sex</td><td>Male n=96
Female n=5</td><td></td><td></td></tr>
<tr><td>AHI</td><td></td><td>37.6 +/-22.8</td><td>38.7 +/-22.2</td></tr>
<tr><td>ESS</td><td></td><td>12.8+/-4.1</td><td>11.1 +/-4.9</td></tr>
<tr><td>BMI</td><td></td><td>32.0 +/-5.5</td><td>1.4 +/-5.7</td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td>-</td><td>-</td></tr>
<tr><td>SAQLI</td><td></td><td>4.2 +/-1.1</td><td>4.2 +/-1.0.</td></tr>
<tr><td>Min SaO2</td><td></td><td>75.8 +/-12.7</td><td>73.6 +/-11.8</td></tr>
</table>
Additional information Outcomes included: AHI, Epworth sleepiness score, minimum SaO2, quality</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td>of life index.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Henke 2001[85]

Setting USA

Design Partial crossover trial.

Duration 6 weeks. Sham-CPAP group received treatment for 15 days then crossed over and received CPAP for rest of treatment period. CPAP received treatment for entire period. No washout period.

Notes only data from the first sequence were used, thus data were treated as parallel data

Inclusion criteria Males and females with diagnosed symptoms of sleep apnea/hypopnea syndrome with an AHI > 10 plus daytime sleepiness or AHI>20 without daytime sleepiness.

Exclusion criteria Oxygen saturation <85% for >50% of sleep</td><td>CPAP (following laboratory titration) Adherence (hrs/nt): First limb 5.9 (SD 1.8); second limb 5.8 (SD 2.0).

Comparator Sham CPAP. Adherence (hrs/nt): First limb 5.2 (SD 2.2); second limb 4.9 (SD 2.4).</td><td>Number randomised Total: 45 CPAP: 27 Comparator: 18

Number of withdrawals Total: 4 (T3 parallel analysis) CPAP: NR Comparator: NR

Reasons for withdrawals Baseline polysomnogram was mistakenly performed on effective CPAP rather than ineffective CPAP for 4 participants from placebo group; data were not included in the analysis.

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>Not reported</td><td>50.2 (SD 10.4)</td><td>50.6 (SD 9.7)</td></tr>
<tr><td>Sex</td><td>Male n=25
Female n=20</td><td>NR</td><td>NR</td></tr>
<tr><td>AHI</td><td>Not reported</td><td>62.1 (SD 27.4)</td><td>68.1 (SD 25.2)</td></tr>
<tr><td>ESS</td><td>16</td><td>16.4 (SD 5.6)</td><td>16.0 (SD 4.8)</td></tr>
<tr><td>BMI</td><td>Not reported</td><td>42.7 (SD 10.5)</td><td>42.2 (SD 11.9)</td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td>-</td><td>-</td></tr>
</table>
Additional information Outcomes were measured on the last day of each treatment: ESS, AHI, ODI, MinSaO2, Steer Clear (see Table 11.13).</td></tr>
</table>

<table>
<tr><td>time, clinical signs of right –sided congestive heart failure, claustrophobia or nasal obstruction preventing use of nasal CPAP.</td><td></td><td></td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Hoekema 2005[102]
Related papers[71, 111, 114, 300]

Setting Netherlands

Design Parallel group trial.

Duration 8 weeks.

Notes Abstract only for main efficacy data. Data for driving simulator test comes from related paper (Hoekema, 2006 #2956). Data for sexual dysfunction (GRISS) has been taken from a related paper (Hoekema 2006 #2955).

Study duration for the two related papers: 8-12 weeks. After 8 weeks of treatment participants were assessed with a second polysomnographic study; for participants with AHI >=5, treatment was adjusted if possible to improve effectiveness, and in these</td><td>CPAP Treatment adherence: Not reported.

Comparator Oral appliance.

Related papers: The oral appliance was a 2 part adjustable appliance set at 5 degrees of patients maximum advancement to begin with; patients could adjust the amount of mandibular advancement in 0.2 increments and were instructed to adjust by o.2 to 0.4 weeks 2-8 untill symptoms abated or any further advancement was uncomfortable.</td><td>Number randomised Total: 103 CPAP: 52 Comparator: 51

Number of withdrawals Not reported

Reasons for withdrawals Not reported

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age, years</td><td>Not reported</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Not reported</td><td></td><td></td></tr>
<tr><td>AHI, median</td><td>Not reported</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>BMI</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>Driving simulator test (N=19):
Lapses of attention, median.</td><td></td><td>10 (IQR 1.0 to 16.8)</td><td>5.0 (IQR 2.0 to 14.0)</td></tr>
<tr><td>GRISS (N=47):
Erectile dysfunction
Premature ejaculation
Nonsensuality
Avoidance
Sexual dissatisfaction</td><td></td><td>
9.5 (SD 4.2)
9.0 (SD 2.7)
5.8 (SD 2.1)
4.0 (IQR 4.0-5.5)
10.2 (SD 4.3)</td><td>
7.9 (SD 3.5)
9.5 (SD 3.5)
5.4 (SD 2.0)
4.0 (IQR 4.0-5.0)
8.5 (SD 3.9)</td></tr>
</table></td></tr>
</table>

<table>
<tr>
<td>participants the follow-up period was extended for another 4 weeks. Adjustment sequence was continued until AHI <5 or until adjustments become uncomfortable.

Inclusion criteria Adults with OSAHS (AHI >5).</td>
<td></td>
<td>
<table>
<tr><td>Infrequency of sexual contact</td><td></td><td>7.0 (SD 1.7)</td><td>5.9 (SD 2.0)</td></tr>
<tr><td>Noncommunication</td><td></td><td>4.6 (SD 1.8)</td><td>4.0 (SD 1.9)</td></tr>
</table>

Additional information Primary outcome for main paper: AHI. Primary outcomes for related papers: driving simulator test, and sexual dysfunction. Participants undertaking the driving simulator test were assessed between noon and 2pm. Room conditions: lights were dimmed, noise was shut out and room temperature was kept at 22C. The driving test was completed in the absence of company. Participants were instructed to refrain from stimulating products such as caffeine 3hrs before testing and not to smoke 30mins before testing. Outcomes were assessed at baseline and after 8 weeks of treatment. In some participants final assessment occurred at a later stage (median final review was 81 days (IQR 72-93) in the OA group and 79 days (IQR 63-102) in the CPAP group).</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Hui 2006 [64]
Related paper [318]

Setting Hong Kong

Design Parallel group trial.

Duration 3 months.

Inclusion criteria CPAP naive adults with OSA. Participants with hypertension were eligible as long as there was no change in antihypertensive medication.

Exclusion criteria Individuals with problems staying awake during</td>
<td>CPAP (following overnight titration using an automated pressure setting device) Treatment adherence (Machine run time): 5.1 hrs/night (SE 0.4).

Comparator Sham CPAP (pressure: 4cm H_20). Treatment adherence (Machine run time): 2.6 hrs/night (SE 0.4).</td>
<td>Number randomised Total: 56 CPAP: 28 Comparator: 28

Number of withdrawals Total: 10 CPAP: 5 Comparator: 5

Reasons for withdrawals CPAP: defaulted ambulatory BP measurement (n=3), and ambulatory BP recording failed to record (n=2).
sham CPAP: discomfort with treatment (n=5)
Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>50.8 (SE 1.7)</td><td>50.3 (SE 1.6)</td><td>51.2 (SE 1.8)</td></tr>
<tr><td>Sex</td><td>Male n=43
Female n=13</td><td>Male n=22
Female n=6</td><td>Male n=21
Female n=7</td></tr>
<tr><td>AHI</td><td>31.2 (SE 2.2)</td><td>32.9 (SE 3.2)</td><td>29.5 (SE 3.1)</td></tr>
<tr><td>ESS</td><td>11.1 (SE 0.7)</td><td>10.7 (SE 1.0)</td><td>11.6 (1.0)</td></tr>
<tr><td>BMI</td><td>27.2 (SE 0.5)</td><td>27.5 (SE 0.6)</td><td>26.9 (SE 0.7)</td></tr>
<tr><td>Blood pressure:</td><td></td><td></td><td></td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>driving, professional drivers, shift workers, recent myocardial infarction, unstable angina, or underlying malignancy.</td>
<td></td>
<td>
<table>
<tr><td>24 hr BP systolic</td><td>123.7 (SE 1.8)</td><td>125.4 (SE 2.6)</td><td>122.0 (SE 2.7)</td></tr>
<tr><td>24 hr BP diastolic</td><td>80.9 (SE 1.2)</td><td>81.8 (SE 1.9)</td><td>80.0 (SE 1.7)</td></tr>
<tr><td>24 hr MAP</td><td>95.2 (SE 1.3)</td><td>96.2 (SE 1.8)</td><td>94.1 (SE 2.0)</td></tr>
<tr><td>Wake time systolic</td><td>127.8 (SE 1.8)</td><td>128.6 (SE 2.6)</td><td>127.2 (SE 2.7)</td></tr>
<tr><td>Wake time diastolic</td><td>83.6 (SE 1.2)</td><td>83.7 (SE 1.9)</td><td>83.7 (SE 1.7)</td></tr>
<tr><td>Wake time MAP</td><td>98.1 (SE 1.5)</td><td>98.3 (SE 1.8)</td><td>97.9 (SE 1.9)</td></tr>
<tr><td>Sleep time systolic</td><td>115.7 (SE 2.0)</td><td>117.7 (SE 2.9)</td><td>113.9 (SE 3.0)</td></tr>
<tr><td>Sleep time diastolic</td><td>74.8 (SE 1.4)</td><td>75.8 (SE 2.1)</td><td>74.1 (SE 2.0)</td></tr>
<tr><td>Sleep time MAP</td><td>89.1 (SE 1.5)</td><td>90.6 (SE 2.1)</td><td>87.8 (SE 2.3)</td></tr>
</table>

28 participants had hypertension (previously documented BP of >140/90 on at least two occasions or receiving antihypertensive medication). There were no changes in antihypertensive medication during the study.

Additional information Outcomes included ESS, change in 24hr arterial BP, change in systolic and diastolic BP, change in mean BP awke and asleep. Outcomes were assessed at baseline and 48 hrs before end of treatment (BP) or 3 mths after treatment (ESS). BP was measured every 30 minutes for 48hrs using cuff inflation; the second 24hrs of data were used.
</td>
</tr>
<tr>
<td>**Study details**</td>
<td>**Intervention**</td>
<td>**Participants**</td>
</tr>
<tr>
<td>Jenkinson 1999 [77]
Related papers[118, 319-324]

Setting UK

Design Parallel group trial.

Duration 4 weeks.

Inclusion criteria Men age 30-75</td>
<td>**CPAP (autotitrating)** Adherence (hrs/nt): 5.4 (2.2-7.4).

Comparator Sham CPAP (pressure: appox. 1cm H_2O). Adherence (hrs/nt): 4.6 (0.7-8.5).</td>
<td>**Number randomised** Total: 107 CPAP: 54 Comparator: 53

Number of withdrawals Total: 6 CPAP: 2 Comparator: 4

Reasons for withdrawals CPAP: Did Not use nCPAP and failed to reattend (n=2). Comparator: did not use nCPAP and failed to reattend (n=3), unexplained collapse (n=1)

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>years with ESS of 10 or more and 10 or more oxygen desaturation (SaO2) > 4%.</td>
<td></td>
<td>
<table>
<tr><td>Age, yrs</td><td>49 (34-70)</td><td>50 (33-71)</td><td>48 (36-68)</td></tr>
<tr><td>Sex</td><td>Male n=107</td><td>Male n=54</td><td>Male n=53</td></tr>
<tr><td>AHI</td><td>Not assessed</td><td>-</td><td>-</td></tr>
<tr><td>ESS</td><td>16.5 (10-)</td><td>16.0 (10.7-21.7)</td><td>17 (10.0-23.0)</td></tr>
<tr><td>BMI</td><td>35 (26-50)</td><td>35.1 (25.8-44.3)</td><td>35.0 (26.9-51.4)</td></tr>
<tr><td>Blood pressure</td><td></td><td></td><td></td></tr>
<tr><td>4% SaO2, dips per hour</td><td>31 (13-65)</td><td>32.9 (15.5-63.4)</td><td>28.5 (10.7-68.7)</td></tr>
<tr><td>MWT</td><td></td><td>22.5 (7.6-40.0)</td><td>20.0 (3.5-40.0)</td></tr>
<tr><td>SF-36*:</td><td></td><td></td><td></td></tr>
<tr><td>Mental component</td><td></td><td>44.8 (SD 10.4)</td><td>43.5 (SD 10.7)</td></tr>
<tr><td>Physical component</td><td></td><td>43.7 (SD 11.6)</td><td>42.6 (SD 10.1)</td></tr>
<tr><td>General health perception</td><td></td><td>59.2 (SD 18.4)</td><td>59.5 (SD 20.4)</td></tr>
<tr><td>Physical functioning</td><td></td><td>80.9 (SD 22.7)</td><td>78.6 (SD 22.1)</td></tr>
<tr><td>Social functioning</td><td></td><td>73.5 (SD 26.1)</td><td>73.0 (SD 26.1)</td></tr>
<tr><td>Physical role</td><td></td><td>62.0 (SD 37.2)</td><td>58.7 (SD 37.0)</td></tr>
<tr><td>Mental role</td><td></td><td>73.7 (SD 33.2)</td><td>68.7 (SD 36.3)</td></tr>
<tr><td>Bodily pain</td><td></td><td>82.1 (SD 23.8)</td><td>76.2 (SD 25.5)</td></tr>
<tr><td>Mental health</td><td></td><td>73.2 (SD 16.8)</td><td>68.7 (SD 18.2)</td></tr>
<tr><td>Energy & vitality</td><td></td><td>35.4 (SD 22.4)</td><td>33.9 (SD 17.5)</td></tr>
</table>
Data are Median (5th-95th centiles) except * mean (SD)

Additional information Outcomes include: Epworth, MWT, daytime saturation, SF-36. Related paper reports cognitive outcomes (#480) (see Table 11.13).
</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Jokic 1999 [108]

Setting Canada</td>
<td>CPAP (following manual titration)

Comparator Postural therapy with backpack with soft ball inside to prevent</td>
<td>Number randomised Total: 14 participants completed study.

Number of withdrawals Total: 1 (exclusion) CPAP: Not reported Comparator: Not reported</td>
</tr>
</table>

<table>
<tr><td>Design Crossover trial.

Duration 2 x 2 weeks (no washout period).

Notes Unclear how many originally eligible.

Inclusion criteria Outpatients referred with daytime sleepiness. Postural OSA (AHI during supine sleep that was two or more times the AHI during sleep in the lateral position; AHI < 15 in lateral position; daytime sleepiness).</td><td>subjects from sleeping supine.</td><td>Reasons for withdrawals Not reported

Baseline characteristics<table><tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr><tr><td>Age</td><td>51 (SD 9)</td><td></td><td></td></tr><tr><td>Sex</td><td>Male n=12
Female n=1</td><td></td><td></td></tr><tr><td>AHI</td><td>17 (SD 8)</td><td></td><td></td></tr><tr><td>ESS</td><td>13 (SD 1.3)</td><td></td><td></td></tr><tr><td>BMI</td><td>30 (SD 4)</td><td></td><td></td></tr><tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr></table>Additional information Outcomes include: MWT, ESS, HAD, UMAC, NHP, Trail A&B, GHQ, Digit symbol modality test, Wechsler Memory Scale I and II, and cognitive outcomes (see Table 11.13).</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>L’Estrange 1999 [104]

Setting UK

Design Crossover trial.

Duration 2 x 2 months (washout period not reported)

Notes Conference abstract - insufficient outcome information.

Inclusion criteria Patients with</td><td>CPAP Treatment adherence not reported

Comparator Oral appliance (mandibular advancement splint)</td><td>Number randomised Total: 15

Number of withdrawals Total: Unclear, appears that 6 participants were not included in the analysis

Reasons for withdrawals 2 participants failed to tolerate CPAP and 4 participants failed to complete OA treatment period.

Baseline characteristics<table><tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr><tr><td>Age</td><td>52.9 (+/-6.3)</td><td></td><td></td></tr><tr><td>Sex</td><td>Not reported</td><td></td><td></td></tr><tr><td>AHI</td><td>63.7 (+/-10.0)</td><td></td><td></td></tr></table></td></tr>
</table>

<table>
<tr><td>severe OSAHS (AHI >50).</td><td></td><td>
<table>
<tr><td>ESS</td><td>17.2 (+/-3.8)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>34.2 (+/-7.2)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
</table>

Additional information Outcomes include: ESS and AHI.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Lam 2006 [70]
Related papers [325, 326]

Setting Hong Kong

Design Parallel group trial.

Duration 10 weeks.

Inclusion criteria Patients with mild to moderate OSA.

Exclusion criteria Sleepiness which may present a risk to self or others, unstable medical disease, co-existence of sleep disorders other than OSA, previous surgery to upper airway (except for nasal problems), and pregnant women.</td><td>CPAP CPAP (at a pre-titrated pressure) and conservative management (CM; advice on sleep hygiene and attendance at a weight control programme if overweight) plus CPAP.

Adherence to active treatment: 4.2 (SEM 0.1) hrs per night and 4.4 (SEM 0.1) nights per wk

Comparator
1. CM (advice on sleep hygiene and attendance at a weight control programme if overweight using Asian criteria of BMI ≥23 kg/m²)
2. CM plus Oral appliance (OA): tailor-made non-adjustable device made of dental acrylic from a functional activator (Harvold type).
Adherence to active treatment (self-reported): 6.4 (SEM 0.2) hrs per night</td><td>Number randomised Total: 101 CPAP: 34 OA:34 CM:33

Number of withdrawals Total: 10 CPAP: 1 OA: 4 CM: 5

Reasons for withdrawals CPAP: intolerance of device (n=1), OA: gum problems (n=4), CM: refused final PSG (n=5).

Baseline characteristics
<table>
<tr><td></td><td>CPAP</td><td>OA</td><td>CM</td></tr>
<tr><td>Age, yrs</td><td>45 (SE 1)</td><td>45 (SE 2)</td><td>47 (SE 2)</td></tr>
<tr><td>Sex</td><td>Male n=27</td><td>Male n=26</td><td>Male n=26</td></tr>
<tr><td>AHI</td><td>23.8 (SE 1.9)</td><td>20.9 (SE 1.7)</td><td>19.3 (SE 1.9)</td></tr>
<tr><td>ESS</td><td>12 (SE 1)</td><td>12 (SE 1)</td><td>12 (SE 1)</td></tr>
<tr><td>BMI</td><td>27.6 (SE 0.6)</td><td>27.3 (SE 0.6)</td><td>27.3 (SE 0.6)</td></tr>
<tr><td>Blood pressure:</td><td></td><td></td><td></td></tr>
<tr><td>Morning systolic BP</td><td>127.9 (SE 2.3)</td><td>127.1 (SE 2.6)</td><td>125.5 (SE 3.5)</td></tr>
<tr><td>Morning diastolic BP</td><td>77.0 (SE 1.8)</td><td>76.2 (SE 2.1)</td><td>74.2 (SE 2.4)</td></tr>
<tr><td>Evening systolic BP</td><td>130.9 (SE 2.4)</td><td>131.9 (SE 3.1)</td><td>127.2 (SE 3.2)</td></tr>
<tr><td>Evening diastolic BP</td><td>78.0 (SE 1.9)</td><td>77.8 (SE 2.2)</td><td>73.5 (SE 1.9)</td></tr>
</table>
19 participants were hypertensive and on treatment (CPAP n=7, OA n=4, CM n=8). There was no change in anti-hypertensive medications during the study period.</td></tr>
</table>

<table>
<tr><td></td><td>and 5.2 (SEM 0.3) nights per week</td><td>Additional information AHI, ESS, Quality of life (SF-36, SAQL), morning (8-9am) BP, evening BP (8-9pm), treatment adherence (assessed at 4 wks and 10 wks) and adverse events. BP was the average of three readings taken at a one minute interval.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Lim 2005[110]

Setting USA

Design Parallel group trial.

Duration 4 weeks.

Notes Abstract – insufficient outcome data.

Inclusion criteria Adults with chronic daily headache and AHI ≥ 5.</td><td>CPAP Adherence (hrs/nt): Not reported

Comparator Conservative management</td><td>Number randomised Total: 23 CPAP: 12 Comparator: 11

Number of withdrawals Total: No dropouts were reported

Reasons for withdrawals NA

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>Not reported</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=5
Female n=18</td><td></td><td></td></tr>
<tr><td>AHI</td><td>Not reported</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>BMI</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
</table>
Additional information There were no changes in medication throughout the study period.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Lojander 1996 [99]
Related paper [113]

Setting Finland.</td><td>CPAP Nasal CPAP (initiated in the hospital). Adherence: 9 out of 10 participants complied with CPAP use (a minimum of 4 hrs a night for at least 5 nights a week).</td><td>Number randomised Total: 27 CPAP: 10 Comparator: 17

Number of withdrawals Total: 9 CPAP: unclear Comparator: unclear

Reasons for withdrawals Refused to attend follow-up visits due to relocation or other personal reason</td></tr>
</table>

Design Parallel group trial.

Duration 52 weeks.

Notes
Consecutive patients were reviewed by a panel of experts and allocated to 2 groups: candidates for UPP surgery (n=23) and candidates for CPAP (n=27). The latter group was randomly allocated to CPAP or conservative follow up

Inclusion criteria Patients with OSA and a BMI of < 40 kg/m2.

Comparator Conservative management (avoidance of alcohol at bedtime and weight reduction).

(n=5). 4 participants randomised to conservative management were put on CPAP (n=3) or operated on (n=1) due to a worsening of symptoms.

Baseline characteristics

	Total	CPAP	Comparator
Age, years		50 (41-60)	51 (43-65)
Sex	Not reported	Not reported	Not reported
AHI	Not assessed	-	-
ESS	Not assessed	-	-
BMI		31 (25-38)	33 (26-41)
Blood pressure	Not assessed	-	-
ODI 4%		31 (10-67)	26 (11-96)
Daytime somnolence: VAS		31 (21-80)	58 (8-90)

Data are median (range)

Additional information Follow up at 3 and 12 months: ODI 4%; ODI 10%; VAS for sleepiness; Frequency and loudness of snoring questionnaire. Cognitive outcomes were also reported (see Table 11.13).

Study details	**Intervention**	**Participants**
Marshall 2005 [79] Related papers[327, 328] **Setting** New Zealand. **Design** Crossover trial. **Duration** 2 x 3 weeks. 2 week	**CPAP** Humidified CPAP. (following manual titration overnight) Adherence (machine run time): 4.9 hrs/night (range 0-8.4). **Comparator** Humidified sham (pressure: <1cm H_20). Adherence to treatment (machine run time): 4.9 hrs/night (range 0-	**Number randomised** Total: 31 **Number of withdrawals** Total: 2 CPAP: 1 Comparator: 1 **Reasons for withdrawals** Non-fatal MI during sham treatment (n=1), and CPAP intolerant (n=1). **Baseline characteristics** (completers only, n=29)

	Total	CPAP	Comparator

washout period.

Notes

Inclusion criteria AHI 5-30; >/=18 years of age; daytime symptoms of sleepiness/ESS >/= 8; CPAP naive; English-speaking.

8.32).

Age (range)	26-67 years		
Sex	Male n=22 Female n=7		
AHI	22 (14.5)		
ESS	12.5 (SE 0.8)		
BMI	Not assessed		
Blood pressure	Not assessed		
MWT	20.9 (SE 2.5)		
SF-36: Mental health Bodily pain Social functioning Vitality Role emotional Role physical Physical functioning General health	 75 (SE 3) 73 (SE 4) 79 (SE 4) 44 (SE 3) 78 (SE 7) 63 (SE 8) 82 (SE 3) 74 (SE 3)		
HADS: Anxiety Depression	 6.8 (SE 0.7) 4.2 (SE 0.5)		
FOSQ: Total Activity Social outcomes Vigilance General product	 12.6 (SE 0.3) 3.0 (SE 0.1) 3.2 (SE 0.1) 3.0 (SE 0.1) 3.3 (SE 0.1)		

Additional information Outcomes: ESS; FOSQ; SF-36; HADS - Anxiety; HADS - Depression;

<table>
<tr><td></td><td></td><td>MWT, and cognitive function (see Table 11.13)..</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>McArdle 2001[95]

Setting UK

Design Crossover trial.

Duration 2 x 4 weeks. No washout phase described.

Inclusion criteria Men and women with AHI>15 and at least two symptoms of obstructive sleep apnoea.

Exclusion criteria Shift workers, those with driving problems due to sleepiness; consumption of >21g alcohol per week, medication/comorbidity likely to disturb sleep quality.</td><td>CPAP Adherence (hrs/nt): Not reported

Comparator Oral placebo (lactose capsule).</td><td>Number randomised Total: 23

Number of withdrawals Total: 1 CPAP: 1 Comparator: 0

Reasons for withdrawals Refused to continue with CPAP treatment.

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age, yrs</td><td>53 (SD 11)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=20
Female n=3</td><td></td><td></td></tr>
<tr><td>AHI (median)</td><td>40 (IQR 25-65)</td><td></td><td></td></tr>
<tr><td>ESS (median)</td><td>14 (IQR 10-17)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>31 (SD 5)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
</table>
Additional information Outcomes: ESS; sleep efficiency.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Monasterio 2001[100]
Related paper[329]

Setting Spain.</td><td>CPAP CPAP plus CM
Adherence (hrs/nt): 4.8 (SD 2.2) at 6mths; at 6mths 64% of participants used CPAP for > 4hrs per night.</td><td>Number randomised Total: 142 CPAP: 77 Comparator: 65

Number of withdrawals Total: 17 CPAP: 11 Comparator: 7

Reasons for withdrawals Not reported</td></tr>
</table>

Design Parallel group trial.

Duration 24 weeks.

Inclusion criteria Men and women with AHI 10-30 and absence of severe daytime sleepiness.

Exclusion criteria Apnoea index greater than 20, hazardous jobs, notable cardiovascular disease, and conditions that may affect cognitive or quality of life evaluation (severe neurological or psychiatric disorder, severe chronic disease, or illiteracy).

Comparator Conservative management (CM): weight loss programme following home diet if BMI >27, avoidance of sedatives, alcohol consumption, and supine position during sleep, and adequate hours of sleep every night.

Baseline characteristics

	Total	CPAP	Comparator
Age	54 (SD 9)	53 (SD 9)	54 (SD 9)
Sex (%)	Male 86%	Male = 81	Male = 91
AHI	20 (SD 6)	20 (SD 6)	21 (SD 6)
ESS	12.6 (SD 4.6)	12.1 (SD 4.9)	13.2 (SD 4.3)
BMI	29 (SD 4)	29.4 (SD 3.7)	29.5 (SD 3.3)
Blood pressure: Systolic BP Diastolic BP		 126 (SD 17) 81 (SD 12)	 132 (SD 17) 84 (SD 11)
FOSQ		101 (SD 18)	100 (SD 15)
NHP		21 (SD 20)	20 (SD 16)
MSLT, min		10 (SD 5)	11 (SD 5)
SAHS related symptoms		21 (SD 4)	21 (SD 3)

Additional information Outcomes were measured at study entry and after 3 months and 6 months of treatment. Outcomes included: symptom measures (SAHS symptom questionnaire), sleepiness (ESS, MSLT), quality of life (NHP, FOSQ), and cognitive function (see Table 11.13).

Study details	**Intervention**	**Participants**
Montserrat 2001[86] **Setting** Spain **Design** Partial crossover trial. **Duration** 6 weeks	**CPAP** (following overnight manual titration) Adherence (hrs/nt): 4.25 **Comparator** Sham CPAP. All participants were encouraged to follow a diet and sleep regimen regardless of	**Number randomised** Total: 48 CPAP: 24 Comparator: 24 (baseline data for age, AHI and BMI n=45; other outcomes n=46) **Number of withdrawals** Total: 2 (first treatment period), 1 (crossover) CPAP: 2 (n=1 first treatment period, n=1 crossover) Comparator: 1 **Reasons for withdrawals** Not reported

Notes CPAP group had 6 weeks study period using the intervention, sham-CPAP group trialled 6 weeks on each intervention. 10 day washout period.

Inclusion criteria Patients previously diagnosed with an AHI>10 and excessive daytime somnolence.

Exclusion criteria Severe or unstable cardiovascular disease or hazardous job (professional driver or handling dangerous machinery).

treatment group assigned.

Baseline characteristics

	Total	CPAP	Comparator
Age		55.65 (SD 9.41)	52.59 (SD 10.93)
Sex	Not reported	Not reported	Not reported
AHI		50.52 (SD 19.83)	57.14 (SD 21.14)
ESS		16.13 (SD 1.03)	16.86 (SD 1.20)
BMI		30.31 (SD 4.49)	33.73 (SD 6.62)
Blood pressure	Not assessed	-	-
SF-36:			
PCS		46.53 (SD 1.92)	45.54 (SD 2.17)
MCS		48.21 (SD 2.06)	48.73 (SD 2.49)
Physical functioning		76.96 (SD 5.66)	78.18 (SD 4.80)
Role-physical		71.74 (SD 8.79)	78.41 (SD 8.11)
Bodily pain		75.26 (SD 5.26)	58.32 (SD 7.27)
General health		60.48 (SD 3.05)	61.55 (SD 5.61)
Vitality		56.52 (SD 5.93)	58.03 (SD 6.23)
Social functioning		82.61 (SD 3.91)	82.39 (SD 5.37)
Role-emotional		84.06 (SD 7.52)	75.76 (SD 8.55)
Mental health		71.83 (SD 3.93)	77.45 (SD 3.67)
FOSQ:			
General productivity		19.18 (SD 1.06)	20.25 (SD 0.89)
Social		18.96 (SD 1.26)	18.00 (SD 1.66)
Activity level		16.71 (SD 0.81)	17.21 (SD 1.23)
Vigilance		13.66 (SD 1.16)	14.17 (SD 1.48)
Intimacy		16.40 (SD 1.57)	17.43 (SD 1.63)
Total score		84.45 (SD 4.63)	86.16 (SD 5.96)
SAHS related symptoms		39.70 (SD 1.14)	38.86 (SD 1.14)

<table>
<tr><td></td><td></td><td>Additional information Outcomes were measured on the last day of each treatment: ESS, SF-36, FOSQ.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Norman 2006[73]
Related papers [116, 302, 330-335]

Setting USA

Design Parallel group trial

Duration 2 weeks

Notes At time of initial screening, CPAP group had a higher baseline SBP than sham CPAP group (p=0.042).

Participants whose BP was >170/105 mmHg were excluded and re-started on BP medication.

Inclusion criteria Men and women between 25 and 65 years within 100% to 170% of their ideal body weight, with an AHI>15.

Exclusion criteria Major ongoing illness other than sleep apnoea and</td><td>CPAP Humidified CPAP (following manual titration) plus an oxygen concentrator that provided room air.
Adherence to treatment: 6.7 hrs/night (SE 1.2).

Comparator Sham CPAP (0-0.5 cm H20) following mock titration plus an oxygen concentrator that provided room air
Adherence to treatment: 6.0 hrs/night (SE 2.4).

Supplemented oxygen (3L/m oxygen concentrator) plus sham CPAP
Adherence to treatment: 6.7 hrs/night (SE 1.2).</td><td>Number randomised Total: 46 CPAP: 18 Sham CPAP: 15 Oxygen: 13

Number of withdrawals No withdrawals reported.

Reasons for withdrawals NA

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Sham CPAP</td></tr>
<tr><td>Age</td><td></td><td>49.7 (SE 2.5)</td><td>49.3 (SE 2.7)</td></tr>
<tr><td>Sex</td><td></td><td>Male n=15</td><td>Male n=13</td></tr>
<tr><td>AHI</td><td></td><td>66.1 (SD 29.1)</td><td>53.9 (SD 29.8)</td></tr>
<tr><td>ESS</td><td></td><td>12.0 (SE 1.3)</td><td>12.0 (SE 1.7)</td></tr>
<tr><td>BMI</td><td></td><td>31.5 (SE 1.4)</td><td>29.9 (SE 1.3)</td></tr>
<tr><td>Blood pressure (mmHg):
Systolic BP
Diastolic BP
MAP</td><td></td><td>
135.1 (SE 3.8)
79.6 (SE 1.7)
98.1 (SE 2.5)</td><td>
122.5 (SE 3.3) 75.6 (SE 2.5)
91.2 (SE 2.5)</td></tr>
</table>
Additional information Outcomes: BP (mean 24-hour ambulatory BP, daytime systolic and diastolic BP, night-time systolic and diastolic BP), AHI, and various polysomnographic parameters. BP was taken every 15 minutes between 6am and 10pm (daytime) and every 30 minutes between 10pm and 6am (night-time) using a cuff. Related papers report psychological symptoms (Bardwell 2007), and cognitive outcomes (Lim 2005) (see Table 11.13).</td></tr>
</table>

<table>
<tr><td>hypertension. Individuals who had had previous treatment with CPAP or undergone pharyngeal surgery for OSA were also excluded.</td><td></td><td></td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Olson 2002[50] (unpublished data from Giles et al., 2006)

Setting

Design Crossover trial

Duration 2 x 6 weeks (2 week washout period).

Inclusion criteria AHI > 15, or apnea index > 5, or AHI > 5 and arousal index > 15.

Exclusion criteria Poor dentition, temporo-mandibular joint pain, or previous treatment with oral appliances or CPAP.</td><td>CPAP Treatment adherence: not reported

Comparator Oral appliance.</td><td>Number randomised Total: Unclear, 24 participants included

Number of withdrawals Not reported

Reasons for withdrawals

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>Not reported</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Not reported</td><td></td><td></td></tr>
<tr><td>AHI, range</td><td>8.1-36.9</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not reported</td><td></td><td></td></tr>
<tr><td>BMI</td><td>Not reported</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not reported</td><td></td><td></td></tr>
</table>
Additional information Outcomes: total sleep time, sleep efficiency, %REM sleep, AHI, Arousal index, Sleep apnoea quality of life index.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Pepperell 2002[87]
Related papers [336, 337]

Setting UK.</td><td>CPAP (following overnight titration using an automated pressure setting device)
Adherence (hrs/nt): 4.5 (SD 2.4)</td><td>Number randomised Total: 118 CPAP: 59 Comparator: 59

Number of withdrawals Total: 14 CPAP: 6 Comparator: 8</td></tr>
</table>

Design Parallel group trial.

Duration 4 weeks.

Notes A specialist nurse helped all participants with advice via telephone, and masks were further adjusted if necessary.

Inclusion criteria Men with > 10 episodes per hour of greater than 4% drop in SaO_2 and ESS ≥10.

Exclusion criteria Required urgent CPAP therapy, where about to lose their job as a result of sleepiness, declined to participate, preferred alternative treatment, unable to give informed consent.

Comparator Subtherapeutic CPAP (pressure: < 1cm water). Adherence (hrs/nt): 4.9 (SD 204)

Reasons for withdrawals CPAP: discontinued CPAP (n=2), did not attend post treatment BP (n=4)
Sham CPAP: discontinued CPAP (n=2), did not attend post treatment BP (n=6).

In addition, post BP recordings were inadequate in 10 participants (n=5 per treatment arm).

Baseline characteristics

	Total	CPAP	Comparator
Age		50.1 (SD 10.4)	51.0 (SD 9.8)
Sex	Male n=118		
AHI	Not assessed		
ESS		16.3 (SD 3.3)	16.0 (SD 3.1)
BMI		34.6 (SD 8.5)	35.3 (SD 6.0)
Blood pressure:			
Systolic BP		132.5 (SD 15.3)	134.9 (SD 18.7)
Diastolic BP		85.1 (SD 8.7)	85.1 (SD 8.9)
24-HR Mean BP		101.0 (SD 9.8)	101.7 (SD 10.8)
Sleep period BP		93.7 (SE 1.6)	96.2 (SE 1.6)
Wake period BP		104.3 (SE 1.3)	104.2 (SE 1.4)

22 participants (11 in each group) were taking medication for hypertension.

Additional information Outcomes: Blood pressure; withdrawal; ESS; AHI. BP was recorded every 30 minutes for a 24 hr period, and measured with a cuff.

Study details	**Intervention**	**Participants**
Randerath 2002[105] Related paper [338] **Setting** Germany.	**CPAP** Treatment adherence (self-reported): hrs/night, %: >8 hrs, 9%; 6-7hrs, 27%; 4-5 hrs, 64%; 2-3 hrs, 0%. All participants used	**Number randomised** Total: 20 **Number of withdrawals** No dropouts reported

<table>
<tr>
<td></td>
<td>CPAP on at least 5 nights per week.</td>
<td>Reasons for withdrawals NA</td>
</tr>
<tr>
<td>Design Crossover trial.

Duration 2 x 6 weeks.

Inclusion criteria Patients with an AHI 5-30 and clinical symptoms of OSAS.

Exclusion criteria AHI >30, temperomandibular joint disorders, bruxism, participants with gaps in their teeth preventing fitting of device.</td>
<td>Comparator Oral appliance (two thin thermoplastic plates, worn on the upper and lower jaws connected by two adjustable telescopic guide rods). The maximum forward protrusion of the mandible was measured and this amount reduced to about 2/3 before mounting the casts.

Treatment adherence (self-reported): hrs/night, %: >8 hrs, 33%; 6-7hrs, 53%; 4-5 hrs, 7%; 2-3 hrs, 7%. All participants used OA on at least 5 nights per week.</td>
<td>Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>56.5 (SD 10.2)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=16
Female n=4</td><td></td><td></td></tr>
<tr><td>AHI</td><td>17.5 (SD 7.7)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>BMI</td><td>31.2 (SD 6.4)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
</table>
Additional information Outcomes: AHI; Snoring (epochs/hr); SaO2 (%); TST (min); Wake after sleep onset; Sleep stage 1, 2, 3, 4; REM sleep; Arousals per/h; Respiration-induced arousals, per/hr of TST.</td>
</tr>
<tr>
<td>Study details</td>
<td>Intervention</td>
<td>Participants</td>
</tr>
<tr>
<td>Redline 1998[59]

Setting USA.

Design Parallel group trial.

Duration 8-16 weeks.

Inclusion criteria Adults, aged 25-65 years, with mild to moderate sleep disorderd breathing (RDI 5-30) without subjective pathologic sleepiness.</td>
<td>CPAP CPAP plus CM (advice on sleep, posture and sleep hygiene. Weight reduction and counselling was provided to patients with a BMI > 29kg/m2 and nasal steroid spray for those with nasal congestion).

Adherence (machine usage): 44% (SD 34) of the time subjects were estimated to be asleep (3.1hrs).

Comparator Conservative treatment (CM). Control patients were also given a</td>
<td>Number randomised Total: 111 CPAP: 59 Comparator: 52

Number of withdrawals Total: 14 CPAP: 8 Comparator: 6

Reasons for withdrawals CPAP: 3 withdrew due to problems in using CPAP, and 5 due to an inability to schedule all day testing battery.
Comparator: all withdrew due to an inability to schedule all day testing battery.

Baseline characteristics (presented for completers only, n=97)
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td></td><td>48.1 years (SD 9.2),</td><td>49.2 years (SD 10.5).</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Exclusion criteria Any severe or unstable medical disease documented in previous 3 months; neurologic disease; alcohol or drug abuse; regular use of medications that impair sensorium and < 8 years of education.</td>
<td>supply of nasal dilators.

Use of mechanical nasal dilators: 82% (SD 28) of intervention nights.</td>
<td>
<table>
<tr><td>Sex</td><td></td><td>Male n=30
Female n=21</td><td>Male n=20
Female n=26</td></tr>
<tr><td>AHI</td><td>Not assessed</td><td>-</td><td>-</td></tr>
<tr><td>ESS</td><td></td><td>10.4 (SD 4.3)</td><td>10.6 (SD 5.6)</td></tr>
<tr><td>BMI</td><td></td><td>33.4 (SD 6.9)</td><td>32.0 (SD 8.5)</td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td>-</td><td>-</td></tr>
<tr><td>RDI</td><td></td><td>14.6 (SD 9.8)</td><td>11.8 (SD 9.6)</td></tr>
<tr><td>MSLT, min</td><td></td><td>9.9 (SD 4.8)</td><td>10.3 (SD 5.0)</td></tr>
<tr><td>POMS:
fatigue score</td><td></td><td>
44.2 (SD 8.2)</td><td>
41.8 (SD 7.6)</td></tr>
<tr><td>SF-36:
fatigue/energy
general health perception
social role functioning
role limitations-physical
role limitation-emotional</td><td></td><td>
51.7 (SD 19.8)
66.4 (SD 18.2)
88.4 (SD 18.3)
70.6 (SD 34.5)
85.6 (SD 26.9)</td><td>
58.3 (SD 19.0)
69.8 (SD 19.5)
91.4 (SD 14.0)
88.1 (SD 22.5)
82.8 (SD 31.1)</td></tr>
<tr><td>PANAS:
positive affect
negative affect</td><td></td><td>
32.9 (SD 7.3)
16.3 (SD 5.4)</td><td>
32.3 (SD 6.8)
16.0 (SD 6.0)</td></tr>
</table>
Additional information Polysomnographic parameters and daytime test battery: mood (Profile of mood states (POMS), and the Positive and Negative Affect Scale (PANAS), well-being and functional status (Medical Outcomes Survey Short Form 36 (SF-36), and objective measure of sleepiness (MSLT). Participants were evaluated at baseline and at 8-16 weeks, and after at least two weeks following any intercurrent illness. Change on these measures was used to calculate an overall treatment response score. ESS was also assessed. Three participants were re-tested after the 16 week period (two at 17 weeks and 1 at 19 weeks).
</td>
</tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
</table>

<table>
<tr>
<td>Robinson 2006[68]
Related paper[339]

Setting UK

Design Crossover trial.

Duration 2 x 4 weeks (2 week washout period).

Inclusion criteria Adults with moderate to severe OSA (without hypersomnolence) and hypertension. Hypertension was defined as BP>140/90mmHg, or currently using hypertensive medication.

Exclusion criteria Respiratory failure.</td>
<td>CPAP (following titration using an automated pressure device)
Treatment adherence (mean machine usage, hrs/night): 5.2 (SD 2.1).

Comparator Sham CPAP (pressure: <1 cm H_20). Treatment adherence (mean machine usage, hrs/night): 4.3 (SD 2.4).</td>
<td>Number randomised Total: 35

Number of withdrawals Total: 3 CPAP: 3 Comparator: 0

Reasons for withdrawals CPAP arm: two before completing first month's treatment period (1 due to intolerance of BP cuff and 1 due to inadequate BP data), and one participant during the second treatment period due to intolerance of BP cuff.

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>54 yrs (SD 8)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=31</td><td></td><td></td></tr>
<tr><td>AHI</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>ESS, median</td><td>5.3 (IQR 3.0-7.0)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>33.2 (SD 5.3)</td><td></td><td></td></tr>
<tr><td>Blood pressure:
24hr BP (mmHg)
24hr systolic BP
24hr diastolic BP
Wake BP
Sleep BP</td><td>Not reported</td><td>
103.4 (SD 11.6)
140.3 (SD 16.1)
85.3 (SD 11.2)
106.1 (SD 13.6)
96.0 (SD 11.5)</td><td>
105.1 (SD 12.1)
143.0 (SD 17.33)
86.7 (SD 11.1)
108.8 (SD 13.0)
98.0 (SD 14.8)</td></tr>
<tr><td>Osler test (min), median</td><td>40 (IQR 40-40)</td><td></td><td></td></tr>
<tr><td>Dips in SaO2 of >4%/hr sleep, median</td><td>28.1(IQR 18.0-38.0)</td><td></td><td></td></tr>
</table>
77% (27) participants were receiving medication for hypertension; these participants were instructed not to change their antihypertensive medication during the study period.</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td>Additional information Outcome: oxygen saturation, ESS, and 24hr BP. Outcomes were assessed before and after each treatment period. BP was measures every 30 minutes over 24hrs using an arm cuff.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Reference Skinner 2004a[60]

Setting New Zealand.

Design Crossover trial.

Duration 2 x 4 weeks (1 week washout period).

Inclusion criteria Men and women with OSA (AHI 10-60 and symptoms of daytime somnolence).

Exclusion criteria History of cardiovascular, neurological, and / or psychological disorders affecting sleep; known cervical, shoulder or thoracic wall abnormalities, and / or chronic pain; or previous treatment for OSA.</td><td>CPAP (the pressure was set following 3-5 nights on an automated titrating device) Adherence to treatment (machine recorded): 4.7 hrs/night (SD 2.6).

Comparator Shoulder-head elevation pillow (SHEP). SHEP is designed to keep the patient in an upright posture (60 degrees) during sleep. Adherence to treatment (self-reported): 6.3 hrs/night (SD 1.6).</td><td>Number randomised Total: 14

Number of withdrawals Total: 1 CPAP: 1 Comparator: 0

Reasons for withdrawals Declined to use portable sleep monitor at end of CPAP treatment phase.

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td>54 years (SD 10)
(range 39-69)</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=12</td><td></td><td></td></tr>
<tr><td>AHI</td><td>27 (SD 12)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>11.9 (SD 4.6)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>34 (SD 7)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>SHS (%)</td><td>53.6 (SD 13.7)</td><td></td><td></td></tr>
<tr><td>SF-36:
Physical score
Mental score</td><td>
42.6 (SD 11.3)
47.9 (SD 12.3)</td><td></td><td></td></tr>
<tr><td>FOSQ</td><td>12.1 (SD 1.9)</td><td></td><td></td></tr>
</table>
Additional information Outcomes: ESS, AHI, Functional Outcomes of Sleep Questionnaire (FOSQ), Medical Outcomes Trust short-form general health survey (SF-36), and the Scottish Sleep Health Symptom questionnaire (SHS) were assessed at study entry and at the end of each treatment period. In addition, adverse events were assessed using a questionnaire at the end of each treatment period;</td></tr>
</table>

<table>
<tr><td></td><td></td><td>questionnaire comprising of 19 adverse events most likely to be associated with SHEP was administered, and a similar questionnaire was completed after CPAP.</td></tr>
<tr><td>Study details</td><td>Intervention</td><td>Participants</td></tr>
<tr><td>Skinner 2004b[61]

Setting New Zealand.

Design Crossover trial.

Duration 2 x 4 weeks (no report of washout period)

Notes

Inclusion criteria Men and women with AHI 10 – 60 and mild to moderate obstructive sleep apnoea.

Exclusion criteria History of cardiovascular, neurologic, or psychological disorders affecting sleep, known cervical or temporomandibular joint dyfunction and/or pain.</td><td>CPAP (the pressure was set following 3-5 nights on an automated titrating device) Adherence to treatment: 68% (SD 24%) of available study nights, mean nightly duration 4.4hrs (SD1.2).

Comparator Cervicomandibular collar (designd to retain the head in the natural head position and prevent jaw opening during sleep). Adherence to treatment: 89% (SD 23%) of total available study nights, mean nightly duration 5.2hrs (SD1.2).</td><td>Number randomised Total: 10

Number of withdrawals Total: 0 CPAP: 0 Comparator: 0

Reasons for withdrawals NA

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age, yrs</td><td>48.6 (SD 14.8).</td><td></td><td></td></tr>
<tr><td>Sex</td><td>Male n=8</td><td></td><td></td></tr>
<tr><td>AHI</td><td>29.4 (SD 13.4)</td><td></td><td></td></tr>
<tr><td>ESS</td><td>13.2 (SD 4.9)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>34.1 (SD 5.6)</td><td></td><td></td></tr>
<tr><td>Blood pressure</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>SF-36:
Physical score
Mental score</td><td>
45.3 (SD 10.4)
43.8 (SD 13.1).</td><td></td><td></td></tr>
<tr><td>FOSQ</td><td>12.2 (SD 3.1)</td><td></td><td></td></tr>
<tr><td>SHS</td><td>59.7 (SD 11.9)</td><td></td><td></td></tr>
</table>
Additional information Outcomes: sleep parameters, ESS, SF-36, FOSQ, and SHS were assessed at before treatment and after each treatment period. Adverse effects of treatment were also assessed at the end of each treatment period (self-reported diary and questionnaire). Mean scores were annotated from responses to 19 self-reported questions (score 0-3). Overall benefit of each treatment was assessed at the end of the study.</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Intervention</th><th>Participants</th></tr>
<tr><td>Spicuzza 2006[66]

Setting Italy

Design Parallel group trial.

Duration 4 weeks.

Notes

Inclusion criteria Men and women with moderate to severe obstructive sleep apnoea.

Exclusion criteria Presence of hypertension and/or other cardiovascular diseases, diabetes, thyroid disorders, chronic obstructive/restrictive lung diseases or respiratory failure, and smokers.</td><td>CPAP (following overnight titration)
Treatment adherence (machine use/hrs on):
CPAP 6.0 (SD 1.1).

Comparator Sham CPAP (pressure: 1-2cm H_20).
Treatment adherence (machine use/hrs on):
6.5 (SD 2.4).</td><td>Number randomised Total:25 CPAP: 15 Comparator: 10

Number of withdrawals The authors do not report withdrawals.

Reasons for withdrawals NA

Baseline characteristics
<table>
<tr><td></td><td>Total</td><td>CPAP</td><td>Comparator</td></tr>
<tr><td>Age</td><td></td><td>55.9 yrs (SD 9.4)</td><td>55.1yrs (SD 9.3)</td></tr>
<tr><td>Sex</td><td>Male n=20</td><td></td><td></td></tr>
<tr><td>AHI</td><td></td><td>55.3 (SD 11.9)</td><td>59.2 (SD 17.3)</td></tr>
<tr><td>ESS</td><td>Not assessed</td><td></td><td></td></tr>
<tr><td>BMI</td><td></td><td>31.1 (SD 4.2)</td><td>33.5 (SD 5.5)</td></tr>
<tr><td>Blood pressure
Systolic BP
Diastolic BP</td><td></td><td>
145.4 (SD 4.7)
87.9 (SD 4.6)</td><td>
149.5 (SD 7.2)
85.0 (SD 3.8)</td></tr>
</table>
Additional information Outcomes: AHI, and ventilatory control measures. Outcomes were assessed at baseline and at the end of the study.</td></tr>
<tr><th>Study details</th><th>Intervention</th><th>Participants</th></tr>
<tr><td>Tan 2002[106]
Related papers [340-342]

Setting UK

Design Crossover trial.</td><td>CPAP Two different models of nCPAP compressor were used. Nasal corticosteroid sprays were prescribed to relieve nasal congestion where necessary.

Adherence (hrs/nt): Not reported</td><td>Number randomised Total: 24

Number of withdrawals Total: 3 CPAP: 2 Comparator: 1

Reasons for withdrawals Two participants did not tolerate nCPAP, one participant did not tolerate MAS.</td></tr>
</table>

Duration 2 x 8 weeks. Two-week washout.

Notes Baseline: O2 desaturation: 7.1 +/- 2.7. Arousals/hr: 19.3 +/- 9.6.

Inclusion criteria Men and women with AHI <50, with adequate dentition and periodontal status for support and retention of oral appliance.

Exclusion criteria
Temporomandibular joint dysfunction, medical contraindications, significant heart disease, co-existent chronic obstructive pulmonary disease, regular hypnotic use, epilepsy, arterial oxygen saturation < 60% during initial sleep study, ability to give informed consent.

Comparator Oral appliance. A soft one-piece MAS was used for the first 10 participants. A two part semi-rigid MAS was used for the remainder of the study; this appliance permitted some mandibular opening during sleep.

Adherence (hrs/nt): Not reported

Baseline characteristics

	Total	CPAP	Comparator
Age	50.9 (SD 10.1)		
Sex	Male n=20 Female n=4		
AHI	22.2 (SD 9.6)		
ESS	13.4 (4.6)		
BMI	31.9 (SD 6.8)		
Blood pressure	Not assessed		

Additional information Outcomes were measured on the last day of each treatment: ESS, AHI, ODI, REM%, Sleep Efficacy, Preference.

Study details	**Intervention**	**Participants**
West [151] (unpublished data supplied by the author) Related papers: [67]	**CPAP** CPAP (auto-titrating). Treatment adherence (machine usage): 3.6 hrs/night (SD 2.8).	**Number randomised** Total: 42 CPAP: 20 Comparator: 22 **Number of withdrawals** Total: 2 CPAP: 2 Comparator: 0

Setting UK

Design Parallel group trial.

Duration 12 weeks.

Notes One participant in the active treatment group received a defective machine which delivered minimal pressure and was analysed with sham CPAP group.

Inclusion criteria Men with OSA (>10 Sa02 dips of greater than 4% per hour) and type 2 diabetes.

Exclusion criteria Urgent CPAP required or unstable diabetes requiring an escalation in treatment. Primary care physicians were requested not to change participants medications, unless essential.

Comparator sham CPAP (pressure: <1cm and >0cm water).

Treatment adherence (machine usage): 3.3 hrs/night (SD 3.0).

Reasons for withdrawals unrelated surgery (n=1), unwilling to continue using CPAP (n=1)

Baseline characteristics

	Total	CPAP	Comparator
Age		57.8 (SD 10.4)	54.5 (SD 9.4)
Sex		Male n=21	Male n=21
AHI	Not assessed	-	-
ESS		14.7 (SD 3.5)	13.5 (SD 3.5)
BMI		36.6 (SD 4.9)	36.8 (SD 4.6)
Blood pressure	Not assessed	-	-
>4% SaO_2 dips/hr		33.1 (SD 21.6)	39.1 (SD 24.8)
MWT, min		21.9 (SD 12.8)	32 (SD 10.8)
SAQLI		4.3 (SD 1.1)	4.4 (SD 0.9)

Additional information Outcomes: ESS, MWT (Osler), SAQLI, and change in HbA1c, insulin sensitivity, and adverse events. Outcomes were assessed at baseline and at end of treatment.

11.6 Economic evaluation data extraction

Surname of first author, date of publication	**Ayas**[122]	**Mar**[123]	**ResMed**[120]	**Trent**[44]
Type of economic evaluation	Cost-utility analysis.	Cost-utility analysis.	Cost-utility analysis and cost-effectiveness analysis	Cost-utility analysis
Currency used, year	US $, 2003.	Euros (converted from Spanish Pesetas), 2000.	UK sterling, 2005	UK sterling, no report of financial year of costs
Study design	Markov model using effectiveness estimates from one study and adjusting these for the impact of RTA, based on a random-effects meta-analysis of 8 before and after studies.	Semi-Markov model using effectiveness estimates from a before and after study.	Markov model using effectiveness estimates from a before and after study	Review synthesis. Effectiveness estimates based on results from two studies. Estimates based on before and after data.
Perspective	Third party payer Societal perspective.	Healthcare perspective.	Healthcare perspective.	Healthcare perspective.
Participants	Data from 99 patients with moderate to severe OSAH were used to establish the proportion of patients in each sex/age group.	Based on a cohort of 5,000 patients with moderate to severe OSAH to establish the proportion of patients in each sex/age group.	Based on a simulated cohort of 2,000 patients with moderate to severe OSAH.	Patients referred to a Sleep Clinic. Typically middle-age group (45+ years old).
Setting, country of study	US	Spain	UK	UK
Intervention group	CPAP.	nCPAP.	CPAP (fixed).	nCPAP.
Control group	No CPAP.	No CPAP.	CPAP (auto) No CPAP.	Dental devices No CPAP.
Resources used	Health care; costs of diagnosis and treatment of OSAS, costs attributable to motor vehicle accidents and maintenance costs of the devices and costs of medical follow-up.	Health care; costs of investigation, diagnosis and treatment of OSAS, costs attributable to CVE morbidity and maintenance costs of the devices and costs of medical follow-up.	Health care; costs of investigation, titration, diagnosis and treatment of OSAS, costs attributable to CVE and RTA morbidity and maintenance costs of the devices and costs of medical follow-up.	Health care; costs of investigation, diagnosis and treatment of OSAS and maintenance costs of the devices and costs of medical follow-up.
Source of effectiveness data	Base-case used single study (Chakravorty *et al*, (2002).[97] For patients who had an RTA, utility estimates were adjusted using the FCI.	Survey of OSAS patients before the initiation of CPAP and three months post CPAP.	Base-case used Mar *et al* (2003) results.	Two studies (Waterhouse *et al*, 2000 and Jenkinson *et al*, 1999) using before and after (up to 4 weeks) initiation of CPAP. [146, 147] Jenkinson, 1999 #494}
Length of follow up	Five years.	Results were extrapolated to five years and over the lifespan of the patient.	14 years. Used results of Marin *et al* (2005)).[130] and Mar *et al* (2003)[123] to calculate annual incidence of fatal and non-fatal CVE and cerebrovascular	Five years.

			events in CPAP treated and untreated patients with severe OSAHS (AHI greater than 30) to 12 years and extrapolated these results over another two years. Used the Mar *et al* (2003))[123] to estimate the ratio of CHD and stroke in patients with untreated severe OSAHS as 1.185 and 1.353 respectively. Estimated the ratio of developing CHD to stroke as 1:1.13. Estimated ratio of CHD to stroke in treated patients as 1:1. Using these estimates, ResMed calculated the annual risk of CVE and stroke.	
Source of resource use data	A primary referral centre and national data. Not all sources of resource use data were reported.	Single sleep centre located in a hospital.	19 clinicians.	Published literature, administrative database and clinical opinion
Source of unit cost data	The cost of CPAP was obtained from Medicare fee schedules. Costs of RTA were obtained from the National Highway Traffic Safety Administration.	The device cost was the price of the CPAP S VI Plus model. Regional hospital costs were used for the healthcare costs.	List prices, published literature, government statistics	Published literature, administrative database and clinical opinion
Link between cost & effectiveness data	Cost & effectiveness data were not linked directly.	Cost & effectiveness data were not linked directly.	Cost & effectiveness data were not linked directly	Cost & effectiveness data were not linked directly
Clinical outcomes measured & methods of valuation used	The base-case used a single study (Chakravorty *et al*, 2002)[97] to obtain the relative treatment effect of CPAP vs. do nothing. The utilities were elicited using patient preferences and were valued using the standard gamble. For the secondary analysis, EQ-5D estimates were used based on societal preferences (Jenkinson *et al*, 1998 and Mar *et al*, 2003).[123] The patients who had an RTA, utility estimates were adjusted using rating scale preference weights obtained from the FCI (Graham *et al*, 1997).	Utility values were obtained using the EQ-5D. The health states for 46 patients were elicited and societal preferences were applied using the time-trade off technique. No data were available on quality of life in OSAS patients with stroke and CHD therefore this was modelled by assigning quality adjustment factors of 0.8 and 0.9 respectively to these health states, based on an estimate in the published literature.	Utility values were obtained from the EQ-5D using the Mar *et al* (2003) results.[123] The health states for 46 patients were elicited and societal preferences were applied using the time-trade off technique. No data were available on quality of life in OSAS patients with stroke and CHD therefore this was modelled by assigning quality adjustment factors of 0.8 and 0.9 respectively to these health states, based on an estimate in the published literature. 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.	Utility values generated via SF-36 survey, using the Brazier *et al* (1998) algorithm. [148] Societal preferences were applied using the TTO and/or standard gamble.
Outcome results/ adverse events	CPAP utility = 0.55, no CPAP utility = 0.32. Treatment with CPAP reduced	Of the patients who were diagnosed with moderate to severe OSAS, there	The utility associated with untreated OSAHS is 0.738 and with treated	The gain in HRQoL as measured by the SF-36 single index was 0.12 QALYs (95%CI,

	the rate of RTA by sevenfold (OR of RTA with CPAP vs. no CPAP = 0.15, 95% CI, 0.10 to 0.22. No consideration was given to the effect of adverse events due to CPAP. The incremental QALY for CPAP was 0.75 QALYs, that is 2.22 QALYs (95% CI, 0.86 to 3.89 vs. 1.47 QALYs (95% CI, 0.28 to 3.08).	was a 10% drop out rate from treatment in the first year. In the analysis this impacted on costs but was not included in terms of outcomes. The mean EQ-5D score was 0.738 (0.646 to 0.829) before beginning nCPAP. The mean gain 3 months later was 0.073 (0.015 to 0.131) QALYs were 3.73 at five years and 14.38 over the lifespan in the nCPAP arm and QALYs 3.39 at five years and 12.90 over the lifespan in the no CPAP arm.	OSAHS is 0.811. The utility of non-fatal stroke in untreated OSAHS patients was 0.590 and in treated patients was 0.649. The utility of non-fatal CVE in untreated OSAHS patients was 0.664 and in treated patients 0.730. The utility of non-fatal RTA in untreated OSAHS patients was 0.701 and 0.771 in treated patients. At 14 years the estimated QALY gains were 7.22 (6.85 to 7.62) for no treatment, 8.19 (7.79 to 8.69) for CPAP (fixed) and 8.32 (7.97 to 8.81) for CPAP (auto). It was estimated that for 79% of patients would continue to use CPAP (fixed) and 84% CPAP (auto) after the first year of treatment and that following this there would be no further loss to compliance.	0.09 to 0.16) over one year.
Cost data handled appropriately	Some unit costs and resource use were reported separately	Unit costs and resource use were reported separately.	Unit costs and resource use were reported separately.	Unit costs and resource use were reported separately.
Cost results	From the third party payer perspective, the incremental cost for CPAP $2,519, that is $4,177 (95% CI, $2,804 to $1,659 (95% CI, $283 to $3,936) From the societal perspective, CPAP was more costly, that is $7,123 (95% CI, $4,324 to $11,906) vs. $6,887 (95% CI, $3,113 to $14,843).	Costs were Euros 2,719 at five years and Euros 7,902 over the lifespan in the nCPAP arm and Euros 55 at five years and Euros 591 over the lifespan in the no CPAP arm.	Costs were estimated over 14 years. From the NHS perspective the cost of no treatment was £10,645 (95% CI £7,912 to £14,177) and £9,086 (95% CI £6,851 to £11,117) for CPAP (fixed) and £8,622 (95% CI £6,712 to £10,947) for CPAP (auto).	Total recurring annual cost of £250 per patient on long-term CPAP therapy.
Sub-group analysis	Not undertaken	Not undertaken.	Not undertaken.	Not undertaken.
Modelling summary	Third party payer perspective: CPAP more costly & more effective than no CPAP. ICER = $3,354 per QALY (95% CI, $1,062 per QALY to $9,715 per QALY). Societal perspective CPAP more costly & more effective. ICER = $314 (95% CI, cost saving to $6,114). From the third party payer & the societal perspective, probabilistic sensitivity analysis if society's willingness to pay for a QALY is	nCPAP was estimated to be more costly and more effective than no CPAP. The ICER for CPAP was Euros 7,861 per QALY over a five year time horizon and Euros 4,938 per QALY for the life time horizon.	CPAP was estimated to be more costly and more effective than no CPAP.	Authors undertook a review of the evidence. nCPAP was estimated to be more costly and more effective than no CPAP. The ICER for CPAP was £8,300 at one year and £3,200 at year five. Small differences in clinical effectiveness and cost were found when comparing nCPAP to dental devices but these were not explicitly quantified.

	$50,000, 100% of simulations favoured the cost-effectiveness of CPAP.			
Direction of result with appropriate quadrant location	North-East quadrant.	North-East quadrant.	South-East quadrant.	North-East quadrant.
Statistical analysis for patient-level stochastic data	Not undertaken.	Not undertaken.	Not undertaken.	Not undertaken.
Appropriateness of statistical analysis	Not undertaken.	Not undertaken.	Yes.	Not undertaken.
Uncertainty around cost-effectiveness expressed & appropriateness of method of dealing with uncertainty around this	Yes.	No.	Yes.	No.
Sensitivity analysis & appropriateness	Sensitivity analysis was undertaken on utility values, the discount rate, the compliance rate, the time horizon, the scaling factor for converting lifetime costs to the 5 year model time frame and the reduction in the rates of RTA according to the 95% confidence limits determined in the meta-analysis. Probabilistic sensitivity analysis was also undertaken. The analyses were appropriate.	A series of univariate and multivariate sensitivity analyses were conducted by age, sex, the relative risk of stroke (untreated), different utility estimates, the benefit of nCPAP on blood pressure, the drop out rate, the cost of nCPAP, the discount rate/s. It was found that the estimation of the ICER was sensitive to the time horizon.	A series of univariate and multivariate sensitivity analyses were conducted as reported in Table 6.7.	A series of univariate sensitivity analyses were conducted by : the impact of the analytical time horizon, costs of investigation for nCPAP, long-term costs of maintenance, follow-up and other healthcare resource usage, the long-term impact of gross annual healthcare costs, the potential impact of improved mortality from use of nCPAP treatment, the impact of uncertainty in morbidity benefits from nCPAP therapy and the discount rate.
Modelling inputs & techniques appropriate	Markov model using second-order Monte Carlo simulations to generate 1,000 incremental cost and effectiveness pairs was appropriate.	Yes.	Yes.	Not undertaken.
Author's conclusions	Treatment for OSAS with CPAP has a cost-effectiveness in line with that of other commonly funded treatments such antihypertensive drugs.	Treatment for OSAS with nCPAP has a cost-effectiveness in line with that of other commonly funded treatments such antihypertensive drugs. The key clinical benefit of nCPAP is improvement in the quality of life of patients with OSAS.	CPAP (fixed) dominates no treatment and CPAP (auto) dominates no treatment after a minimum of two years' treatment. Based on current evidence use of CPAP (auto) is associated with marginally better outcomes and no additional cost, compared to CPAP (fixed).	Treatment for OSAS with CPAP has a cost-effectiveness in line with that of other commonly funded treatments. The incremental cost-effectiveness of nCPAP over dental devices was likely to be highly uncertain.

11.7 Review of utility data

The approach recommended by the National Institute for Health and Clinical Excellence (NICE) and other bodies when undertaking cost-effectiveness analyses is to measure the incremental cost per quality adjusted life year (QALY) gained of the intervention under study versus an appropriate comparator. QALYS are calculated by multiplying the amount of time spent in a health outcome by the preference value or utility attached to that outcome. This latter quality adjustment is based on a set of values or weights for each possible health state, that reflect the relative desirability of that health state as judged by individuals or society. In the case of cost effectiveness studies of CPAP, utility values are required which quantify the impact on HRQoL of experiencing sleep apnoea and also the influence of receiving CPAP therapy on HRQoL. This report reviews the clinical and cost effectiveness literature on CPAP and sleep apnoea in order to identify possible utility values for the economic analysis.

A search was undertaken of the MEDLINE database in order to identify relevant literature. The search strategy identified 160 abstracts. Abstracts were screened by one reviewer (SvH) and copies of those that were considered relevant were obtained. Four papers were identified as containing potentially relevant HRQoL/utility data. These are appraised below with respect to their utility data.

Tousignant, Cosio, Levy and Groome (1994)[124]
This study assessed the impact of nCPAP therapy on the quality of life of 19 patients with sleep apnoea.

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 nCPAP, pre-treatment, full health and immediate death. To assess the reliability of the results patients completed the exercise on two occasions 2 to 3 weeks apart. The mean utility score for the pre-treatment health state was 0.63 (0.29) and the mean utility score for the NCPAP treatment health state was 0.87 (0.17). The intra class correlation coefficients for the retest data were above 0.7 for both the treatment health state and pre-treatment health states.

Comments
As all the patients were currently receiving nCPAP therapy, their valuation of the pre-treatment health state was done retrospectively. As such 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 is reflects some sort of measurement error due to bias in recall.

Jenkinson, Stradling and Petersen (1997)[152]

This study compared the performance of three commonly used quality of life measures (SF-36, EQ-5D and the Functional Limitations Profile) in patients with sleep apnoea before and after nCPAP therapy and compared the data with that for a normal population.

108 male patients (mean age 50 years, SD 10) with a mean baseline ESS of 14 (SD 5) attending a sleep clinic for a therapeutic assessment of nCPAP therapy completed the three HRQOL measures before and five weeks after commencing treatment.

At baseline the mean EQ-5Dindex scores was 0.79 (0.21) and after treatment the score had increased to 0.84 (0.25), which was not statistically significant and indicates only minor benefits from nCPAP therapy. In contrast both SF-36 and the FLP showed statistically significant improvements in scores on the majority of their dimensions. The authors suggest that the failure of EQ-5D to show a similar magnitude of change to the other measures may be because it does not contain that specifically address areas of health thought to be affected by sleep apnoea such as sleep tiredness energy and social functioning. As such they caution the use of measures such as EQ-5D when evaluating therapy in this area.

Comments

Unlike the SF-36 and FLP, EQ-5D does not contain dimensions relating to sleep and or vitality which undoubtedly are of importance in this area, however through it usual activities dimension it does arguably measure aspects of social functioning. If the intention were to measure change in sleepiness or tiredness then EQ-5D would not be the first choice. However if the intention is to measure change in overall HRQOL then EQ-5D is a well validated globally used measure that unlike the other two measures generates a score that is weighted by the values of the general population. The EQ-5D index score is the main output of interest to those who require a score for use in decisions relating to resource allocation, however within the context of this paper it is not clear why the authors restrict their assessment of the performance of EQ-5D to the performance of the EQ-5D index score alone and appear to disregard the EQ-5D visual analogue scale score or indeed the score on the five dimension questions separately.

Chakrovarty, Cayton and Szcepura (2002)[97]

This study compared the effectiveness of CPAP therapy with a conservative lifestyle management as assessed using two different methods for eliciting health utilities (EQ-5D and a SG task).

71 patients referred to a hospital sleep clinic with a history of snoring and excessive daytime sleepiness were recruited to the study and randomised to receive either CPAP therapy or lifestyle management. Each treatment phase lasted for 3 months. Prior to randomisation and at the end of treatment patients completed EQ-5D and a SG task where they were asked whether they would choose to stay in their current state of health or to be treated with two outcomes: either compete cure or failure leading to a worst health state/death.

SG scores showed a mean gain of 0.23 (from 0.32 to 0.55) for the CPAP group compared to a gain of 0.04 (from 0.31 to 0.35) for the Lifestyle group. In comparison EQ-5Dindex scores showed a much smaller mean gain of 0.04 (from 0.73 to 0.77) for the CPAP group and no change for the lifestyle group. Both groups showed significant improvements in their ESS score and the CPAP group but not the Lifestyle group also had significant improvement in their AHI index score.

The authors suggest that the results indicate that EQ-5D may not be an appropriate instrument to use amongst patients with sleep apnoea because it only showed a mild change in patients with an effective positive treatment response to CPAP and failed to record the small improvement seen in the Lifestyle group (as measured using standard gamble). However it should be noted that the lifestyle group did not show significant improvement in terms of the objective polysomnographic measures reported in the study.

Comments

EQ-5D scores were relatively high at baseline and similar to those reported in other studies for this patient group.

It is not surprising that the utility values obtained using the two methods are different as they were elicited via completely different questions As such the authors conclusions about EQ-5D appear to be somewhat unwarranted.

Comparing utility values elicited using two different methods is problematic, the authors appear to treat the utilities elicited using the SG approach as the “gold standard” but their

justifications for doing so in this context other than describing the standard gamble approach as the "classical approach to calculating utilities" are unclear.

Mar, Rueda, Duran-Cantolla *et al* (2003)[123]

This paper aimed to analyse the long-term cost effectiveness of nCPAP treatment in patients with moderate to severe obstructive sleep apnoea in comparison to conventional treatment.

The authors undertook a survey to obtain EQ-5D utility values for patients with sleep apnoea. Forty-six patients referred to a hospital Sleep Unit were recruited and interviewed twice, once before beginning treatment and then after using nCPAP for three months. The mean age of the sample was 53 years (SD 12), 87% were male and their mean ESS was 13.8 (SD 5.8). Before starting nCPAP the mean EQ-5Dindex score for the sample was 0.738 (0.646-0.829), three months later the mean gain was 0.073 (0.015-0.131). Utilities for non-fatal stroke and non-fatal CHD also included in the model were obtained from the literature but were not specific to patients with sleep apnoea.

Comments

EQ-5D utility values were chosen as the study was designed to consider CPAP within the context of resource allocation; in addition EQ-5D has been validated in a Spanish population. Improvement was similar to that reported in the study by Jenkinson *et al*, 1997 (see above) which also used EQ-5D in a similar population.[152] However the authors point out that the lack of a control group is a limitation of most studies that measure utility values in patients with sleep apnoea and warn that the improvement in HRQOL observed may be an overestimation due to placebo.

11.8 Bivariate Random Effects Meta-Analysis in WinBUGS

The randomised controlled trials identified in the systematic review reported a range of outcomes that were potentially relevant to the appraisal of CPAP for the treatment of OSAHS. In Section 5 a separate univariate meta-analysis was performed for each outcome of interest (where there were sufficient data from comparable studies). An alternative approach would be to perform a multivariate meta-analysis to jointly calculate pooled estimates for each outcome. By performing a multivariate meta-analysis the correlation between outcomes can be estimated and incorporated. Under a univariate approach, outcomes that are not reported are assumed to be missing completely at random (MCAR) and the between study correlation between treatment effects on different outcomes is assumed to be zero. Using the mutlivariate approach, outcomes that are not reported are assumed to be missing at random (MAR), with the mechanism for missingness informed by the between study correlation and the treatment effects for those outcomes that are reported.

Two outcomes identified in the systematic review were selected to inform the York economic model: mean difference in ESS score and mean difference in SBP. A random effects analysis was performed in both the univariate and bivariate meta-analysis approaches where it was assumed that each study's summary statistics (ess_i ($essVar_i$), bp_i ($bpVar_i$)) were assumed to represent an estimate of different underlying true values ($essMu_i$, $bpMu_i$), and these underlying true values were assumed to be drawn from a distribution with particular mean (essReMu, bpReMu) and variance (essReVar, bpReVar). The framework for the bivariate approach is as follows:

$$\begin{pmatrix} ess_i \\ \cdot \end{pmatrix} \sim N\left(\begin{pmatrix} essMu_i \\ \cdot \end{pmatrix}, \delta_i \right), \quad \delta_i = \begin{pmatrix} essVar_i & \varphi_i essVar_i \\ \cdot & \cdot \end{pmatrix}$$

$$\begin{pmatrix} essMu_i \\ \cdot \end{pmatrix} \sim N\left(\begin{pmatrix} essReMu \\ \cdot \end{pmatrix}, \Omega_i \right), \quad \Omega_i = \begin{pmatrix} essReVar & \Phi essReVar \\ \cdot & \cdot \end{pmatrix}$$

Where $\varphi_i essVar_i$ is the within-study covariance and $\Phi essReVar$ is the between-study covariance. None of the trials reported within-study covariance between mean difference in ESS and mean difference in SBP, and so a set of patient-level data containing both outcomes

was obtained from which an informative prior could be specified. In addition, due to the small number of studies reporting both outcomes when incorporating only SBP measured by ABPM, an informative prior was specified for the variance ($essVar_i$, $bpVar_i$) to be used where studies did not report one of the outcomes of interest. This prior was specified by multiplying the variance by the sample size, with a crude adjustment for the study design (i.e. doubling the sample size for cross-over studies).

A product-normal approach was used to specify the model to estimate the effect of CPAP compared to conservative management on ESS score and SBP. The WinBUGS code for the model and the datasets used in the analyses are presented below. The output from 10,000 iterations was used to inform the York economic model after discarding the first 50,000 iterations.

WinBUGS code for bivariate random effects meta-analysis

```
model{
            bpReMu ~ dnorm(0,1.0E-6)
            essReMu ~ dnorm(0,1.0E-6)

            essReTau <- 1/pow(essReSe,2)
            zReTau <- 1/(bpReVar - pow(bBeta,2)*essReVar)

            bpReVar <- pow(bpReSe,2)
            essReVar <- pow(essReSe,2)

            bpReSe ~ dunif(0,10)
            essReSe ~ dunif(0,10)

            bPsi ~ dunif(-0.99,0.99)
            bBeta <- (pow(bpReVar,0.5)/pow(essReVar,0.5))*bPsi

            essVarPA ~ dgamma(0.001,0.001)
            essVarPB ~ dgamma(0.001,0.001)

            bpVarPA ~ dgamma(0.001,0.001)
            bpVarPB ~ dgamma(0.001,0.001)

                  for (i in 1:nStudies) {

                        essMu[i] ~ dnorm(essReMu,essReTau)

                        bpMu[i] ~ dnorm(bpReMuD[i],zReTau)

                        bpReMuD[i] <- bpReMu - bBeta*(essReMu-
essMu[i])
                        ess[i] ~ dnorm(essMu[i],essTau[i])

                        essTau[i]  <- 1/essVar[i]
                        essVar[i] <-  essPopVar[i]/(n[i]*typ[i])
                        essPopVar[i] ~ dgamma(essVarPA,essVarPB)

                        bpVar[i] <-  bpPopVar[i]/(n[i]*typ[i])
                        bpPopVar[i] ~ dgamma(bpVarPA,bpVarPB)
```

```
                        bp[i] ~ dnorm(bpMuD[i],zTau[i])
                        bpMuD[i] <- bpMu[i] - wBeta[i]*(essMu[i]-
ess[i])

                        zTau[i] <- 1/(bpVar[i] -
pow(wBeta[i],2)*essVar[i])

                        wBeta[i] <-
pow(bpVar[i],0.5)/pow(essVar[i],0.5)*wPsiD[i]
                        wPsiD[i] ~ dnorm(wPsi,t)I(-1,1)

                                                                }
            wPsi <- 0.2852149
            t <- 1/pow(.0739224,2)

}
```

Data for evidence synthesis with daytime SBP based on ABPM

```
Data
typ   ess   essVar      bp    bpVar n
1     0     1.36515856  3     13.01117041 54
2     -1.2  0.16654561  NA    NA    35
1     -5    1.24835929  NA    NA    105
2     0.1   1.401856    NA    NA    18
2     -6    2.3409      NA    NA    23
1     -1.09 0.5184      NA    NA    111
2     -3    1.138489    NA    NA    37
2     -2.4  0.5041      NA    NA    71
1     -2.2  0.92006464  NA    NA    142
2     -0.6  1.7689      -2.9  29.16 42
1     -3.8  2.46929796  -10.3 27.88473636 60
2     -1    0.32069569  NA    NA    114
2     -2.4  0.84327489  NA    NA    31
1     -1    0.5625      NA    NA    72
1     -1.1  1.99741689  -2.5  8.4681      56
1     -3    1.99741689  NA    NA    101
2     -3.1  0.5041      NA    NA    35
1     -4    2.1904      NA    NA    42
1     -4.8  0.806404    NA    NA    107
1     -4    4.37562724  NA    NA    45
1     -7.94 1.62690025  NA    NA    48
1     -3    2.46929796  NA    NA    71
1     -4.5  1.03083409  NA    NA    118
2     NA    NA    -1    5.6169      13
2     NA    NA    0     4.4521      25
1     NA    NA    -1    15.47399569 21
```

Data for evidence synthesis with daytime SBP based on ABPM and office measurements

```
typ   ess   essVar      bp    bpVar n
1     0     1.36515856  3     13.01117041 54
2     -1.2  0.16654561  NA    NA    35
1     -5    1.24835929  NA    NA    105
2     0.1   1.401856    NA    NA    18
2     -6    2.3409      NA    NA    23
1     -1.09 0.5184      NA    NA    111
2     -3    1.138489    NA    NA    37
2     -2.4  0.5041      NA    NA    71
1     -2.2  0.92006464  -8    11.68545856 142
2     -0.6  1.7689      -2.9  29.16 42
1     -3.8  2.46929796  -10.3 27.88473636 60
```

2	-1	0.32069569	NA	NA	114
2	-2.4	0.84327489	NA	NA	31
1	-1	0.5625	NA	NA	72
1	-1.1	1.99741689	-2.5	8.4681	56
1	-3	1.99741689	-3.6	46.69463	101
2	-3.1	0.5041	-6.7	3.009162849	35
1	-4	2.1904	NA	NA	42
1	-4.8	0.806404	NA	NA	107
1	-4	4.37562724	NA	NA	45
1	-7.94	1.62690025	NA	NA	48
1	-3	2.46929796	NA	NA	71
1	-4.5	1.03083409	NA	NA	118
2	NA	NA	-1	5.6169	13
2	NA	NA	0	4.4521	25
1	NA	NA	-1	15.47399569	21