TRENT INSTITUTE

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for Health Services Research

# WORKING GROUP ON ACUTE PURCHASING

## Nasal Continuous Positive Airways Pressure in the Management of Sleep Apnoea

October 2000

# GUIDANCE NOTE FOR PURCHASERS 00/06

# Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 10 October 2000 at which this Guidance Note for Purchasers (in a draft form) was considered.

## NASAL CONTINUOUS POSITIVE AIRWAYS PRESSURE IN THE MANAGEMENT OF SLEEP APNOEA

**AUTHORS:** Chilcott J, Clayton E, Chada N, Hanning CD, Kinnear W, Waterhouse JC. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 2000. Guidance Note for Purchasers: 00/06.

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*(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)*

**DECISION: The Committee recommended that continuous positive airways pressure (CPAP) in the management of sleep apnoea be supported for all those patients who would benefit from it.**

October 2000

# NASAL CONTINUOUS POSITIVE AIRWAYS PRESSURE IN THE MANAGEMENT OF SLEEP APNOEA


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GUIDANCE NOTE FOR PURCHASERS 00/06

Published by the Trent Institute for Health Services Research



ISBN 1 900752 15 8

Referencing information:
Chilcott J, Clayton E, Chada N, Hanning CD, Kinnear W, Waterhouse JC. *Nasal Continuous Positive Airways Pressure in the Management of Sleep Apnoea.* Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield, 2000. Guidance Note for Purchasers: 00/06.

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***Conflict of Interest*** None of the authors of this document has any financial interest in the product being evaluated here.

***Acknowledgements***

The authors would like to acknowledge gratefully the help and advice of the following people: Dr J Mar (Clinical Management Unit, Alto Deba Hospital, Mondragon, Spain); Ms V Stevens (Royal Hallamshire Hospital, Sheffield); Dr S Matuesiewicz (Consultant Respiratory Physician, Lincoln County Hospital); Dr D Baldwin (Consultant in Respiratory Medicine, Nottingham City Hospital); Dr S Crookes (Medical Consultant, Chesterfield & North Derbyshire Royal Hospital); Professor T Higenbottom (Director of Clinical Sciences, Royal Hallamshire Hospital, Sheffield) and Dr P Anderson (Respiratory & Chest Diseases, Northern General Hospital, Sheffield).

Grateful acknowledgements are also due to Suzy Paisley (Information Resources, ScHARR) for her help with literature searching and obtaining articles. Also, Pat Holmes, Mike Jacobs and Danny Hind (ScHARR) for their invaluable help in the editing, formatting and proof-reading of this document.

***Expiry Date***

The authors are not aware of any major studies in progress which would impact on the conclusions reached in this Guidance Note. Therefore, given potential developments in alternative technologies, the conclusions should be reviewed after a period of approximately three years.

## ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor M Clarke (Leicester); and
Professor H Williams (Nottingham).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

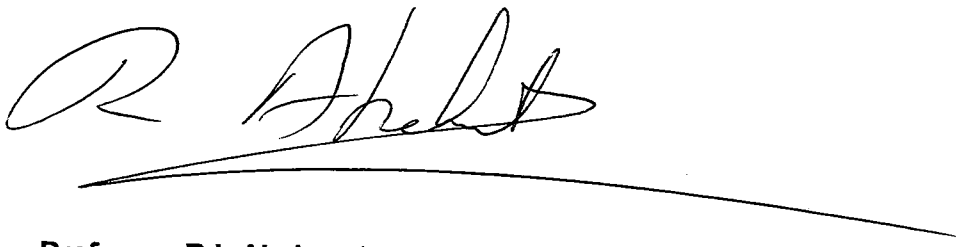
A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

## FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Mr Steve Beard.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority and Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterTASC, with units in other regions. These are: The Wessex Institute for Health Research and Development, The University of Birmingham Department of Public Health and Epidemiology and the Centre for Research and Dissemination, University of York.



**Professor R L Akehurst**

**Chairman, Trent Working Group on Acute Purchasing**

CONTENTS

## LIST OF TABLES AND FIGURES

## SUMMARY


### Description of Proposed Service

Obstructive sleep apnoea syndrome (OSAS) is defined by intermittent complete or partial upper airway obstruction during sleep, causing mental and physical effects. The consequences of these include depression, irritability, sexual dysfunction, learning and memory difficulties as well as falling asleep at inappropriate times such as whilst at work, on the telephone or driving. OSAS is also thought to be associated with premature death, hypertension, coronary heart disease, stroke and road traffic accidents. For many patients who use it regularly at home, nasal continuous positive airways pressure (nCPAP) administered through a nasal mask can eliminate the sleep apnoea symptoms resulting in improved sleep patterns and reduced daytime sleepiness.

### Epidemiology

The Royal College of Physicians, in its review of the topic, estimated a prevalence of symptomatic obstructive sleep apnoea (OSA) of 1-2% of middle-aged men and about half that in women. This is a fairly conservative estimate in relation to much of the literature, and is based on a definition of OSA that takes into account the Apnoea Hypopnea Index (AHI), as well as attributable symptoms. Though a specific definition of 'middle age' is not given, these figures, when applied to the population aged over 45 years, suggest that in a 'typical' health authority population of 500,000, the prevalence of sleep apnoea would be approximately 900 males and 450 females.

Literature concerning annual incidence figures for OSA is scarce and, due to overlapping catchment populations for sleep clinics, a 'typical' workload for a specific region is hard to define. According to current workloads quoted by sleep clinics within Trent, an annual incidence has been estimated at 150 referrals per 'typical' health authority population of 500,000.

### Number and Quality of Studies and Direction of Evidence

Five studies that focussed on the impact of nCPAP on morbidity were included, all of which were prospective, randomised and placebo-controlled. One study used a sham nCPAP in the control arm, that allowed blinding, and the others used an oral placebo on the basis that sham nCPAP might disrupt sleep. Disease specific instruments used within the studies include the Epworth Sleepiness Scale, the Maintenance of Wakefulness Test and the

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AHI | Apnoea Hypopnea Index |
| ANTADIR | Association Nationale pour le Traitement À Domicile de l'Insuffisance Respiratoire chronique |
| EEG | Electroencephalogram |
| ESS | Epworth Sleepiness Score |
| MAD | Mandibular Advancement Device |
| MSLT | Multiple Sleep Latency Test |
| MWT | Maintenance-of-Wakefulness Test |
| nCPAP | Nasal Continuous Positive Airways Pressure |
| NHP | Nottingham Health Profile |
| NICE | National Institute for Clinical Excellence |
| OSA | Obstructive Sleep Apnoea |
| OSAS | Obstructive Sleep Apnoea Syndrome |
| PSG | Polysomnography |
| QALY | Quality Adjusted Life Year |
| QOL | Quality Of Life |
| RCP | Royal College of Physicians |
| RCT | Randomised Controlled Trial |

## 1. AIM OF THE REVIEW

The paper addresses the current uncertainty surrounding both the economic and clinical effectiveness of nasal Continuous Positive Airways Pressure (nCPAP) as a treatment for Obstructive Sleep Apnoea (OSA). This issue is characterised by contradictory views on the definition of the disease itself, the association with morbidity and mortality, as well as the efficacy of available treatments. The report defines the disease and outlines the comparator treatments. Associated morbidity and mortality are explored in the light of evidence regarding the short-term and long-term effectiveness of treatment. Critiques surrounding OSA/nCPAP literature and trial data are addressed. The clinical effect of OSA in a 'typical' district is quantified and the cost-effectiveness of setting up and maintaining a satisfactory sleep service estimated. Finally, quality of life (QOL) assessments are presented for patients with OSA, before and after nCPAP treatment.

# 2. BACKGROUND

## 2.1 DESCRIPTION OF THE UNDERLYING DISEASE

OSA is a disorder characterised by a periodic reduction (hypopnea) or cessation (apnoea) in breathing due to the narrowing of the upper airways during sleep.[1] As the patient falls into deeper sleep, the muscle tone of his/her upper airways decreases, hence, narrowing the upper airway and hindering breathing. There is then an increase in respiratory effort, leading to transient arousal, which restores tone in the upper airway, allowing it to reopen. The arousal consequent on the irregularity in breathing results in an increase of heart rate and blood pressure. This can occur many hundreds of times in a single night, leading to disturbed, unsatisfying and fragmented sleep.[2] The main nocturnal symptoms of OSA are loud and irregular snoring, breathing pauses, restless sleep and frequent arousals. Due to these serious disturbances within the sleep pattern, people with OSA often feel very sleepy during the day, with their concentration and daytime performance suffering as a result.

In the past, this abnormality has been narrowly defined in terms of the average number of apnoeas and hypopneas per hour of sleep; the Apnoea Hypopnea Index (AHI). Many workers have considered an AHI of >15 to be diagnostic of OSA, however, this arbitrary cut off correlates poorly with clinical manifestations. Therefore, more flexible clinical definitions have been formulated recently, which combine episodic increases in upper airways resistance with daytime sleepiness.

The condition is considered to be a significant public health problem. The consequences of OSA range from annoying to life-threatening. They include depression, irritability, sexual dysfunction, learning and memory difficulties as well as falling asleep whilst at work, on the telephone or driving. OSA is also thought to be associated with premature death, hypertension, coronary heart disease, stroke and road traffic accidents. The strength of these associations is a very controversial point which will be addressed further in Section 3.3.4.

## 2.2 DIAGNOSIS AND SCREENING

Many authorities state that a 'full polysomnography is the gold standard for the diagnosis of OSA'. However, it is open to debate exactly which variables constitute full polysomnography

(PSG). A PSG is a test which records a variety of body functions during sleep, such as the electrical activity of the brain, eye movement, muscle activity, heart rate, respiratory effort, air flow, and blood oxygen levels. Most would agree that oximetry is essential together with some measure of respiration. Opinions divide as to whether respiration should be assessed by chest and abdominal wall movement alone or whether a measure of airflow is necessary. Some would insist upon oesophageal pressure as an index of respiratory effort.

Detection of arousals is equally controversial, as conventional analysis of electroencephalogram (EEG), electro-oculogram and electromyogram by Rechtstaffen and Kales rules may miss brief micro-arousals. Modern computer analysis, either mimicking the Rechtstaffen and Kales rules or using waveform and frequency analysis, may be an improvement. Physiological measures of arousal, such as increases in heart rate and blood pressure, may be as effective, and even able to replace electrophysiological measures.

All authorities are agreed that in-patient laboratory testing is expensive and in short supply. Several approaches have been suggested to reduce waiting times and costs. Technical advances have permitted an increasing number of variables to be recorded in a home setting. 'Limited somnography', generally the recording of cardio-respiratory variables, snoring sound and body position, has been evaluated and found to be comparable to 'full PSG' in the diagnosis of OSA. These devices are less expensive than those for full PSG, and are less demanding on technician time.[3]

An alternative approach has been to screen patients with oximetry. The pulse oximeter is a spectrophotometric device that detects and calculates the differential absorption of light by oxygenated and reduced haemoglobin to produce a measurement called $SpO_2$, an estimate of arterial oxygen saturation. These devices are relatively cheap and easy to use. However, there may be significant differences between the instruments of different manufacturers, which are relevant to their use in a home setting. Key factors, not always considered in the choice of instrument, include probe design, averaging time, artefact rejection capability and sampling frequency. Different methods of oximetry signal analysis have been used, including the number of dips greater than an agreed value (often 4%), the time spent below an agreed $SpO_2$ (often 90%) and spectral analysis.

Studies of oximetry as a screening tool for OSA are summarised in Table 1. In general, oximetry detects severe OSA well, but is less useful for milder cases.

**Table 1 Oximetry as a Screening Tool for OSA**

| Author | Sensitivity | Specificity | +ve pred | -ve pred | Number | Comments |
|---|---|---|---|---|---|---|
| Vazquez et al. 2000[4] | 98% | 88% | na | Na | 246 | Randomised control trial (RCT). Patients selected as probable OSA |
| Baltzan et al. 2000[5] | 86% | 74% | na | na | 55 | Oximetry and nasal airflow |
| Herer et al. 1999[6] | 94% | 72.5% | 94% | 90% | 102 | Obese patients |
| Golpe et al. 1999[7] | 97% | 38% | 38% | 84% | 116 | 'Useful to rapidly identify severe OSA' |
| Zamarron et al. 1999[8] | 78-94% | 89-65% | 89% | 78% | 233 | Spectral analysis, different parameters |
| Olson et al. 1999[9] | 88-91% | 40-70% | na | na | 793 | 'Sensitive but non-specific' |

Given that resources are likely to be limited for the foreseeable future, some means of identifying patients at high risk of severe OSA, for early confirmation of diagnosis and treatment, would seem to be essential. There are no studies comparing the different approaches outlined above and, thus, no firm recommendations can be made, although purchasers should satisfy themselves that suppliers of nCPAP services have put in place means of prioritising new referrals.

## 2.3 THE SCALE OF THE PROBLEM IN A 'TYPICAL' DISTRICT

Although a large body of literature exists describing the epidemiology of sleep apnoea, there are large variations in quoted prevalence due to varying definitions, as well as differences between study populations and study designs. Depending on the definition of OSA (which is still controversial), the prevalence within the general population may vary. OSA may be under-diagnosed in women, because it is thought of as a predominantly male disease, and the symptoms experienced and expressed by women may be different from those apparent in men. The Royal College of Physicians (RCP), in its review of the topic, quotes a figure of 1-2% of middle aged men and about half that in women.[10] This is a fairly conservative estimate in relation to much of the literature, and takes into account the AHI index as well as attributable symptoms.

Using the RCP figures in a 'typical' health authority population of 500,000, the prevalence of sleep apnoea would be approximately 900 males and 450 females. Literature concerning annual incidence figures for OSA is scarce and, due to overlapping catchment populations for sleep clinics, a 'typical' workload for a specific region is hard to define. According to current workloads quoted by sleep clinics, an annual incidence has been estimated at 150 referrals per 'typical' health authority population of 500,000. The Sleep Disorders Clinic at Leicester General Hospital recorded 450 OSA referrals between 1999 and 2000, for a large catchment population of approximately one to one and a half million people. The Sleep Clinics in Nottingham receive a similar number of referrals; audit of referral patterns in 1998 showed that 180 were from the Nottingham Health Authority population of approximately 600,000. These numbers have increased steadily in the intervening interval.

The estimated prevalence of symptomatic OSA of 900 males and 450 females in a 'typical' health authority population, when taken together with the estimated annual incidence of 150 new referrals for OSA implies an average duration of disease of nine years. This low implied

disease duration again may imply that the RCP estimates of prevalence may be conservative and/or the current levels of referrals are likely to be stable.

## 2.4 CURRENT SERVICE PROVISION

Sleep services, including the provision of nCPAP appliances, have been emerging haphazardly and sporadically throughout the UK. Health authorities, unconvinced of the mortality and morbidity associated with the condition, have been somewhat reluctant to commit themselves wholeheartedly to the development of sleep services. Moreover, there has been a real concern that, with large estimates of the condition's potential prevalence, purchasers would be overburdened by an expensive service, subject to ever-increasing demand, with maintenance costs escalating exponentially.

Other potential treatments for sleep apnoea apart from nCPAP are:

- Changes of lifestyle, including positional training, weight loss or the avoidance of alcohol and sedative drugs;
- Upper airways surgery;
- A mandibular advancement device (MAD).

### 2.4.1 Changes of Lifestyle

Obesity is an underlying cause of OSA and, for that reason, obese patients should be enrolled in a weight loss programme in addition to other therapies. However, weight loss and/or decreased alcohol consumption alone are not usually very successful and are typically used in conjunction with another treatment option such as nCPAP.

### 2.4.2 Surgical Treatment

Surgical treatment is a last resort, only considered for a patient whose apnoea is severe and remains uncontrolled by all other alternative treatments. It is, therefore, excluded from detailed review in the evaluation.

### 2.4.3 Mandibular Advancement Devices

A degree of retrognathia is common in patients with OSA. Over the past 10-12 years a number of intra-oral devices have been described which protrude the mandible by 2-5mm during sleep. They vary in complexity, some being adjustable with others giving a fixed degree of protrusion. All require the services of a dentist and a dental laboratory. Typically,

at least three visits are required to achieve an acceptable fit. The costs of manufacture depend upon the device chosen, but are, typically, around £200-300.

There have been a large number of studies examining the efficacy of a particular device in patients with varying degrees of OSA. In general, they have shown that the devices are reasonably well tolerated, with compliance rates comparable to nCPAP.[11] Side effects are generally those of dental and temperomandibular joint pain in the longer term and hypersalivation in the short term. Concern is expressed in the dental literature on the long-term effects on the bite and temperomandibular joint. Most authors have concluded that the MAD is indicated only for snoring and mild to moderate OSA.[12]

There are two randomised crossover trials of MAD versus nCPAP. Ferguson et al.[13] in 1997 compared 24 patients with mild to moderate OSA (AHI 26.8±11.9). 55% were regarded as a treatment success with the MAD compared with 70% on nCPAP. More subjects were compliant with the MAD (50% cf 30%) and patient satisfaction was greater. Clark et al.[14] in a similar study in 1996, including a similar group of patients again showed that the MAD was less effective than nCPAP but was preferred by patients.

### 2.4.4 nCPAP Therapy

nCPAP equipment includes a pump, tubing and nasal mask with an exhalation port. Patients undergoing nCPAP are required to wear the mask at night. Air is blown gently into the nose of the patient, keeping the upper airway patent by means of a pneumatic splint. Essentially, the pharynx is blown open so that it no longer obstructs.

## 2.5 nCPAP COMPLIANCE

Compliance with nCPAP ranges from 64-90% (Table 2). Interpretation of these figures is difficult, as criteria for selecting patients for a nCPAP trial will vary from centre to centre and most studies report neither average AHI values nor sleepiness scores. Most dropouts appear to occur within the first few months of use and compliance rates seem to change little with time thereafter.[15]

Most studies have suggested that severity of disease, as measured by AHI and sleepiness, are predictors of compliance. Increasing age and previous palatal surgery reduce the likelihood of success (Table 3 refers). Standard polysomnographic variables such as AHI,

micro-arousal index and hypoxaemia were poor predictors of response to nCPAP therapy in a recent prospective study.[16] Compliance is increased by close follow-up and patient support. It is not affected by automatic rather than manual titration and is not reduced by the use of split-night studies.

**Table 2 Compliance with nCPAP**

| Author | Compliance (%) | Follow-up (month) | Number | Comments |
|---|---|---|---|---|
| Findley et al, 2000[17] | 72 | 24 | 50 | Patients in RTA study, subjective monitoring |
| Pepin et al, 1999[18] | 77, 82, 79 | 1, 2, 3 | 121 | Multi-centre EC study. Not all subjects objectively monitored |
| McArdle et al, 1999[15] | 68 | 60 | 1,211 | Methods of survival analysis, 11 year experience |
| MarquezBaez et al, 1998[19] | 80 | ? | 65 | Questionnaire study |
| Kiely & McNicholas 1997[20] | 78 | 2-12 | 91 | Questionnaire study |
| Krieger et al, 1996[21] | 90, 85 | 36, 84 | 575 | Objective measurement, Kaplan-Meir modelling |
| Stradling et al, 1997[22] | 64, 73 | 1½ | 122 | Randomised trial of automatic titration |

**Table 3 Factors Affecting nCPAP Compliance**

| Author | Factors increasing compliance | Number | Comments |
|---|---|---|---|
| Janson et al, 2000[23] | ↑ disease severity, ↓ age, no previous Uvulopalatopharyngoplasty, no nasal problems | 40+63 | Case control study |
| Kingshott et al, 2000[16] | Polysomnography variables *not* predictive | 62 | Prospective study |
| McArdle et al, 1999[15] | ↑ disease severity | 1211 | Observational study |
| Tiihonen et al, 1998[24] | ↑ effectiveness of treatment (Maintenance-of-Wakefulness Test) | 10 | Small prospective study |
| Chervin et al, 1997[25] | ↑ intensity of early follow-up and support | 33 | RCT |
| Likar et al, 1997[26] | Regular follow-up (group clinics), ↑ disease severity | 73 | Retrospective study |

# 3. THE USE OF nCPAP FOR THE TREATMENT OF SLEEP APNOEA: SUMMARY OF EVIDENCE OF EFFECTIVENESS

## 3.1. METHODS FOR REVIEWING EFFECTIVENESS

Due to the systematic review involving OSA and nCPAP published in 1997,[1] evidence was sought through the years 1996-2000. Trials regarding the effectiveness of nCPAP were identified through searching medical and health databases; MEDLINE, EmBASE, BIDS, the Cochrane Database of Systematic Reviews, NAPS and BEDS and other OSA specific web sites. The search terms featured the following: 'obstructive sleep apnoea', 'OSA', 'continuous positive airway pressure' and 'CPAP'. Studies addressing the effect of nCPAP on daytime symptoms in adults were identified, and those that were randomised and included a placebo or comparator therapy in the control arm extracted. Data were extracted from copies of the published articles, and the quality of the study assessed on the randomisation procedure, matching of placebo and nCPAP groups, and consideration of order effects.

The evidence was separated into two categories:

- short-term effectiveness, and
- long-term effectiveness.

The short-term evidence identifies recent trials and summarises a range of different outcomes, which measure the immediate health effects of treatment. The long-term evidence features literature surrounding the controversial link between OSA and long-term morbidities and mortality.

## 3.2 SHORT-TERM EFFECTIVENESS

### 3.2.1 Outcome Measures

The Epworth Sleepiness Score (ESS) is an index widely used to measure sleep apnoea subjectively. It uses eight questions regarding the tendency to fall asleep in situations of variable stimulation, for example, watching television, or talking to someone. Each question is scored from 0 to 3, to show an increased tendency to fall asleep in each situation. The

total score ranges from 0 (no sleepiness) to 24 (extremely sleepy); a score of 9 is the upper limit of normal.[27]

The SF-36 is a standardised general measure of health status developed in the USA,[28] with a validated anglicised version.[29] It asks 36 questions about health over the past four weeks; these measure eight dimensions of health status: physical functioning; role limitation because of physical health; social functioning; vitality or energy; bodily pain; mental health; role limitation because of emotional problems; and general health. The responses to questions within each dimension are aggregated and transformed to generate a dimension score ranging from 0 ('poor health') to 100 ('good health').

The Maintenance-of-Wakefulness test (MWT) and the Multiple Sleep Latency Test (MSLT) are both objective measures of sleepiness. Essentially, after a full night's monitored sleep, the subject sits in a darkened room and is asked either to go to sleep (MSLT) or stay awake (MWT) on four occasions spread throughout the day. Each test period is terminated after either the patient falls asleep or 20-40 minutes has elapsed. Patients are not allowed to use active methods, such as singing or pinching themselves, to keep themselves awake. In one commonly used version of the MWT, the Osler test, the patient must repeatedly tap a detector in response to a dim red light that flashes every three seconds. The responses are recorded electronically and null response to 21 consecutive flashes is defined as sleep. The time taken for them to fall asleep is measured and the average of the four time periods is the final test result. In the UK the MWT is favoured as it more closely resembles 'real life' and does not need EEG monitoring.

Part One of the Nottingham Health Profile (NHP) questionnaire measures patients' perception of their quality of life. This part includes 38 items exploring six dimensions of perceived health: energy, pain, sleep, physical mobility, emotional reactions and social isolation, yes = 1 and no = 0. Each item is weighted and a final score is calculated for each dimension by adding the weighted answer of each item. For each dimension the scores range from 0 (excellent perception of health) to 100 (very poor perception of health).

### 3.2.2 Quantity and Quality of Research Available

Five studies were included (Table 4), all of which were prospective, randomised and placebo-controlled. The study of Jenkinson[27] was by far the largest. Two forms of placebo have been used:

**Table 4 Characteristics of Studies**

| Author | Design | Number in Trial | Severity of OSA | Placebo | Duration | **ESS** Subjective scale, 0–24, lower better | **MWT** Objective measure of time | **SF36** Scales of 0 – 100 lower poor health | **MSLT** Objective measure of time | **NHP** Scale of 0 – 100 lower good health |
|---|---|---|---|---|---|---|---|---|---|---|
| Jenkinson 1999[27] | Parallel group | 107 | >10 dips /hr | Sham nCPAP | 4 weeks | 15.5 to 7 on nCPAP; 15 to 13 on sham. | 22.5 to 32.9 minutes on nCPAP; no significant change on sham. | Significant positive changes in all domains on nCPAP; 4 domains on sham. | - | - |
| Engleman 1999[30] | Cross-over | 34 | AHI 5-15/hr | Oral placebo | 4 weeks | 11 to 8 on nCPAP. | No significant change. | Significant changes in 5 domains. | - | - |
| Engleman 1998[31] | Cross-over | 23 | AHI >15 /hr | Oral placebo | 4 weeks | 12 to 6 on nCPAP | - | - | 6.8 to 9.2 minutes on nCPAP. | No significant change. |
| Engleman 1997[32] | Cross-over | 16 | AHI 5-15 /hr | Oral placebo | 4 weeks | No significant change. | - | - | No significant change. | No significant change. |
| Engleman 1994[33] | Cross-over | 35 | AHI >5 /hr | Oral placebo | 4 weeks | - | - | - | 7.2 to 6.1 minutes on nCPAP. | Significant decrease. |

ESS=Epworth Sleepiness Score (subjective sleepiness)
MWT=Maintenance of Wakefulness Test (objective wakefulness)
MSLT=Multiple Sleep Latency Test (objective sleepiness)
AHI=Apnoea Hypopnea Index
NHP=Nottingham Health Profile

- Oral tablet placebo, (ranitidine);
- 'Sham', sub-therapeutic nCPAP.

Four of the five studies used the oral placebo on the basis that sham nCPAP might disrupt sleep.

The most robust of these studies is that of Jenkinson, both on account of size and the use of the most appropriate control. The placebo effect of sham nCPAP in this study justifies our exclusion from the current analysis of those studies which did not include a placebo in the control arm. In the Jenkinson study, the patients had fairly severe OSA, with around 30 hypoxic dips/hr and high ESS scores before treatment. In this group, the beneficial effects of nCPAP are clear. The 1994[33] and 1998[31] studies of Engleman had similar severity of OSA (median AHI 28 and 43/hr respectively, 20 desaturations/hr in the 1998 study) and, again, showed a clear benefit from nCPAP.

The 1997 and 1999 studies of Engleman looked at a group of patients with milder OSA (AHI of 11 and 10/hr). The changes in this group were less marked, but still clearly present. Tolerance of nCPAP in this milder group was less and anxieties about the cost implications of widespread use of nCPAP for mild OSA are probably unfounded. A small number of patients derive dramatic benefit, and the remainder will not wish to continue with this form of treatment. Identification of which patients should be referred for a trial of nCPAP remains difficult although, in general, the severity of disease (estimated by AHI or desaturations) is a predictor of long-term compliance with nCPAP. Some patients, whose OSA could be graded as 'mild' on the basis of their sleep study, derive great symptomatic benefit from nCPAP.

### 3.3 LONG-TERM EFFECTIVENESS

The evidence linking sleep disordered breathing to systemic and pulmonary hypertension, myocardial infarction and stroke, is outlined below. What is currently missing is incontrovertible evidence that treating OSA reduces the cardiovascular risk and increases life expectancy. Such evidence is unlikely to emerge for some years, if at all, not least because the evidence for improvement in life quality with nCPAP is such that a long-term randomised control trial (RCT) of nCPAP versus placebo or dummy treatment would be unethical and impractical. Studies of patients who decline nCPAP are unlikely to be helpful as they are a self-selected group who differ from patients who accept nCPAP, not least in

the severity of their OSA. Multi-centre studies would be necessary to recruit sufficient patients to enable a meaningful comparison.

### 3.3.1 Hypertension

The large Wisconsin Sleep Cohort study, in both cross-sectional and prospective studies, has shown a clear, dose-dependant relationship between sleep-disordered breathing and hypertension.[34-36] Further evidence comes from surveys of patients referred for investigation of sleep-disordered breathing[37,38] and surveys of snorers.[39] Other, earlier studies are reviewed by Grunstein.[40] OSA has been shown to be more common than expected in hypertensives.[41]

Several studies have shown differences in autonomic control between patients with OSA and those without, some of which were reversed with nCPAP.[42-48]

The effects of nCPAP on established hypertension are less conclusive. Dimsdale et al. showed a significant effect on nocturnal blood pressure, compared with placebo in an RCT, but not for daytime blood pressure[49] (see also Davies et al.[50]). Voogel et al. were able to demonstrate a mean reduction in daytime mean arterial pressure and diastolic blood pressure of –11 and –7mmHg respectively.[51] Akashiba et al. showed that the normal circadian blood pressure pattern was restored by nCPAP in patients with OSA.[52]

### 3.3.2 Cardiac Disease

The independent association between OSA and cardiac disease has been demonstrated for coronary artery disease,[53,54] left ventricular failure,[55] left ventricular hypertrophy[56] (although not confirmed by Davies et al.[50]) and right ventricular dysfunction and pulmonary hypertension, which is reversible with nCPAP.[57-59] A decrease in Factor VII clotting activity has been shown with nCPAP in patients with OSA.[60]

### 3.3.3 Mortality

Evidence of increased mortality in patients with OSA comes from a Finnish study of sudden deaths. Habitual snorers were significantly more likely to die of cardiovascular causes in their sleep or in the morning.[61] A prospective observational study was undertaken by the

Association Nationale pour le Traitement À Domicile de l'Insuffisance Respiratoire chronique (ANTADIR), a French national observatory for respiratory home care. This study of 5,669 OSA patients on nCPAP showed that they had the same mortality as the general French population. A case control study of mortality within this population, undertaken to identify risk factors against an age-sex match, identified an excess of cardiovascular deaths compared to case controls.[62]

### 3.3.4 Driving Accidents

The relationship between the excessive daytime sleepiness and OSA and road traffic accidents is now beyond doubt, as is the beneficial effect of nCPAP. This has been shown both in driving simulators[63] and in a survey of accidents.[64] The latter study showed that patients with OSA had almost 20 times the accident rate per $10^6$ km of normal subjects (13 vs 0.78). In those patients treated with nCPAP the rate decreased from 10.6 to 2.7 per $10^6$ km.

### 3.3.5 Weight Loss as a Treatment for OSA

Most patients with OSA are obese and there is no doubt that weight loss is an effective treatment. However, the proportion of patients who are successful in the long-term is low, only 9% at two years despite a well structured cognitive behavioural programme.[65] Using a similar programme and a very low calorie diet, Lojander et al. achieved a mean weight loss of only 11kg (110-99kg) in one year.[66] While all obese patients with OSA should be encouraged to lose weight, nCPAP should be offered, initially, to treat the presenting symptoms, and withdrawn in those patients who are successful. It should be noted, however, that weight loss is rarely a sufficient treatment for patients with OSA who are obese.

## 3.4 SUMMARY OF EFFECTIVENESS

For patients with OSA who comply with long-term usage the nCPAP appliance is effective in providing symptomatic relief. The symptomatic relief can be measured both in disease specific measures, that focus on daytime sleepiness and through generic measures that assess the improvements in quality of life across a range of dimensions. Statistically significant improvements in both these aspects are associated with nCPAP use.

OSA has been shown to be independently associated with excess mortality associated with coronary heart disease, stroke and road traffic accidents. There is no RCT evidence to demonstrate that this excess mortality is reduced through nCPAP use. However, evidence exists from cohort studies focussing directly on mortality, from studies focussing on surrogate physiological outcome measures, and from simulated driving experiments that is strongly suggestive of potential benefits from nCPAP use in reducing long-term mortality.

# 4. HEALTH ECONOMIC IMPACT OF nCPAP WITHIN THE UK

## 4.1 ANALYTIC OVERVIEW

The aim of this section is to evaluate the cost-effectiveness of nCPAP appliances in the treatment of OSA in comparison with other comparator treatments. Available treatments for OSA include:

- no treatment;
- mandibular advancement devices;
- surgical treatment.

Surgical treatment is usually used as a treatment of last resort and only considered for patients whose apnoea remains uncontrolled by all other treatments. Therefore, It does not constitute a comparator therapy in this evaluation. It follows that comparator therapies are 'no treatment' and 'mandibular advancement devices'. The comparative economic potential of the mandibular advancement devices is presented in Section 4.7.

In order to determine the health economics of treatment, the health outcomes, resource utilisation and costs are estimated for an annual incidence cohort of patients. The evaluation takes a health service perspective of costs; indirect and societal costs have not been included within the scope of this evaluation. All costs have been discounted at 6%, and life years at 1.5%, as recommended by the National Institute for Clinical Excellence (NICE) and the UK Treasury. In addition, a range of discount rates from 0% to 10% has also been investigated.

The costs associated with providing nCPAP treatment can be divided into the following categories: investigation and diagnosis, initial purchase of the nCPAP machine, follow-up of the patient and maintenance of the appliance. Section 4.2 focuses on the investigation and diagnosis of patients for nCPAP treatment and provides a summary of these costs. Other costs are described in Section 4.3.

Health benefits, in terms of both morbidity and mortality, have been associated with nCPAP treatment for OSA. In terms of morbidity, health benefits are measured through the QOL improvements associated with treatment. Different generic and disease specific QOL instruments have been used in assessments of the nCPAP devices and the evidence in this

area is summarised in Section 3.2. The evaluation presented in Section 4.5 focuses on determining a cost per Quality Adjusted Life Year (QALY) based upon the SF-36 single index measure.

Long-term mortality benefits have been attributed to nCPAP therapy, associated with reductions in hypertension and road traffic accidents etc. The clinical evidence in this area is summarised in Section 3.3. Due to the historical controversies regarding the quality of this evidence, and in the light of the economic analyses undertaken by Rueda et al.[67] and Chervin et al.,[68] the analysis presented here focuses on the morbidity benefits of treatment, whilst recognising that the benefits arising from any impact on mortality will be underestimated.

The Chervin study,[68] which focuses on the economics of different approaches to the diagnosis of obstructive sleep apnoea syndrome (OSAS), uses a baseline estimate of reduced life expectancy from OSAS of 0.3 years over a five year time horizon. Due to the recognised uncertainty about the impact of nCPAP treatment on mortality,[1] the impact of varying the life years gained between 0 years (i.e. no benefit in mortality from nCPAP treatment) and 0.5 years is assessed. The impact of mortality benefits is found to be small compared to the morbidity benefits in terms of QALYs gained. This result over a five year horizon is supported by the similar conclusions reached by Rueda et al.,[67] who considered treatment over a patient's full life.

## 4.2 INVESTIGATION AND DIAGNOSIS OF OSA

There is a wide variation in the procedures undertaken in the investigation and diagnosis of patients with OSA. These procedures may vary according to the severity of disease in individual patients or the facilities, historic practice or resource constraints on the centre undertaking the investigation. There is currently no consensus or guidance in the UK, on a procedure for the investigation of OSA, although such work is ongoing under the auspices of the British Thoracic Society and the Scottish Intercollegiate Guideline Network (SIGN).

The investigation procedure is usually made up of a combination of certain procedures including:

- Initial out-patient appointments;

- home oximetry;
- nCPAP questionnaire;
- out-patient appointment with lung function technician;
- nCPAP education hour;
- follow-up consultations;
- polysomnography;
- wakefulness tests;
- home trial with nCPAP.

Based on clinical opinion, two potential modes of investigation, basic and intensive, have been defined for this analysis, and are set down in Table 5. The basic evaluation procedure costs approximately £370 and the intensive procedure £750. The baseline analysis uses the costs from the basic investigation. Sensitivity analysis has been undertaken for a range of costs and is reported in Section 4.5.4.

**Table 5 Costs of Investigation and Diagnosis for OSA and nCPAP**

| **Basic Investigation** | **Unit Cost (£)** |
|---|---|
| Out-patient appointment X 2 | 120.00 |
| Home oximetry | 50.00 |
| Questionaire | 10.00 |
| Out-patient – lung function technician | 60.00 |
| nCPAP education and home trial | 20.00 |
| Home oximetry | 50.00 |
| Follow-up consultation | 60.00 |
| **Total cost** | **370.00** |

| **Intensive Investigation (in addition to intermediate)** | **Unit Cost (£)** |
|---|---|
| Polysomnography | 200.00 |
| Wakefulness test (1 day and 1 night) | 100.00 |
| 2 X follow-up consultations | 120.00 |
| **Total cost** | **750.00** |

The initial investigative procedures would result in a decision to refer or not to refer for a trial period of nCPAP. The initial trial of nCPAP would then result in a further proportion of patients who would drop out either because nCPAP does not result in a relief of symptoms or because the individual patient finds the nCPAP appliance excessively intrusive. As

identified in the discussion of compliance presented in Section 2.5, compliance with nCPAP ranges from 64-90% (Table 2).

## 4.3 COSTS ASSOCIATED WITH THE USE OF nCPAP APPLIANCES

Patients with OSA have been shown to have a lower general health status, independent of other factors such as age, body mass index, alcohol and smoking usage.[69] Ronald et al.[70] report that, in the 10 years prior to diagnosis, OSA patients had more utilisation of health care resources than age, sex and class matched controls both for physician claims ($3,972 vs. $1,969) and hospitalisation (6.2 vs. 3.7 days). The same group then examined health care utilisation in OSA patients two years after diagnosis and treatment compared to a matched control group. Physician claims decreased significantly from $260 to $174 and hospitalisation from 1.27 to 0.54 days in those patients who were compliant with nCPAP. No changes were found in those patients who were not compliant.[71] A retrospective Swedish study of hospital admissions for cardiovascular and pulmonary disease in patients with OSA showed a marked reduction in the number of in-hospital days in the two years after nCPAP was initiated, compared to the preceding two years, and compared with a group who did not use nCPAP (413 compared to 54 days and 137 compared to 188 days respectively).[72]

The initial purchase cost of a nCPAP appliance is approximately £250, reported by the sleep units at Leicester General Hospital, Queen's Medical Centre, Nottingham and the Royal Hallamshire Hospital, Sheffield. In addition to this one-off cost, appliances require an annual electrical test, at a cost of approximately £60 per machine, as well as renewal of disposables including mask, harness and tubes, estimated at around £100 per year.

Patients on nCPAP therapy would require long-term follow-up through out-patient appointments, usually with one or two appointments per year with a sleep technician or equivalent. A cost of £60 per appointment gives an expected cost in the region of £90 per year.

Therefore, a total recurring annual cost of £250 per patient on long-term nCPAP therapy is assumed. However, it should be noted that this model will overstate the likely gross Health Service cost, as no account will be taken of potential reductions in the utilisation of other healthcare resources.

## 4.4 QUALITY OF LIFE EFFECTIVENESS OF nCPAP TREATMENT

### 4.4.1 Estimating Health State Utility Values from the SF-36

The SF-36 is a standardised questionnaire used to assess patient health across eight dimensions.[29] It consists of items or questions, which present respondents with choices relating to how they perceive their own health. The physical functioning dimension, for example, has ten items to which the patient can make one of three responses: 'limited a lot', 'limited a little' or 'not limited at all'. These responses are coded 1, 2 and 3 respectively, and the ten coded responses summed to produce a score from 10 to 30. These raw dimension scores are transformed onto a scale of 0 to 100, which are not comparable across dimensions.

There is extensive evidence of the ability of the dimension scores to describe the health differences between different patient groups and, more importantly, for evaluation, their ability to detect health changes in populations following intervention.[29,73-75] However, in its current form, the SF-36 cannot be used to undertake economic evaluations since it does not incorporate preference information and cannot be used to calculate QALYs. It was decided, therefore, to apply the results of a research study, recently undertaken by a team in the School of Health and Related Research, to derive a preference-based single index measure of health from the SF-36 that can be used to derive QALYs.[76] Essentially, the algorithm applies preference-based weights to the item responses to derive the single index.

Two preference-based algorithms have been used. Both were estimated from a valuation survey where respondents were asked to value health states derived from the SF-36 using the standard gamble technique for eliciting preferences. The methods and results of the first survey, including a demonstration of the validity of the derived measure, have been published elsewhere.[76] In summary, the study undertook a parsimonious restructuring of the SF-36, using explicit criteria to form the SF-6D health state classification. A sample of multi-dimensional health states, defined by this classification, were valued by a convenience sample of 165 health professionals, managers and patients, who responded to a set of visual analogue scale rating and standard gamble questions with highly complete and consistent answers. Statistical models were estimated to predict single index scores for all 9,000 health states defined by the new classification. The same methodology has been used in a second and much larger study, where the valuation exercise was undertaken by a

representative sample of 781 members of the UK general population, using standard gamble.

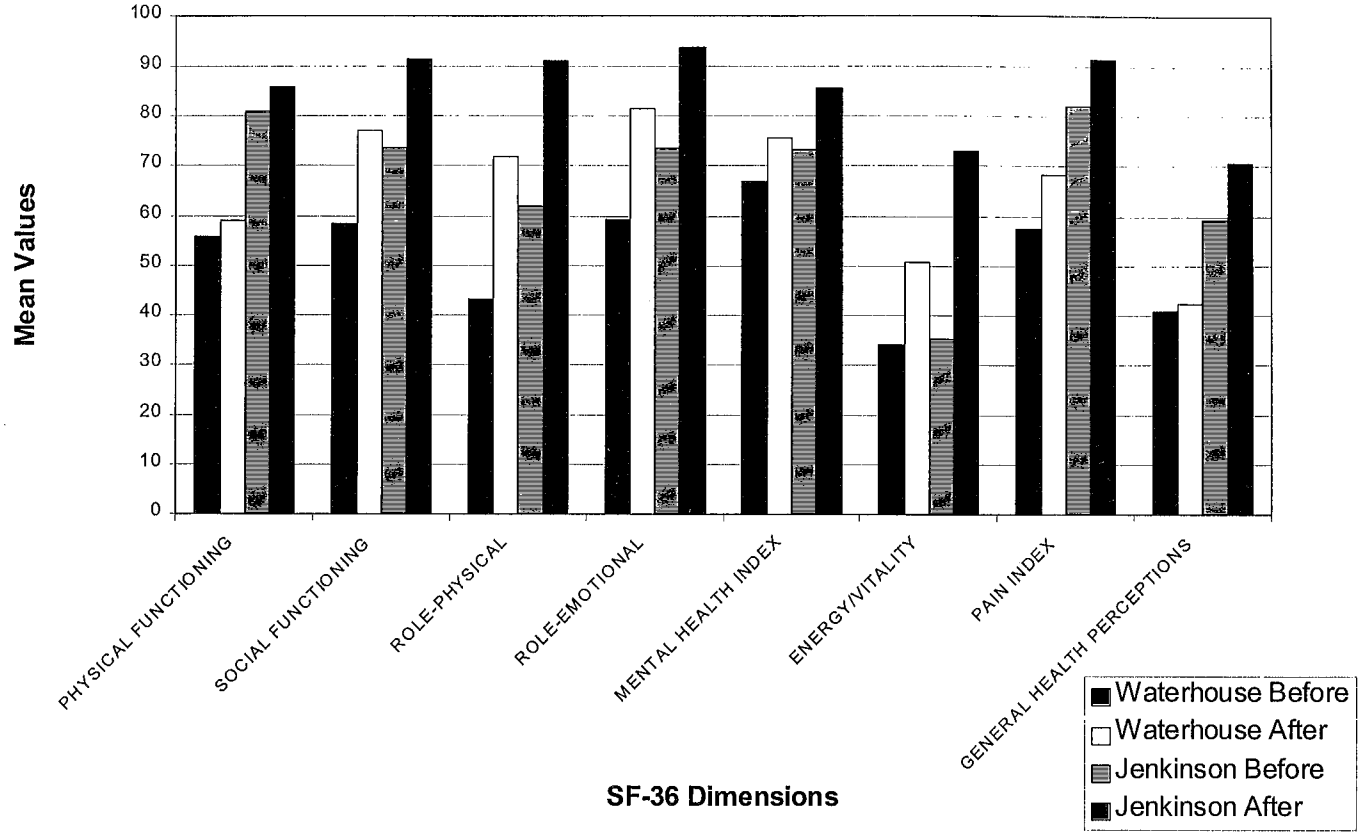
The algorithms can be applied to existing SF-36 data to generate preference-based indexes for each respondent to the SF-36 on a QALY scale, where one is full health and zero is for states equivalent to death.

### 4.4.2 The SF-36

None of the currently available randomised studies that have used the SF36 QOL instrument presents the single index form of the SF36 results. However, the Sleep Disorders Unit at the Royal Hallamshire Hospital in Sheffield has been using the SF36 questionnaire within a cohort study, as part of initial investigations of patients referred with potential OSA; the resulting data allow the generation of the single index. The methodology of and results from the Royal Hallamshire cohort study have been reported by Waterhouse et al. at the Year 2000 meeting of the European Respiratory Society in Florence and published in abstract form.[77,78]

As mentioned above, the Royal Hallamshire Hospital study reported by Waterhouse is of a case series design and is not randomised. Therefore, in order to validate the results of this study, they are compared to the randomised study reported by Jenkinson et al.[27] Figure 1 presents the before and after data from the Waterhouse cohort study and the before and after results from the treatment arm in the Jenkinson randomised study. As can be seen from Figure 1, the differences between the before and after results are broadly similar for all SF-36 dimensions in the two studies, although the population in the Waterhouse study appears to start from a lower baseline health status.

**Figure 1** **Comparison of the Waterhouse and Jenkinson Studies**



The before and after results from the Waterhouse study in terms of the SF36 single index are given in Table 6. The overall quality of life (0-1 scale) of patients receiving a trial of nCPAP increased by 0.10 (0.07,0.12). The overall quality of life in those patients who were subsequently offered a nCPAP appliance based on the results of this trial increased by 0.12 (0.09, 0.16).

Assuming that the improvement in health status follows immediately from use of the nCPAP appliance, this relates to a gain of 0.12 QALYs for each person who receives nCPAP over the course of one year.

**Table 6 Gain in Health Related Quality of Life as Measured by the SF36 Single Index**

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

## 4.5 COST-EFFECTIVENESS OF nCPAP

### 4.5.1 Cost per Quality Adjusted Life Year Gained

Table 7 presents the cost per QALY gained obtained from nCPAP treatment. The evidence of effectiveness is obtained from relatively short studies, the Waterhouse study was of two weeks' duration and the randomised Jenkinson study[27] was of four weeks' duration. The health economic results over the limited period covered by these studies are presented, together with extrapolations to one year, two years and five years. Due to the short period of study, the benefits accrued in terms of QALYs over this period are small. This, together with the fact that the majority of costs are incurred over this period, means that the cost-effectiveness over the trial period is poor. If benefits from continued use beyond the trial period are assumed to be maintained, then the cost-effectiveness over one year is £8,300 per QALY and over five years is £3,200 per QALY or £4,400 per QALY, including the purchase of a second machine at five years.

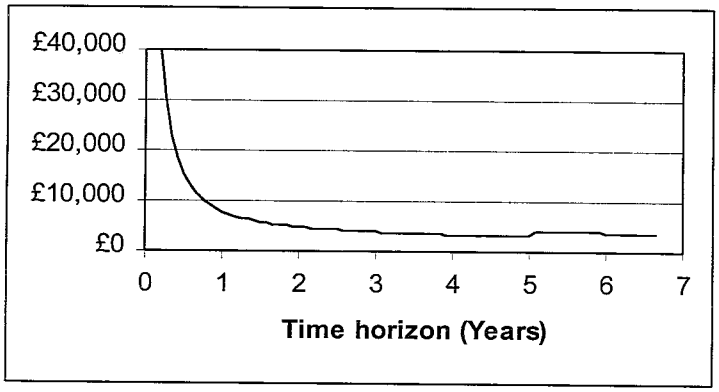
**Table 7** **Baseline Cost Per Quality Adjusted Life Year Gained**

| Time Horizon | Cost per QALY Gained |
|---|---|
| 1 month | £99,000 |
| 1 year | £8,300 |
| 2 years | £5,200 |
| 5 years | £3,200 |

### 4.5.2 Impact of Analytical Time Horizon

As can be seen from Figure 2, the cost-effectiveness is highly sensitive to the time horizon used for the analysis up to one year. However, for time horizons beyond one year, the cost-effectiveness is relatively stable. The slight jump at five years is due to the purchase of a new nCPAP appliance at five years.

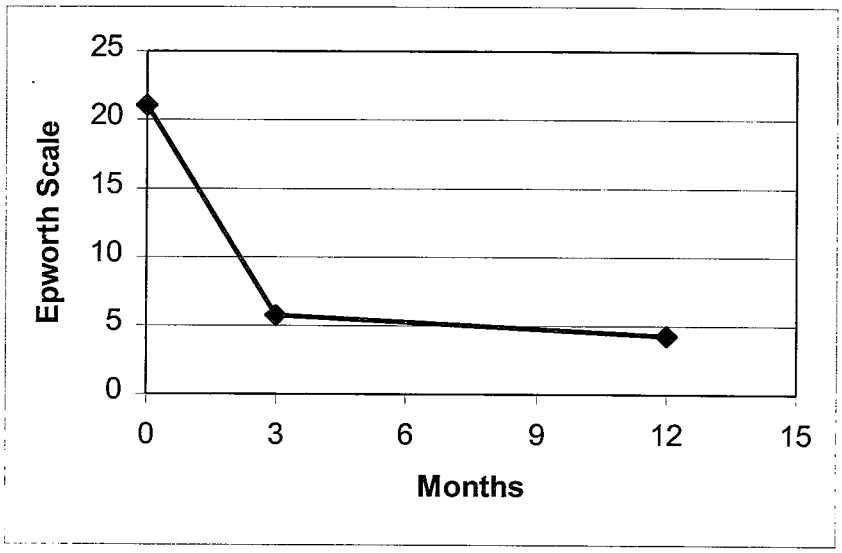
**Figure 2** **Cost per Quality Adjusted Life Year Gained against the Time Horizon of the Analysis**




### 4.5.3 Long-term Benefit

Munoz et al.[79] provide evidence that the long-term use of nCPAP significantly improves levels of somnolence, as measured by the Epworth scale, and vigilance; they also demonstrate that these benefits are maintained. Their study[79] shows that benefits of treatment continue to improve, slightly but significantly, after three months of treatment through to month 12. As shown in Figure 3, the Epworth scale improved from month 3 to month 12 from 5.8 (+/- 0.4) to 4.3 (+/- 0.4) [$p<0.05$].

**Figure 3** **Maintenance of Long-term Benefit from nCPAP Treatment (After Munoz et al.[79])**




### 4.5.4 Sensitivity Analysis for the Costs of Investigation for nCPAP Treatment

Two modes of investigation have been detailed; basic and intensive. The baseline analysis uses the costs from the basic mode detailed earlier. Table 8 presents the cost-effectiveness at 12 months using the costs of the basic and intensive investigation and for a mixed protocol where 90% of patients require basic investigation and the remaining 10% require the intensive investigation.

**Table 8** **Cost per QALY for Different Modes of Investigation**

| Mode of Investigation | Cost per Investigation | Cost per QALY (12 months) |
|---|---|---|
| Basic | £370 | £8,300 |
| 90% Basic / 10% Intensive | £412 (Average per patient) | £9,000 |
| Intensive | £790 | £15,400 |

### 4.5.5 Sensitivity Analysis for Long-term Costs of Maintenance, Follow-up and Other Healthcare Resource Usage

An annual recurring cost of £250 per appliance is included in the baseline analysis. This cost includes the cost of servicing the appliance and of patient follow-up, based upon an average

of 1.5 out-patient sessions per person per year. This annual cost is not incurred in the first year and, thus, does not affect the cost-effectiveness analysis at 12 months. The impact of doubling this annual cost is presented in Table 9. In addition, the available evidence from studies undertaken in other European and North American countries indicates that OSAS is associated with an increased use of health resources and that this is reduced following nCPAP treatment. The breakeven point for cost recovery would be an approximate annual gross healthcare cost reduction of £300 per patient, including the cost of follow-up.

**Table 9 Impact of Long-term Gross Annual Healthcare Costs on Cost-effectiveness**

| Gross Annual Healthcare Cost (Year 2 onwards) | Cost per QALY (5 years) |
|---|---|
| -£300 | £0 |
| £0 | £1,700 |
| £250 | £3,200 |
| £500 | £4,600 |

### 4.5.6 Potential Impact of Improved Mortality from Use of nCPAP Treatment

Chervin[68] used an estimate, based on earlier epidemiological studies, of improved life expectancy of 0.3 years (range 0 to 0.5 years) from the use of nCPAP over a five-year period. The cost-effectiveness of nCPAP therapy based upon these figures is presented in Table 10.

**Table 10 Potential Impact of Improvements in Mortality on Cost-effectiveness**

| Improvement in Life Expectancy (over 5 years) | Cost per QALY (5 years) |
|---|---|
| 0 years | £3,200 |
| 0.3 years | £2,100 |
| 0.5 years | £1,700 |

### 4.5.7 Impact of Uncertainty in Morbidity Benefits from nCPAP Therapy

The 95% confidence interval for the benefit from nCPAP therapy in terms of the SF36 single index, derived from the before and after study undertaken at the Royal Hallamshire Hospital, gives the range of cost-effectiveness presented in Table 11.

**Table 11 Sensitivity Analysis for Morbidity Benefits from nCPAP Therapy**

| SF36 single index benefit | Cost per QALY | |
|---|---|---|
| | (1 year) | (5 years) |
| 0.09 | £11,000 | £4,200 |
| 0.12 | £8,300 | £3,200 |
| 0.16 | £6,200 | £2,400 |

### 4.5.8 Impact of Assumptions Regarding Discounting of Future Benefits and Costs

The baseline analysis discounts costs at 6% and benefits at 1.5% per year in line with current NICE and Treasury guidelines. The impact of different assumptions regarding the discounting of both costs and benefits is presented in Table 12. As can be seen from Table 12 the economics of nCPAP treatment are not at all sensitive to the assumptions regarding discounting.

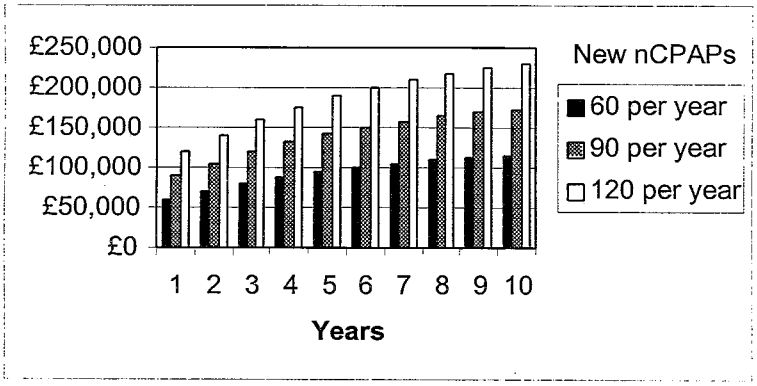
**Table 12 Sensitivity Analysis for Different Assumptions Regarding Discounting**

| Time horizon | Discounting assumptions (Benefits, Costs) | | | |
|---|---|---|---|---|
| | 0%, 0% | 1.5%, 6% | 6%, 6% | 10%, 10 % |
| 1 year | £8,250 | £8,300 | £8,500 | £8,600 |
| 2 years | £5,170 | £5,200 | £5,400 | £5,500 |
| 5 years | £3,300 | £3,200 | £3,500 | £3,700 |

## 4.6 ANNUAL COSTS OF PROVIDING nCPAP

Health authorities have expressed concern about the potential long-term costs associated with maintaining an ever-increasing pool of nCPAP appliances. Current referrals for OSA to the clinics at Leicester and Nottingham are estimated at approximately 150 cases per year leading to approximately 60 new appliances per year. At this rate of new appliances the annual cost of the nCPAP service, including new investigations and maintenance of the pool of nCPAP users, increases from approximately £60,000 in year one, to around £95,000 in year five and £115,000 in year ten. If the rate increases to 90 new appliances per year the equivalent annual costs will be £90,000, £140,000 and £170,000 at years one, five and ten respectively and at a rate of 120 new appliances will be £120,000, £190,000 and £230,000.

**Figure 4 Annual Discounted Cost to a 'Typical' Health Authority**




## 4.7 COMPARATIVE ECONOMIC POTENTIAL OF nCPAP AND MANDIBULAR ADVANCEMENT DEVICES

The costs associated with treatment of OSAS patients with a mandibular advancement device are likely to be similar to the costs of nCPAP treatment. Firstly, the diagnostic and investigative procedures used in the work-up of patients and hence, costs, for both treatment types would be very similar, if not identical. Secondly, the cost of providing the mandibular device is estimated at approximately £200-£300 as compared to a purchase cost of £250 for a nCPAP appliance. Thirdly, due to the concerns surrounding the potential long-term effects of using the mandibular device, at least some follow-up of patients would be required.

The available evidence on the comparative effectiveness of the mandibular advancement devices come from two studies[13,14] comparing MAD and nCPAP, these are both small cross-over randomised studies. Both studies indicate that the MADs have either similar or inferior effectiveness to nCPAP therapy, although, interestingly, both studies showed that patients preferred, or were more satisfied with the mandibular advancement device. This preference possibly arose because: a) the patients' subjective snoring complaint was managed by the MAD; b) subjective evidence suggests that the MAD is more convenient and easier to use than nCPAP; and c) in one of the studies the MAD was free to the patient whereas the nCPAP device had to be purchased.

Thus, the cost-effectiveness of treatment with the MAD compared to no treatment is likely to be similar or worse than the cost-effectiveness of nCPAP therapy compared to no treatment. Due to the implied small differences in clinical effectiveness, costs between the two therapies and the relatively large uncertainties in both, the incremental-cost effectiveness of nCPAP over MAD treatment is likely to be prone to very high uncertainty.

## 4.8 CONCLUSION ON THE COST-EFFECTIVENESS OF nCPAP THERAPY

The baseline estimate of the cost-effectiveness of nCPAP therapy for the treatment of OSA over a one-year period is approximately £8,300 per QALY gained. This gives a cost-effectiveness that is comparable to other treatments that are, currently, routinely funded.

This estimate of cost-effectiveness is likely to be biased through the exclusion of reduced healthcare costs associated with nCPAP use, and increased mortality benefits from improvements in road traffic accident rates and hypertension. Against this, however, is the uncertainty associated with the short-term nature of the randomised evidence concerning morbidity. All these sources of bias are examined within the one–way sensitivity analyses presented here and all estimates of cost-effectiveness over one year are less than £16,000 per QALY gained.

## 5. IMPLICATIONS FOR OTHER PARTIES

Studies of the clinical effectiveness of nCPAP have focused on the morbidity, disease specific and generic, of the OSAS for the sufferer. As has been identified, the depression, irritability, sexual dysfunction and nocturnal snoring, associated with this syndrome, can also have a severe impact on the life of partners. In severe cases the loss of employment due to excessive waking sleepiness can have a major impact on families. The impact of nCPAP treatment on a partner's life is not clear cut, however, as anecdotal evidence exists that the nCPAP appliance can also cause disturbance sufficient to dislodge a partner from the shared bed.

An important factor in the cost-effectiveness of nCPAP treatment is the number of initial examinations required to identify each final nCPAP patient. Therefore, it is imperative that awareness is raised, among GPs, of the characteristics of people who may benefit from this service, and that referral criteria are clarified and promoted.

'Current Medical Standards of Fitness to Drive',[80] published by the Driver and Vehicle Licensing Agency states that Group1 drivers (non-commercial) with sleep disorders causing excessive awake time sleepiness *must* cease to drive and that Group 2 drivers (commercial) are *recommended to cease driving* until such time that their condition is controlled adequately. In the case of Group 2 drivers, this controlled status must be confirmed by specialist assessment and reviewed annually. As has been demonstrated, nCPAP has the capability to return people to a 'normal' state, and the ESS and MWT can be used to demonstrate the level of control achieved.

## 6. FACTORS RELEVANT TO NHS POLICY

As previously discussed, current service provision has developed very unevenly in terms of geographical distribution. Consequently, access to services varies greatly between health authorities and resolving these inequalities is of high importance.

The British Thoracic Society, in co-operation with the Scottish Intercollegiate Guidelines Network, is developing guidelines for the diagnosis and management of OSA. This initiative is due to report at the end of 2001. The Guidelines may clarify some of the uncertainties in the diagnosis and investigation of sleep apnoea identified in this assessment. The impact on the economics of nCPAP treatment should be reviewed on their publication.

## 7. OPTIONS FOR PURCHASERS/COMMISSIONERS

Three options present themselves to commissioning bodies.

1. Do not invest at all in nCPAP for the treatment of OSA.

   This option would not appear to be tenable in the light of the evidence provided in this report, particularly with respect to short-term improvements in quality of life derived from treatment with nCPAP. The available evidence is also strongly suggestive that nCPAP use may be effective in reducing long-term mortality associated with hypertension, cardiac disease and road traffic accidents.

2. Continue current commissioning patterns.

   There is a great deal of variation across the Region in the pattern and range of service available for the diagnosis and treatment of OSA. This perpetuates inequity across the NHS.

3. Provide nCPAP for those likely to benefit the most from the treatment.

   On the basis of the evidence reviewed in this report, nCPAP provides an effective treatment for patients with OSA at a cost-effectiveness that is in line with other commonly funded procedures. There needs to be robust assessment and diagnostic facilities providing efficient investigation of potential candidates for nCPAP, together with clear criteria for referral for investigation and prioritisation of cases.

## 8. DISCUSSION AND CONCLUSIONS

- *Discussion of the issues raised by the Cochrane Systematic Review of Sleep Apnoea*[1]

The Wright review[1] was undertaken with the aim of assessing the evidence for claims that OSA was as harmful to the public health as smoking.[81] The report provided a summary of the evidence surrounding the health effects of sleep apnoea and the effectiveness of nCPAP. Wright et al. commented on the poorly designed epidemiological studies as well as on the weak and contradictory evidence other than that for sleepiness. The authors concluded that treatment with nCPAP was difficult to justify, because much of the published evidence was inconclusive and called for further trials with more appropriate placebos. The review created great controversy and considerable response. Although the review was seen by some to 'state the obvious',[82] a large proportion of the responses contained strong criticism.

The main criticisms have been addressed below:[83-88]

- *The authors were criticised for having little understanding of OSA. The report seemed to suggest that OSA was not a 'separate disease entity,'[1] but merely a consequence of obesity. They prescribed weight-loss as a more effective treatment than nCPAP.*

OSA cannot be labelled as a side-effect of obesity, as many sufferers are not overweight. If obesity is a factor, dietary measures are often the first option. However, even within this class of patients, it is inappropriate to deny immediate treatment such as nCPAP, usually prescribed alongside a weight-loss programme. There is much less evidence to support the effectiveness of dietary treatment than that of nCPAP.[85]

- *Wright et al. concluded that the relationships between OSA and hypertension, coronary heart disease, stroke and premature death were poorly established. The varying degrees of OSA were not acknowledged and the authors used studies in which people had mild OSA to suggest that there was no association between OSA and long-term medical problems.*

The varying degrees of OSA were not acknowledged and the authors used studies in which people had mild OSA, to suggest that there was no association between this condition and

long-term medical problems. Current available evidence regarding the link between OSA and increased mortality, cardiac disease and hypertension is most compelling (Section 3.3) though the evidence that nCPAP reverses these conditions is weaker.

- *There was a failure to explain that nCPAP was given primarily for the relief of disabling daytime sleepiness. The authors ignored even their own conclusion, that OSA caused sleepiness, possibly road accidents and, thereby, injury and death. The final conclusion was completely opposed to that drawn by other reports, including that of The Royal College of Physicians.*[10]

There was concern that this misleading inference could lead to patients being denied treatment, which is capable of curing excessive sleepiness for the rest of their lives. Two recent studies have demonstrated therapeutic benefit in patients with OSA.[27,31] nCPAP has been shown to reduce sleepiness, mood and quality of life measures. Wright concluded that nCPAP would only be of benefit to patients with severe OSA. Since the systematic review, Engleman's 1998 study has found nCPAP to provide clinically significant benefits to daytime function for patients with mild OSA.[31]

Wright's call for further trials with more appropriate placebos was answered by the Jenkinson trial.[27] Jenkinson et al. proved that such a trial was possible and also that patients receiving sham nCPAP showed significant and, at times, large effects in key dimensions of QOL and a subjective measure of sleepiness.

## REFERENCES


1 Wright J, Johns R, Watt I, et al. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. *British Medical Journal* 1997; 314: 851-860.

2 Neill AM, McEvoy RD. Obstructive sleep apnoea and other sleep breathing disorders. *Medical Journal of Australia* 1997; 167-381.

3 Whittle AT, Finch SP, Mortimore IL, et al. Use of home sleep studies for diagnosis of the sleep apnoea/hypopnoea syndrome. *Thorax* 1997; 52: 1068-1073.

4 Vazquez J, Tsai W, Flemons W, et al. Automated analysis of digital oximetry in the diagnosis of obstructive sleep apnoea. *Thorax* 2000; 55: 302-307.

5 Baltzan M, Verschelden P, Aljahdali H, et al. Accuracy of oximatry with thermistor (Oxiflow) for diagnosis of obstructive sleep apnoea and hypopnea. *Sleep* 2000; 23: 61-69.

6 Herer B, Roche N, Carton M, et al. Value of clinical, functional and oximetric data for the prediction of obstructive sleep apnoea in obese patients. *Chest* 1999; 116: 1537-1544.

7 Golpe R, Jimenez A, Carpizo R, et al. Utility of home oximetry as a screening test for patients with moderate to severe symptoms of obstructive sleep apnea. *Sleep* 1999; 22: 932-937.

8 Zamarron C, Romero P, Rodriguez J, et al. Oximetry spectral analysis in the diagnosis of obstructive sleep apnoea. *Clinical science* 1999; 97: 467-473.

9 Olson L, Ambrogetti A, Gyulay S. Prediction of sleep-disordered breathing by unattended overnight oximetry. *Journal of Sleep Research* 1999; 8: 51-55.

10 Gibson GJ, Douglas NJ, Stradling JR, et al. Sleep apnoea: clinical importance and facilities for investigation and treatment in the UK. Addendum to the 1993 Royal College of Physicians Sleep Apnoea report. *Journal of the Royal College of Physicians of London* 1998; 32: 540-544.

11 Ivanhoe JR, Cibirka RM, Lefebvre CA, et al. Dental considerations in upper airway sleep disorders: a review of the literature. *Journal Of Prosthetic Dentistry* 1999; 82: 685-698.

12 Tegelberg A, Wilhelmsson B, WalkerEngstom ML, et al. Effects and adverse events of a dental appliance for treatment of obstructive sleep apnoea. *Swedish Dental Journal* 1999; 23: 117-126.

13 Ferguson KA, Ono T, Lowe AA, et al. A short term controlled trial of ant adjustable oral appliance for the treatment of mild to moderate obstructive sleep apnoea. *Thorax* 1997; 52: 362-368.

14 Clark GT, Blumenfeld I, Yoffe N, et al. A crossover study comparing the efficacy of continuous positive airway pressure with anterior mandibular positioning devices on patients with obstructive sleep apnoea. *Chest* 1996; 109: 1477-1483.

15 McArdle N, Devereux G, Heidarnejad H, et al. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *American Journal Of Respiratory And Critical Care Medicine* 1999; 159: 1108-1114.

16 Kingshott R, Vennelle M, Hoy C, et al. Predictors of improvement in daytime function outcomes with CPAP therapy. *American Journal of Respiratory & Critical Care Medicine* 2000; 161: 866-871.

17 Findley L, Smith C, Hooper J, et al. Treatment with nasal CPAP decreases automobile accidents in patients with Sleep apnea. *American Journal Of Respiratory And Critical Care Medicine* 2000; 161: 857-859.

18 Pepin JL, Krieger J, Rodenstein D, et al. Effective compliance during the first 3 months of continuous positive airway pressure: A European prospective study of 121 patients. *American Journal Of Respiratory And Critical Care Medicine* 1999; 160(4): 1124-1129.

19 MarquezBaez C, PaniaguaSoto J, CastillaGarrido J. Treatment of sleep apnea syndrome with CPAP: Compliance withtreatment, its efficacy and secondary effects. *Revista De Neurologia* 1998; 26: 375-380.

20 Kiely J, McNicholas W. Bed partners' assessment of nasal continuous postive airway pressure therapy in OSA. *Chest* 1997; 111: 1261-1265.

21 Krieger J, Kurtz D, Petiau C, et al. Long-term compliance with CPAP therapy on obstructive sleep apnea patients and in snorers. *Sleep* 1996; 19: S136-S143.

22 Stradling JR, Barbour C, Pitson DJ, et al. Automatic nasal continuous positive airway pressure titration in the laboratory: Patient outcomes. *Thorax* 1997; 52: 72-75.

23 Janson C, Noges E, SvedbergBrandt S, et al. What characterizes patients who are unable to tolerate continuous positive airway pressure (CPAP) treatment? *Respiratory Medicine* 2000; 94: 145-149.

24 Tiihonen M, Partinen M. Polysomnography and maintenance of wakefulness test as predictors of CPAP effectiveness in obstructive sleep apnea. *Electroencephalography and Clinical Neurophysiology* 1998; 107: 383-386.

25 Chervin RD, Theut S, Bassetti C, et al. Compliance with nasal CPAP can be improved by simple interventions. *Sleep* 1997; 20: 284-289.

26 Likar LL, Panciera TM, Erickson AD, et al. Group education sessions and compliance with nasal CPAP therapy. *Chest* 1997; 111: 1273-1277.

27 Jenkinson C, Davies RJ, Mullins R, et al. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. *Lancet* 1999; 353: 2100-2105.

28 Ware J, Sherbourne C. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1993; 30: 473-483.

29 Brazier J, Harper R, Jones N. Validating the SF-36 Health survey questionaire: new outcome measures for primary care. *British Medical Journal* 1992; 305: 160-164.

30 Engleman HM, Kingshott RN, Wraith PK, et al. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep Apnea/Hypopnea syndrome. *American Journal of Respiratory & Critical Care Medicine* 1999; 159: 461-467.

31 Engleman HM, Martin SE, Kingshott RN, et al. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. *Thorax* 1998; 53: 341-345.

32 Engleman HM, Martin SE, Deary IJ, et al. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. *Thorax* 1997; Thorax. 1997; 52: 114-119.

33 Engleman HM, Martin SE, Deary IJ, et al. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. *Lancet* 1994; 343: 572-575.

34 Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep disordered breathing and hypertension. *New England Journal of Medicine* 2000; 342: 1378-1384.

35 Nieto FJ, Young T, Samet J. Sleep apnea and systemic hypertension. The sleep heart health study. *Circulation* 1998; 97: 53

36 Young T, Peppard PE, Palta M, et al. Population-based study of sleep disordered breathing as a risk factor of hypertension. *Archives of Internal Medicine* 1997; 157: 1746-1752.

37 Grote L, Hedner J, Peter JH. Sleep related breathing disorder is an independent risk factor for uncontrolled hypertension. *Journal of Hypertension* 2000; 18: 679-685.

38 Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *British Medical Journal* 2000; 320: 479-482.

39 Lindberg E, Janson C, Gislason T, et al. Snoring and hypertension: a 10 year follow-up. *European Respiratory Journal* 1998; 11: 884-889.

40 Grunstein R. Obstructive sleep apnoea as a risk factor for hypertension. *Journal of Sleep Research [Supplement]* 1995; 4: 1-170).

41 Worsnop CJ, Naughton MT, Barter CE. The prevalence of obstructive sleep apnea in hypertensives. *American Journal of Respiratory And Critical Care Medicine* 1998; 157: 111-115.

42 Phillips BG, Somers VK. Neural and humoral mechanisms mediating cardiovascular responses to obstructive sleep apnea. *Respiration Physiology* 2000; 119: 181-187.

43 Garcia-Rio F, Racionero MA, Pino JM, et al. Sleep apnea and hypertension - The role of peripheral chemoreceptors and the sympathetic system. *Chest* 2000; 117: 1417-1425.

44 Wiklund U, Olofsson BO, Franklin K, et al. Autonomic cardiovascular regulation in patients with obstructive sleep apnoea: a study based on spectral analysis of heart rate variability. *Clinical Physiology* 2000; 20: 234-241.

45 Salo TM, Jula AM, Piha JS. Comparison of autonomic withdrawal in men with obstructive sleep apnea syndrome, systemic hypertension, and neither condition. *Americal Journal of Cardiology* 2000; 85: 232-238.

46 Duchna HW, Guilleminault C, Stoohs RA, et al. Vascular reactivity in ostructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine* 2000; 161: 187-191.

47 Narkiewicz K, vandeBorne P, Dyken ME, et al. Does the altered cardiovascular variability associated with obstructive sleep apnea contribute to development of cardiovascular disease in patients with obstructive sleep apnea syndrome? Response. *Circulation* 1999; 100: E136-E137.

48 Roche F, Court-Fortune I, Pichot V, et al. Reduced cardiac sympathetic autonomic tone after long-term nasal continuous positive airway pressure in obstructive sleep apnoea syndrome. *Clinical Physiology* 1999; 19: 127-134.

49 Dimsdale JE, Loredo JS, Profant J. Effect of continuous positive airway pressure on blood pressure - a placebo trial. *Hypertension* 2000; 35: 144-147.

50 Davies RJO, Crosby JH, Prothero A, et al. Ambulatory blood-pressure and left ventricular hypertrophy in subjects with untreated obstructive sleep-apnea and snoring, compared with matched control subject, and their response to treatment. *Clinical Science* 1994; 86: 417-424.

51 Voogel AL, van Steenwijk RP, Karemaker JM et al. Effects of treatment of obstructuve sleep apnea on circadian hemodynamics. *Journal of the Autonomic Nervous System*. 1999; 77(2-3): 117-183.

52 Akashiba T, Kurashina K, Minemura H, et al. Daytime hypertension and the effects of short-term nasal continuous positive airway pressure treatment in obstructie sleep apnea syndrome. *Internal Medicine* 1995; 34: 528-532.

53 Peker Y, Kraiczi H, Hedner J. An independent association between obstructive sleep apnea and coronary artery disease. *European Respiratory Journal* 1999; 14: 179-184.

54 Sanner B, Sturm A, Konermann M. Coronary heart disease in patients with obstructive sleep apnea. *Deutsche Medizinische Wochenschrift* 1996; 121: 931-935.

55 Tremel F, Pepin J-L, Veale D, et al. High prevalence and persistence of sleep apnoea in patients referred for acute left ventricular failure and medically treated over 2 months. *European Heart Journal* 1999; 20(16):1201-9.

56 Schafer H, Berner S, Ewig S. Cardiovascular morbidity in patients with obstructive sleep apnoea in relation to their severity of respiratory disorder. *Deutsche Medizinische Wochenscrift* 1998; 123: 1127-1133.

57 Kessler R, Chaouat A, Weitzenblum E, et al. Pulmonary hypertension in the obstructive sleep apnoea syndrome: prevalence, causes and therapeutic consequences. *European Respiratory Journal* 1996; 9: 787-794.

58 Hu FB, Willett WC, Manson JE, et al. Snoring and risk of cardiovascular disease in women. *Journal of The American College Of Cardiology* 2000; 35: 308-313.

59 Sanner BM, Doberauer C, Konermann M. Pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Archives of Internal Medicine* 1997; 157: 2483-2487.

60 Chin K, Kita H, Noguchi T, et al. Improvement of Factor VII clotting activity following long-term nCPAP treatment in obstructive sleep apnoea syndrome download full text of article. *Qjm-Monthly Journal of the Association of Physicians* 1998; 91: 627-633.

61 Seppala T, Paartinen M, Penttila A, et al. Sudden death and sleeping history among Finnish Men. *Journal of Internal Medicine* 1991; 229: 23-28.

62 Veale D, Chailleux E, HoorelbekeRamon A, et al. Mortality of sleep apnoea patients treated by nasal continuous positive airway pressure registered in the antadir observatory. *European Respiratory Journal* 2000; 15: 326-331.

63 Risser MR, Ware JC, Freeman FG. Driving simulation with EEG monitoring in normal and obstructive sleep apnea patients. *Sleep* 2000; 23: 393-398.

64 Horstmann S, Hess CW, Bassetti C, et al. Sleepiness-related accidents in sleep apnea patients. *Sleep* 2000; 23: 383-389.

65 Kajaste S, Telakivi T, Mustajoki P. Effects of a cognitive-behavioral weight loss program on overweight obstructive sleep apnea patients. *Journal of Sleep Research* 1994; 3: 245-249.

66 Lojander J, Mustajoki P, Ronka S, et al. A nurse-managed weight reduction programme for obstructive sleep apnoea syndrome. *Journal of Internal Medicine* 1998; 244(3): 251-255.

67 Rueda J, Asua J, Mar J, et al. Cost-utility analysis of the treatment of severe sleep apnea with CPAP. *Book of Abstracts: 16th Annual Meeting of the International Society of Technology Assessment in Health Care* 2000; 18-21. 2000.

68 Chervin RD, Murman DL, Malow BA, et al. Cost-utility of three approaches to the diagnosis of sleep apnea: polysomnography, home testing, and empirical therapy. *Annals of Internal Medicine* 1999; 130: 496-505.

69 Finn L, Young T, Palta M, et al. Sleep-disordered breathing and self-reported general health status in the Wisconsin sleep cohort study. *Sleep* 1998; 21: 701-706.

70 Ronald J, Delaive K, Roos L, et al. Health care utilization in the 10 years prior to diagnosis in obstructive sleep apnea syndrome patients. *Sleep* 1999; 22: 225-229.

71 Bahammam A, Kryger M. Decision making in obstructive sleep-disordered breathing: Putting it all together. *Otolaryngol Clinics of North America* 1999; 2: 333-348.

72 Peker Y, Hedner J, Johansson A, et al. Reduced hospitalization with cardiovascular and pulmonary disease in obstructive sleep apnea patients on nasal CPAP treatment. *Sleep* 1997; 20: 645-653.

73 Garratt A, Ruta D, Aballa M. The SF-36 health survey questionnaire: an outcome measure suitable for routine use within the NHS. *British Medical Journal* 1993; 306: 1440-1444.

74 Hollingworth W, Mackensie R, Todd C, et al. Measuring changes in quality-of-life following magnetic-resonance- imaging of the knee -SF-36, Euroqol((c)) or Rosser index. *Quality of Life Research* 1995; 4: 325-334.

75 Harper R, Brazier J, Waterhouse J, et al. A comparison of outcome measures for patients with chronic obstructive pulmonary disease (COPD) in an outpatient setting. *Thorax* 1997; 52: 879-887.

76 Brazier J, Harper R, Thomas K, et al. Deriving a preference based single index measure from the SF-36 Measure. *Journal of Clinical Epidemiology* 1998; 51: 1115-1129.

77 Waterhouse JC, Brazier JE, Billings CG et al. Can a two week trial of CPAP treatment return patients' perception of vitality to that of the local population? *European Respiratory Journal* 16 (suppl. 31): 167s. 2000.

78 Waterhouse JC, Brazier JE, Billings CG et al. Can a health status questionnaire demonstrate change after a two week trial of CPAP treatment? *European Respiratory Journal* 16 (suppl. 31): 269s. 2000.

79 Munoz A, Mayoralas L, Barbe F, et al. Long-term effects of CPAP on daytime functioning in patients with sleep apnoea syndrome. *European Respiratory Journal* 2000; 15: 676-681.

80 Drivers Medical Unit DVLA. Current Medical Standards of Fitness to Drive. Swansea: DVLA. 1999.

81 Wright J, Sheldon TA, Watt I. Sleep apnoea [letter; comment]. *Lancet* 1999; 354(9178):600.

82 Wright J, Sheldon T. Sleep apnoea and its impact on public health. *Thorax* 1998; 53: 410-413.

83 Shneerson J, Smith I. False impression of objectivity may deny patients affordable treatment. *British Medical Journal* 1997; 315(7104): 367.

84 Pack AI, Young T. Superficial analysis ignores evidence on efficacy of treatment. *British Medical Journal* 1997; 315(7104):367-368.

85 Gibson GJ, Prowse K. Review was misleading and may deny cost-effective treatment to patients. *British Medical Journal* 1997; 315(7104): 368.

86 Semple SJG, London DR. Treatment prevents road accidents, injury, and death caused by daytime sleepiness. *British Medical Journal* 1997; 315(7104): 368-9.

87 Engleman HM, Martin SE, Deary IJ, et al. Some criticisms of studies are unfounded. *British Medical Journal* 1997; 315(7104): 369.

88 Wright J, Sheldon T. Authors' reply. *British Medical Journal* 1997; 315(7104): 369.

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