Obstructive Sleep Apnoea Syndrome

A Systematic Literature Review

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Obstructive Sleep Apnoea Syndrome –
Report of a Joint Nordic Project

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Content

Summary and Conclusions

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Conclusions

Cardiovascular complications, diabetes mellitus and death

- ❑ Obstructive sleep apnoea syndrome covaries with cardiovascular disease, including stroke and early death in men (Evidence Grade 2). There is insufficient evidence for women. There is insufficient scientific evidence of a relationship between obstructive sleep apnoea syndrome and arterial hypertension or diabetes mellitus.

Traffic accidents

- ❑ Obstructive sleep apnoea covaries with traffic accidents independent of daytime sleepiness and driving exposure among men (Evidence Grade 3).

Diagnostic procedures

- ❑ The apnoea-hypopnoea index (AHI) shows good agreement between two nights of polysomnographic recordings (Evidence Grade 2).

- ❑ Manually scored portable devices including airflow, respiratory movements and pulse oximetry during one night of sleep have high sensitivity and specificity to identify a pathologic apnoea-hypopnoea index compared with polysomnography (Evidence Grade 1). Automatic scoring of the results of portable devices has high sensitivity and identifies most patients with a pathologic apnoea-hypopnoea index, but specificity is low (Evidence Grade 1). Automatic scoring programs cannot score sleep time and it is unclear whether these programs can differentiate obstructive from central apnoeas.

- ❑ Pulse oximetry with results from the oxygen desaturation index is insufficient to identify a pathologic apnoea-hypopnoea index and there is a high risk that patients with sleep apnoea syndrome will be incorrectly classified as normal (Evidence Grade 1).

- ❑ A global impression from a case history and a physical examination alone are insufficient to identify or to rule out obstructive sleep apnoea syndrome (Evidence Grade 1).

Treatments

Continuous positive airway pressure therapy (CPAP)

- ❑ There is strong evidence that CPAP reduces daytime sleepiness regardless of the severity of the sleep apnoea syndrome (Evidence Grade 1). CPAP is highly effective in reducing obstructive sleep apnoeas (Evidence Grade 1). There is contradictory scientific evidence concerning the effect of CPAP on quality of life (measured as functional outcomes and vitality) or arterial blood pressure.

- ❑ Tolerance and compliance with CPAP is good, and about 70% of patients still use it after 1–4 years for a mean of 5.3 (range 4.4–6.2) hours per night (Evidence Grade 2) – provided that patients and their CPAP equipment are seen by physicians shortly after treatment starts and subsequently at individual intervals, but always at least once a year.

- ❑ Mild to moderate discomfort from the CPAP mask – pain at the bridge of the nose, skin problems, air leaks and disturbing noise from the CPAP machine – are common adverse effects of CPAP (Evidence Grade 2). Mild nasal adverse effects, such as rhinitis, are common (Evidence Grade 3). Auto-CPAP utilises a lower mean pressure than fixed CPAP, but the effects on daytime sleepiness, apnoea reduction and compliance are the same (Evidence Grade 1).

Mandibular repositioning appliances (MRAs)

- ❑ Custom-made mandibular repositioning appliances reduce daytime sleepiness in patients with mild to moderate sleep apnoea syndrome (Evidence Grade 3). They reduce apnoea frequency but to a lesser extent than CPAP (Evidence Grade 3). There is insufficient evidence concerning the effect of MRAs on quality of life (measured as functional outcomes and vitality) or arterial blood pressure.

- ❑ MRAs are still used by 76% of patients after one year and 56% after five years (Evidence Grade 3). A majority of patients experience mild adverse effects – including discomfort in the teeth, hypersalivation and minor reductions in overjet and overbite – during the first few months (Evidence Grade 3).

Surgery

- ❑ There is insufficient scientific evidence for the effect of any surgical modality on daytime sleepiness or quality of life. There is contradictory scientific evidence for the effect of laser-assisted uvulopalatoplasty (LAUP) in reducing apnoea frequency. There is insufficient scientific evidence for other surgical interventions in reducing apnoea frequency.

- ❑ The adverse effects of uvulopalatopharyngoplasty (UPPP) due to snoring or obstructive sleep apnoea include serious perioperative and postoperative complications, including death, bleeding and respiratory compromise (Evidence Grade 2). Persistent adverse effects are frequent, and difficulty in swallowing occurs in about 28% of patients (Evidence Grade 2). Voice changes are also common (Evidence Grade 3).

- ❑ The adverse effects of uvulopalatoplasty (UPP) and laser-assisted uvulopalatoplasty (LAUP) due to snoring or obstructive sleep apnoea include serious postoperative complications (Evidence Grade 3). Persistent adverse effects occur in 50–60% of patients and difficulty swallowing in about 26% (Evidence Grade 2). Globus sensation in the throat and voice changes are common (Evidence Grade 3).

Other treatments and lifestyle modifications

- ❑ No studies that meet the present inclusion criteria show that weight reduction programmes, bariatric surgery, drugs, pacemakers, devices for sleep in lateral position, didgeridoo-playing or any other suggested treatment or lifestyle modification for obstructive sleep apnoea syndrome have any effect.

Fact Box 1 Study Quality and Relevance, Evidence Grade.

Study quality and relevance refers to the scientific quality of a particular study and its ability to reliably address a specific question.

Evidence Grade refers to the total scientific evidence for a conclusion, ie, how many high-quality studies support the conclusion.

Evidence Grade 1 – Strong Scientific Evidence
A conclusion assigned Evidence Grade 1 is supported by at least two studies with high study quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the evidence grade may be lower.

Evidence Grade 2 – Moderately Strong Scientific Evidence
A conclusion assigned Evidence Grade 2 is supported by at least one study with high study quality and relevance as well as two studies with medium study quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Evidence Grade 3 – Limited Scientific Evidence
A conclusion assigned Evidence Grade 3 is supported by at least two studies with medium study quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Insufficient Scientific Evidence
If no studies meet the study quality and relevance criteria, the scientific evidence is rated as insufficient to draw any conclusions.

Contradictory Scientific Evidence
If different studies are characterized by equal study quality and relevance but generate conflicting results, the scientific evidence is rated as contradictory and no conclusions can be drawn.

Summary

Background

An estimated 4% of men and 2% of women have obstructive sleep apnoea syndrome (OSAS), ie, daytime sleepiness and obstructive apnoeas during sleep. The apnoea-hypopnoea index (AHI) is the mean number of apnoeas and hypopnoeas per hour of sleep, and an AHI greater than 5 is considered pathological. Overnight polysomnography – including respiratory monitoring, pulse oximetry, electrocardiogram (ECG) and sleep staging with electroencephalogram (EEG) – is the reference diagnostic procedure.

Daytime sleepiness and snoring are the most common symptoms. OSAS is considered a risk for traffic accidents due to sleepiness. It has also been suggested that sleep apnoea is a risk factor for cardiovascular disease, diabetes mellitus and early death. The most common treatments are continuous positive airway pressure (CPAP), mandibular repositioning appliances and various surgical modalities. A number of other treatments and lifestyle modifications have been suggested. A diversity of portable simplified diagnostic equipment has been introduced due to the high cost of overnight polysomnograms.

This report contains the results of a systematic review regarding diagnosis and treatment of OSAS in adults. The aim of the review was to investigate:

- Consequences of OSAS on cardiovascular morbidity, diabetes mellitus, death and traffic accidents.
- How to diagnose OSAS.
- The effects of various treatment modalities, including compliance and adverse effects.

Methodology

The inclusion criteria and quality assessments were predefined. Systematic literature searches were performed in Medline, Embase and Cochrane Library. Randomised controlled trials, including a minimum of 20

subjects with a follow-up of at least 4 weeks, were included with daytime sleepiness as the primary outcome. Any trial design was considered for adverse effects, and a minimum of 100 patients and follow-up of at least one year were considered for compliance. Portable devices measuring airflow, oxygen saturation, respiratory movements, pulsoximetry alone and global impression were compared with polysomnography during the same night, with pooled sensitivity and specificity for the AHI or oxygen desaturation index as the outcome measure. The search also included night-to-night variability of polysomnography. Meta-analyses were performed for the effect of different treatment modalities and for different diagnostic methods compared to polysomnography. Prospective trials were considered when investigating the relationship of obstructive sleep apnoea to cardiovascular disease, death and diabetes mellitus.

Because the assessed surgical modalities are used for treating both snoring and OSAS, all adverse effects of these procedures were included in this report, regardless of diagnosis.

Titles and abstracts of all identified trials were screened by two independent investigators, and full reports were requested for all possible relevant articles. Data were independently extracted by two reviewers. The authors were contacted if any questions arose.

Cardiovascular diseases, diabetes mellitus and death

A covariation between OSAS and cardiovascular disease or early death in men was shown in 4 studies of medium or high quality comprising a total of 2 979 patients. Only 307 were women. Five prospective studies, 4 in the general population, investigated the association of obstructive sleep apnoea (ie an AHI over a critical level) with the above conditions. A dose-dependent association between apnoea-hypopnoea frequency and hypertension was found in one population study. Reduced survival was not found in a population study of seniors. The AHI was related to neither diabetes in a third population study nor stroke in a fourth. One prospective study on patients with coronary artery disease reported an independent covariation between an AHI greater than 10 and the incidence of stroke.

Traffic accidents

Four studies of medium quality investigated the effect of obstructive sleep apnoea on traffic accidents. All 4 reported an increased frequency of accidents in obstructive sleep apnoea subjects independent of driving exposure. One study reported an adjusted odds ratio of 2.6 (95% CI 1.1–64) for accidents when the AHI was above 20, regardless of whether they had daytime sleepiness. Another study reported an odds ratio of 11 (95% CI 4.0–30) at an AHI greater than 5 regardless of daytime sleepiness. A third study reported that patients with OSAS had more traffic accidents. Only the fourth study included a sufficient number of women. Obstructive sleep apnoea in men, but not in women, covaried with traffic accidents in this study.

Diagnostics

Night-to-night variability in polysomnographic recordings was investigated in 5 studies of medium quality that included patients seeking medical attention for sleep apnoea and 5 studies of medium quality in the general population. Between 81% and 90% of patients in 3 studies did not cross a certain AHI level when two recordings were compared. One study reported an interclass correlation of 0.92 (95% CI 0.90–0.95) during 4 nights. Between 64% and 87% in 4 studies of subjects in the general population did not cross a certain level of the AHI when two recordings were compared. One study reported an interclass correlation of 0.80 (95% CI 0.71–0.86) and another study of 0.80 (95% CI 0.69–0.87).

Manual scoring of portable simplified sleep apnoea investigations (n = 6) compared with in-lab polysomnography during the same night had a pooled LR+ of 9.95 (95% CI 4.01–24.6), LR– of 0.09 (95% CI 0.05–0.16), sensitivity of 0.93 (95% CI 0.89–0.97) and pooled specificity of 0.92 (95% CI 0.87–0.96), suggesting that about 7% will be false negative and 8% false positive. The scoring was performed by professionals trained in polysomnographic scoring. Automatic scoring of portable simplified devices (n = 3) compared with polysomnography had a pooled LR+ of 6.6 (95% CI 1.3–34.0) with heterogeneity, LR– of 0.11 (95% CI 0.05–0.16) with heterogeneity, sensitivity of 0.92 (95% CI 0.83–0.97) with

heterogeneity and pooled specificity of 0.85 (95% CI 0.73–0.93) with heterogeneity, suggesting that about 8% will be false negative and 15% false positive. Whether the automatic scoring systems can differentiate obstructive from central sleep apnoeas has not been tested.

Using pulse oximetry with ODI (oxygen desaturation index) 4% as a measure of sleep apnoea, the pooled LR+ was 10.4 (95% CI 5.0–21.4) with heterogeneity, LR– was 0.32 (95% CI 0.21–0.52), specificity was 0.93 (95% CI 0.91–0.95) and sensitivity was 0.69 (95% CI 0.66–0.72) with heterogeneity, suggesting that about 31% of patients with sleep apnoea will be classified as normal and 7% will obtain false positive results. Desaturations defined at 2% had better sensitivity of 0.87 (95% CI 0.83–0.90) with heterogeneity but lower specificity of 0.64 (95% CI 0.59–0.69) with heterogeneity.

A global impression from a case history and physical examination had a pooled LR+ of 1.7 (95% CI 1.5–2.0), LR– of 0.68 (95% CI 0.59–0.77), sensitivity of 0.54 (95% CI 0.49–0.58) with heterogeneity and specificity of 0.69 (95% CI 0.65–0.72) with heterogeneity, suggesting that about 46% will be false negative and 31% false positive.

Treatment

Continuous positive airway pressure (CPAP)

Continuous positive airway pressure treatment (CPAP) significantly reduced subjective sleepiness measured with the Epworth sleepiness scale by –2.7 (95% CI –3.2 to –2.2) and objective measurements of sleep latency as a proxy for daytime sleepiness according to the multiple sleep latency test and maintenance of wakefulness test. The frequency of apnoeas and hypopnoeas was significantly reduced by CPAP by –13.0 (95% CI –17.7 to –8.25) to a mean apnoea-hypopnoea index of 5.4 ± 4.8. There were conflicting results regarding quality of life measured as the short form-36 subscale vitality and functional outcome of sleep questionnaire. There were also conflicting results regarding the effect on blood pressure in patients with OSAS.

About 70% of patients still used CPAP after 4 years for a mean of 5.3 (range 4.4–6.2) hours per night, provided that patients and their equipment were seen by physicians after about 1 month and subsequently every 6–12 months with additional phone support. Mild to moderate discomfort from the CPAP mask – pain at the bridge of the nose, skin problems, air leaks and disturbing noise from the CPAP machine – were common adverse effects of CPAP. Mild nasal adverse effects, such as rhinitis, were also common.

The utilised pressure was lower using auto-CPAP than fixed CPAP –2.2 (–1.9 to 2.5) cm – but the effect on daytime sleepiness, apnoea reduction and compliance was the same according to 4 systematic reviews of medium and high quality. Most participants preferred auto-CPAP to fixed CPAP when their preference was measured. Auto-CPAP has not been tested for subjects with central apnoea.

Mandibular repositioning appliances (MRAs)

A number of different oral appliances have been suggested for the treatment of snoring and OSAS. Custom-made oral appliances for mandibular advancement significantly reduce subjective sleepiness measured as the Epworth sleepiness scale and objective measurements according to the multiple sleep latency test and maintenance of wakefulness test. The AHI was significantly less when using MRAs than a placebo device, but the difference was smaller compared to CPAP. Only single studies measured the functional outcome of sleep questionnaire and short form 36 subscale vitality. Thus, no conclusions regarding these variables can be drawn. Pooled data from 2 studies did not demonstrate any effect on blood pressure.

Two studies of medium quality that assessed compliance reported that 76% of patients used the appliance after 1 year and 56% after 5 years. Patients using MRAs reported temporary discomfort in the jaw or teeth in the mornings more often than those who used placebo devices or CPAP. Excessive salivation or dry mouth, pain, soreness or other discomfort in the teeth were also common during the first few months of

treatment. Small reductions (less than one millimetre) in overjet and overbite were reported. No increase in symptoms in the masticatory system could be seen during an observation period of 4 years.

Surgery

Only three randomised controlled studies comparing surgical treatment with sham surgery or conservative treatment were identified. Two studies investigated the effect after laser-assisted uvulopalatoplasty (LAUP) and one after temperature-controlled radio frequency tissue volume ablation (TCRAFTA). We did not find any studies fulfilling the inclusion criteria that reported treatment effects from uvulopalatopharyngoplasty (UPPP) or any other surgical modality. Regarding adverse effects from surgery, all studies were included regardless of indication for surgery, ie, obstructive sleep apnoea or snoring.

Uvulopalatopharyngoplasty

No randomised controlled trial fulfilling inclusion criteria investigated the treatment effects of uvulopalatopharyngoplasty (UPPP) for OSAS. But severe complications – including death, bleeding and loss of airway in up to 16% of patients – in the perioperative and postoperative period have been reported for this surgical modality when it comes to obstructive sleep apnoea or snoring. A total of 30 cases of death were reported in 6 studies. Respiratory compromise, bleeding, intubation difficulties, infections and cardiac arrest were the main causes of death. A recent study of high quality comprising 3 130 operations reported perioperative and postoperative death in 7 patients (0.2%). Persistent adverse effects occurred in 14–62%. Adverse effects included difficulty in swallowing in 13–36% and voice changes in 7–14%.

Uvulopalatoplasty

Two randomised controlled trials compared laser-assisted uvulopalatoplasty (LAUP) with sham surgery or conservative treatment for OSAS. One LAUP study reported a slight reduction in the AHI. But the other study found no difference. There were no effects on subjective sleepiness measured with the Epworth sleepiness scale. No effects were reported on sleep latency, wakefulness, quality of life or blood pressure. Uvulopalatoplasty performed with a scalpel (UPP) or laser-assisted uvulopa-

latoplasty (LAUP) for obstructive sleep apnoea or snoring was followed by perioperative and postoperative complications – including postoperative bleeding and infections with one report of death from septicaemia – in up to 5%. Persistent adverse effects were reported in 52–62%. Adverse effects included difficulty in swallowing in 19–29%, globus sensation in 17–36% and voice changes in 6–10%.

Radio frequency tissue volume ablation

One randomised controlled study compared temperature-controlled radio frequency tissue volume ablation (TCRAFTA) with sham surgery for OSAS. There was no effect on either the functional outcome of the sleep questionnaire or subjective sleepiness measured with the Epworth sleepiness scale. TCRAFTA used for obstructive sleep apnoea or snoring reported adverse effects that included palatal mucosal breakdown, mucosal ulcers, palatal fistula, uvula loss, haemorrhage and infections. Treatment of the tongue was associated with case reports of tongue base abscess, tongue swelling and mouth floor oedema. Long-term follow-up studies on adverse effects are lacking.

Other treatments and lifestyle modifications

No trials that fulfilled the inclusion criteria were found regarding the effects of weight reduction programmes, bariatric surgery, different drugs, pacemakers, devices to avoid sleep supine position or any other treatment for OSAS, except for one small study on didgeridoo playing. But there was no effect of didgeridoo playing vs no treatment at follow-up.

Future research

If surgery for OSAS or snoring is to be considered in the future, controlled trials for efficacy and long-term follow-up for adverse effects are necessary.

The covariation between cardiovascular disease and OSAS needs to be further elucidated. The effects of CPAP and/or MRAs on traffic accidents, morbidity and mortality are still unknown.

The effects of lifestyle changes are important issues, given that patients with OSAS often carry other risk factors for conditions such as obesity.

The Board of SBU is responsible for the conclusions of the report. The conclusions are not necessarily in accordance with the opinions of external experts.

Preface

In recent years, obstructive sleep apnoea syndrome (OSAS) has received increasing attention in most Western countries. Excessive daytime sleepiness is one of the major symptoms. People with the syndrome may be at risk for traffic accidents. There may also be an increased risk for other diseases, as well as higher mortality. Because about 4% of men and 2% of women have OSAS, questions about risks, diagnosis and treatment options are of importance to both the clinician and those who plan health care.

The Nordic health technology assessment (HTA) agencies decided jointly in 2004 to conduct a systematic literature review concerning diagnostic procedures and treatment effects on OSAS in adults. The significance of OSAS for traffic accidents, deaths and conditions such as cardiovascular disease and diabetes mellitus was also systematically assessed. The sections on prevalence and pathophysiology of OSAS (Chapter 1), as well as ethical considerations (Chapter 6), are general in character and not based on systematic literature searches. An assessment of economic evaluations of the diagnosis and treatment of OSAS is not included in this systematic literature review.

In order to investigate current practice in the Nordic countries, a postal questionnaire regarding 2003 was sent to primary and specialist care departments. Health economic aspects have not been dealt with in this report due to the difficulty of finding data and differences among the Nordic countries. Methodological aspects differ somewhat among the various chapters. Thus, they are specified in each chapter.

The aim of the report was to assess the scientific evidence in order to address the following questions:

- Are people with OSAS at increased risk of contracting other conditions, such as cardiovascular disease and diabetes mellitus?
- Is mortality greater among OSAS patients than non-OSAS patients?
- Which is the most reliable and accurate procedure for diagnosing OSAS?
- What are the effects, compliance rates and adverse effects of different treatment modalities?

A number of databases were searched for relevant literature. In order to be accepted for inclusion, the studies had to investigate OSAS in adults. Diagnostic procedures were to be compared with polysomnography. The various elements of these procedures were not assessed separately. In order to assess increased risks for traffic accidents, mortality and co-morbidity, a comparison group should have been set up. The main outcomes for effect were to be symptoms of sleepiness as reported or measured in patients, as well as self-reported measures of functioning and well-being. Prospective studies of at least one year with a minimum of 100 patients were reviewed in order to address the issue of compliance. All types of studies, regardless of design, that reported adverse effects were included.

The titles and abstracts of all identified studies were screened by two independent investigators, and full reports were requested for all possible relevant articles. Based on assessment protocols, at least two independent reviewers assessed each article that met the inclusion criteria. The quality and clinical relevance of each study was assessed as high, medium or low. Detailed information on the inclusion criteria and assessment process is found in each chapter. Data were extracted and summarised in tables. The authors were contacted if there were any questions.

The scientific evidence for each conclusion was rated as strong, moderately strong, limited or insufficient, depending on the quality of the studies assessed.

1. The Obstructive Sleep Apnoea Syndrome

Definitions according to the American Academy of Sleep Medicine

Obstructive sleep apnoea syndrome (OSAS) is characterised by recurrent episodes of partial or complete upper airway obstructions during sleep [1]. This manifests as a reduction (hypopnoea) in or complete cessation (apnoea) of airflow despite ongoing inspiratory efforts resulting in oxygen desaturations and arousals. Daytime symptoms such as excessive sleepiness are thought to be related to sleep disruption (repetitive arousals) and possibly to recurrent hypoxemia.

Diagnostic criteria

A person must fulfil criterion A or B, as well as criterion C.

A. Excessive daytime sleepiness that is not better explained by other factors.

B. Two or more of the following that are not better explained by other factors:
   – choking or gasping during sleep
   – recurrent awakenings from sleep
   – unrefreshing sleep
   – daytime fatigue
   – impaired concentration.

C. Overnight monitoring demonstrating five or more obstructive breathing events per hour during sleep. These events may include any combination of obstructive apnoeas/hypopnoeas or respiratory effort-related arousals.

Obstructive apnoea/hypopnoea event

A transient reduction or complete cessation of breathing. In routine clinical practice it is not considered necessary to distinguish obstructive hypopnoeas from apnoeas. The events must fulfil criterion 1 or 2, plus criterion 3, of the following:

1. A clear decrease (greater than 50%) from baseline in the amplitude of a valid measure of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event, or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern).

2. A clear amplitude reduction of a validated measure of breathing during sleep that does not meet the above criterion but is associated with either oxygen desaturation of >3% or an arousal.

3. The event lasts 10 seconds or longer.

Severity criteria

Severity of the obstructive sleep apnoea-hypopnoea syndrome has two components: severity of daytime sleepiness and overnight monitoring. A severity level should be specified for both components. The rating of severity for the syndrome should be based on the most severe component.

A. Sleepiness

1. Mild: Unwanted sleepiness or involuntary sleep episodes occur during activities that require little attention. Examples include sleepiness that is likely to occur while watching television, reading, or travelling as a passenger. Symptoms produce only minor impairment of social or occupational function.

2. Moderate: Unwanted sleepiness or involuntary sleep episodes during activities that require some attention. Examples include uncontrol-

lable sleepiness that is likely to occur while attending activities such as concerts, meetings, or presentations. Symptoms produce moderate impairment or social or occupational function.

3. Severe: Unwanted sleepiness or involuntary sleep episodes during activities that require more active attention. Examples include uncontrollable sleepiness while eating, during conversation, walking, or driving. Symptoms produce marked impairment in social or occupational function.

B. Sleep related obstructive breathing events

Mild: 5 to 15 events per hour
Moderate: 15 to 30 events
Severe: more than 30 events per hour.

Overnight polysomnography – including respiratory monitoring, pulse oximetry, ECG and sleep staging with EEG – is the reference diagnostic procedure. A diversity of portable simplified diagnostic equipment has been introduced in order to reduce the costs for investigating the huge number of people seeking medical attention for sleep apnoea recordings.

Obstructive apnoeas are due to an obstruction, usually by the tongue, of the upper airways during sleep. The person is aroused at the end of apnoea with a short awakening of 5–15 seconds due to a struggle for air. Snoring starts at sleep onset and is followed by repetitive apnoeas, arousals, snoring, etc. Sleep quality is disturbed by frequent arousals, as well as reduced REM and slow wave sleep, causing daytime sleepiness. There is a continuum from simple snoring to snoring with a struggle for air and increased upper airway resistance to obstructive sleep apnoea with repetitive apnoeas and periodic snoring [2]. Apnoeas are followed by oxygen desaturations. Intrathoracic pressure decreases as the person struggles for air with persisting respiratory movements during apnoea, causing elevated venous pressure and intracranial pressure [3,4]. Sympathetic activity and blood pressure increase during the end of apnoea [5,6]. Cerebral blood flow increases concomitant with arterial pressure during

apnoea and rapidly decreases after apnoea termination to below resting values when hypoxemia occurs [7,8].

Central apnoeas differ from obstructive apnoeas in that there is no effort to breathe. Central apnoeas are most common in patients with heart failure and Cheyne-Stokes respiration. There is a regular waxing and waning breathing pattern, ie, increases and decreases in tidal volume followed by a central apnoea [9]. Some people exhibit both central and obstructive apnoeas.

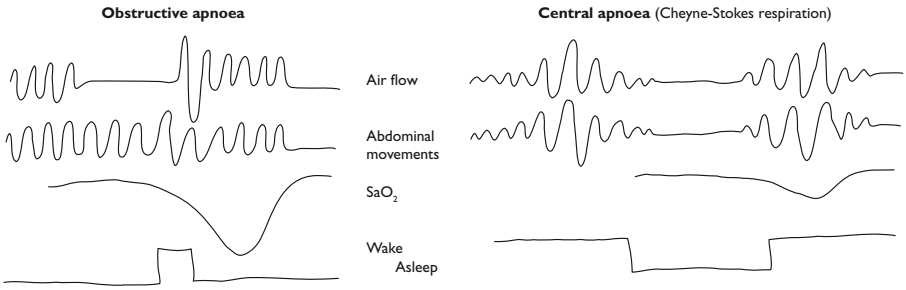

Figure 1.1 *Respiration and sleep during obstructive and central apnoeas (Illustration K Franklin).*

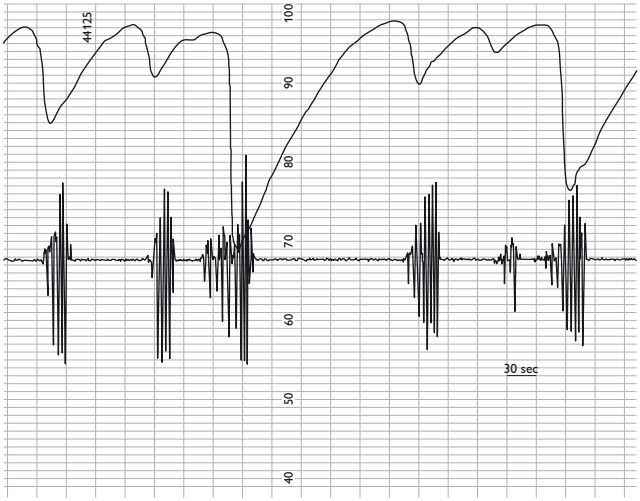

Figure 1.2 *Repetitive obstructive apnoeas with a three-minute long obstructive apnoea followed by a desaturation to 68%.*

Risk factors

Apnoeas and snoring are signs of increased upper airway resistance. They are usually due to anatomical factors that narrow the upper airway. Such factors are overweight with increased fat surrounding the pharynx, a large tongue or a retro positioned tongue from mandibular retrognathia or large tonsils. Sleep apnoea is also more prevalent among men and during sleep in the supine position as well as during alcohol intoxication.

Obesity is believed to predispose to OSAS because of mass loading of the upper airway [10]. Recent volumetric magnetic resonance suggests that patients with OSAS have smaller calibre upper-airway lumen than healthy controls, mainly due to lateral narrowing of the pharyngeal walls [11]. Despite the relationship between OSAS and obesity, it is important to remember that many slender people have sleep apnoea [12].

Smoking is related to sleep apnoea in a dose-response relationship [13]. Several surveys have reported a higher prevalence of snoring among smokers and passive smokers than non-smokers [14–16].

Heredity has been suggested as a risk for sleep apnoea, given that a number of studies have reported a significantly higher prevalence of sleep-disordered breathing in relatives of OSAS patients than controls, a difference that can not be explained by obesity alone [17–19]. Among 2 350 OSAS patients diagnosed in Iceland, the risk ratio for a first-degree relative of a patient with OSAS was 2.0 (95% CI 1.7–2.8), while the risk ratio of the more severely affected patients with OSAS was slightly higher [20]. Differences in facial structure have been suggested as a plausible cause of the familial aggregation [17]. Significantly lower hypoxic responses among the first-degree relatives of sleep apnoea families than among controls was reported by Redline et al [19], indicating that the familial aggregation of OSAS may be based partly on a familial abnormality in ventilatory control.

Other risk factors are endocrinological disorders, such as hypothyroidism [21] and acromegalia [22]. OSAS is also over-represented in rheumatoid arthritis, probably because of temporomandibular joint destruction with retrognathia or subluxation of the cervical spine as a result, leading to narrowing of the upper airways [23,24].

Symptoms

The most common symptom of obstructive sleep apnoea is excessive daytime sleepiness. Headache, concentration difficulties, depression, fatigue, nocturnal diuresis and gastroesophageal reflux are other prevalent symptoms. Typically, patients are drowsy in the morning, tired during the day and prone to fall asleep when sitting down. They have short sleep latency but they are often awakened 1–4 times during sleep. Other common symptoms are morning headache, fatigue and nycturia. Most patients with obstructive sleep apnoea snore. Snoring and daytime sleepiness are a common reason that people seek medical attention for sleep apnoea recordings.

Prevalence of obstructive sleep apnoea[1]

Sleep apnoea recordings in the general population identify subjects with not only OSAS, but asymptomatic subjects apnoea-hypopnoea index >5 who do not meet the criteria for OSAS. These subjects are sometimes classified in epidemiological studies as having obstructive sleep apnoea (OSA).

Studies of the prevalence of OSA (percentage of people with AHI ≥5) in a general population are usually carried out through a two-phase strategy [25–28]. The first phase, which is based on a random sample from the study population, aims at a rough discrimination between a group in which OSA is expected and one in which it is expected to be rare.

The first phase may include questions on daytime sleepiness and/or snoring and/or the number of transient desaturations and/or the number of apnoeas found in simplified sleep apnoea recordings. The second phase includes more resource-demanding methods, often polysomnography. The results of polysomnography are used to compute AHI scores, which are the accepted measure of OSA. To estimate OSAS, the AHI scores are combined with estimates of objective and/or subjective daytime sleepiness [25–30].

Figure 1.3 illustrates how snoring, sleep apnoea and (excessive) daytime sleepiness may be related in a theoretical middle-aged population at a given time. The circles represent those reporting habitual snoring and/or daytime sleepiness and/or having an AHI ≥5 events per hour based on polysomnography. The percentage meeting the traditional definition of OSAS [1] is shaded.

[1] This part has not been systematically reviewed.

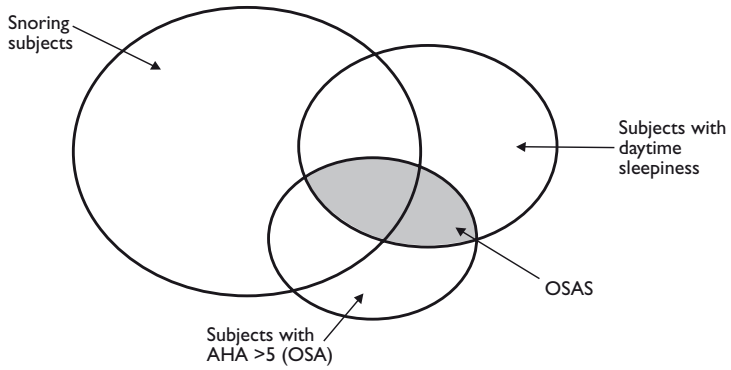

Figure 1.3 *A schematic illustration of the relationships between snoring, excessive daytime sleepiness, obstructive sleep apnoea (OSA = AHI >5) and OSAS (OSAS = AHI >5 and daytime sleepiness) in a theoretical population.*

Four population studies that reported the prevalence of obstructive sleep apnoea by age and gender were identified [25–27,31]. Studies carried out in Wisconsin (subjects aged 30–60), Pennsylvania (subjects aged 20–100) and Spain (subjects aged 30–70) used 2-stage stratified probability sampling with appropriate weighting techniques, similar measurement methods and definitions of AHI cut points [25–27,31] (Tables 1.1 and 1.2).

Table 1.1 *Population frequencies of obstructive sleep apnoea (OSA) with regard to apnoea-hypopnoea.*

Source Population	Gender	AHI ≥5	AHI ≥10	AHI ≥15
Young et al 1993 [25], USA Ages 30–60 Number = 602	Female Male	9% (6–12%) 24% (19–28%)	5% (2–8%) 15% (12–19%)	4% (2–7%) 9% (6–11%)
Bixler et al 1998, 2001 [27,31], USA Ages 20–100 Number = 1 741	Female Male All	17% (15–20%)	11% (8–13%)	2.2% 7.2% 6% (4–7%)
Durán et al 2001 [26], Spain Ages 30–70 Number = 555	Female Male	28% (20–35%) 26% (20–32%)	15% (9–20%) 19% (12–24%)	7% (3–11%) 14% (10–18%)

AHI = Apnoea-hypopnoea index

AHI and daytime sleepiness in population studies

The relationship between AHI level and excessive daytime sleepiness can be illustrated by the results of a cross-sectional cohort study of community-dwelling adults participating in the Sleep Heart Health Study [32]. The study sample consisted of 886 men and 938 women, with mean age of 65 (±11). Sleepiness was quantified using the Epworth Sleepiness Scale (ESS, see Appendix). Sleep-disordered breathing was quantified by AHI measured during in-home polysomnography. When AHI was categorised into 4 groups (<5, 5–14, 15–29, ≥30 events per hour), values on the Epworth Sleepiness Scale were found to be above normal (≥11) for 21%, 28%, 28% and 35%, respectively, in the four categories of AHI severity. Thus, even in individuals categorised as having severe OSA (≥30 events per hour), excessive daytime sleepiness may be present in only one third of the population.

OSAS in epidemiological studies

OSAS defined as AHI ≥5 and excessive daytime sleepiness are more common in men than women [25–27,31]. The most oft-cited figures come from the Young et al study, which reported that 4% of men and 2% of women have OSAS [25].

Table 1.2 *Prevalence of obstructive sleep apnoea.*

Author **Year** **Reference** **Country**	**Study group** **1. Type of population** **2. Number in phase 1** **3. Number in phase 2** **4. Age range**	**Outcomes reported** **1. For EDS** **2. For AHI categories** **3. For OSAS categories**
Young et al 1993 [25] USA	1. State employees 2. n=3 513 3. n=602 4. 30–60 years	1. BNSQ. Sleepiness >3 days/week 2. 3 (AHI ≥5; ≥10; ≥15) 3. Only summary
Durán et al 2001 [26] Spain (Basque)	1. Random population sample 2. n=2 148 3. n=555 4. 30–70 years	1. 4 subjective questions 2. 5 (AHI ≥5; ≥10; ≥15; ≥20; ≥30) 3. Only summary
Bixler et al 1998, 2001 [27,31] USA	1. Random population sample 2. n=16 583 3. n=1 741 4. 20–100 years	1. Not specified 2. 3 (AHI ≥5; ≥10; ≥20) 3. Not reported

AHI = Apnoea-hypopnoea index
BNSQ = Basic nordic sleep questionnaire
EDS = Excessive daytime sleepiness
OSAH = Obstructive sleep apnoea-hypopnoea
SDC = Smallest detectable change

Results	
1. EDS by gender	1. "Higher among females" ($p<0.01$) when AHI ≥5, 23% of ♀ and 16% of ♂
2. EDS by age	2. Did not vary by age ($p>0.10$)
3. AHI by gender	3. ♀ 9% and ♂ 24% When AHI ≥5: ♀ 6–16%; ♂ 17–31% When AHI ≥15: ♀ 3.7–4.0%; ♂ 6.2–11%
4. AHI by age	4. AHI increases with age
5. OSAS by gender	5. ♀ 2%; ♂ 4% at AHI ≥5
6. OSAS by age	6. Not reported
	1. ♀ 22%; ♂ 14%
	2. Not associated with age
	3. When AHI <8, no gender difference When AHI ≥8, ♂ had higher prevalence than ♀
	4. Not reported
	5 and 6. "The prevalence of OSAH increased with age in both sexes", "Daytime hypersomnolence was not associated with OSAH". At an AHI ≥10 plus EDS, the prevalence of OSAH syndrome was 3.4% in ♂ and 3% in ♀ at AHI ≥10
	1. Not reported
	2. Not reported
	3. At AHI ≥15: ♀ 2.2%, ♂ 7.2%
	4. At AHI ≥15: 0.6% in age group 20–44, 2.0% in age group 45–64 and 7.0% in age group 65–100 year
	5. ♀ 1.2% and ♂ 3.9% at AHI ≥10
	6. 0.7% in age group 20–44, 1.1% in age group 45–64 and 3.1% in age group 65–100 (based on SDC definition (sleep laboratory plus clinical findings))

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2. **Cardiovascular Disease, Diabetes Mellitus and Death**

Conclusions

- Obstructive sleep apnoea syndrome covaries with cardiovascular disease, including stroke and early death in men (Evidence Grade 2). There is insufficient evidence for women. There is insufficient scientific evidence of a relationship between obstructive sleep apnoea syndrome and arterial hypertension or diabetes mellitus.

Background

Several authors have suggested that sleep apnoea is a risk factor for cardiovascular disease, including arterial hypertension, diabetes mellitus and early death.

Objectives

To address the question of whether OSAS is related to cardiovascular disease, diabetes mellitus or early death.

Inclusion criteria

- Prospective design
- A control group should be present
- Objective outcomes
- A diagnosis of sleep apnoea from polysomnography or the equivalent.

Search strategies

PubMed was searched on 1 March 2006 for "Sleep Apnoea Syndromes/complications" [MeSH] AND "Cardiovascular diseases/aetiology" [MeSH] OR "Sleep Apnoea Syndromes" [MeSH] AND "Risk Factors"

[MeSH] OR "Diabetes Mellitus" [MeSH] OR "Mortality/mortality" [MeSH] NOT Case Reports; Comment; Editorial; Letter, News. Limits: 19+ years, Danish, English, Finnish, French, German, Norwegian, Spanish, Swedish. Titles and abstracts were screened for relevance.

Titles and abstracts of all identified trials were screened by two independent investigators, and full reports were requested for all possible relevant articles. Data were extracted by two independent reviewers. The authors ware contacted if questions arose. Fourtyeight articles were read, 9 of which were included in the final analysis. Data extractions of included studies are shown in Table 2.1 and excluded articles in Tables 2.2 and 2.3.

Quality assessment

1. Prospective design
2. Control group
3. Objective outcome
4. Adjustments for confounders
5. Power
6. Distinguishing between obstructive and central apnoeas
7. Defined population
8. <30% loss to follow-up

High quality: Requires an affirmative answer to all questions.
Medium quality: Requires an affirmative answer to questions 1–4.
Low quality: A negative answer to any of questions 1–4.

Grading of evidence

See summary of the report.

Description of included studies

Seven prospective studies of medium quality and two of high quality were included. The studies comprised 163–1 387 subjects, the majority of whom were men. Four studies investigated patients who had been referred for sleep apnoea recordings. Four studies were made in the general population, while one investigated patients with coronary artery disease.

Results

Patients admitted for sleep apnoea investigation (OSAS)

He et al 1988, followed 385 male patients and reported an increased risk of death when the apnoea index exceeded 20 [1]. Medium quality.

Peker et al 2002, followed 185 male patients who were free of cardiovascular disease for 7 years and reported an increased risk of developing cardiovascular disease – defined as hypertension, angina pectoris, myocardial infarction, stroke, cardiovascular death, cardiac arrhythmia's or congestive heart failure – among subjects with sleep apnoea, independent of body mass index, blood pressure and age at baseline with adjusted odds ratio: 4.9 (1.8–13.6) [2]. Medium quality.

Yaggi et al 2005, followed 1 022 patients (71% men) for a median of 3.4 years and reported a doubled risk for stroke or death at AHI >5, regardless of confounders and treatment for sleep apnoea at baseline [3]. Adjusted hazard ratio 1.97 (1.12–3.48). High quality.

Marin et al 2005, followed 1 387 male patients for 10 (1.6) years and reported that untreated patients with severe sleep apnoea syndrome and AHI >30 had a greater risk than controls of fatal and non-fatal cardiovascular events [4]. Adjusted odds ratio for fatal events: 2.87 (1.17–7.51), non-fatal events 3.17 (1.12–7.51). Medium quality.

General population studies (OSA)

Mant et al 1995, followed 163 seniors, 79% of whom were women, for 4 years. AHI >15 was not associated with reduced survival [5]. However, only 15 subjects had AHI >15. This study did not discriminate between obstructive and central apnoeas. Medium quality.

Peppard et al 2000, followed 709 subjects (55% men) in Wisconsin for 4 years [6]. Sleep apnoea was independent of confounders related to hypertension in a dose-dependent relationship. High quality.

Reichmuth et al 2005, followed 978 men and women (56% men) in Wisconsin for 4 years [7]. They reported an increased risk of developing diabetes mellitus in the prospective analysis among subjects with an AHI >15 vs AHI <5 in the univariate analysis, but not when adjusting for sex, age and waist girth adjusted odds ratio 1.62 (95% CI 0.67–3.65). Medium quality.

Arzt et al 2005, followed 1 189 subjects (55% men) in Wisconsin for 4 years [8]. AHI >20 was related to a risk of stroke in the univariate analysis, odds ratio 4.31 (1.31–14.2), but not after adjustments for confounders, adjusted odds ratio 3.08 (0.74–12.8). But the power was low, given that only 14 subjects developed a stroke. Medium quality.

Sleep apnoea in patients with coronary artery disease (OSA)

Mooe et al 2001, followed 407 patients with coronary artery disease for 5 years after a sleep apnoea investigation [9]. They reported an increased risk of the combined endpoint of death, stroke and myocardial infarction among patients with sleep apnoea, defined as ODI4 >5 (at least five desaturations per hour sleep) with a hazard risk of 1.59 (1.00–2.51). There was a tripled risk of stroke in the subanalysis for AHI >10 – adjusted hazard risk: 2.98 (1.43–6.20) – but no increased risk of death or myocardial infarction. Medium quality.

Table 2.1 *Data extraction. Sleep apnoea, cardiovascular disease, death and diabetes mellitus.*

Author **Year, reference** **Country**	**1. Study design** **2. Type of population** **3. Time of follow-up** **4. Number** **5. Age** **6. % women**	**1. Outcomes** **2. Risk factor** **3. Covariates = adjustments**
General population		
Mant et al 1995 [5] Australia	1. Prospective cohort 2. Two groups of retirement village residents 3. 4 years 4. 163 5. ≥70 years 6. 79	1. Death 2. RDI ≥15 vs RDI <15 3. Age, sex
Peppard et al 2000 [6] USA	1. Prospective 2. General population (Wisconsin) 3. 4 years 4. 709 (of 957 invited) 5. 46±7 years (30–60) 6. 45	1. Hypertension (140/90 or medication) 2. AHI 3. Age, sex, BMI, neck circumference, waist/hip, skin-fold, smoking status, alcohol, exercise, menopausal status
Reichmuth et al 2005 [7] USA	1. Prospective 2. General population (Wisconsin cohort) 3. 4 years 4. 978 5. 49±8.3 years 6. 44	1. Diabetes mellitus type 2 2. AHI >15 vs AHI <5 3. Age, sex, waist girth

	Results (odds ratio/hazard ratio = 95% CI)	Comments	Quality 1. Prospective 2. Controls 3. Objective outcome 4. Adjust for confounders 5. Power 6. Obstructive/central in separate 7. Defined population 8. <30% loss to follow-up
	Adjusted OR for AHI >15 and death: 0.95 (0.27–3.38) 4/15 subjects with RDI >15 had died. 33/148 subjects with RDI <15 had died	Only 7/34 men and 8/129 women had AHI >15. AHI did not relate to EDS, snoring or obesity. Simplified scoring could not differentiate between OSA and CSA Most senior women and very few with sleep apnoea	Medium 1. 1 2. 1 3. 1 4. 1 5. 0 6. 0 7. 0 8. 0
	Adjusted OR AHI 0: 1.0 AHI 0.1–4.9: 1.42 (1.13–1.78) AHI 5–14.9: 2.03 (1.29–3.17) AHI ≥15: 2.89 (1.46–5.64) p-trend: 0.002	PSG	High 1. 1 2. 1 3. 1 4. 1 5. 1 6. 1 7. 1 8. 1
	Adjusted OR: 1.62 (0.67–3.65)		Medium 1. 1 2. 1 3. 1 4. 1 5. 1 6. 0 7. 1 8. 1

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Table 2.1 *continued*

Author **Year, reference** **Country**	**1. Study design** **2. Type of population** **3. Time of follow-up** **4. Number** **5. Age** **6. % women**	**1. Outcomes** **2. Risk factor** **3. Covariates = adjustments**
Arzt et al 2005 [8] USA	1. Prospective and cross-sectional 2. General population (Wisconsin) 3. 4 years 4. 1 189 5. 47±8 years 6. 45	1. Stroke 2. AHI >20 vs AHI <5 3. Age, sex, BMI, smoking, hypertension
Patient cohorts		
He et al 1988 [1] USA	1. Cohort 2. Patients from sleep apnoea evaluation 3. 5 years and 8 years survival 4. 385 of 709 men with AI >5 investigated 1978–1986 5. 51±12 years 6. 0	1. Death 2. AI ≤20, AI >20, treated, untreated 3. Age
Peker et al 2002 [2] Sweden	1. Prospective patient series 2. Men investigated for sleep apnoea in 1991 free from cardiovascular disease and diabetes age 30–69 years 3. 7 years 4. 182 5. 46.8±9.3 6. 0	1. Cardiovascular disease with combined endpoint of either: Hypertension, angina pectoris, myocardial infarction, stroke, cardiovascular death, cardiac arrhythmias and congestive heart failure 2. OSA = 30 oxygen desaturation/night 3. BMI, blood pressure, age

	Results (odds ratio/hazard ratio = 95% CI)	Comments	Quality 1. Prospective 2. Controls 3. Objective outcome 4. Adjust for confounders 5. Power 6. Obstructive/central in separate 7. Defined population 8. <30% loss to follow-up
	AHI >20 compared with AHI <5 *Cross-sectional analysis* Adjusted OR: 3.83 (1.17–12.6) *Prospective* Unadjusted OR: 4.31 (1.31–14.2) Adjusted OR: 3.08 (0.74–12.8)	During the 4 years follow-up, only 14 persons suffered a first ever stroke Large confidence interval. Power problem	Medium 1. 1 2. 1 3. 1 4. 1 5. 0 6. 1 7. 1 8. 1
	AI >20 increased mortality vs subjects with AI <20 Only 22 had died		Medium 1. 1 2. 1 3. 1 4. 1 5. 1 6. 1 7. 1 8. 0
	22/60 patients with OSA developed cardiovascular disease (CVD) vs 8/122 non-OSA subjects Adjusted OR for CVD among OSA patients: 4.9 (1.8–13.6)		Medium 1. 1 2. 1 3. 1 4. 1 5. 1 6. 0 7. 1 8. 1

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Table 2.1 *continued*

Author **Year, reference** **Country**	**1. Study design** **2. Type of population** **3. Time of follow-up** **4. Number** **5. Age** **6. % women**	**1. Outcomes** **2. Risk factor** **3. Covariates = adjustments**
Yaggi et al 2005 [3] USA	1. Prospective patient cohort 2. Patients referred for sleep apnoea recordings >50 years old 3. Median 3.4 years 4. 1 022 5. 60.2 years 6. 29	1. Stroke and death 2. AHI ≥5 vs AHI <5 3. Sex, age, atrial fibrillation, hypertension, BMI, diabetes mellitus, race, smoking, alcohol and hyperlipidemia
Marin et al 2005 [4] Spain	1. Prospective 10 years 2. Patients referred for sleep apnoea recordings and age and BMI matched controls 3. 10.1±1.6 years 4. 1 387 patients investigated 1992–1994 and 264 healthy controls 5. 50±8 years 6. 0	1. Fatal cardiovascular events (death of stroke or AMI) and non fatal cardiovascular events (stroke, AMI, CABG, PTCA) 2. Untreated AHI >30, untreated AHI 5–30, untreated snorer AHI <5, AHI >5 + CPAP 3. BMI, sex, diabetes, smoking, alcohol, cholesterol, triglycerides, hypertension, cardiovascular disease, lipid lowering drugs and antihypertensive
CAD or stroke patients		
Mooe et al 2001 [9] Sweden	1. Prospective 2. Patients with coronary artery disease 3. Median 5.1 years 4. 407 5. <70 years 6. 32	1. Stroke, death and myocardial infarction 2. AHI >10 or ODI >5 3. Diabetes, LVEF, Coronary intervention, age, sex, BMI and hypertension

AHI = Apnoea-hypopnoea index; AI = Apnoea index; AMI = Acute myocardial infarction;
BMI = Body mass index; CABG = Coronary artery bypass graft (surgery); CI = Confidence interval;
CPAP = Continuous positive airway pressure; CSA = Central sleep apnoea; CVD = Cardiovascular disease;

	Results (odds ratio/hazard ratio = 95% CI)	Comments	Quality 1. Prospective 2. Controls 3. Objective outcome 4. Adjust for confounders 5. Power 6. Obstructive/central in separate 7. Defined population 8. <30% loss to follow-up
	Adjusted hazard ratio at AHI ≥5 for stroke and death was 1.97 (CI 1.12–3.48) Increased risk with increased levels of AHI	68% had AHI >5	High 1. 1 2. 1 3. 1 4. 1 5. 1 6. 1 7. 1 8. 1
	Untreated severe OSA AHI >30 compared with age and BMI matched controls had adjusted OR for fatal cardiovascular events = 2.87 (1.17–7.51) and non-fatal events = 3.17 (1.12–7.51)		Medium 1. 1 2. 1 3. 1 4. 1 5. 1 6. 1 7. 0 8. 1
	Adjusted hazard ratio at AHI ≥10 vs AHI <10 for stroke was 2.98 (1.43–6.20)	Simplified recording, not PSG	Medium 1. 1 2. 1 3. 1 4. 1 5. 1 6. 0 7. 1 8. 1

EDS = Excessive daytime sleepiness; LVEF = Left ventricular ejection fractions; ODI = Oxygen desideration index; OR = Odds ratio; OSA = Obstructive sleep apnoea; PSG = Polysomnography; PTCA = Percutaneous coronary angiography; RDI = Respiratory disturbance index

Table 2.2 *Excluded studies. Obstructive sleep apnoea, cardiovascular disease and death.*

Reason for exclusion	References
Snoring and not sleep apnoea	[10,11]
No data on OSA vs controls	[12]
Non RCT treatment study	[13–15]
No outcome such as death or cardiovascular disease	[16,17]
Mostly CSA and Cheyne-Stokes respiration	[18]
Low power	[19]
Low quality	[15,20–30]

CSA = Central sleep apnoea; RCT = Randomised controlled trial

Table 2.3 *Excluded studies. Obstructive sleep apnoea and diabetes mellitus.*

Reason for exclusion	References
No sleep apnoea investigation	[31–36]
Only a very small fraction of patients investigated	[37]
Small study <10 subjects	[38]
Treatment study, not RCT	[39,40]
A study of daytime sleepiness and not OSA and diabetes	[41]
Metabolic syndrome as the outcome and not diabetes, insulin resistance or glucose intolerance	[42]
Cross-sectional study	[43–47]
Low quality	[48,49]

RCT = Randomised controlled trial

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3. Traffic Accidents

Conclusion

- Obstructive sleep apnoea covaries with traffic accidents independent of daytime sleepiness and driving exposure among men (Evidence Grade 3).

Background

Daytime sleepiness is the most common symptom of obstructive sleep apnoea syndrome (OSAS). Sleepiness is also regarded as a risk for traffic accidents. It is against the law in many countries to drive when experiencing daytime sleepiness and snoring or obstructive sleep apnoea unless successfully treated.

Objectives

To address the question of whether OSAS is related to an increased frequency of traffic accidents.

Inclusion criteria

- A sleep apnoea diagnosis with polysomnography or the equivalent.
- A control group should be present.
- Measures of outcome should represent the number of actual traffic accidents, not events on simulated driving performance tests.

Exclusion criteria

Results that did not adjust for driving exposure. Titles and abstracts of all identified trials were screened by two independent investigators, and full reports were requested for all possible relevant articles. Data were extracted by two independent reviewers. Sixteen articles were read, 4 of which were included in the final analysis. Data extractions of included studies are shown in Table 3.2 and excluded articles in Table 3.3.

Quality assessment

1. Objective accidents records
2. Adjusted for driving exposure
3. Prospective design.

High quality: Required an affirmative answer to all questions
Medium quality: Required an affirmative answer to question 2.

Description of included studies

Four studies of medium quality were included (Table 3.1). One was a population-based study with retrospective data on objective accidents [1]. Three were case-control studies; 1 investigated the frequency of sleep apnoea in patients with a recent traffic accident [2] and 2 investigated accidents of patients with and without sleep apnoea [3,4]. The response rate was more than 70% in all studies.

Results

Young et al reported that men, but not women, with snoring or OSA and AHI >5 had experienced more traffic accidents during the past five years after adjustments for age and annual miles driven [1]. There was no relationship between sleepiness and accident risk.

Terán-Santos et al investigated the frequency of AHI among 102 subjects who required emergency care after highway crashes and 152 age-matched and sex-matched controls without traffic accidents during the past two months [2]. AHI ≥5 was related to traffic accidents with an adjusted OR of 11 (95% CI 4.0–30) independent of alcohol, visual refraction disorders, body mass index, years of driving, kilometres of driving a year and work schedules. ESS was 5.9 for cases and 5.7 for controls.

Barbé et al investigated the frequency of traffic accidents resulting in personal injury or property damage of 500 US dollars or more in patients with AHI >20 in a sleep clinic population with healthy controls [3].

They reported an adjusted odds ratio of 2.6 (95% CI 1.1–6.4) for traffic accidents among subjects with sleep apnoea, after controlling for annual kilometres driven and alcohol consumption.

Horstmann et al investigated the frequency of traffic accidents associated with sleepiness during the past three years in 156 patients with AHI >10 from a sleep clinic and compared them with 160 controls [4]. They reported a much higher frequency of traffic accidents per kilometre driven in patients with obstructive sleep apnoea.

Table 3.1 *Obstructive sleep apnoea and traffic accidents.*

Author Year, reference	Study design	% men	Outcomes	Results OSA (OR (95% CI) or frequency)/Controls	p-value	Quality
Young et al 1997 [1]	Retrospective. Population based	59%	OR for accident past 5 years. Controls: AHI <5 non snore	*Men* Snorers: 3.4 (1.8–6.9)/1 AHI 5–15: 4.2 (1.6–11.3)/1 AHI ≥15: 3.4 (1.4–8.0)/1 OR for women, no significant results		Medium
Barbé et al 1998 [3]	Case-control	98%	OR for accident ≥1 accident/ 3 years Accidents/ driver/year	AHI ≥20: 2.6 (1.1–6.4)/1 AHI ≥20: 33%/18% AHI ≥20: 0.17/0.07	0.06 <0.05	Medium
Terán-Santos et al 1999 [2]	Case-control	77%	OR for motor vehicle accidents	AHI ≥5: 11.1 (4.0–30.5)/1 AHI ≥10: 7.2 (2.4–21.8)/1 AHI ≥15: 8.1 (2.4–26.5)/1		Medium
Horstmann et al 2000 [4]	Case-control	91%	≥1 accident/ 3 years Accidents/ driver/ 1 million km during 3 years	AHI ≥10: 12.4%/2.9% AHI ≥10: 6.8/0.78	0.005 0.005	Medium

AHI = Apnoea-hypopnoea index; CI = Confidence interval; OR = Odds ratio; OSA = Obstructive sleep apnoea

Table 3.2 *Data extraction. Obstructive sleep apnoea and traffic accidents.*

Author **Year** **Reference** **Country**	**Study design**	**Subject characteristics** **1. Number** **1b. Participation rate of eligible** **2. Mean age (SD)** **3. Women (%)** **4. Mean AHI (SD)** **5. Type of population**	**Methods** **1. AHI level for OSA diagnosis** **2. Retrospective reference period for accidents** **3. Subgroups** **4. Method specific of the individual study**
Young et al 1997 [1] USA	Cross-sectional, retrospective Population-based sample aged 30–60 years	1. 913 1b. 95% 2. 45.1 (7.8) 3. 371 (41%) 4. – 5. AHI >5: 221 AHI <5, non snorer: 318 AHI <5 snorer: 374	1. ≥5 2. 5 years 3. AHI 5–15 AHI >15 4. Accident risk was analysed for men and women separately. Accidents defined as those resulting in personal injury and/or property damage >$500
Barbé et al 1998 [3] Spain	Case-control study, retrospective	*OSA* 1. 60 1b. 87% 2. 47 (1) 3. 1 (2%) 4. 58 (3) 5. Sleep clinic population with AHI ≥20 *Control* 1. 60 2. 47 (1) 3. 1 (2%) 4. Not reported 5. Healthy volunteers, non-medical workers or visitors to the hospital	1. ≥20 2. 3 years 3. – 4. Accidents defined as those resulting in personal injury and/or property damage >$500

	Accident risk	Comments	Quality 1. Objective accident records? 2. Adjusted for driving exposure? 3. Prospective design? 4. Sum of 1–3
	OR (95% CI) for having at least 1 accident during the reference period <u>*Men*</u> AHI <5, snore: 3.4 (1.8–6.9) AHI 5–15: 4.2 (1.6–11.3) AHI ≥15: 3.4 (1.4–8.0) <u>*Women*</u> AHI <5, snore: 0.9 (0.5–1.6) AHI 5–15: 0.8 (0.3–2.0) AHI ≥15: 0.6 (0.2–2.5)	OR adjusted for age, miles driven/year Risk increased for men with an AHI ≥5 but not for women No relationship between sleepiness and accident risk	Medium 1. 1 2. 1 3. 0 4. 2
	% of drivers with at least 1 accident during the reference period. OSA: 33% Control: 18% p=0.06 OR (95% CI) for having at least 1 accident during the reference period, adjusted for km driven/year and alcohol consumption. OSA: 2.6 (1.1–6.4) Accidents/driver/year. OSA: 0.17 Control: 0.07 p<0.05	Accident risk was not related to the severity, as measured by different markers (ie AHI, ESS)	Medium 1. 1 2. 1 3. 0 4. 2

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Table 3.2 *continued*

Author **Year** **Reference** **Country**	**Study design**	**Subject characteristics** **1. Number** **1b. Participation rate of eligible** **2. Mean age (SD)** **3. Women (%)** **4. Mean AHI (SD)** **5. Type of population**	**Methods** **1. AHI level for OSA diagnosis** **2. Retrospective reference period for accidents** **3. Subgroups** **4. Method specific of the individual study**
Terán-Santos et al 1999 [2] Spain	Case-control	*Cases* 1. 102 1b. 71% 2. 44 (9) 3. Not reported 4. Not reported 5. Drivers aged 30–70 receiving emergency care after highway accidents *Controls* 1. 152 1b. 89% 2. 43 (9) 3. Not reported 4. Not reported 5. Randomly selected from 3 primary care centres matched for age and sex 23% of participants were women	1. ≥5 2. Not available (case-control design) 3. AHI ≥5 AHI ≥10 AHI ≥15 4. All subjects were investigated at home with PSG. Suspected OSA was confirmed with PSG

	Accident risk	Comments	Quality 1. Objective accident records? 2. Adjusted for driving exposure? 3. Prospective design? 4. Sum of 1–3
	Adjusted OR (95% CI) for having at least 1 accident during the reference period. AHI ≥5 11.1 (4.0–30.5) AHI ≥10 7.2 (2.4–21.8) AHI ≥15 8.1 (2.4–26.5)	Adjusted for alcohol, visual-refraction disorder, BMI, years of driving, km of driving/year, sedative medications, work schedule ESS was 5.9 for cases and 5.7 for controls	Medium 1. 1 2. 1 3. 0 4. 2

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Table 3.2 *continued*

Author **Year** **Reference** **Country**	**Study design**	**Subject characteristics** **1. Number** **1b. Participation rate of eligible** **2. Mean age (SD)** **3. Women (%)** **4. Mean AHI (SD)** **5. Type of population**	**Methods** **1. AHI level for OSA diagnosis** **2. Retrospective reference period for accidents** **3. Subgroups** **4. Method specific of the individual study**
Horstmann et al 2000 [4] Switzerland	Case-control, retrospective	*OSA* 1. 156 1b. 72% 2. 56.5 (10.4) 3. 10% 4. 35 5. Sleep clinic population with AHI >10 from 1993–1996 *Controls* 1. 160 1b. 70% 2. 56.2 (12.5) 3. 8% 4. Not reported 5. Subjects examined for lower back pain or carpal tunnel syndrome	1. ≥10 2. 3 years 3. AHI <35 AHI ≥35 4. Only accidents due to sleepiness. Analysed both all types of traffic accidents, and traffic accidents causing personal injury and/or property damage >$500

AHI = Apnoea-hypopnoea index; BMI = Body mass index; CI = Confidence interval; ESS = Epworth sleepiness scale; OR = Odds ratio; OSA = Obstructive sleep apnoea; PSG = Polysomnography; SD = Standard deviation

	Accident risk	Comments	Quality 1. Objective accident records? 2. Adjusted for driving exposure? 3. Prospective design? 4. Sum of 1–3
	% of drivers with at least 1 accident during the reference period. *AHI ≥10* OSA: 12.4% Control: 2.9% p<0.005 *AHI 10–35* OSA: 6% *AHI ≥35* OSA: 19% Accidents/driver/1 million km. OSA: 6.8 Controls: 0.78 p<0.005	OSA patients had significant increased risk of motor vehicle accidents/km driving p<0.005 No relationship between ESS score and accident risk	Medium 1. 0 2. 1 3. 0 4. 1

Table 3.3 *Excluded studies. OSA and traffic accidents.*

Data not adjusted for driving exposure	[5–11]
Low response rate	[12]
No data presented regarding accident risk in OSA patients	[13,14]
OSA not diagnosed with PSG or equivalent	[15,16]

OSA = Obstructive sleep apnoea; PSG = Polysomnography

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4. Diagnostic Procedures

Conclusions

- The apnoea-hypopnoea index (AHI) shows good agreement between two nights of polysomnographic recordings (Evidence Grade 2).

- Manually scored portable devices including airflow, respiratory movements and pulse oximetry during one night of sleep have high sensitivity and specificity to identify a pathologic apnoea-hypopnoea index compared with polysomnography (Evidence Grade 1). Automatic scoring of the results of portable devices has high sensitivity and identifies most patients with a pathologic apnoea-hypopnoea index, but specificity is low (Evidence Grade 1). Automatic scoring programs cannot score sleep time and it is unclear whether these programs can differentiate obstructive from central apnoeas.

- Pulse oximetry with results from the oxygen desaturation index is insufficient to identify a pathologic apnoea-hypopnoea index and there is a high risk that patients with sleep apnoea syndrome will be incorrectly classified as normal (Evidence Grade 1).

- A global impression from a case history and a physical examination alone are insufficient to identify or to rule out obstructive sleep apnoea syndrome (Evidence Grade 1).

Background

Polysomnography

The reference standard for diagnostic sleep apnoea recording is overnight polysomnography (Figure 4.1). The method includes measurements of airflow with oronasal thermistors or pressure transducers for apnoea and hypopnoea detection. Respiratory effort is measured with chest and abdominal piezo sensors, strain gauges or oesophageal pressures to differentiate between obstructive and central apnoeas. Electroenceph-

alograms (EEG), electro-oculograms (EOG) and chin-electromyograms (EMG) measure sleep time, sleep stages, arousals and awakenings. Oxygen saturation is measured with finger or ear oximetry, ECG (V5), and often with a body position sensor. Manual scoring of apnoeas and sleep staging according to Rechtschaffen and Kales is the standard procedure [1].

The apnoea-hypopnoea index (AHI), which measures the mean number of apnoeas and hypopnoeas per hour of sleep, is the major outcome of polysomnography. Other outcomes include total sleep time, sleep efficiency, sleep latency, arousal index, sleep staging, mean and lowest oxygen saturation during the night, and apnoea frequency in different body positions and sleep stages.

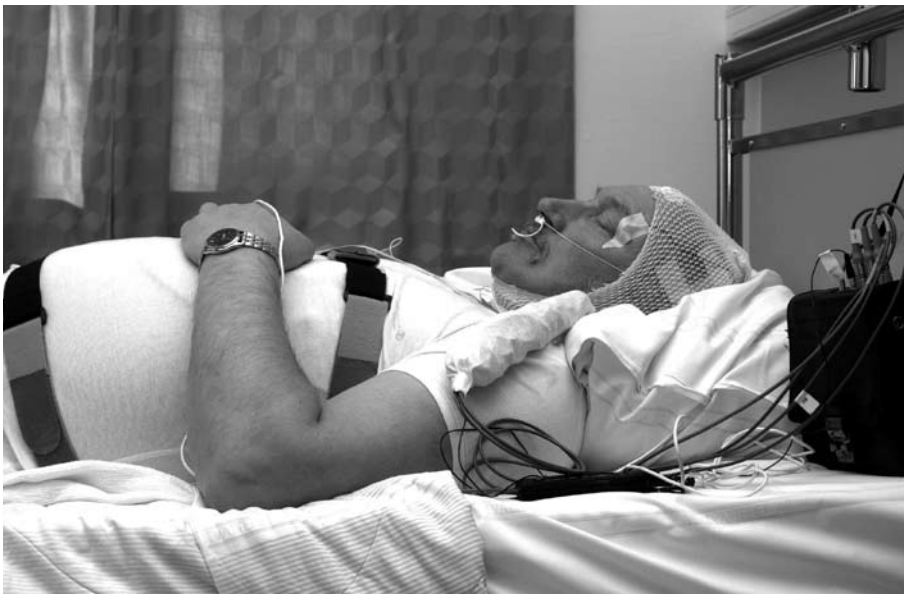

Figure 4.1 *Overnight polysomnography.*

Apnoeas are more prevalent in the supine position and after alcohol ingestion, while they are less frequent in slow wave sleep. The amount of sleep in different positions and sleep stages, and alcohol consumption can explain some of the night-to-night variability of the AHI.

Portable simplified sleep apnoea recordings

Simplified sleep apnoea recordings without EEG recordings of sleep time are commonly used in home settings. In such cases, sleep time is often approximated as recording time or time-in-bed. Because time-in-bed is almost always longer than sleep time, this approach introduces a risk of underestimating the average number of obstructive events per hour of sleep. Other approaches are based on the patient's subjective experience of sleep, ie, sleep diaries, actigraphy or estimating sleep from respiratory signals. Airflow, respiratory effort and oxygen saturation are mandatory for defining apnoeas and hypopnoeas, as well as for differentiating obstructive from central apnoeas.

Nocturnal pulse oximetry

Pulse oximetry, which is the simplest screening tool, measures oxygen saturation non-invasively from a probe on a finger or ear. Oxygen saturation is normally 96–98%, but transient desaturations occur after apnoeas. Oxygen desaturation is often defined as an absolute reduction of the oxygen saturation by 4% or more from baseline. But other definitions, such as 2% or 3%, have also been used. The oxygen desaturation index (ODI) measures the mean number of episodes of oxygen desaturation per estimated sleep hour and is sometimes used as a surrogate for the AHI. Oxygen desaturations defined as decreases by 2%, 3%, 4%, etc, are designated as ODI2, ODI3, and ODI4, etc. The degree of desaturation may differ according to brand, signal averaging time, type of probe and whether the probe is placed on a finger or ear [2]. Pulse oximetry alone cannot differentiate central from obstructive apnoeas.

Measurements of excessive daytime sleepiness

Excessive daytime sleepiness is measured either subjectively with different questionnaires or objectively with sleep latency as a proxy.

Epworth sleepiness scale (ESS)

The ESS is a self-administered questionnaire and the most frequently used outcome of daytime sleepiness in treatment studies of sleep apnoea [3]. Respondents are asked to rate their likelihood of dozing in eight different situations on a 4-point scale – 0: would never doze; 1: slight chance of dozing; 2: moderate chance of dozing; 3: high chance of dozing. The summary score varies from 0 to 24. A score of above 10 indicates daytime sleepiness [4,5]. The questionnaire appears in Figure 4.6.

Multiple Sleep Latency Test (MSLT)

The MSLT measures the time required to fall asleep under conditions that favour sleep. The subject is instructed to try to fall asleep on a comfortable bed in a dark, quiet room while standard EEG is being recorded. The time interval from start of the test to the onset of sleep is defined as sleep latency. The test is repeated 4–5 times for one day [6]. Severe sleepiness is defined as an MSLT score of 5 minutes or less, moderate sleepiness as 5–10 minutes and normal as 10–20 minutes [7].

Maintenance of Wakefulness Test (MWT)

The MWT resembles the MSLT, but the patient is asked to try to stay awake and resist sleep for 20 (or sometimes 40) minutes [8]. The test consists of 4 trials [8]. A mean MWT latency of less than 11 minutes identifies abnormally low sleep resistance.

Reliability of ESS, MSLT, and MWT

There were 2 studies of test-retest reliability on the ESS and 1 on the MSLT. The reliability of the MSLT has been reported from 1 small study of healthy men (n = 14) [9]. The second test was administered 4–14 months after the first. The Pearson correlation was found to be r = 0.97. The MWT has not undergone any reliability testing. A test-retest trial of the ESS in 104 healthy medical students was reported [10]. The test was repeated after a five-month interval. A high Pearson correlation of r = 0.822 between the results was found. The second test-retest trial of the ESS (n = 56 healthy subjects) found that the paired scores did

not differ, or differed by 1 point, for 54% of the sample, by 2 points in 20%, by 3 or 4 points in 23% and by 5 points in 4% [11]. No study was identified that tested the variability of ESS in patients with OSAS.

Associations between AHI, MSLT, MWT and ESS

A number of studies present statistical relationships between the AHI, MSLT, MWT and ESS [3,11–31]. Common to all the studies is that these measures of daytime sleepiness are only weakly correlated with the AHI ($0 < r < 0.55$).

Functional outcomes of sleep questionnaire (FOSQ)

The FOSQ is a self-administered, 35-item questionnaire designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living, ie, activity level, vigilance, intimacy, general productivity and social outcome [32]. Subjects are asked whether they have difficulty performing specific activities due to sleepiness or tiredness on a 4-point scale ranging from "no difficulty" to "extreme difficulty", or if they do not engage in the activity for reasons other than their sleep disorder.

Objectives

To examine night-to-night variability in diagnosing obstructive sleep apnoea from overnight polysomnography. To evaluate portable simplified sleep apnoea recordings, pulse oximetry and global impressions from case histories and physical examinations to diagnose obstructive sleep apnoea with polysomnography as the reference standard.

Methods

Inclusion criteria

Studies using overnight polysomnography in at least 10 subjects on two separate occasions to detect night-to-night variability of the AHI.

Studies comparing portable devices (including airflow measurements, respiratory movements and pulse oximetry) or pulse oximetry or global impression (from a case history and physical examination) with overnight polysomnography during the same night in at least 10 subjects who had been referred for sleep apnoea recordings with the AHI or ODI as outcomes.

Exclusion criteria

- Selected patients or subjects not representative of patients who will be given the test in practice
- Portable devices that include EEG recordings
- An index test not independent of polysomnography.

Search strategies

PubMed was searched on 7 February 2006 for "Sleep apnoea syndromes/diagnosis" [MeSH Major Topic] NOT ("case reports" [Publication Type] OR "comment" [Publication Type] OR "editorial" [Publication Type] OR "letter" [Publication Type]) AND Polysomnography, Field: All Fields, Limits: All Adult: 19+ years.

Articles were also searched in "related articles" of PubMed, in earlier systematic reviews [33–35] and through reference lists of identified articles.

Two independent readers went through 117 articles, 29 of which were included in the final analysis. Data extractions of included studies appear in Tables 4.7–4.10 and excluded articles in Tables 4.11–4.14.

Data collection

For each included study, the following data were abstracted:

- Referral process and selection criteria
- Number of patients eligible and examined
- Percentage of women, mean age, mean BMI, mean ESS and mean AHI
- Equipment used

- Scoring technique
- Definition of hypopnoea
- Cut-off levels for diagnosis of OSA
- Number of patients above the cut-off levels
- True positive, false positive, true negative, false negative.

Quality assessment

The following criteria modified from QUADAS were used for quality assessment [36]:

1. Was the spectrum of patients representative of those who will be given the test in practice?
2. Is the reference standard likely to classify the target condition correctly?
3. Is the period between reference standard and index test short enough to provide reasonable assurance that the target condition did not change between the two tests?
4. Was the whole sample or a random selection verified using a reference standard of diagnosis?
5. Did the patients receive the same reference standard regardless of index test result?
6. Was the reference standard independent of the index test (ie, the index test was not part of the reference standard)?
7. Was the performance of the index test described in sufficient detail to permit replication?
8. Was the execution of the reference standard described in sufficient detail to permit replication of the test?
9. Were the index test results interpreted without knowing the results of the reference standard?
10. Were the reference standard results interpreted without knowing the results of the index test?

Each question could be answered with "Yes", "No" or "Unclear".

High quality
An affirmative answer on all 10 questions.

Medium quality
An affirmative answer on questions 2–5.

Low quality
A negative answer on any of questions 1, 6, 9 or 10.

Grading of evidence

See summary of the report.

Statistical analysis

Sensitivity, specificity and likelihood ratios from studies of medium and high quality were pooled using Meta-analysis of Diagnostic and Screening Tests, Meta-DiSc Version Beta 1.1.0, Universidad Complutense, Madrid, Spain. Cut-off levels closest to AHI >15 were used in the meta-analysis. Variables and values are otherwise given as percentages in the individual studies.

Description of included studies

Night-to-night variability

Ten studies of medium quality and 1 of high quality comparing polysomnography during two or more nights were included (Table 4.7). They comprised 662 subjects. Two studies compared home polysomnography with in-lab polysomnography. Five studies included a total of 339 patients, of whom 16–30% were women, investigated for suspicion of obstructive sleep apnoea. Five studies included a total of 286 subjects from the general population with 0–68% women, and one investigated 37 men due to erectile dysfunction.

Six studies were excluded, the reasons for which are given in Table 4.11.

Portable devices vs polysomnography

Eight studies were included in the final analysis (Table 4.8) [37–44]. Five studies were of high quality and 3 of medium quality. Analysis was done manually by experienced polysomnographic scorers in 6 studies and automatically in 3 studies. One study reported the results of both automatic and manual analysis. A total of 435 patients, of whom 8–26% were women, were investigated. Manual analysis was reported on 349 patients and automatic analysis on 125 patients. All included patients were referred for an investigation based on suspicion of obstructive sleep apnoea. Five studies reported results from more than one cut-off level to defined sleep apnoea. AHI >5 was reported in 3 studies, AHI >10 in 4 studies, AHI >15 in 6 studies and AHI >20 in 3 studies. All of the studies used different brands of portable devices.

Fifty-one studies were excluded, the reasons for which are given in Table 4.12.

Pulse oximetry vs polysomnography

Seven studies were included in the final analysis (Table 4.9) [45–51]. Three studies were of high quality and 4 of medium quality. A total of 1 735 patients, 11–30% of whom were women, were investigated for suspicion of sleep apnoea. Automatic analysis was performed in 5 studies and manual analysis in 2 studies. Patients were consecutive in 4 studies and randomly selected in two. All studies used different brands of pulse oximeters. Finger probe was used in 4 studies and ear probe in 2. One study did not specify the probe used. Two studies reported more than one cut-off for diagnosis. AHI >5 was used in 2 studies, AHI >10 in 2 studies, AHI >15 in 5 studies and AHI >20 in 1 study. Six studies defined desaturations as a decline of 4% or more. Four studies presented results from desaturations of 3%, and 3 studies presented results from desaturations of 2%.

Thirty-five studies were excluded, the reasons for which are given in Table 4.13.

Global impression, from case history and physical examination

Three studies were included (Table 4.10) [52–54]. Two studies were of high quality and one was of medium quality. A total of 1 102 patients, 18–21% of whom were women, were investigated, all for suspicion of sleep apnoea. Two studies used a cut-off level of AHI >10, and 1 study used a cut-off level of AHI >15. Global impression was rated by a physician based on a case history and physical examination of patients in all studies. The possibility that some patients were included in 2 studies cannot be ruled out [52].

Eight studies were excluded, the reasons for which are given in Table 4.14.

Results

Night-to-night variability (Table 4.1)

Patients seeking medical attention for sleep apnoea

The AHI correlated significantly between 2 nights ($r = 0.86$ and $r = 0.77$) in 2 studies [55,56]. The interclass correlation was 0.92 (0.90–0.95) during 4 nights in another study of 20 patients with AHI >10 at baseline [57]. Eighty-one to ninty percent of patients in 3 studies did not cross a certain cut-off level between the two recordings [55,56,58].

Studies in the general population

Two studies reported an interclass correlation of 0.80 [59,60]. Three other studies reported a correlation of 0.66–0.79 and a small difference in the mean AHI between the nights [61–63]. Sixty-four to eighty-seven percent of subjects in 4 studies did not cross a certain cut-off level between the two recordings [60–62,64].

Table 4.1 *Night-to-night variability.*

Author Year, reference	n	Correlation	Cut-off	Unchanged, %	Increased, %	Decreased, %	Quality
Patients seeking medical attention for sleep apnoea (OSAS)							
Wittig et al 1984 [65]	22	r=0.91, p<0.01 frequent apnoea group r=–0.19 infrequent apnoea group					Medium
Mendelson 1994 [55]	50	r=0.86, p<0.001	AHI 10	88	10	2	Medium
Portier et al 2000 [58]	78		AHI 15	90	9	1	Medium
Le Bon et al 2000 [56]	169	r=0.77, p=0.0001 Mean AHI: 12±15 and 16±17	AHI 20	81	15	4	Medium
Bittencourt et al 2001 [57]	20	Interclass correlation 4 nights: 0.92 (0.90–0.95)					Medium
General population studies (OSA)							
Mosko et al 1988 [63]	46	r=0.70					Medium
Aber et al 1989 [61]	14	r=0.66, p<0.01 Mean AHI: 6.6±6.6 and 7.7±9.4	AHI 5 AHI 10	64 86	21 0	14 14	Medium
Chediak et al 1996 [62]	37	r=0.79, p<0.05 Mean AHI: 15±19 and 12±12	AHI 5	68	22	11	Medium

The table continues on the next page

Table 4.1 *continued*

Author Year, reference	n	Correlation	Cut-off	Unchanged, %	Increased, %	Decreased, %	Quality
Bliwise et al 1991 [64]	71		AHI 5 AHI 10	86 83			Medium
Quan et al 2002 [60]	91	Interclass correlation: 0.80 (0.71–0.86)	AHI 5 AHI 10 AHI 15	80 84 87	7 8 10	13 9 2	High
Iber et al 2004 [59]	64	Interclass correlation: 0.80 (0.69–0.87)					Medium

AHI = Apnoea-hypopnoea index; OSA = Obstructive sleep apnoea; OSAS = Obstructive sleep apnoea syndrome

Diagnostic measurements vs polysomnography for diagnosing OSAS

Table 4.2 *Pooled sensitivity, specificity and likelihood ratio at a cut-off closest to AHI 15 for the different diagnostic measurements vs polysomnography.*

	Portable, Manual scoring	Portable, Automatic scoring	Global impression
Number of studies	6	3	3
Pooled sensitivity (95% CI) Heterogeneity (p-value)	0.93 (0.89–0.97) 0.206	0.92 (0.83–0.97) 0.429	0.54 (0.49–0.58) 0.001
Pooled specificity (95% CI) Heterogeneity (p-value)	0.92 (0.87–0.96) 0.076	0.85 (0.73–0.93) 0.010	0.69 (0.65–0.72) 0.017
Pooled LR+ (95% CI) Heterogeneity (p-value)	9.95 (4.01–24.6) 0.007	6.6 (1.3–34.0) 0.005	1.7 (1.5–2.0) 0.917
Pooled LR– (95% CI) Heterogeneity (p-value)	0.09 (0.05–0.16) 0.515	0.11 (0.05–0.25) 0.576	0.68 (0.59–0.77) 0.278

CI = Confidence interval; LR = Likelihood ratio

Table 4.3 *Pooled sensitivity, specificity and likelihood ratio at a cut-off closest to AHI 15 pulse oximetry vs polysomnography.*

	Pulse oximetry ODI 4%	**Pulse oximetry ODI 3%**	**Pulse oximetry ODI 2%**
Number of studies	6	4	3
Pooled sensitivity (95% CI) Heterogeneity (p-value)	0.69 (0.66–0.72) 0.000	0.82 (0.79–0.85) 0.000	0.87 (0.83–0.90) 0.000
Pooled specificity (95% CI) Heterogeneity (p-value)	0.93 (0.91–0.95) 0.000	0.83 (0.79–0.86) 0.010	0.64 (0.59–0.69) 0.000
Pooled LR+ (95% CI) Heterogeneity (p-value)	10.4 (5.0–21.4) 0.000	4.83 (3.00–7.78) 0.002	2.2 (1.2–4.3) 0.000
Pooled LR– (95% CI) Heterogeneity (p-value)	0.32 (0.21–0.52) 0.000	0.18 (0.07–0.47) 0.000	0.14 (0.03–0.71) 0.000

CI = Confidence interval; LR = Likelihood ratio; ODI = Oxygen desaturation index

Portable devices vs polysomnography

Manual scoring of portable devices (n = 6) compared with polysomnography during the same night in hospital had high pooled sensitivity of 0.93 (95% CI 0.89–0.97) and high specificity of 0.92 (95% CI 0.87–0.96). There was no heterogeneity, even though 6 different portable equipment brands were used (Table 4.2, 4.4 and Figure 4.2).

Table 4.4 *Manual scoring of portable devices vs polysomnography.*

Author Year, reference	Brand	n	Cut-off	Sensitivity	Specificity	Quality
Emsellem et al 1990 [38]	Eden-Trace	63	AHI 5	0.95	0.96	Medium
White et al 1995 [39]	Night-Watch	30	AHI 10	1.00	0.64	Medium
Man et al 1995 [41]	PolyG	104	AHI 15	0.86	0.95	High
Verse et al 2000 [40]	Poly-mesam	53	AHI 10 AHI 15	0.92 0.87	0.96 0.97	High
Dingli et al 2003 [42]	Embletta	39	AHI 10 AHI 15	0.88 0.96	1.00 0.87	High
Núñez et al 2003 [37]	Breas SC20	60	AHI 10 AHI 15	0.97 0.97	0.76 0.92	Medium

AHI = Apnoea-hypopnoea index

Automatic scoring of portable devices (n = 3) compared with polysomnography had a pooled sensitivity of 0.92 (95% CI 0.83–0.97) without heterogeneity and a pooled specificity of 0.85 (95% CI 0.73–0.93) with heterogeneity (p = 0.010). The automatic systems investigated identified most patients with obstructive sleep apnoea, but specificity was low due to a high number of false positive results in the study by Dingli et al using the Embletta automatic scoring system [42]. Three different automatic systems were used. The results of one system are not applicable to another (Table 4.2, 4.5 and Figure 4.3). No study included a sufficient number of patients with central sleep apnoea. It is not clear whether the automatic scoring systems can differentiate obstructive from central sleep apnoeas.

Table 4.5 *Automatic scoring of portable devices vs polysomnography.*

Author Year, reference	Brand	n	Cut-off	Sensitivity	Specificity	Quality
Claman et al 2001 [44]	Bedbugg	42	AHI 15	0.86	0.95	High
Dingli et al 2003 [42]	Embletta	39	AHI 10 AHI 15	0.87 0.95	0.33 0.57	High
Reichert et al 2003 [43]	Novasom	60	AHI 15	0.95	0.91	High

AHI = Apnoea-hypopnoea index

Pulse oximetry vs polysomnography

Using pulse oximetry with ODI 4% as a measure of sleep apnoea compared with polysomnography during the same night in hospital, the pooled sensitivity was 0.69 (0.66–0.72) with heterogeneity ($p < 0.0001$). The pooled specificity was 0.93 (0.91–0.95), also with heterogeneity ($p < 0.0001$). Pulse oximetry using ODI 4% as a cut-off for sleep apnoea is not a good screening tool, given that as many as 31% of patients with sleep apnoea will be classified as normal and heterogeneity among different studies is large (Table 4.3, 4.5 and Figure 4.4).

A definition of 2% desaturation instead of 4% increases pooled sensitivity from 0.69 to 0.87 with high heterogeneity and reduces specificity from 0.93 to 0.64 with high heterogeneity. These data indicate that a lower desaturation level of 2% is better when pulse oximetry is used as an opportunistic screening tool to exclude patients without sleep apnoea (Table 4.3). But the pooled values of sensitivity and specificity are doubtful because of high heterogeneity among studies.

Table 4.6 *Pulse oximetry vs polysomnography.*

Author Year, reference	Brand	n	Cut-off	ODI threshold	Sensitivity	Specificity	Quality
Douglas et al 1992 [47]	Ohmeda 3700	200	AHI 15	4%	0.41	0.97	High
Yamashiro et al 1995 [48]	Ohmeda 3740	269	AHI 5	3%	0.94	0.76	Medium
Chiner et al 1999 [49]	Nellcor	275	AHI 15	4%	0.62	0.93	Medium
Zamarrón et al 1999 [50]	Criticare 504	233	AHI 10	2%, 3%, 4%	0.57	0.84	High
Vázquez et al 2000 [51]	Health-dyne	241	AHI 10 AHI 15	4%	0.97 0.98	0.80 0.88	High
Oeverland et al 2002 [46]	Nonin 8500	93	AHI 15	2%, 3%, 4%	0.64	1.00	Medium
Nakano et al 2004 [45]	3i, Minolta	424	AHI 15	2%, 3%, 4%	0.86	0.89	Medium

AHI = Apnoea-hypopnoea index

Global impression, from case history and physical examination

Pooled sensitivity was low, 0.54 (95% CI 0.49–0.58), with heterogeneity p = 0.0014. Pooled specificity was also low, 0.69 (95% CI 0.65–0.72), with heterogeneity p = 0.0167. (Table 4.2, Figure 4.5).

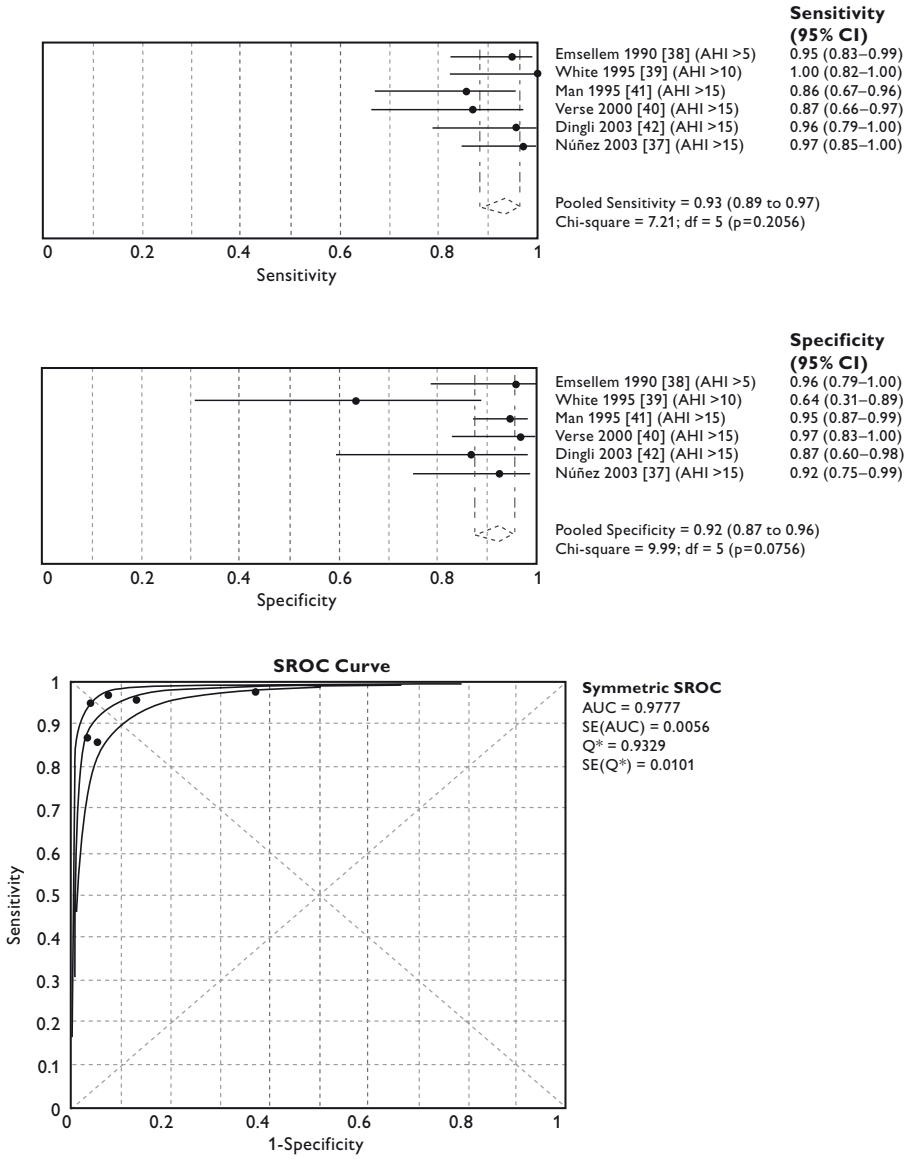

Figure 4.2 *Portable simplified devices vs polysomnography, manual scoring.*

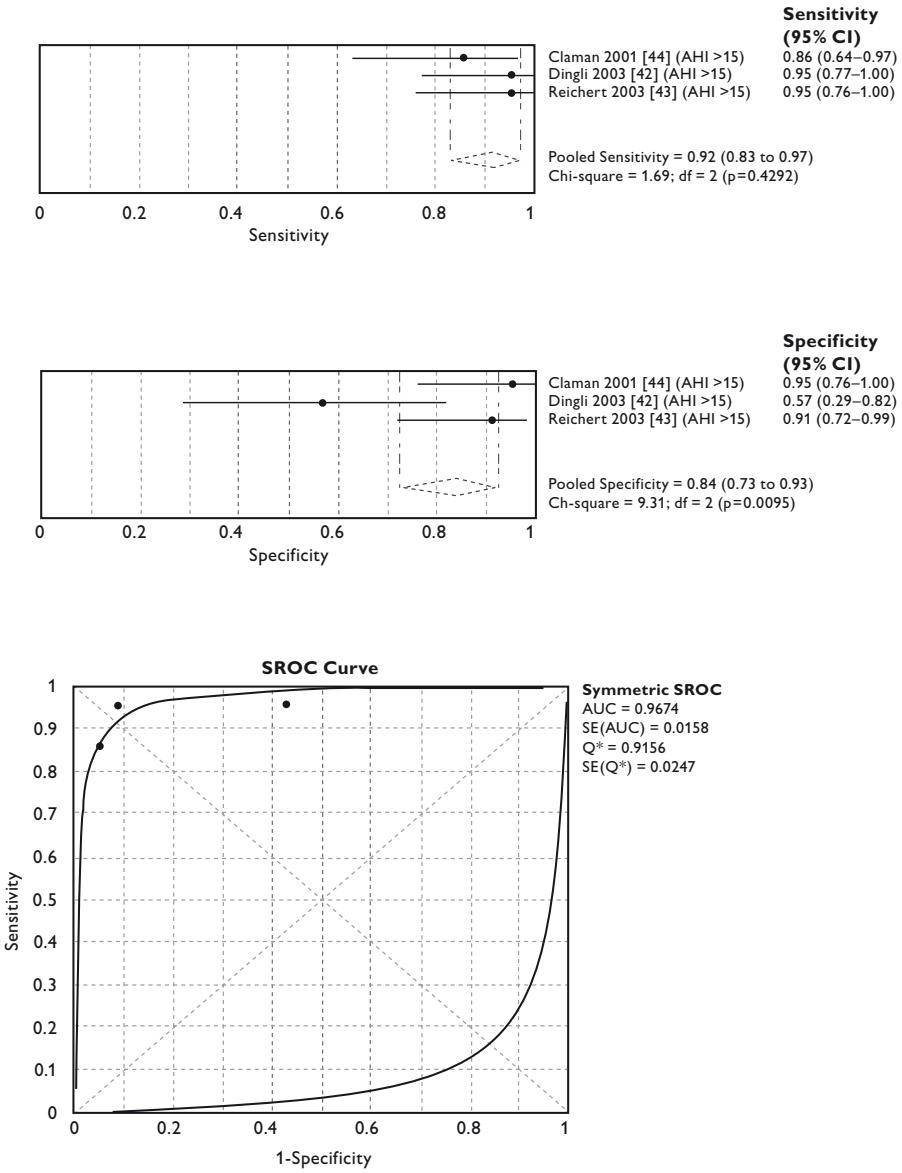

Figure 4.3 *Portable simplified devices vs polysomnography, automatic scoring.*

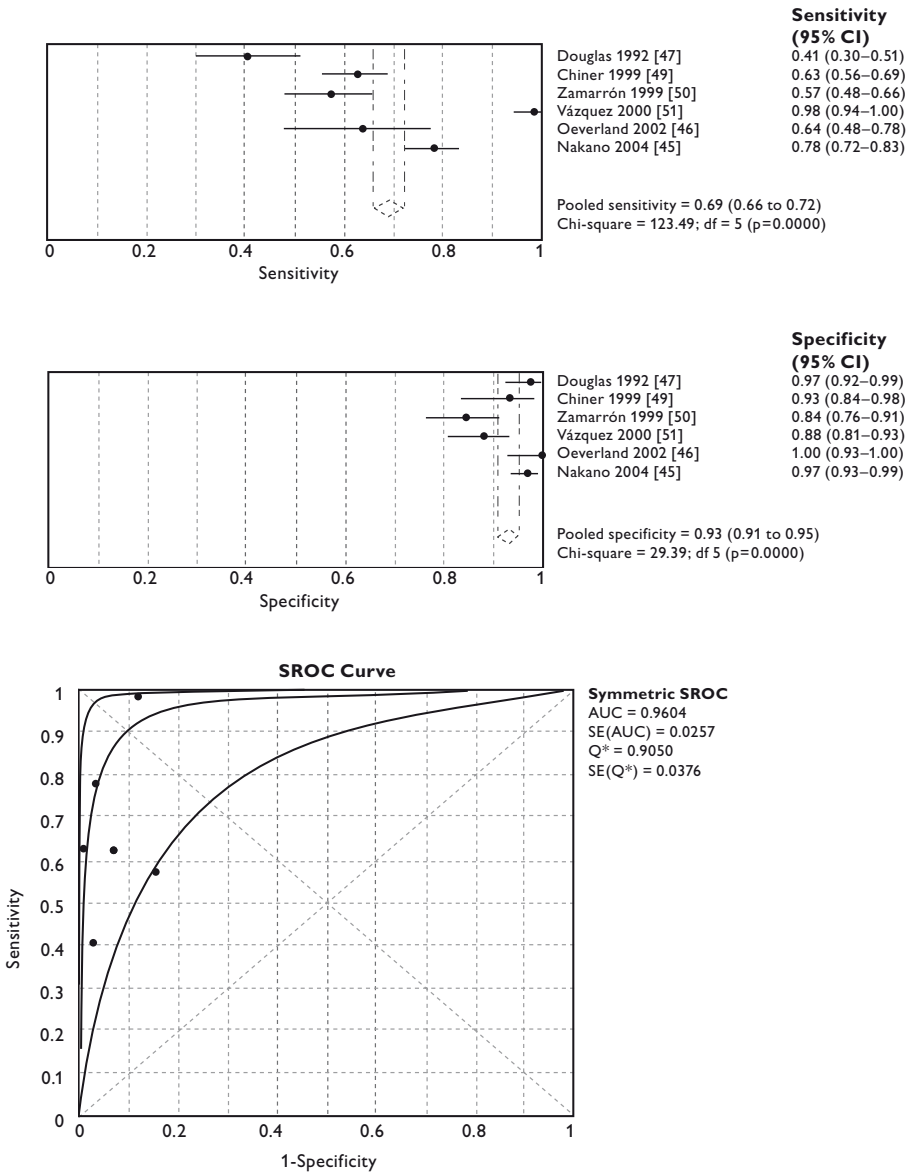

Figure 4.4 *Pulse oximetry vs polysomnography.*

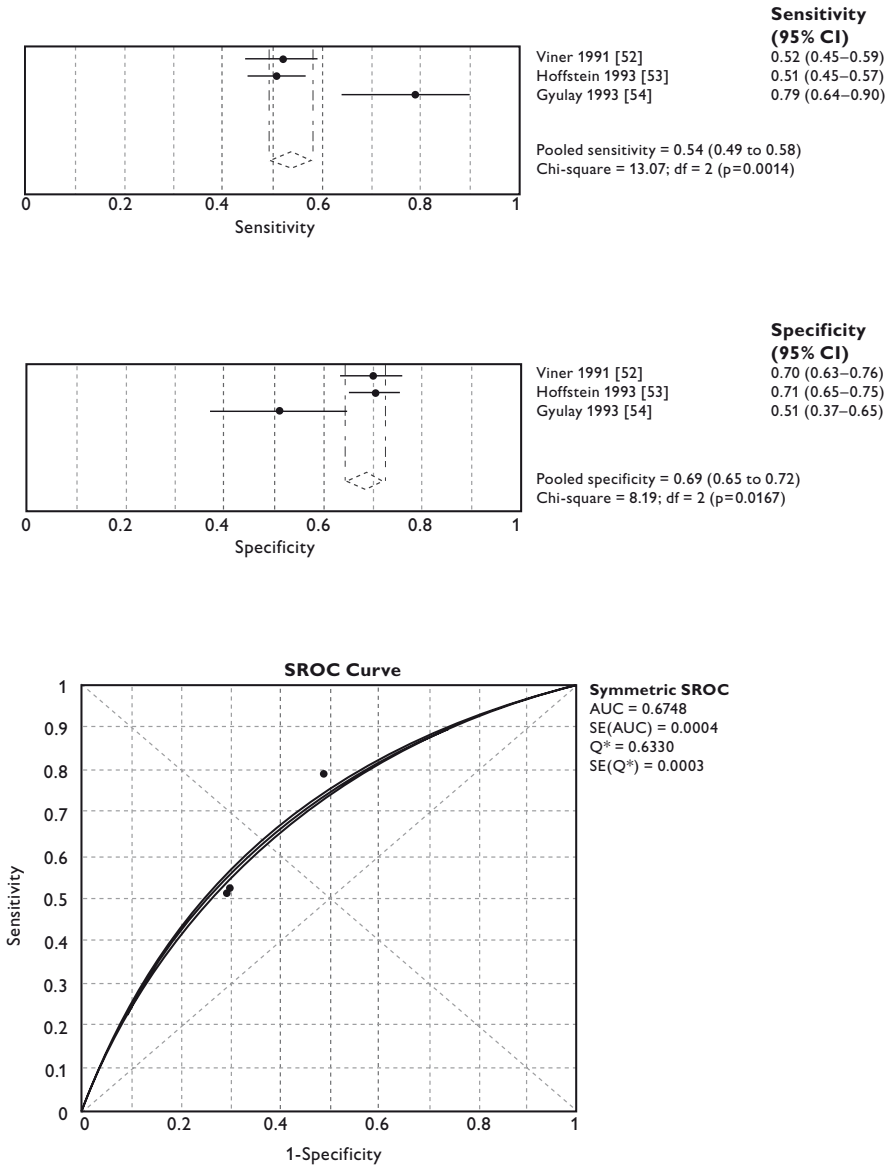

Figure 4.5 *Global impression vs polysomnography.*

Table 4.7 *Data extraction. Night-to-night variability polysomnography.*

Author Year, reference	**n Eligible**	**% women Age BMI ESS**	**Hypopnoea definition Scoring subject Inter/intra rater correlation Time between recordings**	**AHI treshold for diagnosis**	**n > treshold night 1 n > treshold night 2**
Studies on patients referred for sleep apnoea recordings (OSAS)					
Wittig et al 1984 [65]	22 50	Missing data 49.7±9.8 Missing data Missing data	Only apnoeas Missing data Missing data <90 days	100 apnoeas	
Mendelson 1994 [55]	50	16% 50.2±16.2 Missing data Missing data	–/4%/10 s* Missing data Missing data 2 consecutive nights	AHI >10	42 46
Portier et al 2000 [58]	78 103	18% 52±10 31±6 Missing data	25–50%/–/10 s* Trained specialist Missing data 14±18 days	AHI >15	Lab: 37 Home: 31
Le Bon et al 2000 [56]	169 243	Missing data 48.4±11.9 28.7±5.8 Missing data	50–80%/3%/–* Trained technologist Yes Consecutive nights	AHI >5	
Bittencourt et al 2001 [57]	20	30% 50±14 30±6 16±6	50%/3% or arousals/–* Trained physician Missing data 4 consecutive nights		

	Mean AHI night 1 Mean AHI night 2	Correlation night 1 and 2	Unchanged	Increase above threshold	Decrease below threshold	Quality Comments
	Group >100 apnoeas Group <100 apnoeas	r=0.91 p<0.01 r=0,35 p>0.10 –0.19				Medium Good correlation when frequent apnoeas night 1
	Missing data Missing data	r=0.86 p<0.001	44 (88%)	5 (10%)	1 (2%)	Medium
	Lab: 26±31 Home: 23±32	Missing data	70 (90%)	7 (9%)	1 (1%)	Medium Home vs in lab PSG random order. Home = "reference night"
	12.3±14.7 15.5±17.4	r=0.77 p=0.0001	137 (81%)	25 (15%)	7 (4%)	Medium Only 1/3 of patients with AHI >20 during night 1 (n=27) was included in a second night
		Interclass correlation =0.92 95% CI: 0.90–0.95				Medium Patients with AHI >10 were included during 4 consecutive nights

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Table 4.7 *continued*

Author Year, reference	**n Eligible**	**% women Age BMI ESS**	**Hypopnoea definition Scoring subject Inter/intra rater correlation Time between recordings**	**AHI treshold for diagnosis**	**n > treshold night 1 n > treshold night 2**
Epidemiological studies (OSA)					
Mosko et al 1988 [63]	46	68% 68.7±6.7 Missing data Missing data	Decrease+ arousal Manually Missing data 3 consecutive nights	AHI >5	
Aber et al 1989 [61]	14 19	0 66±6 Missing data Missing data	50%/7%/–* Missing data Missing data 2 consecutive nights	AHI >5	5 6
Bliwise et al 1991 [64]	71	32% 74.6±8.8 34.9±4.6 Missing data	Missing data Single technologist Missing data Missing data	AHI >5	
Chediak et al 1996 [62]	37	0% 52±14 27±4 Missing data	Gould 1988 [66] Missing data Missing data 2 consecutive nights	AHI >5	21 26 18 (for AHI >10 night 1) 18 (for AHI >10 for night 2)

	Mean AHI night 1 Mean AHI night 2	Correlation night 1 and 2	Unchanged	Increase above threshold	Decrease below threshold	Quality Comments
		r=0.70				Medium Healthy volunteers over 60 years old
	6.6±6.6 7.7±9.4	r=0.655 p<0.01	9 (64%) 12 (86%) (for individuals AHI >10)	3 (21%) 0 (0%) (for individuals AHI >10)	2 (14%) 2 (14%) (for individuals AHI >10)	Medium Healthy elderly men recruited from newspapers advertisements. Some were offered 2 nights but not everyone
	13.2±17.6 11.5±5.1		10 (86%) 12 (83%) (for individuals AHI >10)			Medium Elderly volunteers in a cohort study of sleep and breathing
	15±19 12±12	r=0.79 p<0.05	25 (68%)	8 (22%)	4 (11%)	Medium Retrospective on consecutive patients with erectile dysfunction. Letter sent/ received

The table continues on the next page

Table 4.7 *continued*

Author Year, reference	**n Eligible**	**% women Age BMI ESS**	**Hypopnoea definition Scoring subject Inter/intra rater correlation Time between recordings**	**AHI treshold for diagnosis**	**n > treshold night 1 n > treshold night 2**
Quan et al 2002 [60]	91 99	44% 40–87 28.3 Missing data	–/4%/–* Experienced scorers Missing data Within 4 months (77±18 days)	AHI >5 AHI >10 AHI >15	
Iber et al 2004 [59]	64 76	47% Median 57 31.3±10.5 7.5±4.8	30%/3%/–* SHHS Yes 2 weeks		

* % decrease breathing/desaturation/time of event.

AHI = Apnoea-hypopnoea index; BMI = Body mass index; CI = Confidence interval; ESS = Epworth sleepiness scale; OSA = Obstructive sleep apnea; OSAS = Obstructive sleep apnoea syndrome; PSG = Polysomnography; r = Coefficient of correlation; SHHS = Sleep heart health study

	Mean AHI night 1 Mean AHI night 2	Correlation night 1 and 2	Unchanged	Increase above threshold	Decrease below threshold	Quality Comments
		Interclass correlation 0.80, 95% CI 0.71–0.86	73 (80%) 76 (84%) 79 (87%)	6 (7%) 7 (8%) 9 (10%)	12 (13%) 8 (9%) 2 (2%)	High 2 home PSG within sleep heart health study. Representative patients
	Home: 12.4 Lab: 9.5	Interclass correlation 0.80, 95% CI 0.69–0.87				Medium Healthy volunteers in SHHS, home vs in lab PSG in random orders

Table 4.8 *Data extraction. Portable recordings vs polysomnography.*

Author Year, reference	**n Eligible**	**% women Age BMI ESS AHI**	**Portable brand and measures**	**Portable score (automatic/ manual) Hypopnoea definition Sleep time measures Scoring subjects Inter/intra rater correlation Portable AHI**	**AHI tres-hold for dia-gnosis**
Emsellem et al 1990 [38]	63 67	Missing data 45 years Missing data Missing data Missing data	EdenTrace N/o ther-mistors, SaO_2, chest impedance, ECG	Manual 50%/–/10 s* From signals 2 independent No Missing data	AHI >5
White et al 1995 [39]	30	23% 51±3 33±2 Missing data 31±6	NightWatch Oronasal thermistors, SaO_2, leg movements, thorax/ abdominal belts, EOG, body move-ments, body position	Manual 50% + arousals or desaturations EOG+body move-ment Blinded PSG-technicians No 32±6	AHI >10 AHI >20
Man et al 1995 [41]	104	22% 47±12 30 Missing data 17±26	PolyG Oronasal thermistors, SaO_2, tho-rax/abdom-inal belts, ECG, body position	Manual 50%/–/10 s* Recording time 2 blinded techni-cians No 15±22	AHI >15 AI >5
Verse et al 2000 [40]	53 53	8% 48±11 27±5 Missing data 18±18	POLYME-SAM Oronasal flow, SaO_2, thorax/ abdominal belts, ECG, body posi-tion, micro-phone	Manual correction of auto 50–80%/–/–* 22:30–05:30 Blinded, expe-rienced No 16±17 man, 16±17 auto	AHI >10 AHI >15 AHI >20

	n > AHI threshold	Sensitivity	Specificity	True positive	False positive	True negative	False negative	Quality Comments
	39	0.95	0.96	37	1	23	2	Medium
	19 13	1.00 0.77	0.64 0.88	19 10	4 2	7 15	0 3	Medium
	28 23	0.86 0.83	0.95 0.91	24 19	4 7	72 74	4 4	High
	25 23 21	0.92 0.87 0.71	0.96 0.97 0.97	24 20 15	1 1 1	26 29 31	2 3 6	High

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Table 4.8 *continued*

Author Year, reference	**n Eligible**	**% women Age BMI ESS AHI**	**Portable brand and measures**	**Portable score (automatic/ manual) Hypopnoea definition Sleep time measures Scoring subjects Inter/intra rater correlation Portable AHI**	**AHI tres-hold for dia-gnosis**
Claman et al 2001 [44]	42	26% 54±12.9 30.6±6.7 Missing data 25.5±28.1	Bedbugg (sleep solu-tions Inc) Microphone 1 (respire) microphone 2 (snoring), pulsoximet-ry, respir-atory effort	Automatic Missing data Recording time Auto PSG-technicians Missing data 22.9±31.2	AHI >15
Dingli et al 2003 [42]	39 40	18% 46±10 32±6 Missing data 35±6	Embletta Nasal pres-sure, SaO_2, thorax/ abdominal belts, body position	Automatic and manual 50%/–/10 s* From signals PSG scorer No 27±3	Manual AHI >10 Manual AHI >15 Auto AHI >10 Auto AHI >15
Reichert et al 2003 [43]	44 51	25% 52±2 30±1 Missing data Missing data	NovaSom QSG Oronasal airflow from micro-phone, SaO_2, respiratory effort	Automatic 50%/2%/10 s* Recording time Automatic pro-gram, blinded PSG scorer No Missing data	AHI >15
Núñez et al 2003 [37]	60 70	23% 52±13 30±5 13.6±5.0 31±28	Breas SC 20 Nasal can-nula, thorax/ abdominal belts, SaO_2, microphone, leg move-ments	Manual 50%/3% or arousals/–* Time in bed No 28±24	AHI >5 AHI >10 AHI >15 AHI >20 AHI >30

* % decrease breathing/desaturation/time of event.

AHI = Apnoea-hypoapnea index; AI = Apnoea index; BMI = Body mass index; EOG = Electrooculography; ESS = Epworth sleepiness scale

	n > AHI threshold	Sensitivity	Specificity	True positive	False positive	True negative	False negative	Quality Comments
	21	0.86	0.95	18	1	20	3	Medium Author is paid consultant for the company
	33	0.88	1.00	29	0	6	4	High
	24	0.96	0.87	23	2	13	1	Letter to and answer from author
	30	0.87	0.33	26	4	2	4	
	22	0.95	0.57	21	6	8	1	
	22	0.95	0.91	20	2	21	1	High
	50	0.98	0.70	49	3	7	1	Medium
	39	0.97	0.76	38	5	16	1	
	34	0.97	0.92	33	2	24	1	
	31	0.94	0.97	29	1	28	2	
	29	0.79	1.00	23	0	31	6	

Table 4.9 *Data extraction. Polysomnography vs pulse oximetry.*

Author Year, reference	**n Eligible**	**% women Age BMI ESS AHI**	**Hypo-pnoea definition Scoring subject Inter/intra rater correlation**	**Oximeter brand Ear or finger Auto or manual ODI-Sleep time Mean ODI**	**AHI (PSG) threshold for diagnosis**	**n > AHI threshold**
Douglas et al 1992 [47]	200	18% 50±13 Missing data Missing data Missing data	Missing data Automatic program, blinded Missing data	Ohmeda 3700 Ear Automatic Time in bed Missing data	AHI >15	91
Yamashiro et al 1995 [48]	269 300	30% 47±13 Missing data Missing data Missing data	Missing data Blinded 3 PSG scorer + 3 doctors Yes, inter	Ohmeda 3740 Ear Manual Recording time? Missing data	AHI >5	137
Chiner et al 1999 [49]	275	11% 52±11 32±5 13±5 42±20	50%+arousal/4%/–* 2 blinded observers No	Nellcor Finger Manual review Time in bed	AHI >15	216
Zamarrón et al 1999 [50]	233 240	20% 56±13 30±6 Missing data 22±17	50%/4%/–* 3 blinded observers Missing data	Criticare 504 AHI >10	AHI >10	124
Vázquez et al 2000 [51]	241 245	22% 45±11 31±6 11±5 26±17	30%/4%/10 s* Automatic program Missing data	Healthdyne 202-11 Finger 138, ear 108 Automatic Probe on recording time Missing data	AHI >10 AHI >15 AHI >20 AHI >30	142 118 92 65

	Cut-off oximeter (no of desaturations/hour)	Sensitivity	Specificity	True positive	False positive	True negative	False negative	Quality Comments
	ODI4 >5	0.67	0.92	61	9	100	30	High
	ODI4 >10	0.53	0.97	48	3	106	43	
	ODI4 >15	0.41	0.97	37	3	106	54	Letter to and answer from author
	ODI3 >5	0.94	0.76	133	31	96	9	Medium Letter to and answer from author
	ODI4 >5	0.82	0.76	178	14	45	38	Medium
	ODI4 >10	0.71	0.90	154	6	53	62	
	ODI4 >15	0.62	0.93	135	4	55	81	
	ODI4 >10	0.57	0.84	71	17	92	53	High
	ODI3 >10	0.60	0.80	74	22	87	50	
	ODI2 >10	0.68	0.78	84	24	85	40	
	ODI4 >10	0.97	0.80	138	20	79	4	High
	ODI4 >15	0.98	0.88	116	15	108	2	
	ODI4 >20	0.97	0.85	89	22	127	3	
	ODI4 >30	0.95	0.93	62	12	164	3	

The table continues on the next page

Table 4.9 *continued*

Author Year, reference	**n Eligible**	**% women Age BMI ESS AHI**	**Hypo-pnoea definition Scoring subject Inter/intra rater correlation**	**Oximeter brand Ear or finger Auto or manual ODI-Sleep time Mean ODI**	**AHI (PSG) threshold for diagnosis**	**n > AHI threshold**
Oeverland et al 2002 [46]	93 100	21% 44 (27–76) 28 (21–56) Missing data 23 (0–78)	>50% or <50%+3% desaturations or arousal Missing data Missing data	Nonin 8500 Missing data automatic Registration time	AHI >5 AHI >15	 44
Nakano et al 2004 [45]	424 431	19% 49±13 26±2 11±5 29±24	50%/–/10 s* Manual PSG, automatic oximetry Missing data	Pulseox3i, Minolta Finger Automatic Hours of examination ODI4: 21±19	AHI >15	241

* % decrease breathing/desaturation/time of event.

AHI = Apnoea-hypoapnea index; BMI = Body mass index; ODI = Oxygen desaturation index; PSG = Polysomnography

	Cut off oximeter (no of desaturations/hour)	Sensitivity	Specificity	True positive	False positive	True negative	False negative	Quality Comments
	ODI2 >5	1.00	0.00					Medium
	ODI3 >5	0.91	0.67					
	ODI4 >5	0.73	1.00					
	ODI5 >5	0.57	1.00					
	ODI2 >15	1.00	0.27	44	36	13	0	
	ODI3 >15	0.86	0.88	38	6	43	6	
	ODI4 >15	0.64	1.00	28	0	49	16	
	ODI5 >15	0.52	1.00	23	0	49	21	
	ODI4 >15	0.78	0.97	188	6	177	53	Medium
	ODI3 >15	0.86	0.89	208	20	163	33	
	ODI2 >15	0.95	0.66	228	63	120	13	Letter and answer from author

Table 4.10 *Data extraction. Global impression vs polysomnography.*

Author Year, reference	**n Eligible**	**% women Age BMI ESS AHI**	**Hypopnoea definition Scoring subject Inter/intra correlation**	**Global impression**	**AHI (PSG) treshold for diagnosis**	**n > AHI treshold**
Viner et al 1991 [52]	410 410?	18% 46±11 28±5 Missing data	Missing data Experienced technologist Missing data	One physician based on patients history and physical examination	AHI >10	190
Hoffstein et al 1993 [53]	Automatic	21% 47±12 29±6 Missing data	>50% reduction	One physician based on patients history and physical examination	AHI >10	275
Gyulay et al 1993 [54]	98 126	21% 50±2.5 30±1.2	>50% reduction	Patients were seen by 1 of 4 clinicians who rated them as clinically significant OSA or not	AHI >15	43

AHI = Apnoea-hypoapnea index; BMI = Body mass index; ESS = Epworth sleepiness scale; OSA = Obstructive sleep apnea; PSG = Polysomnography

	Sensitivity	Specificity	True positive	False positive	True negative	False negative	Quality
	0.52	0.70	99	66	154	91	High
	0.51	0.71	140	94	225	135	Medium
	0.79	0.51	34	27	28	9	Medium

Table 4.11 *Excluded studies. Day-to-day variability polysomnography.*

Reason for exclusion	References
Not polysomnograms	[67–70]
Selected patients	[71,72]
Less than 10 patients included	[72]

Table 4.12 *Excluded studies. Portable simplified recordings vs polysomnography.*

Reason for exclusion	References
Do not include pulse oximetry + recordings of airflow and respiratory movements	[73–97]
Include EEG in the portable device	[75]
Outcomes not recorded in AHI vs AHI	[98]
Not AHI vs AHI, but a difference of >10 of AHI to score a false result	[99]
Partial night recordings	[100]
Investigations during two different nights	[96,101–111]
Selected patients or subjects not representative of patients who will receive the test in practice	[111–114]
No polysomnography	[115–118]
Polysomnographic score included recording time instead of total sleep time	[119]
Not portable devices	[120–122]
Index test not independent of polysomnography	[120,121]

AHI = Apnoea-hypoapnea index; EEG = Electroencephalograms

Table 4.13 *Excluded studies. Pulse oximetry vs polysomnography.*

Reasons for exclusion	References
Outcomes not presented in ODI vs AHI	[2,91,123–132]
Not pure ODI, but defined desaturation as >4% and below 90%	[128]
No polysomnography	[116]
Sensitivity or specificity not given and not possible to calculate	[80,81]
Investigations during two different nights	[54,76,133–142]
Selected patients	[93,140,142,143]
Not pulse oximetry alone	[76,77,80,81,85,87,91,144]
Index test not independent of polysomnography	[122,144]
Results from patients included in another article	[145]

AHI = Apnoea-hypoapnea index; ODI = Oxygen desaturation index

Table 4.14 *Excluded studies. Global impression vs polysomnography.*

Reason for exclusion	References
Nocturnal observation of patient and not global impression	[146]
Questionnaire and/or specific characteristics and not global impression	[25,76,147–149]
Selected patients	[147]
Outcomes not presented and not possible to calculate	[150]
No polysomnography	[151]

THE EPWORTH SLEEPINESS SCALE

Name: _____

Today's date: _____ Your age (years): _____

Your sex (male = M; female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would *never* doze
1 = *slight* chance of dozing
2 = *moderate* chance of dozing
3 = *high* chance of dozing

Situation	**Chance of dozing**
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (e.g. a theatre or a meeting)	_____
As a passenger in a car for an hour without break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____

Thank you for your cooperation

Figure 4.6 *The Epworth sleepingness scale.*

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5. Treatment

Background

Treatment options

Suggested treatment modalities include:

- Continuous positive airways pressure (CPAP) devices
- Oral appliances – mandibular repositioning appliances (MRAs)
- Surgical procedures
- Pharmacological agents
- Weight reduction, various therapies and lifestyle modifications.

Continuous positive airways pressure (CPAP) devices

In 1981, Sullivan et al introduced continuous positive airway pressure (CPAP) applied to the nostrils in the treatment of obstructive sleep apnoea [1]. They wrote: "Five patients with severe obstructive sleep apnoea were treated with continuous positive airway pressure (CPAP) applied via a comfortable nose mask through the nares. Low levels of pressure (range 4.5–10 cm H_2O) completely prevented upper airway occlusion during sleep in each patient and allowed an entire night of uninterrupted sleep. Continuous positive airway pressure applied in this manner provides a pneumatic splint for the nasopharyngeal airway and is a safe, simple treatment for the obstructive sleep apnoea syndrome".

CPAP acts as a pneumatic splint and prevents upper airway occlusion by pushing the soft palate and tongue forward and away from the posterior oropharyngeal wall (Figure 5.1) [1]. The CPAP device consists of a blower with a pressure control unit, a tube and a nasal or oronasal mask. Adequate pressure must be titrated, and a recoding must be made to verify that apnoeas have been eliminated at a given pressure before CPAP is prescribed for home use. Choosing a well-fitting mask is critical. Regular follow-up with technical assistance is mandatory for compliance with the treatment [2]. Interventions to improve compliance with

CPAP were recently reviewed by the Cochrane Collaboration. Among the interventions are auto-CPAP, Bi-level PAP, heated humidification, patients-titrated CPAP, cognitive-behavioural therapy and educational programmes [3].

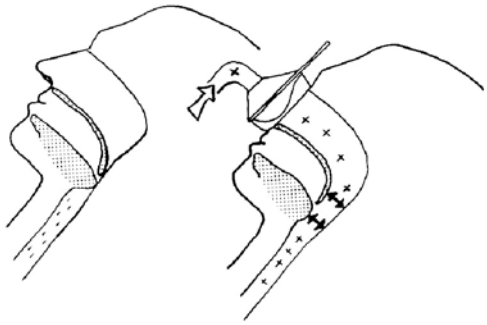


Figure 5.1 *Nasal CPAP prevents upper airway occlusion by increasing upper airway pressure (Illustration K Franklin).*

Mandibular repositioning appliances

A number of different mandibular repositioning appliances (MRAs) have been suggested for the treatment of snoring and obstructive sleep apnoea. MRAs, which were introduced by Soll and George in 1985, are by far the most commonly used appliances [4]. These appliances are also referred to as mandibular advancement devices/appliances or oral appliances. The upper airway is widened by anterior displacement of the base of the tongue, epiglottis and soft palate, produced by the MRA [5]. The device also prevents posterior displacement of the mandible in the supine position. Factors of importance for successful treatment with MRAs are severity of disease, degree of mandibular protrusion, supine position-related apnoea and BMI (Body mass index) [6]. The devices are individually fabricated and advance the mandible by about 5 mm or 50–75% of maximum protrusion. Protrusion by 75% of maximal range has been shown to decrease AHI more than protrusion by 50% in patients with severe OSAS [7]. This effect was not seen in patients with a mild to moderate form of the disease [8]. The appliances may be of a soft or hard material, either monoblock or adjustable two-piece devices (Figure 5.2). Patients must have their own teeth, and children should not be treated due to the

high risk of dental displacement. Patients are usually treated and followed up by dentists. A sleep apnoea investigation during treatment is needed to monitor the effect on apnoea and hypopnoea reduction.

Other oral devices suggested as a treatment of OSAS include tongue retaining devices that hold the tongue anteriorly in a plastic bulb, mouth shields to prevent mouth breathing and soft palate lifters to reduce soft palate vibrations.

Figure 5.2 *Two different kinds of individually adjusted mandibular repositioning appliances.*

Surgical treatments

Surgical treatments for obstructive sleep apnoea aim to increase the upper airway cross-sectional area, remove obstructing tissues or bypass the upper airway. The objective of surgical treatment is to provide lifelong relief of symptoms with one intervention. Uvulopalatopharyngoplasty (UPPP), which was introduced in 1981 [9], shortly became a common procedure worldwide for snoring and obstructive sleep apnoea. Postoperative sleep apnoea recordings are recommended, given that apnoeas may be present even when snoring is reduced [10,11]. During the last few years, a number of other surgical methods – including laser and radiofrequency ablation techniques – have been introduced.

Various surgical techniques:

1. Tracheostomy, which bypasses the upper airway.
2. Uvulopalatopharyngoplasty (UPPP) – removal of the tonsils, uvula and a small portion of the soft palate to enlarge the oropharyngeal airspace (Figure 5.3).
3. Uvulopalatoplasty (UPP) – removal of the uvula and a small portion of the soft palate. Referred to as laser-assisted uvulopalatoplasty (LAUP) when a laser is used.
4. Temperature-controlled radio frequency tissue volume ablation (TCRAFTA) – applies energy to the base of the tongue and/or the soft palate.
5. Inferior sagittal mandibular osteotomy and genioglossus advancement with hyoid myotomy and suspension aiming to enlarge the retrolingual airway.
6. Laser midline glossectomy and lingual plasty.
7. Maxillo-mandibular osteotomy and advancement, which enlarges both the retrolingual and retropalatal airway.
8. Nasal airways enlargement.
9. Epiglottoplasty for selected cases of laryngomalacia.
10. Removal of specific obstructing pathological lesions, ie, hypertrophy of the tonsils.

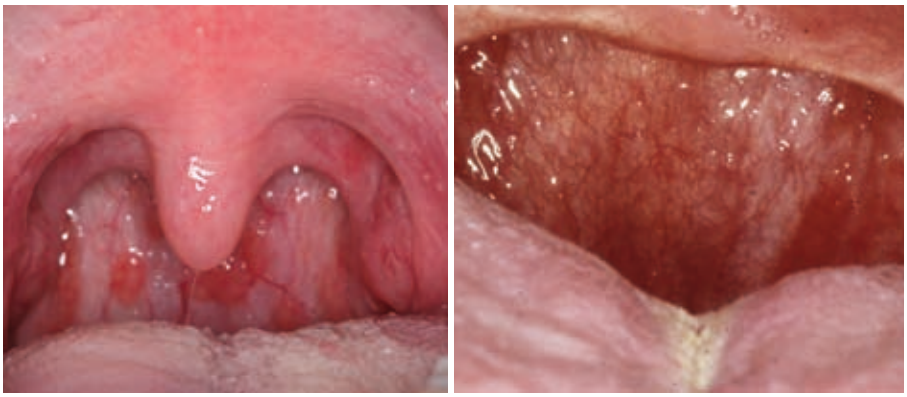


Photo: B Forssell

Figure 5.3 *Normal pharynx vs after uvulopalatopharyngoplasty (UPPP).*

Drug treatment

A number of different classes of drugs have been suggested as possible treatments for obstructive sleep apnoea. Sex hormones, ie medroxyprogesterone and oestrogen, have been suggested, given that sleep apnoea is more prevalent among men and increases in women after menopause. Ventilatory stimulants include theophylline, medroxyprogesterone and azetazolamide. Azetazolamide increases ventilatory drive by metabolic acidosis. Antidepressants have been suggested as a means of reducing sleep apnoea during REM sleep. Other suggested treatments are opoid antagonists, nicotine gum or transdermal nicotine, nasal corticosteroids, antihypertensive agents and physiostigmine.

Other treatments, including lifestyle modifications

A variety of different treatment modalities has been suggested, including cardiac pacemakers, submental electrical stimulation, weight reduction programmes, bariatric surgery, nasal dilators, didgeridoo playing, and various means of avoiding sleep in the supine position. Life style modifications include smoking cessation, as well as avoidance of alcohol and sleep deprivation.

Objectives

To examine the benefits of treatment for OSAS on daytime impairment and blood pressure in randomised controlled trials (RCTs). To examine types and frequencies of adverse effects from treatment and compliance regardless of study design.

Methods

Inclusion criteria

Benefits of treatment trial criteria:

- Randomised controlled trials of any intervention aimed at reducing obstructive apnoeas/hypopnoeas.
- At least 20 adults followed for a minimum of 4 weeks.

- Trials including patients investigated for suspicion of OSAS and studies including subjects with OSAS.
- The primary end point was daytime sleepiness. Secondary end-points were the results of standardised generic or disease-specific, self-reported measures of functioning and well-being. The AHI and blood pressure were based on 24-hour monitoring.

Adverse effects study criteria

- Studies on CPAP, mandibular advancement appliances and surgical modalities used in treating obstructive sleep apnoea.
- Studies that reported any kind of clinical or patient-experienced adverse effect, including technical failures.
- Regardless of trial design without any restrictions on number of adults included, presence or absence of a comparison group, observation time or indication of the treatment.

Compliance study criteria

- At least 100 adults followed up for at least one year. Compliance with CPAP measured objectively.
- No restrictions regarding comparison group.

Exclusion criteria

- Studies of drugs aiming at reducing daytime sleepiness but not obstructive sleep apnoeas.
- Studies written in languages other than Danish, English, Finnish, French, German, Icelandic, Norwegian, Spanish or Swedish.

End-points for beneficial effects

- Excessive daytime sleepiness: Subjective sleepiness assessed with the Epworth sleepiness scale (ESS). Objective sleepiness was assessed with the multiple sleep latency test (MSLT) and the maintenance of wakefulness test (MWT).
- Generic or disease-specific, self-reported measures of functioning and well-being: Functional Outcome of Sleep Questionnaire (FOSQ), Nottingham Health Profile (NHP) subscale on Energy and the subscale measuring Vitality from the Short Form 36 (SF-36) questionnaire.
- Frequency of sleep apnoeas: AHI or respiratory disturbances index (RDI), defined as the mean number of apnoeas and hypopnoeas per hour of sleep.
- Blood pressure: 24-hour blood pressure monitoring.

Search strategies

Benefits of treatment

PubMed, Embase and the Cochrane Controlled Trials Register were searched for randomised control trials (RCT) on 1 March 2006. The following search terms were used: Sleep apnoea syndromes [MeSH]; randomised control trial or clinical trial; all adult 19+ year. Titles and abstracts of all identified trials were first screened for relevance.

Reviews and meta-analyses were also searched. "Randomised control trial" or "clinical trial" was substituted for "review" or "meta-analysis". Twenty-one reviews were identified through the PubMed and Embase searches: [3,12–31]. Furthermore, the reference lists of all identified RCTs were checked for identification of additional trials.

All RCTs included in earlier reviews or reference lists were identified by the current PubMed search.

For all potentially relevant articles, the full reports were requested. Two independent readers went through 113 articles, of which 30 were included

in the final analysis. There was no disagreement between the reviewers concerning inclusion and exclusion of trials.

Data was independently extracted by two reviewers and presented in the form of means and standard deviations. Authors were contacted when needed. Data extractions of included studies are presented in Table 5.21 and excluded articles in Tables 5.22–5.24.

Adverse effects and compliance with therapy

PubMed was searched for reports of adverse effects of treatments until 1 March 2006. The following search terms were used: Sleep apnoea syndromes [MeSH] AND adverse effects [MeSH Subheading] OR complications [MeSH subheading] OR complication [Text Word] OR complications [Text Word], All Adult: 19+ years. RCTs reporting benefits for treatment were also screened for information on adverse effects.

PubMed was searched for compliance with treatments until 1 March 2006. The following search terms were used for finding reports on compliance: Sleep apnoea syndromes [MeSH], compliance [Text Word], adherence [Text Word], dropout [Text Word], attrition [Text Word], patient satisfaction [MeSH], questionnaires [MeSH], patient preference [Text Word]. RCTs reporting benefits of treatment were also screened for information on compliance.

Titles and abstracts were screened for relevance. A total of 131 articles were read, of which 82 were included in the final analysis. Data extractions of included studies are presented in Tables 5.25, 5.26, 5.28, 5.30 and excluded articles in Tables 5.27 and 5.29.

Quality assessment

Randomised controlled trials of treatment benefits

The following modified Jadad rating scale was used [32]:

1. Was the trial described as randomised? Yes = 1 No or not reported = 0
2. Was the allocation concealed? (performed by non-involved source) Yes = 1 No or not reported = 0

3. Were patients blinded to treatment alternative?	Yes = 1	No or not reported = 0
4. Were investigators blinded to treatment alternative?	Yes = 1	No or not reported = 0
5. Was there a description of withdrawals? Lost to follow-up less than 30%	Yes = 1	No or not reported = 0

Trials with a summary rating of 0 or 1 were rated low quality, those with a rating of 2 or 3 were rated medium high quality, and those with a rating of 4 or 5 were rated high quality.

Reports of adverse effects and compliance

High quality required fulfilment of criteria 1–4:

1. Prospective study
2. Before and after data for adverse effects
3. Defined groups of patients, detailed description of methods, adverse effects and compliance
4. Assessment of outcomes either objective or blinded to exposure.

Medium quality required fulfilment of criteria 1–3:

1. Prospective design or consecutive patients
2. Baseline data (for adverse effects not attributable to the device)
3. Summary description of patients, methods, adverse effects or compliance.

Low quality was assigned to a study if at least one of the following was true:

1. Retrospective study
2. Only follow-up data (for adverse effects not attributed to the device)
3. Loss to follow-up >30%
4. No description of patients, methods, adverse effects or compliance.

Grading of evidence

See summary of the report.

Statistical analysis

Data are expressed as means and standard deviations or as percentages. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). For meta-analysis, we used Review Manager (RevMan) version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003. Weighted mean difference was used for comparisons, except when testing the MWT, MSLT and FOSQ, for which standard mean difference was used, given that the results were presented in different scales. Outcome values at follow-up were compared in the analysis. A p-value of <0.05 was considered significant. A random model was used when the p-value for heterogeneity was less than 0.10.

Baseline data, study design, outcome measures and quality ratings of included RCT studies

All in all, 30 trials were included that investigated a total of 1 850 subjects. Baseline mean values are given in Table 5.1.

CPAP vs placebo or conservative treatment was investigated in 17 studies that included a total of 1212 subjects, of whom 19% were women. Mean age was 50, mean BMI was 32 kg/sq m, mean ESS was 13 and mean AHI was 33. Studies included patients with mild, moderate and severe sleep apnoea. Ten studies were of parallel design and 7 of cross-over design. Six studies were rated high quality and 11 were rated medium quality (Table 5.2).

Mandibular repositioning appliances (individually produced) vs placebo was investigated in 4 studies that included a total of 277 patients, of whom 20% were women. Mean age was 48, mean BMI was 30 kg/sq m, mean ESS was 11 and mean AHI was 26. All studies were of crossover design. One study was rated high quality and 3 were rated medium quality (Table 5.3).

CPAP vs individually produced mandibular repositioning appliances was investigated in 5 studies that included 230 patients, of whom 20% were women. Mean age was 46, mean BMI was 31 kg/sq m, mean ESS was 11 and mean AHI was 25. All studies were of cross-over design and rated medium quality (Table 5.4).

Surgery vs sham or conservative treatment was investigated in 3 parallel studies that included a total of 134 patients, of whom 17% were women. Mean age was 47, mean BMI was 30 kg/sq m, mean ESS was 11 and mean AHI was 17. One study of high quality investigated the effect of temperature-controlled radio frequency tissue volume ablation (TCRAFTA) and 2 studies of medium quality evaluated laser-assisted uvulopalatoplasty (LAUP) (Table 5.5).

One study of high quality compared uvulopalatopharyngoplasty (UPPP) with mandibular repositioning appliances. One study of medium quality compared the effect of lateral pharyngoplasty with UPPP, and one study of medium quality compared the effect of didgeridoo playing with subjects on a waiting list for didgeridoo lessons (Table 5.6).

No study reported any outcomes on cardiovascular morbidity, including hypertension or mortality.

Table 5.1 *Baseline characteristics of subjects in included trials (means weighted by sample size).*

	CPAP vs placebo/ conservative	MRA vs placebo/ conservative	CPAP vs MRA
No of included trials	17	4	5
No of subjects	1 212	277	230
Range	23–142	21–104	24–104
Age			
No of trials reporting	17	4	5
Mean age	50	48	46
Range of means	46–54	46–55	44–51
Gender			
No of trials reporting	16	4	5
Percent female (%)	19	20	20
Range of percentages	0–48	19–21	17–25
Body mass index			
No of trials reporting	17	4	5
Mean, kg/m^2	32	30	31
Range of means	29–37	29–31	29–32
Epworth Sleepiness Scale			
No of trials reporting	16	3	4
Mean score	13	11	11
Range of means	7–17	10–14	10–14
Apnoea-hypopnoea index			
No of trials reporting	17	4	5
Mean, events/hour	33	26	25
Range of means	10–64	22–32	22–31

CPAP = Continuous positive airway pressure; MRA = Mandibular repositioning appliance

Surgery vs placebo/ conservative	Surgery vs surgery, surgery vs MRA, didgeridoo	All trials
3	3	30
134	132	1 850
28–60	16–52	21–142
3	2	29
47	50	49
44–49	49–50	44–55
3	2	28
17	4	16
09–24	0–16	0–48
3	3	30
30	27	31
27–32	26–29	26–37
3	2	26
11	13	13
10–12	12–14	7–17
3	3	29
17	19	30
15–18	19–39	10–64

Table 5.2 *CPAP vs placebo/conservative.*

Author, year, reference	Design	Duration	No	Men %	Age
Engleman et al, 1994 [33]	Cross-over	4 weeks	35	81	49±8
Engleman et al, 1998 [34]	Cross-over	4 weeks	24	81	47±12
Redline et al, 1998 [35]	Parallel	8 weeks	111	52	491±0
Ballester et al, 1999 [36]	Parallel	3 months	105	88	53±10
Engleman et al, 1999 [37]	Cross-over	4 weeks	37	62	44±8
Jenkinson et al, 1999 [38]	Parallel	4 weeks	107	100	49
Faccenda et al, 2001 [39]	Cross-over	4 weeks	71	83	50
McArdle et al, 2001 [40]	Cross-over	4 weeks	23	92	52±11
Monasterio et al, 2001 [41]	Parallel	6 months	142	86	54±9
Montserrat et al, 2001 [42]	Parallel	6 weeks	47	91	54±10
Barbé et al, 2001 [43]	Parallel	6 weeks	55	91	53±15
Barnes et al, 2002 [44]	Cross-over	3 months	42	83	46±11
Chakravorty et al, 2002 [45]	Parallel	3 months	71		50±11
Pepperell et al, 2002 [46]	Parallel	4 weeks	118	100	50±10
Becker et al, 2003 [47]	Parallel	2 months	60	90	53±9
Woodson et al, 2003 [48]	Parallel	8 weeks	60	72	49±8
Barnes et al, 2004 [49]	Cross-over	3 months	104	79	46±9

AHI = Apnoea-hypopnoea index; BMI = Body mass index; BP = Blood pressure;
ESS = Epworth sleepiness scale; FOSQ = Functional outcomes of sleep questionnaire;
MSLT = Multiple sleep latency test; MWT = Maintenance of wakefulness test

Table 5.3 *Mandibular repositioning appliance vs placebo/conservative.*

Author, year, reference	Design	Duration	No	Men %	Age
Gotsopoulos et al, 2002 [50]	Cross-over	4 weeks	85	81	48±11
Johnston et al, 2002 [51]	Cross-over	4–6 weeks	21	81	55±7
Gotsopoulos et al, 2004 [52]	Cross-over	4 weeks	67	79	48±11
Barnes et al, 2004 [49]	Cross-over	3 months	104	79	46±9

AHI = Apnoea-hypopnoea index; BMI = Body mass index; BP = Blood pressure;
ESS = Epworth sleepiness scale; FOSQ = Functional outcomes of sleep questionnaire;
MSLT = Multiple sleep latency test; MWT = Maintenance of wakefulness test

	BMI	Baseline Mean AHI	Baseline Mean ESS	Outcomes	Quality
	33±9	Median 28		MSLT	Medium
	30±7	43±37	12±4	ESS, MSLT	Medium
	33±7	13±10	10±5	ESS, MSLT, AHI	Medium
	32±5	56±29	12±5	ESS	Medium
	30±5	10±3	13±3	ESS, MWT, SF-36	Medium
	30±5	Median ODI4: 31	Median 16.5	ESS, MWT, SF-36	High
	30±5	Median 35	Median 15	ESS, FOSQ, BP	Medium
	31±5	Median 42	Median 14	ESS	High
	29±4	20±6	13±5	ESS, MSLT, AHI, FOSQ	Medium
	31±6	54±19	15±7	ESS, FOSQ, SF-36	High
	29±5	55±25	7±3	ESS, MSLT, FOSQ, BP	High
	30±5	13±6	11±5	ESS, MSLT, FOSQ, SF-36, BP	Medium
	37±12	47±25	15±5	ESS, AHI	Medium
	35±7	Mean ODI4: 37±20	16±4	BP	High
	33±6	64±22	14±3	ESS, AHI, BP	Medium
	29±4	18±9	12±4	ESS, AHI, FOSQ	
	31±5	22±11	10±3	ESS, MWT, AHI, FOSQ, SF-36, BP	Medium

	BMI	Baseline Mean AHI	Baseline Mean ESS	Outcomes	Quality
	29±5	27±17	11±5	ESS, MSLT, AHI	Medium
	32±6	32±21	14±6	ESS, AHI	Medium
	29±5	27±15		BP	High
	31±5	22±11	10±3	ESS, MWT, AHI, FOSQ, SF-36, BP	Medium

Table 5.4 *CPAP vs Mandibular repositioning appliance.*

Author, year, reference	Design	Duration	No	Men %	Age
Ferguson et al, 1996 [53]	Cross-over	4 months	27	89	46±11
Ferguson et al, 1997 [54]	Cross-over	4 months	24	79	44±11
Tan et al, 2002 [55]	Cross-over	2 months	24	83	51±10
Engleman et al, 2002 [56]	Cross-over	8 weeks	51	75	46±9
Barnes et al, 2004 [49]	Cross-over	3 months	104	79	46±9

AHI = Apnoea-hypopnoea index; BMI = Body mass index; BP = Blood pressure;
ESS = Epworth sleepiness scale; FOSQ = Functional outcomes of sleep questionnaire;
MWT = Maintenance of wakefulness test

Table 5.5 *Surgery vs placebo/conservative.*

Author, year, reference	Type	Design	Duration	No	Men %
Woodson et al, 2003 [48]	TCRAFTA	Parallel	8 weeks	60	80
Ferguson et al, 2003 [6]	LAUP	Parallel	7 months	46	76
Larrosa et al, 2004 [57]	LAUP	Parallel	3 months	28	100

AHI = Apnoea-hypopnoea index; BMI = Body mass index; ESS = Epworth sleepiness scale;
FOSQ = Functional outcomes of sleep questionnaire; LAUP = Laser-assisted uvulopalatoplasty;
TCRAFTA = Temperature-controlled radio frequency tissue volume ablation

Table 5.6 *Other comparisons.*

Author, year, reference	Type	Design	Duration	No	Men %
Wilhelmsson et al, 1999 [58]	UPPP vs MRA	Parallel	1 year	80	100
Cahali et al, 2004 [59]	Lateral pharyngoplasty vs UPPP	Parallel	8 months	27	
Puhan et al, 2006 [60]	Didgeridoo vs waiting list	Parallel	4 months	25	84

AHI = Apnoea-hypopnoea index; Body mass index; ESS = Epworth sleepiness scale;
MRA = Mandibular repositioning appliance

	BMI	Baseline Mean AHI	Baseline Mean ESS	Outcomes	Quality
	30±5	25±9		AHI	Medium
	32±8	27±12	11±3	ESS, AHI	Medium
	32±7	22±10	13±5	ESS, AHI	Medium
	29±5	31±26	14±4	ESS, MWT, AHI, FOSQ	Medium
	31±5	22±11	10±3	ESS, MWT, AHI, FOSQ, SF-36, BP	Medium

	Age	BMI	Baseline Mean AHI	Baseline Mean ESS	Outcomes	Quality
	49±8	29±4	18±9	12±4	ESS, AHI, FOSQ	High
	45±8	32±5	17±4	10±4	ESS, AHI	Medium
	44±7	27±3	15±13	11±5	ESS, AHI	Medium

	Age	BMI	Baseline Mean AHI	Baseline Mean ESS	Outcomes	Quality
	50	27	19±9		AHI	High
		29±5	39±22	14±12	AHI	Medium
	49±7	26±3	21±5	12±5	ESS, AHI, SF-36	Medium

Treatment effect on excessive daytime sleepiness

Conclusions

- There is strong evidence that CPAP reduces daytime sleepiness regardless of the severity of the sleep apnoea syndrome (Evidence Grade 1).

- Custom-made mandibular repositioning appliances reduce daytime sleepiness patients with mild to moderate sleep apnoea syndrome (Evidence Grade 3).

- There is insufficient scientific evidence for the effect of any surgical modality on daytime sleepiness.

- No studies that meet the present inclusion criteria show that weight reduction programmes, bariatric surgery, drugs, pacemakers, devices for sleep in lateral position, didgeridoo-playing or any other suggested treatment or lifestyle modification for obstructive sleep apnoea syndrome have any effect.

Results

A total of 22 studies investigated the effect of treatment on subjective sleepiness measured with the Epworth sleepiness scale (ESS). Thirteen studies measured sleep latency as an objective proxy for daytime sleepiness using the multiple sleep latency test (MSLT) and maintenance of wakefulness test (MWT). A summary of the results of a meta-analysis (Figures 5.4–5.12) and the evidence for the effects of included studies are presented in Tables 5.7 and 5.8.

Table 5.7 *The effect of different treatments on ESS*.*

	Number of studies	Weighted mean difference (95% confidence interval)	Evidence for included studies
CPAP vs placebo	15**†	–3.0 (–4.1; –1.9) p<0.00001‡	Evidence Grade 1
MRA vs placebo	3**	–1.1 (–2.1; –0.1) p=0.03	Evidence Grade 3
CPAP vs MRA	4**	–1.06 (–3.0; 0.9) p=0.28‡	Contradictory scientific evidence
LAUP vs placebo	2	–1.2 (–3.9; 1.6) p=0.40	Insufficient scientific evidence
TCRAFTA vs placebo	1†	–0.8 (–3.1; 1.5) p=0.50	Insufficient scientific evidence
CPAP vs TCRAFTA	1†	0.5 (–2.3; 3.3) p=0.72	Insufficient scientific evidence
Didgeridoo vs conservative	1	–2.2 (–5.9; 1.5) p=0.25	Insufficient scientific evidence

* A decrease in ESS denotes less sleepiness.
** One study included 3 arms with CPAP, MRA and placebo.
† One study included 3 arms with TCRAFTA, CPAP and placebo.
‡ Analysed in a random model due to heterogeneity.

CPAP = Continuous positive airway pressure; LAUP = Laser-assisted uvulopalatoplasty; MRA = Mandibular repositioning appliance; TCRAFTA = Temperature-controlled radio frequency tissue volume ablation

Table 5.8 *The effect of different treatments on MSLT and MWT*.*

	Number of studies	Standardised mean difference (95% confidence interval)	Evidence for included studies
CPAP vs placebo	9**	0.23 (0.08; 0.38) p=0.003	Evidence Grade 1
MRA vs placebo	2**	0.23 (0.01; 0.45) p=0.04	Evidence Grade 3
CPAP vs MRA	2**	0.09 (–0.15; 0.33) p=0.46	Insufficient scientific evidence

* An increase in MSLT or MWT denotes less sleepiness.
** One study included 3 arms with CPAP, MRA and placebo.

CPAP = Continuous positive airway pressure; MRA = Mandibular repositioning appliance

Daytime sleepiness (subjective and objective) was significantly less after CPAP than after placebo or conservative treatment (Tables 5.7 and 5.8). When comparing the effect on daytime sleepiness with regard to baseline mean AHI or ESS, CPAP was found to reduce subjective sleepiness among patients with mild, moderate and severe sleep apnoea. But the effect size was greater when mean AHI was above 30. A total of 712 patients in 18 studies were followed regarding ESS after active CPAP treatment. Their baseline mean ESS decreased from 12.4 ± 4.2 to 8.1 ± 4.5 during treatment, ie, from abnormal to normal values for daytime sleepiness.

Daytime sleepiness (subjective and objective) was significantly less after a mandibular repositioning appliance had been worn during sleep than after placebo (Tables 5.7 and 5.8). The effect size was greater for CPAP than for mandibular repositioning appliances compared with placebo on subjective sleepiness. However, there was no significant difference in effect size for studies that compared CPAP with mandibular repositioning appliances in a pooled analysis. A total of 250 patients in 6 studies who were treated with active mandibular advancement were monitored with the ESS, which decreased from a mean of 11.4 ± 4.9 to 9.0 ± 5.5, ie, from abnormal to normal values for daytime sleepiness.

Neither LAUP nor TCRAFTA had any effect on subjective sleepiness. No surgical study was identified that included any objective test for sleep latency.

One study that compared didgeridoo playing with being on a waiting list for didgeridoo reported an effect on subjective sleepiness when the standard was baseline (–2.8 (–5.4; –0.2) p=0.04) [60]. But there was no difference in ESS at follow-up when comparing the results of didgeridoo playing with being on a waiting list (–2.2 (–5.9; 1.5) p=0.25).

Treatment effect on sleep apnoeas and hypopnoeas (AHI)

Conclusions

- There is strong evidence that CPAP is highly effective in reducing the frequency of obstructive sleep apnoeas among patients with mild, moderate and severe obstructive sleep apnoea to normal values (Evidence Grade 1).

- There is limited evidence that mandibular repositioning appliances reduce apnoea frequency – but to a lesser degree than CPAP – among patients with mild to moderate obstructive sleep apnoea (Evidence Grade 3).

- The scientific evidence is contradictory regarding the effect of laser-assisted uvulopalatopharyngoplasty (LAUP). There is insufficient scientific evidence for the effect of any other treatment modality – including surgery, pharmacological drugs, weight reduction and lifestyle changes – in reducing the frequency of obstructive sleep apnoeas.

Results

A total of 17 studies investigated the effect of treatment on the AHI. A summary of the results of a meta-analysis (Figures 5.13–5.16) and the evidence for an effect are presented in Table 5.9.

Table 5.9 *The effect of different treatments on apnoea-hypopnoea index (AHI)*.*

	Number of studies	Weighted mean difference (95% confidence interval)	Evidence for included studies
CPAP vs placebo	6**†	–13.0 (–17.7; –8.25) p<0.00001‡	Evidence Grade 1
MRA vs placebo	3**	–9.8 (–15.5; –4.2) p<0.0007‡	Evidence Grade 3
CPAP vs MRA	5**	–7.6 (–9.2; –6.1) p<0.00001	Evidence Grade 3
LAUP vs placebo	2	–3.1 (–14.3; 8.1) p=0.59‡	Contradictory scientific evidence
TCRAFTA vs placebo	1†	3.2 (–2.3; 8,7) p=0.25	Insufficient scientific evidence
CPAP vs TCRAFTA	1†	–12.2 (–18.0; –6.4) p<0.0001	Insufficient scientific evidence
MRA vs UPPP	1	–4.5 (–8.5; –0.50) p=0.03	Insufficient scientific evidence
Lateral pharyngoplasty vs UPPP	1	–14.5 (–27.8; –1.2) p=0.03	Insufficient scientific evidence
Didgeridoo vs conservative	1	–3.8 (–11.0; 3.4) p=0.3	Insufficient scientific evidence

* A reduction in the AHI denotes a reduction in the frequency of apnoeas and hypopnoeas.
** One study included 3 arms with CPAP, MRA and placebo.
† One study included 3 arms with TCRAFTA, CPAP and placebo.
‡ Analysed in a random model due to heterogeneity.

CPAP = Continuous positive airway pressure; LAUP = Laser-assisted uvulopalatoplasty; MRA = Mandibular repositioning appliance; TCRAFTA = Temperature-controlled radio frequency tissue volume ablation; UPPP = Uvulopalatopharyngoplasty

The frequency of apnoeas and hypopnoeas (the AHI) was significantly less during CPAP treatment than during placebo or conservative treatment. The AHI was also significantly smaller using mandibular repositioning appliances than during placebo, but to a lesser extent than with CPAP (Table 5.9).

A total of 390 patients in 10 studies were followed regarding the AHI after active CPAP treatment. Their baseline mean AHI of 31.7 ± 14.6

decreased to 5.4 ± 4.8 during treatment. A total of 332 patients in 8 studies were treated with active mandibular repositioning appliances. Their mean AHI decreased from 23.5 ± 13.7 to 11.9 ± 12.3 during active treatment.

Two studies were identified on LAUP vs placebo or conservative treatment and one on TCRAFTA. One study found no effect of LAUP vs placebo/conservative treatment at follow-up AHI +3.6 (95% CI –7.7; 14.9) [57], while the other study found a reduction of AHI, –8.0 (95% CI –14.9; –1.1) [6]. TCRAFTA had no effect on AHI compared with placebo at follow-up [48]. One study found a better effect on AHI after lateral pharyngoplasty than after uvulopalatopharyngoplasty [59]. One study found that MRA had a significantly better effect than UPPP. But the study did not investigate patients who did not comply with MRA at follow-up [58].

One study that examined didgeridoo playing vs being on a waiting list for lessons on didgeridoo reported an effect when results were compared with baseline in relation to no treatment (–6.6 (–13.3; –0.1) p=0.05) [60]. But there was no difference at follow-up of AHI when comparing didgeridoo playing with being on the waiting list (–3.8 (–11.0; 3.4) p=0.3).

Treatment effect on quality of life measured as functional outcomes and vitality

Conclusions

- There is contradictory scientific evidence concerning the effect of CPAP on quality of life measured with the Functional Outcome of Sleep Questionnaire (FOSQ) or SF-36 vitality subscale.

- There is insufficient scientific evidence for any effect on quality of life measured with the FOSQ or SF-36 vitality subscale on any treatment modality for sleep apnoea syndrome.

Results

A total of 9 studies investigated the effect of treatment on the FOSQ, 6 studies on the quality of life questionnaire's Short form 36 (SF-36) subscale measuring Vitality, and 1 study on the Nottingham Health Profile (NHP) subscale measuring Energy. A summary of the results of the meta-analysis (Figures 5.17–5.19) and the evidence for the effect are presented in Tables 5.10 and 5.11. Because the results of the FOSQ were given in three different ways, standardised mean difference was used in the meta-analysis.

Table 5.10 *The effect of different treatments on FOSQ*.*

	Number of studies	**Standardised mean difference (95% confidence interval)**	**Evidence for included studies**
CPAP vs placebo	8**†	0.21 (–0.01, 0.44) p=0.06‡	Contradictory scientific evidence
MRA vs placebo	1**	0.00 (–0.30, 0.30) p=1.0	Insufficient scientific evidence
CPAP vs MRA	2**	0.14 (–0.10, 0.38) p=0.26	Insufficient scientific evidence
TCRAFTA vs placebo	1†	0.24 (–0.33, 0.81) p=0.41	Insufficient scientific evidence
CPAP vs TCRAFTA	1†	0.09 (–0.69, 0.52) p=0.78	Insufficient scientific evidence

* An increase in FOSQ denotes a better functional outcome.
** One study included 3 arms with CPAP, MRA and placebo.
† One study included 3 arms with TCRAFTA, CPAP and placebo.
‡ Analysed in a random model due to heterogeneity.

CPAP = Continuous positive airway pressure; MRA = Mandibular repositioning appliance; TCRAFTA = Temperature-controlled radio frequency tissue volume ablation

Table 5.11 *The effect of different treatments on SF-36 subscale vitality*.*

	Number of studies	**Weighted mean difference (95% confidence interval)**	**Evidence for included studies**
CPAP vs placebo	5**	8.0 (–0.98, 17.0) p<0.08‡	Contradictory scientific evidence
MRA vs placebo	1**	0.60 (–5.4, 6.6) p=0.84	Insufficient scientific evidence
CPAP vs MRA	1**	2.1 (–3.8, 8.0) p=0.48	Insufficient scientific evidence
Didgeridoo vs conservative	1	–4.4 (–14.7, 5.9) p=0.40	Insufficient scientific evidence

* An increase in SF-36 subscale vitality denotes a better quality of life regarding the vitality.
** One study included 3 arms with CPAP, MRA and placebo.
‡ Analysed in a random model due to heterogeneity.

CPAP = Continuous positive airway pressure; MRA = Mandibular repositioning appliance

There was an improvement in quality of life measured with the SF-36 vitality subscale (8.2 (4.5; 11.8) p<0.0001) and FOSQ (0.21 (0.06; 0.37) p<0.007) in a fixed model, but the results were heterogeneous and did not reach significance in a random model (Table 5.10 and 5.11). No effect was seen for any other treatment modality, but only a few studies were available. One trial reported an effect of CPAP vs conservative treatment on NHP (energy) when compared with baseline. But here was no significant difference of NHP at follow-up between patients given CPAP and conservative treatment (–9.5 (–21; 2.2) p=0.11) [36].

As regards effects on generic measures of quality of life, follow-up periods of 1–3 months may be considered too short for the full effect of the treatment to take hold. It is possible that a considerable percentage of subjects need more time to adjust to the device so as to benefit from its use and experience any adverse effects.

Treatment effect on 24-hour blood pressure

Conclusions

- There is contradictory scientific evidence concerning the effect of CPAP on arterial blood pressure among patients with obstructive sleep apnoea syndrome.

- There is insufficient scientific evidence that any other treatment for obstructive sleep apnoea syndrome reduces arterial blood pressure.

Results

A total of 7 studies investigated the effect on 24-hour blood pressure. A summary of the results of a meta-analysis (Figures 5.20–5.23) and the evidence for the effect are presented in Table 5.12.

Table 5.12 *The effect of different treatments on systolic blood pressure.*

	Number of studies	Weighted mean difference (95% confidence interval)	Evidence for included studies
Systolic blood pressure			
CPAP vs placebo	6*	–1.5 (–3.4; 0.5) p=0.14	Contradictory scientific evidence
MRA vs placebo	2*	–1.5 (–3.9; 0.8) p=0.20	Insufficient scientific evidence
Diastolic blood pressure			
CPAP vs placebo	6*	–1.3 (–3.4; 0.9) p=0.24‡	Contradictory scientific evidence
MRA vs placebo	2*	–1.3 (–2.8; 0.2) p=0.08	Insufficient scientific evidence

* One study included 3 arms with CPAP, MRA and placebo.
‡ Analysed in a random model due to heterogeneity.

CPAP = Continuous positive airway pressure; MRA = Mandibular repositioning appliance

All studies of blood pressure were conducted on patients who had sought medical attention due to suspicion of sleep apnoea. No study investigated the effect on blood pressure among untreated patients with arterial hypertension. The frequency of patients with hypertension in the present studies varied from 0% to 39%.

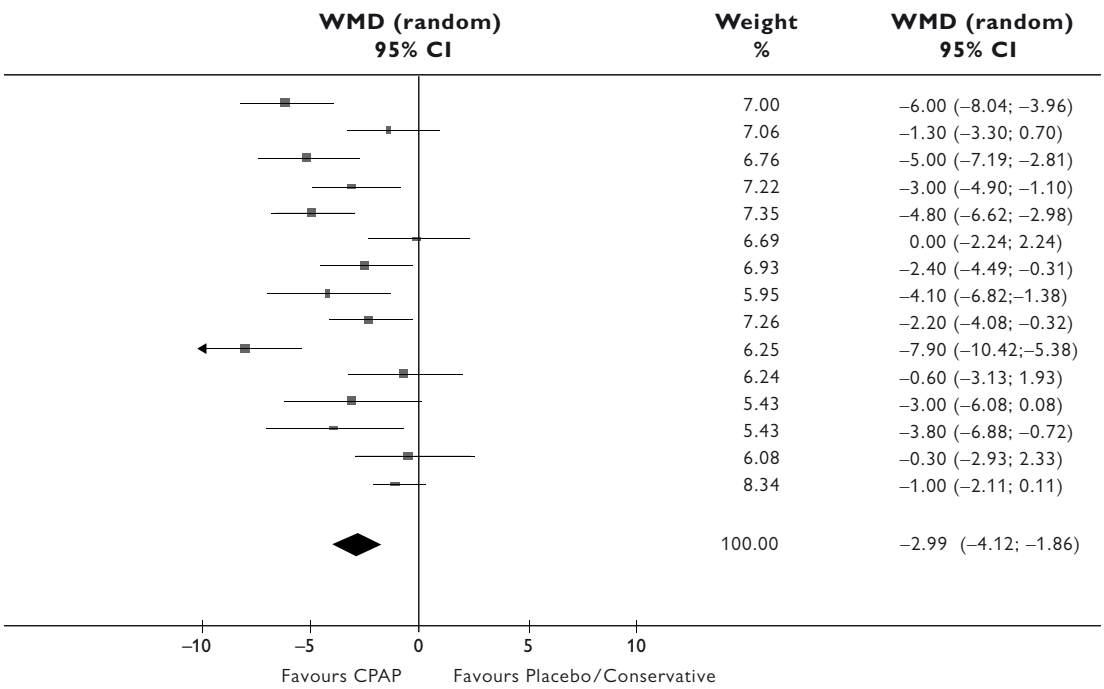
According to the meta-analysis, there was no significant effect on blood pressure from CPAP or mandibular repositioning appliances. One study showed significantly lower blood pressure using CPAP than placebo [47]. But the study had a large loss to follow-up. No study was identified that tested the effect on blood pressure after surgery.

Review: Obstructive sleep apnoea
Comparison: 13 CPAP vs Placebo/conservative
Outcome: 02 Epworth sleepiness scale (ESS)

Study or sub-category	N	CPAP Mean (SD)	N	Placebo/conservative Mean (SD)
Engleman 1998 [34]	23	6.00 (3.00)	23	12.00 (4.00)
Redline 1998 [35]	51	8.90 (4.30)	46	10.20 (5.60)
Ballester 1999 [36]	68	5.60 (4.10)	37	10.60 (6.10)
Engleman 1999 [37]	34	8.00 (4.00)	34	11.00 (4.00)
Jenkinson 1999 [38]	52	7.50 (4.50)	49	12.30 (4.80)
Barbé 2001 [43]	29	8.00 (3.00)	25	8.00 (5.00)
Faccenda 2001 [39]	68	10.10 (5.80)	68	12.50 (6.60)
McArdle 2001 [40]	22	8.00 (4.50)	22	12.10 (4.70)
Monasterio 2001 [41]	66	9.60 (5.50)	59	11.80 (5.20)
Montserrat 2001 [42]	23	6.70 (3.30)	22	14.60 (5.10)
Barnes 2002 [44]	28	8.90 (4.90)	32	9.50 (5.10)
Chakravorty 2002 [45]	32	8.00 (6.40)	21	11.00 (5.00)
Becker 2003 [47]	16	5.10 (3.80)	16	8.90 (5.00)
Woodson 2003 [48]	19	10.30 (5.00)	25	10.60 (3.50)
Barnes 2004 [49]	89	9.20 (3.80)	90	10.20 (3.80)
Total (95% CI)	620		569	

Test for heterogeneity: Chi2=59.92, df=14 (p<0.00001), I2=76.6%
Test for overall effect: Z=5.18 (p<0.0001)

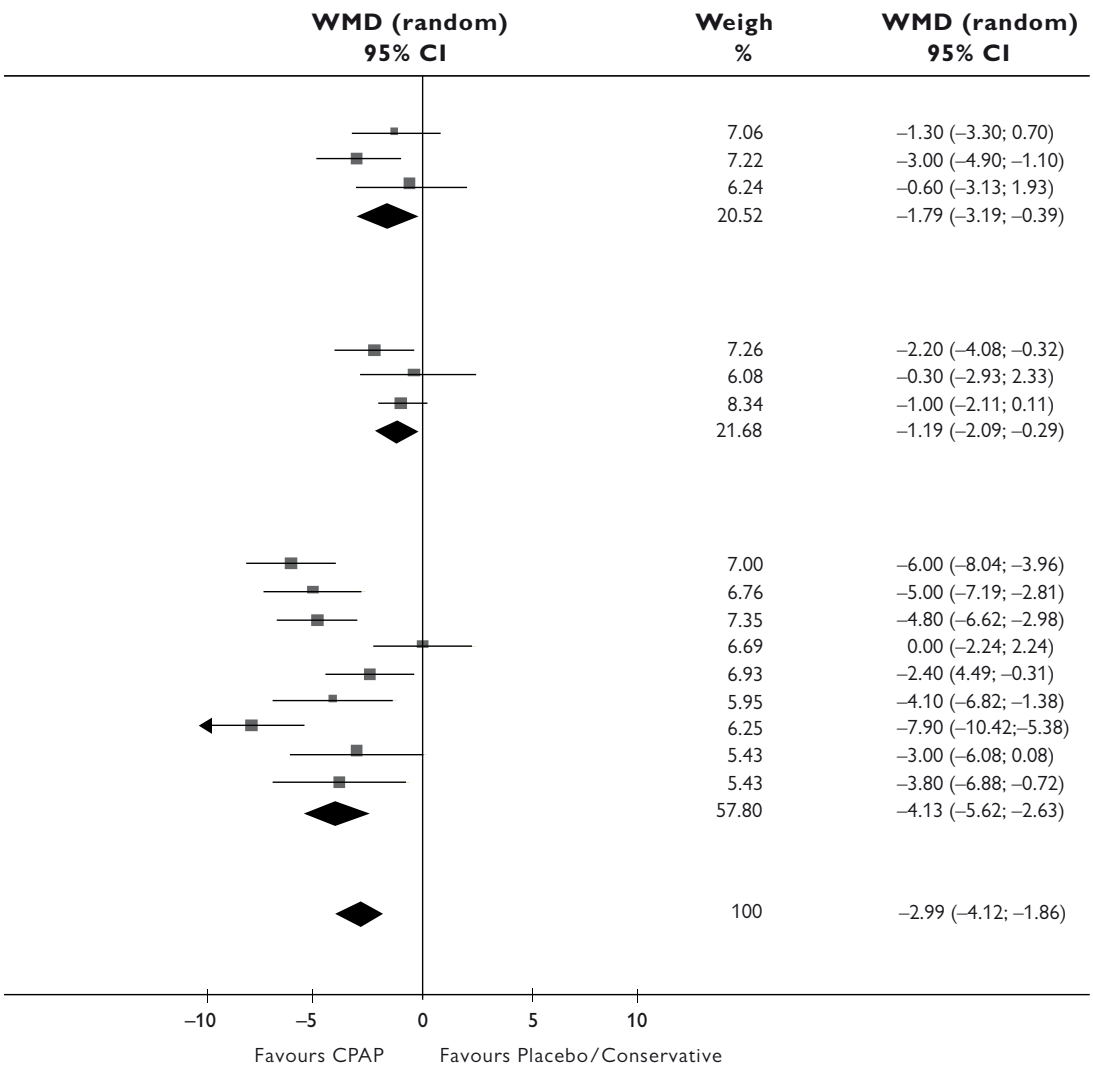
Figure 5.4 *CPAP, effect on Epworth sleepiness scale (ESS).*


WMD (random)
95% CI
Weight
%
WMD (random)
95% CI
7.00 –6.00 (–8.04; –3.96)
7.06 –1.30 (–3.30; 0.70)
6.76 –5.00 (–7.19; –2.81)
7.22 –3.00 (–4.90; –1.10)
7.35 –4.80 (–6.62; –2.98)
6.69 0.00 (–2.24; 2.24)
6.93 –2.40 (–4.49; –0.31)
5.95 –4.10 (–6.82;–1.38)
7.26 –2.20 (–4.08; –0.32)
6.25 –7.90 (–10.42;–5.38)
6.24 –0.60 (–3.13; 1.93)
5.43 –3.00 (–6.08; 0.08)
5.43 –3.80 (–6.88; –0.72)
6.08 –0.30 (–2.93; 2.33)
8.34 –1.00 (–2.11; 0.11)
100.00 –2.99 (–4.12; –1.86)
–10
–5
0
5
10
Favours CPAP
Favours Placebo/Conservative

Review: Obstructive sleep apnoea
Comparison: 13 CPAP vs Placebo/conservative
Outcome: 10 CPAP effect on Epworth sleepiness scale in relation to baseline mean Apnoea-hypopnea index (AHI)

Study or sub-category	N	CPAP Mean (SD)	N	Placebo/conservative Mean (SD)
01 mean AHI 5–15				
Redline 1998 [35]	51	8.90 (4.30)	46	10.20 (5.60)
Engleman 1999 [37]	34	8.00 (4.00)	34	11.00 (4.00)
Barnes 2002 [44]	28	8.90 (4.90)	32	9.50 (5.10)
Subtotal (95% CI)	113		112	
Test for heterogeneity: Chi2=2.63, df=2 (p=0.27), I2=23.9%				
Test for overall effect: Z=2.50 (p=0.01)				
02 mean AHI 15–30				
Monasterio 2001 [41]	66	9.60 (5.50)	59	11.80 (5.20)
Woodson 2003 [48]	19	10.30 (5.00)	25	10.60 (3.50)
Barnes 2004 [49]	89	9.20 (3.80)	90	10.20 (3.80)
Subtotal (95% CI)	174		174	
Test for heterogeneity: Chi2=1.66, df=2 (p = 0.44), I2=0%				
Test for overall effect: Z=2.60 (p=0.009)				
03 mean AHI >30				
Engleman 1998 [34]	23	6.00 (3.00)	23	12.00 (4.00)
Ballester 1999 [36]	68	5.60 (4.10)	37	10.60 (6.10)
Jenkinson 1999 [38]	52	7.50 (4.50)	49	12.30 (4.80)
Barbé 2001 [43]	29	8.00 (3.00)	25	8.00 (5.00)
Faccenda 2001 [39]	68	10.10 (5.80)	68	12.50 (6.60)
McArdle 2001 [40]	22	8.00 (4.50)	22	12.10 (4.70)
Montserrat 2001 [42]	23	6.70 (3.30)	22	14.60 (5.10)
Chakravorty 2002 [45]	32	8.00 (6.40)	21	11.00 (5.00)
Becker 2003 [47]	16	5.10 (3.80)	16	8.90 (5.00)
Subtotal (95% CI)	333		283	
Tests for heterogeneity: Chi2=29.14, df=8 (p=0.0003, I2=72.5%				
Tests for overall effect: Z=5.40 (p<0.00001)				
Total (95% CI)	620		569	
Test for heterogeneity: Chi2=59.92, df=14 (p<0.00001), I2=76.6%				
Test for overall effect: Z=5.18 (p<0.00001)				

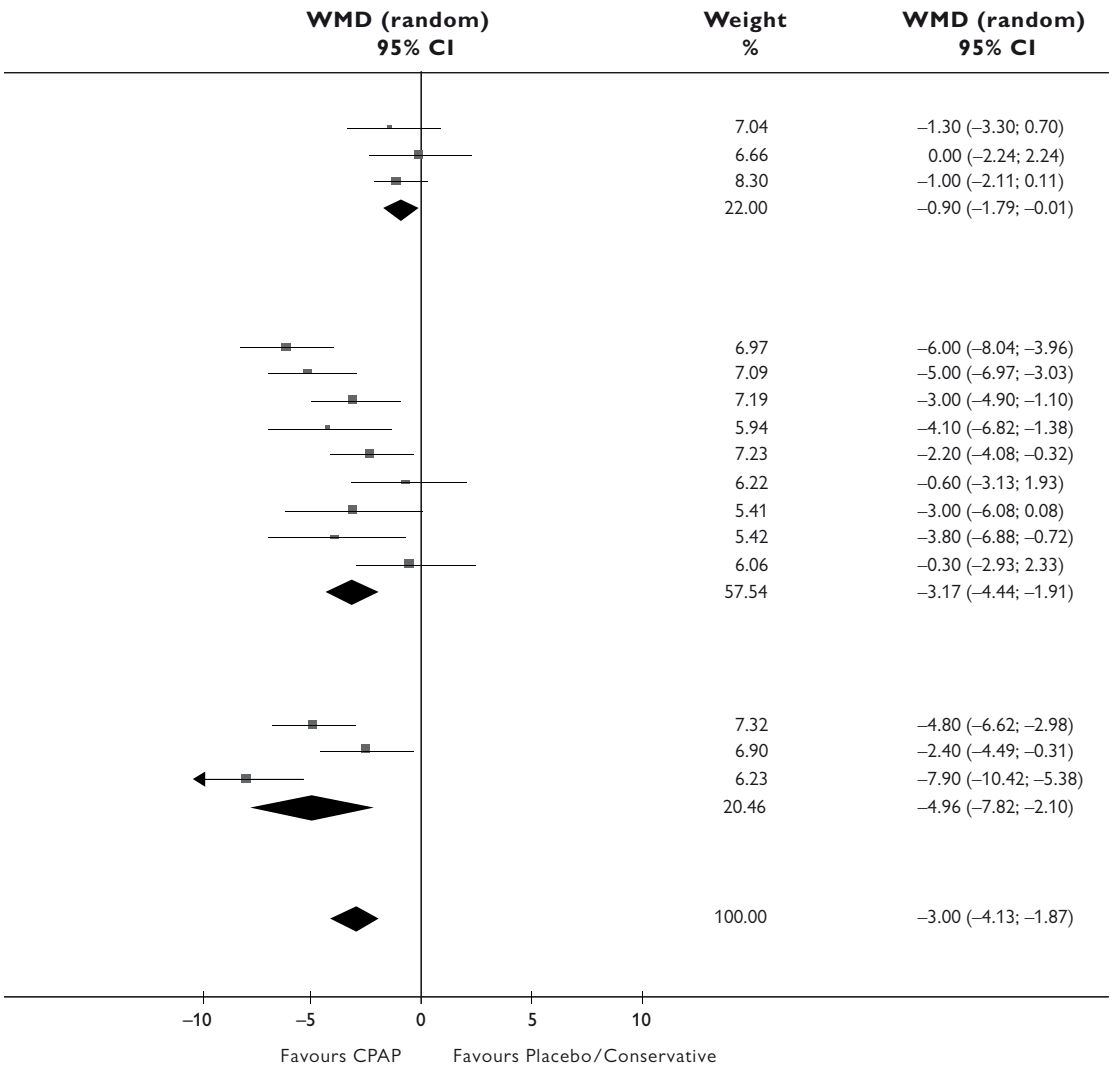
Figure 5.5 *CPAP, effect on Epworth sleepiness scale (ESS) in relation to baseline AHI.*


WMD (random)
95% CI
Weigh
%
WMD (random)
95% CI
7.06
–1.30 (–3.30; 0.70)
7.22
–3.00 (–4.90; –1.10)
6.24
–0.60 (–3.13; 1.93)
20.52
–1.79 (–3.19; –0.39)
7.26
–2.20 (–4.08; –0.32)
6.08
–0.30 (–2.93; 2.33)
8.34
–1.00 (–2.11; 0.11)
21.68
–1.19 (–2.09; –0.29)
7.00
–6.00 (–8.04; –3.96)
6.76
–5.00 (–7.19; –2.81)
7.35
–4.80 (–6.62; –2.98)
6.69
0.00 (–2.24; 2.24)
6.93
–2.40 (4.49; –0.31)
5.95
–4.10 (–6.82; –1.38)
6.25
–7.90 (–10.42;–5.38)
5.43
–3.00 (–6.08; 0.08)
5.43
–3.80 (–6.88; –0.72)
57.80
–4.13 (–5.62; –2.63)
100
–2.99 (–4.12; –1.86)
–10
–5
0
5
10
Favours CPAP
Favours Placebo/Conservative

Review: Obstructive sleep apnoea
Comparison: 13 CPAP vs Placebo/conservative
Outcome: 11 CPAP effect in Epworth sleepiness scale (ESS) score in relation to baseline mean ESS

Study or sub-category	CPAP N	CPAP Mean (SD)	Placebo/conservative N	Placebo/conservative Mean (SD)
01 mean ESS <11				
Redline 1998 [35]	51	8.90 (4.30)	46	10.20 (5.60)
Barbé 2001 [43]	29	8.00 (3.00)	25	8.00 (5.00)
Barnes 2004 [49]	89	9.20 (3.80)	90	10.20 (3.80)
Subtotal (95% CI)	169		161	
Test for heterogeneity: Chi2=0.80, df=2 (p=0.67), I2=0%				
Test for overall effect: Z=1.98 (p=0.05)				
02 mean ESS 11–<15				
Engleman 1998 [34]	12	6.00 (3.00)	23	12.00 (4.00)
Ballester 1999 [36]	68	5.60 (0.10)	37	10.60 (6.10)
Engleman 1999 [37]	34	8.00 (4.00)	34	11.00 (4.00)
McArdle 2001 [40]	22	8.00 (4.50)	22	12.10 (4.70)
Monasterio 2001 [41]	66	9.60 (5.50)	59	11.80 (5.20)
Barnes 2002 [44]	28	8.90 (4.90)	32	9.50 (5.10)
Chakravorty 2002 [45]	32	8.00 (6.40)	21	11.00 (5.00)
Becker 2003 [47]	16	5.10 (3.80)	16	8.90 (5.00)
Woodson 2003 [48]	19	10.30 (5.00)	25	10.60 (3.50)
Subtotal (95% CI)	308		269	
Test for heterogeneity: Chi2=20.81, df=8 (p=0.008), I2=61.6%				
Test for overall effect: Z=4.93 (p<0.00001)				
03 mean ESS 15 and over				
Jenkinson 1999 [38]	52	7.50 (4.50)	49	12.30 (4.80)
Faccenda 2001 [39]	68	10.10 (5.80)	68	12.50 (6.60)
Montserrat 2001 [42]	23	6.70 (3.30)	22	14.60 (5.10)
Subtotal (95% CI)	143		139	
Test for heterogeneity: Chi2=10.86, df=2 (p=0.004), I2=81.6%				
Test for overall effect: Z=3.40 (p=0.0007)				
Total (95% CI)	620		569	
Test for heterogeneity: Chi2=60.94, df=14 (p<0.00001), I2=77.0%				
Test for overall effect: Z=5.19 (p<0.0001)				

Figure 5.6 *CPAP, effect on Epworth sleepiness scale (ESS) in relation to baseline ESS.*


WMD (random)
95% CI
Weight
%
WMD (random)
95% CI
7.04
–1.30 (–3.30; 0.70)
6.66
0.00 (–2.24; 2.24)
8.30
–1.00 (–2.11; 0.11)
22.00
–0.90 (–1.79; –0.01)
6.97
–6.00 (–8.04; –3.96)
7.09
–5.00 (–6.97; –3.03)
7.19
–3.00 (–4.90; –1.10)
5.94
–4.10 (–6.82; –1.38)
7.23
–2.20 (–4.08; –0.32)
6.22
–0.60 (–3.13; 1.93)
5.41
–3.00 (–6.08; 0.08)
5.42
–3.80 (–6.88; –0.72)
6.06
–0.30 (–2.93; 2.33)
57.54
–3.17 (–4.44; –1.91)
7.32
–4.80 (–6.62; –2.98)
6.90
–2.40 (–4.49; –0.31)
6.23
–7.90 (–10.42; –5.38)
20.46
–4.96 (–7.82; –2.10)
100.00
–3.00 (–4.13; –1.87)
–10
–5
0
5
10
Favours CPAP
Favours Placebo/Conservative

Review: Obstructive sleep apnoea syndrome
Comparison: 02 Mandibular repositioning appliance (MRA) vs Placebo
Outcome: 02 Epworth sleepiness scale (ESS)

Study or sub-category	MRA N	MRA Mean (SD)	Placebo N	Placebo Mean (SD)
Gotsopoulos 2002 [50]	73	7.00 (8.50)	73	9.00 (8.50)
Johnston 2002 [51]	18	11.60 (6.70)	18	12.60 (6.30)
Barnes 2004 [49]	85	9.20 (3.70)	90	10.20 (3.80)
Total (95% CI)	176		181	

Test for heterogeneity: Chi2=0.44, df=2 (p=0.80), I2=0%
Test for overall effect: Z=2.21 (p=0.03)

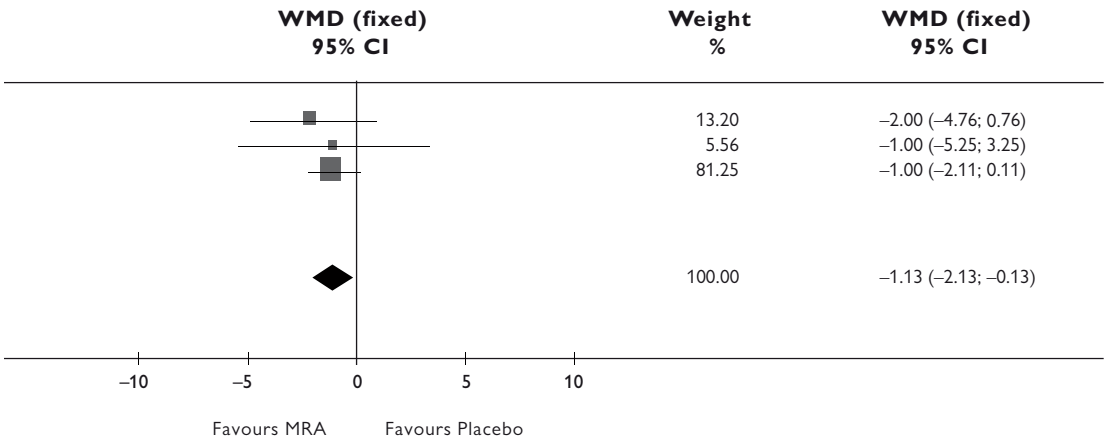
Figure 5.7 *Mandibular repositioning appliance (MRA), effect on Epworth sleepiness scale (ESS).*

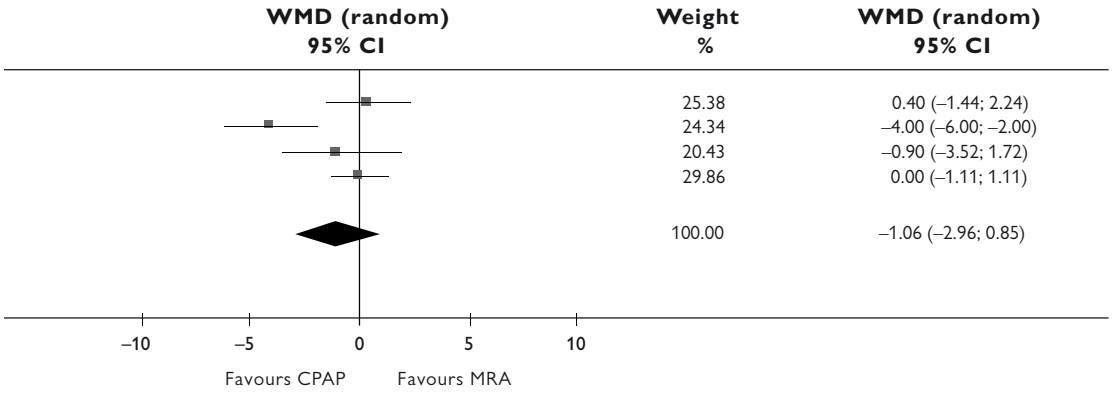
Review: Obstructive sleep apnoea
Comparison: 03 CPAP vs Mandibular repositioning appliance (MRA)
Outcome: 02 Epworth sleepiness scale (ESS)

Study or sub-category	CPAP N	CPAP Mean (SD)	MRA N	MRA Mean (SD)
Ferguson 1997 [54]	20	5.10 (3.30)	20	4.70 (2.60)
Engleman 2002 [56]	48	8.00 (5.00)	48	12.00 (5.00)
Tan 2002 [55]	24	8.10 (4.10)	24	9.00 (5.10)
Barnes 2004 [49]	89	9.20 (3.80)	85	9.20 (3.70)
Total (95% CI)	181		177	

Test for heterogeneity: Chi2=13.36, df=3 (p=0.004), I2=77.5%
Test for overall effect: Z=1.09 (p=0.28)

Figure 5.8 *CPAP vs mandibular repositioning appliance (MRA), effect on Epworth sleepiness scale (ESS).*

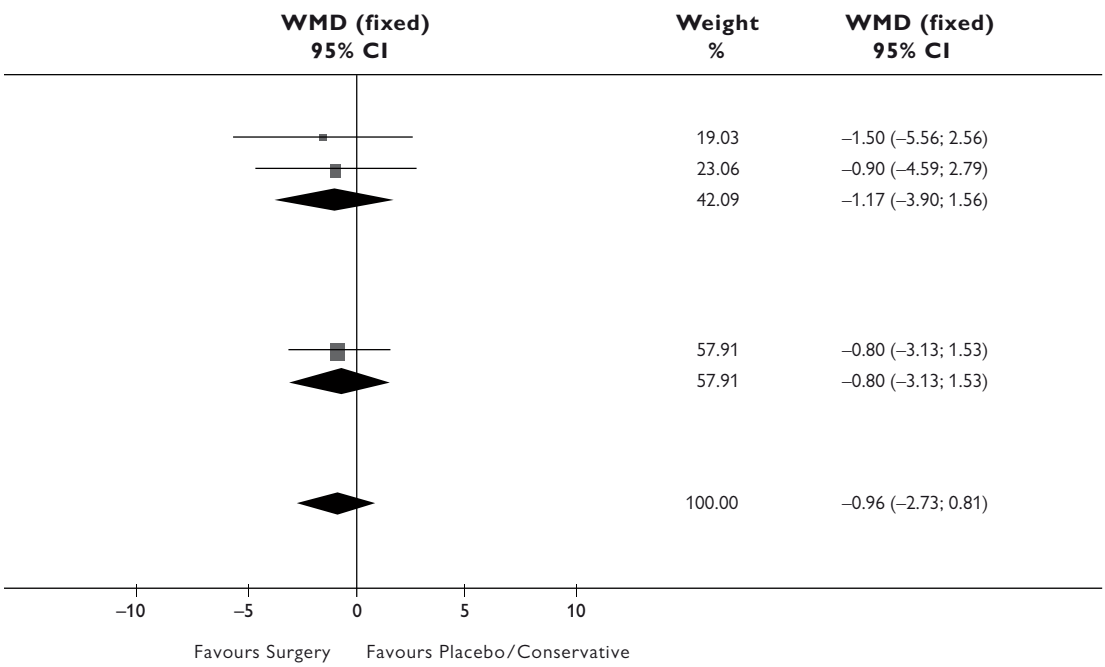

WMD (fixed)
95% CI
Weight
%
WMD (fixed)
95% CI
13.20
–2.00 (–4.76; 0.76)
5.56
–1.00 (–5.25; 3.25)
81.25
–1.00 (–2.11; 0.11)
100.00
–1.13 (–2.13; –0.13)
–10
–5
0
5
10
Favours MRA
Favours Placebo


WMD (random)
95% CI
Weight
%
WMD (random)
95% CI
25.38
0.40 (–1.44; 2.24)
24.34
–4.00 (–6.00; –2.00)
20.43
–0.90 (–3.52; 1.72)
29.86
0.00 (–1.11; 1.11)
100.00
–1.06 (–2.96; 0.85)
–10
–5
0
5
10
Favours CPAP
Favours MRA

Review: Obstructive sleep apnoea
Comparison: 13 CPAP vs Placebo/conservative
Outcome: 10 CPAP effect on Epworth sleepiness scale in relation to baseline mean Apnoea-hypopnea index (AHI)

Study or sub-category	Surgery N	Surgery Mean (SD)	Conservative/placebo N	Conservative/placebo Mean (SD)
01 Laser-assisted uvulopalatoplasty				
Ferguson 2003 [6]	21	9.30 (3.80)	24	10.80 (9.30)
Larrosa 2004 [57]	13	9.60 (3.80)	12	10.50 (5.40)
Subtotal (95% CI)	34		36	
Test for heterogeneity: Chi2=0.05, df=1 (p=0.83), I2=0%				
Test for overall effect: Z=0.84 (p=0.40)				
02 Temperature-controlled radio-frequency tissue ablation				
Woodson 2003 [48]	23	9.80 (4.60)	25	10.60 (3.50)
Subtotal (95% CI)	23		25	
Test for heterogeneity: not applicable				
Test for overall effect: Z=0.67 (p=0.50)				
Total (95% CI)	57		61	
Test for heterogeneity: Chi2=0.09, df=2 (p=0.96), I2=0%				
Test for overall effect: Z=1.06 (p=0.29)				

Figure 5.9 *Surgery, effect on Epworth sleepiness scale (ESS).*


WMD (fixed)
95% CI
Weight
%
WMD (fixed)
95% CI
19.03
–1.50 (–5.56; 2.56)
23.06
–0.90 (–4.59; 2.79)
42.09
–1.17 (–3.90; 1.56)
57.91
–0.80 (–3.13; 1.53)
57.91
–0.80 (–3.13; 1.53)
100.00
–0.96 (–2.73; 0.81)
–10
–5
0
5
10
Favours Surgery
Favours Placebo/Conservative

Review: Obstructive sleep apnoea
Comparison: 13 CPAP vs Placebo/conservative
Outcome: 09 Multiple sleep latency test (MSLT) and Maintenance of wakefulness test (MWT)

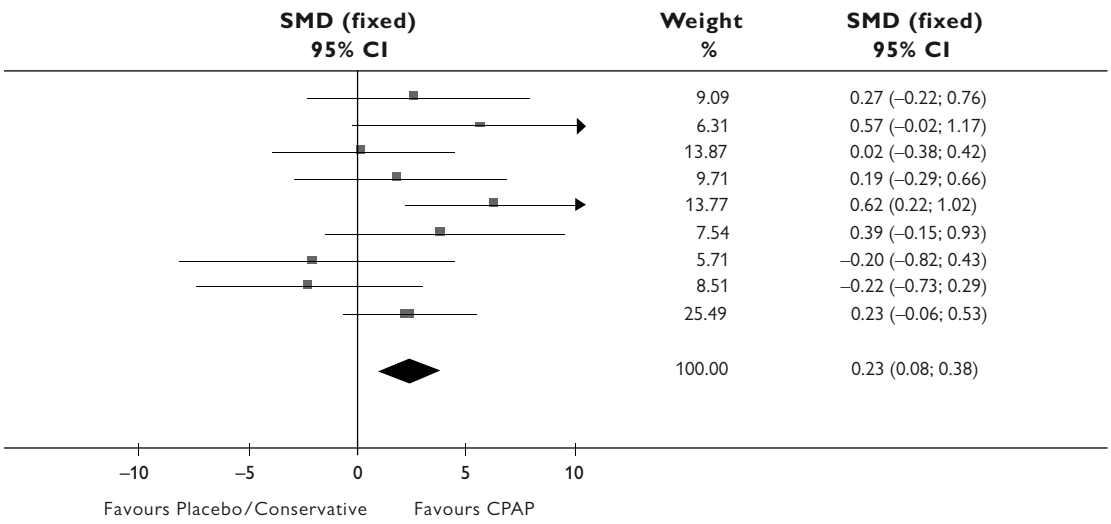
Study or sub-category	CPAP N	CPAP Mean (SD)	Placebo/conservative N	Placebo/conservative Mean (SD)
Engleman 1994 [33]	32	7.20 (4.00)	32	6.10 (4.00)
Engleman 1998 [34]	23	9.20 (3.90)	23	6.80 (4.30)
Redline 1998 [35]	51	10.40 (4.80)	46	10.30 (5.00)
Engleman 1999 [37]	34	16.20 (10.60)	34	14.40 (8.50)
Jenkinson 1999 [38]	52	30.40 (10.00)	49	23.90 (10.70)
Barbé 2001 [43]	29	13.00 (5.00)	25	11.00 (5.00)
Monasterio 2001 [41]	20	10.00 (5.00)	20	11.00 (5.00)
Barnes 2002 [44]	28	11.50 (4.90)	32	12.60 (5.10)
Barnes 2004 [49]	89	30.00 (8.50)	90	28.00 (8.50)
Total (95% CI)	358		351	
Test for heterogeneity: Chi2=11.27, df=8 (p=0.19), I2=29.0%				
Test for overall effect: Z=3.00 (p=0.003)				

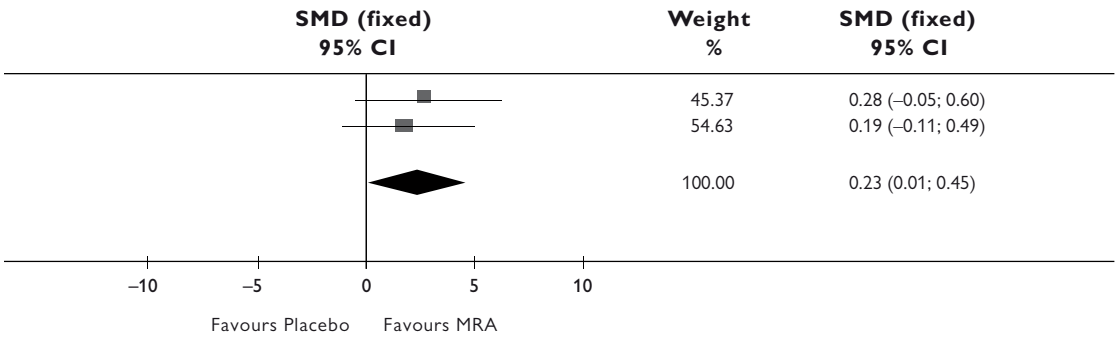
Figure 5.10 *CPAP, effect on Multiple sleep latency test (MSLT) or Maintenance of wakefulness test (MWT).*

Review: Obstructive sleep apnoea
Comparison: 02 Mandibular repositioning appliance (MRA) vs Placebo
Outcome: 03 Multiple sleep latency test (MSLT) and Maintenace of wakefulness test (MWT)

Study or sub-category	MRA N	MRA Mean (SD)	Placebo N	Placebo Mean (SD)
Gotsopoulos 2002 [50]	73	10.30 (4.30)	73	9.10 (4.30)
Barnes 2004 [49]	85	29.60 (8.30)	90	28.00 (8.50)
Total (95% CI)	158		163	
Test for heterogeneity: Chi2=0.15, df=1 (p=0.70), I2=0%				
Test for overall effect: Z=2.05 (p=0.04)				

Figure 5.11 *Mandibular repositioning appliance (MRA), effect on MSLT or MWT.*


SMD (fixed)
95% CI
Weight
%
SMD (fixed)
95% CI
9.09
0.27 (–0.22; 0.76)
6.31
0.57 (–0.02; 1.17)
13.87
0.02 (–0.38; 0.42)
9.71
0.19 (–0.29; 0.66)
13.77
0.62 (0.22; 1.02)
7.54
0.39 (–0.15; 0.93)
5.71
–0.20 (–0.82; 0.43)
8.51
–0.22 (–0.73; 0.29)
25.49
0.23 (–0.06; 0.53)
100.00
0.23 (0.08; 0.38)
–10
–5
0
5
10
Favours Placebo/Conservative
Favours CPAP


SMD (fixed)
95% CI
Weight
%
SMD (fixed)
95% CI
45.37
0.28 (–0.05; 0.60)
54.63
0.19 (–0.11; 0.49)
100.00
0.23 (0.01; 0.45)
–10
–5
0
5
10
Favours Placebo
Favours MRA

Review: Obstructive sleep apnoea
Comparison: 03 CPAP vs Mandibular repositoning appliance (MRA)
Outcome: 03 Maintenance of wakefulness test (MWT)

Study or sub-category	CPAP N	CPAP Mean (SD)	MRA N	MRA Mean (SD)
Engleman 2002 [56]	48	24.00 (12.00)	48	22.00 (12.00)
Barnes 2004 [49]	89	30.00 (8.50)	85	29.60 (8.30)
Total (95% CI)	137		133	

Test for heterogeneity: Chi2=0.21, df=1 (p=0.64), I2=0%
Test for overall effect: Z=0.73 (p=0.46)

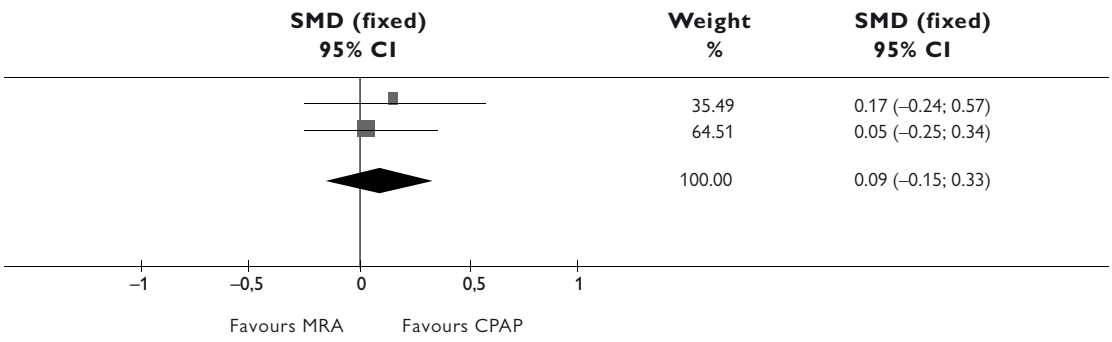
Figure 5.12 *CPAP vs mandibular repositioning appliance (MRA), effect on MWT.*

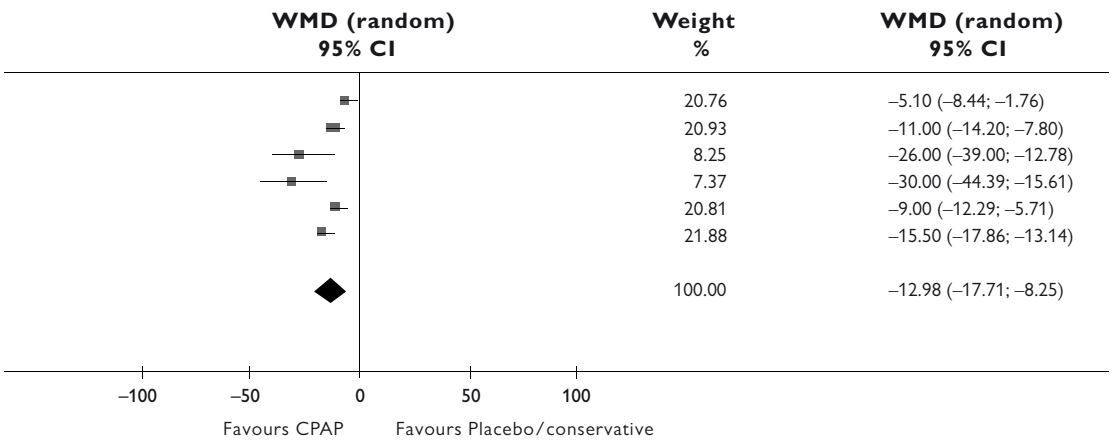
Review: Obstructive sleep apnoea
Comparison: 13 CPAP vs Placebo/conservative
Outcome: 01 Apnea hypopnea index (AHI)

Study or sub-category	CPAP N	CPAP Mean (SD)	Placebo/conservative N	Placebo/conservative Mean (SD)
Redline 1998 [35]	51	4.70 (7.20)	46	9.80 (9.30)
Monasterio 2001 [41]	66	6.00 (8.00)	59	17.00 (10.00)
Chakravorty 2002 [45]	32	8.00 (28.00)	21	34.00 (21.00)
Becker 2003 [47]	16	3.40 (3.10)	16	33.40 (29.20)
Woodson 2003 [48]	19	4.60 (2.70)	25	13.60 (7.80)
Barnes 2004 [49]	89	4.80 (4.70)	90	20.30 (10.40)
Total (95% CI)	273		257	

Test for heterogeneity: Chi2=38.45, df=5 (p<0.00001), I2=87.0%
Test for overall effect: Z=5.38 (p<0.00001)

Figure 5.13 *CPAP, effect on apnoea-hypopnoea index (AHI).*


SMD (fixed)
95% CI
Weight
%
SMD (fixed)
95% CI
35.49
0.17 (–0.24; 0.57)
64.51
0.05 (–0.25; 0.34)
100.00
0.09 (–0.15; 0.33)
–1
–0,5
0
0,5
1
Favours MRA
Favours CPAP


WMD (random)
95% CI
Weight
%
WMD (random)
95% CI
20.76
–5.10 (–8.44; –1.76)
20.93
–11.00 (–14.20; –7.80)
8.25
–26.00 (–39.00; –12.78)
7.37
–30.00 (–44.39; –15.61)
20.81
–9.00 (–12.29; –5.71)
21.88
–15.50 (–17.86; –13.14)
100.00
–12.98 (–17.71; –8.25)
–100
–50
0
50
100
Favours CPAP
Favours Placebo/conservative

Review: Obstructive sleep apnoea
Comparison: 02 Mandibular repositioning appliance (MRA) vs Placebo
Outcome: 01 Apnea hypopnea index (AHI)

Study or sub-category	MRA N	MRA Mean (SD)	Placebo N	Placebo Mean (SD)
Gotsopoulos 2002 [50]	73	12.00 (17.00)	73	25.00 (17.00)
Johnston 2002 [51]	20	22.90 (22.80)	20	37.70 (24.90)
Barnes 2004 [49]	85	14.00 (10.10)	90	20.30 (10.40)
Total (95% CI)	178		183	

Test for heterogeneity: Chi2=5.17, df=2 (p=0.08), I2=61.3%
Test for overall effect: Z=3.39 (p=0.0007)

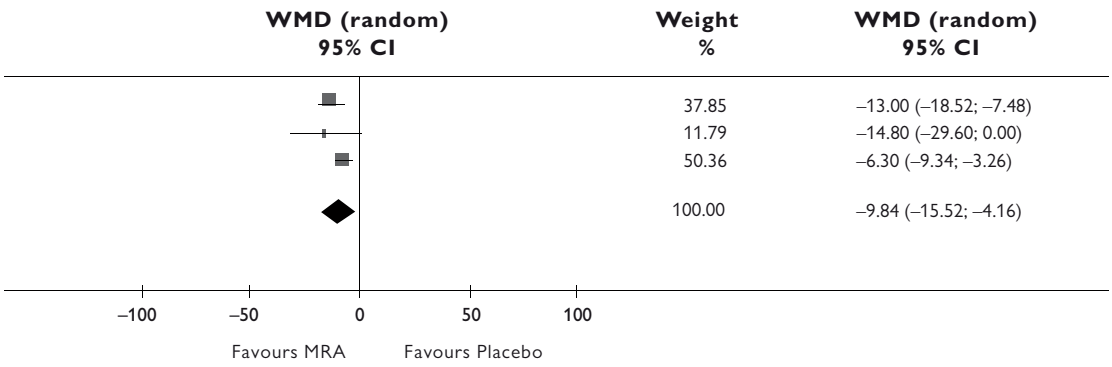
Figure 5.14 *Mandibular repositioning appliance (MRA), effect on apnoea-hypopnoea index (AHI).*

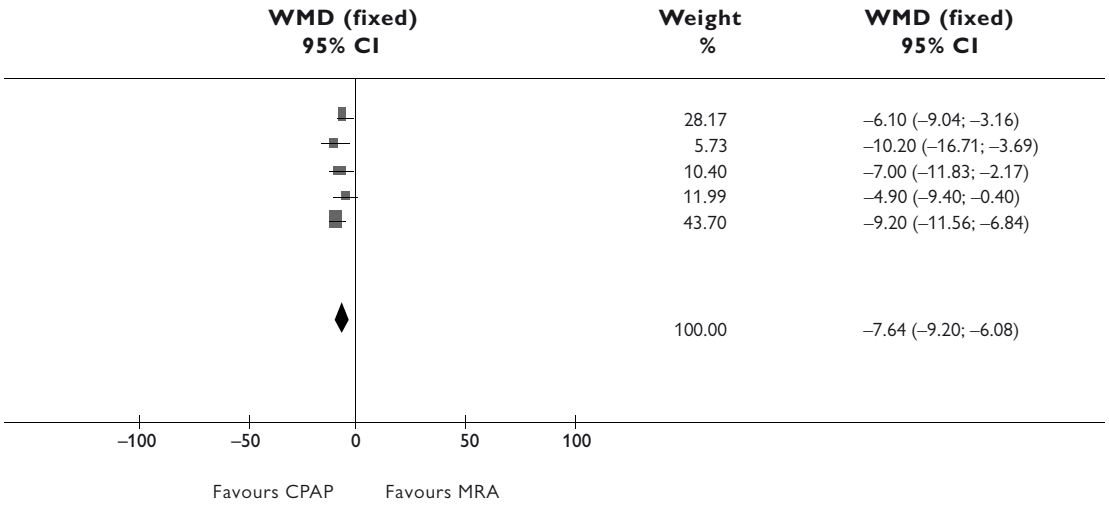
Review: Obstructive sleep apnoea syndrome
Comparison: 03 CPAP vs Mandibular repositioning appliance (MRA)
Outcome: 01 Apnea hypopnea index (AHI)

Study or sub-category	CPAP N	CPAP Mean (SD)	MRA N	MRA Mean (SD)
Ferguson 1996 [53]	25	3.60 (1.70)	25	9.70 (7.30)
Ferguson 1997 [54]	20	4.00 (2.20)	20	14.20 (14.70)
Engleman 2002 [56]	48	8.00 (6.00)	48	15.00 (16.00)
Tan 2002 [55]	24	3.10 (2.80)	24	8.00 (10.90)
Barnes 2004 [49]	89	4.80 (4.70)	85	14.00 (10.10)
Total (95% CI)	206		202	

Test for heterogeneity: Chi2=4.82, df=4 (p=0.31), I2=17.0%
Test for overall effect: Z=9.60 (p<0.00001)

Figure 5.15 *CPAP vs mandibular repositioning appliance (MRA), effect on apnoea-hypopnoea index (AHI).*

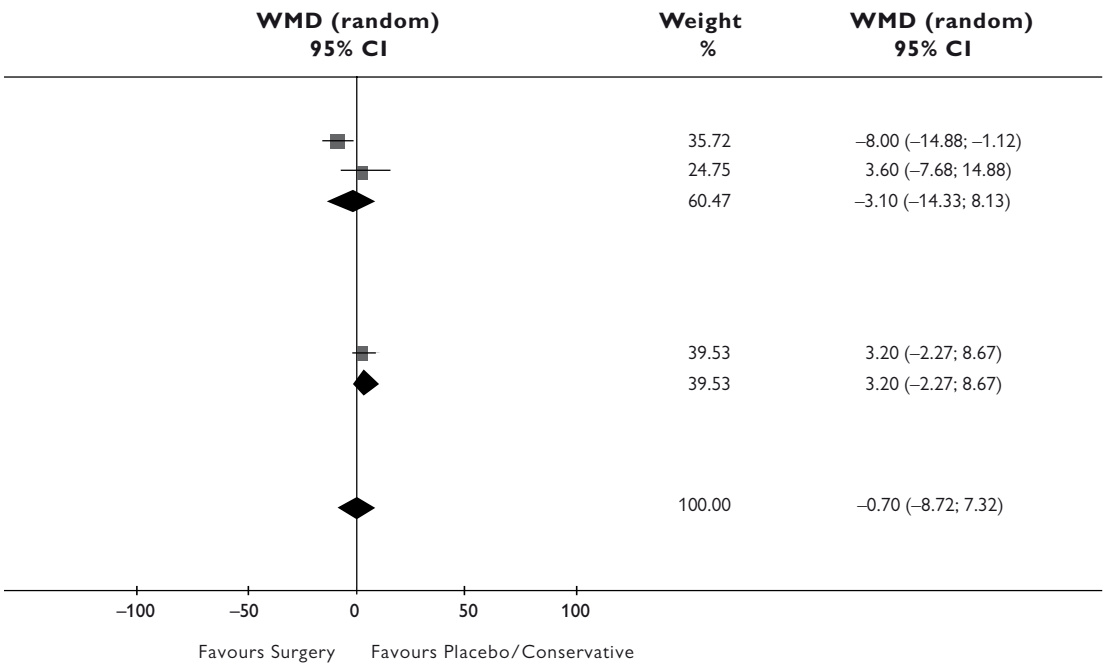

WMD (random)
95% CI
Weight
%
WMD (random)
95% CI
37.85
–13.00 (–18.52; –7.48)
11.79
–14.80 (–29.60; 0.00)
50.36
–6.30 (–9.34; –3.26)
100.00
–9.84 (–15.52; –4.16)
–100
–50
0
50
100
Favours MRA
Favours Placebo


WMD (fixed)
95% CI
Weight
%
WMD (fixed)
95% CI
28.17
–6.10 (–9.04; –3.16)
5.73
–10.20 (–16.71; –3.69)
10.40
–7.00 (–11.83; –2.17)
11.99
–4.90 (–9.40; –0.40)
43.70
–9.20 (–11.56; –6.84)
100.00
–7.64 (–9.20; –6.08)
–100
–50
0
50
100
Favours CPAP
Favours MRA

Review: Obstructive sleep apnoea
Comparison: 01 Surgery vs Placebo/conservative
Outcome: 02 Apnoea hypopnea index

Study or sub-category	Surgery N	Surgery Mean (SD)	Placebo/conservative N	Placebo/conservative Mean (SD)
01 Laser-assisted uvulopalatoplasty				
Ferguson 2003 [6]	21	14.70 (7.50)	24	22.70 (15.20)
Larrosa 2004 [57]	13	15.10 (17.50)	12	11.50 (10.70)
Subtotal (95% CI)	34		36	
Test for heterogeneity: Chi2=2.96, df=1 (p=0.09), I2=66.3%				
Test for overall effect: Z=0.54 (p=0.59)				
02 Temperature-controlled radio-frequency tissue ablation				
Woodson 2003 [48]	23	16.80 (11.10)	25	13.60 (7.80)
Subtotal (95% CI)	23		25	
Test for heterogeneity: not applicable				
Test for overall effect: Z=1.15 (p=0.25)				
Total (95% CI)	57		61	
Test for heterogeneity: Chi2=6.84, df=2 (p=0.03), I2=70.7%				
Test for overall effect: Z=0.17 (p=0.86)				

Figure 5.16 *Surgery, effect on apnoea-hypopnoea index (AHI).*


WMD (random)
95% CI
Weight
%
WMD (random)
95% CI
35.72
–8.00 (–14.88; –1.12)
24.75
3.60 (–7.68; 14.88)
60.47
–3.10 (–14.33; 8.13)
39.53
3.20 (–2.27; 8.67)
39.53
3.20 (–2.27; 8.67)
100.00
–0.70 (–8.72; 7.32)
–100
–50
0
50
100
Favours Surgery
Favours Placebo/Conservative

Review: Obstructive sleep apnoea
Comparison: 13 CPAP vs Placebo/conservative
Outcome: 05 Functional outcome of sleep questionnaire (FOSQ)

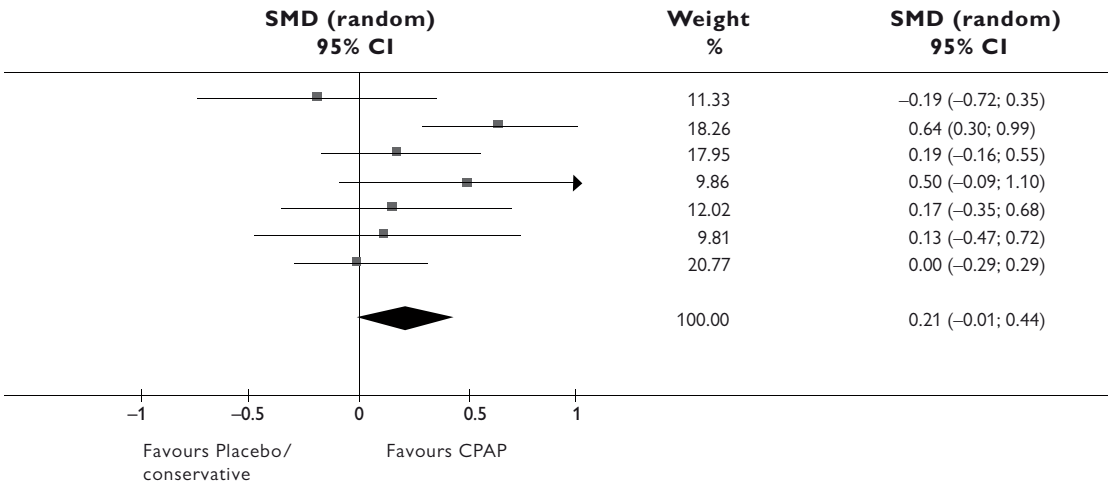
Study or sub-category	CPAP N	CPAP Mean (SD)	Placebo/conservative N	Placebo/conservative Mean (SD)
Barbé 2001 [43]	29	108.00 (11.00)	25	110.00 (10.00)
Faccenda 2001 [39]	68	111.30 (17.00)	68	100.60 (16.00)
Monasterio 2001 [41]	66	106.00 (20.00)	59	102.00 (21.00)
Montserrat 2001 [42]	23	109.40 (12.50)	22	100.70 (20.60)
Barnes 2002 [44]	28	3.45 (0.43)	31	3.38 (0.40)
Woodson 2003 [48]	19	17.50 (2.60)	25	17.20 (2.10)
Barnes 2004 [49]	89	3.30 (0.90)	90	3.30 (0.90)
Total (95% CI)	322		320	
Test for heterogeneity: Chi2=11.22, df=6 (p=0.08), I2=46.5%				
Test for overall effect: Z=1.87 (p=0.06)				

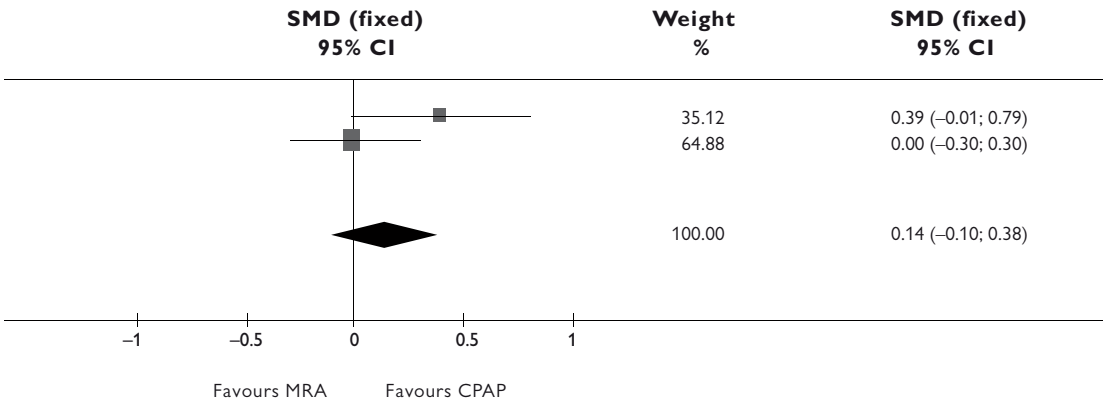
Figure 5.17 *CPAP, effect on Functional outcome of sleep questionnaire (FOSQ).*

Review: Obstructive sleep apnoea syndrome
Comparison: 03 CPAP vs Mandibular repositioning appliance (MRA)
Outcome: 05 Functional outcome of sleep questionnaire (FOSQ)

Study or sub-category	CPAP N	CPAP Mean (SD)	MRA N	MRA Mean (SD)
Engleman 2002 [56]	48	14.00 (2.00)	48	13.00 (3.00)
Barnes 2004 [49]	89	3.30 (0.90)	85	3.30 (0.90)
Total (95% CI)	137		133	
Test for heterogeneity: Chi2=2.31, df=1 (p=0.13), I2=56.7%				
Test for overall effect: Z=1.12 (p=0.26)				

Figure 5.18 *CPAP vs mandibular repositioning appliance (MRA), effect on FOSQ.*


SMD (random)
95% CI
Weight
%
SMD (random)
95% CI
11.33
–0.19 (–0.72; 0.35)
18.26
0.64 (0.30; 0.99)
17.95
0.19 (–0.16; 0.55)
9.86
0.50 (–0.09; 1.10)
12.02
0.17 (–0.35; 0.68)
9.81
0.13 (–0.47; 0.72)
20.77
0.00 (–0.29; 0.29)
100.00
0.21 (–0.01; 0.44)
–1
–0.5
0
0.5
1
Favours Placebo/
conservative
Favours CPAP


SMD (fixed)
95% CI
Weight
%
SMD (fixed)
95% CI
35.12
0.39 (–0.01; 0.79)
64.88
0.00 (–0.30; 0.30)
100.00
0.14 (–0.10; 0.38)
–1
–0.5
0
0.5
1
Favours MRA
Favours CPAP

Review: Obstructive sleep apnoea
Comparison: 13 CPAP vs Placebo/conservative
Outcome: 06 SF-36 vitality

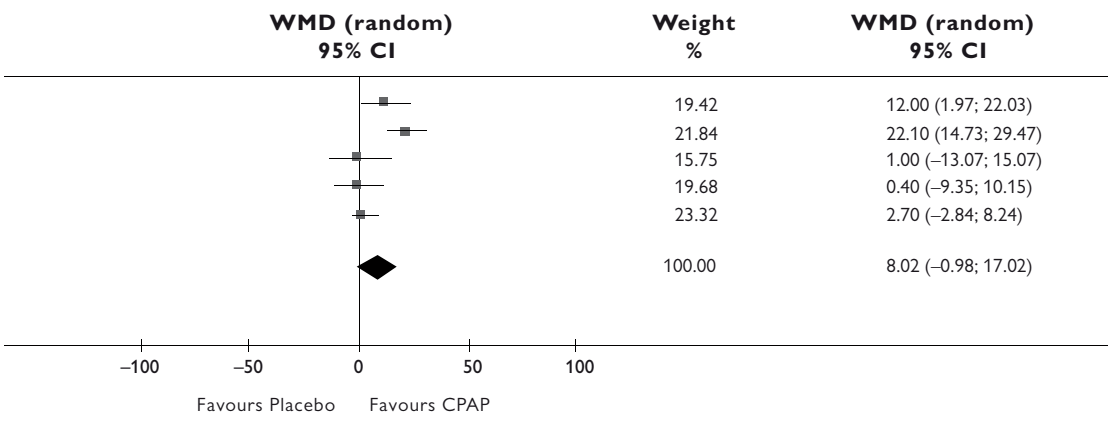
Study or sub-category	CPAP N	CPAP Mean (SD)	Placebo N	Placebo Mean (SD)
Engleman 1999 [37]	34	58.00 (19.00)	34	46.00 (23.00)
Jenkinson 1999 [38]	52	73.00 (17.00)	49	50.90 (20.50)
Montserrat 2001 [42]	23	69.40 (27.30)	22	68.40 (20.50)
Barnes 2002 [44]	28	59.80 (19.40)	32	59.40 (19.00)
Barnes 2004 [49]	88	58.70 (18.20)	88	56.00 (19.30)
Total (95% CI)	225		225	
Test for heterogeneity: Chi2=21.47, df=4 (p=0.0003), I2=81.4%				
Test for overall effect: Z=1.75 (p=0.08)				

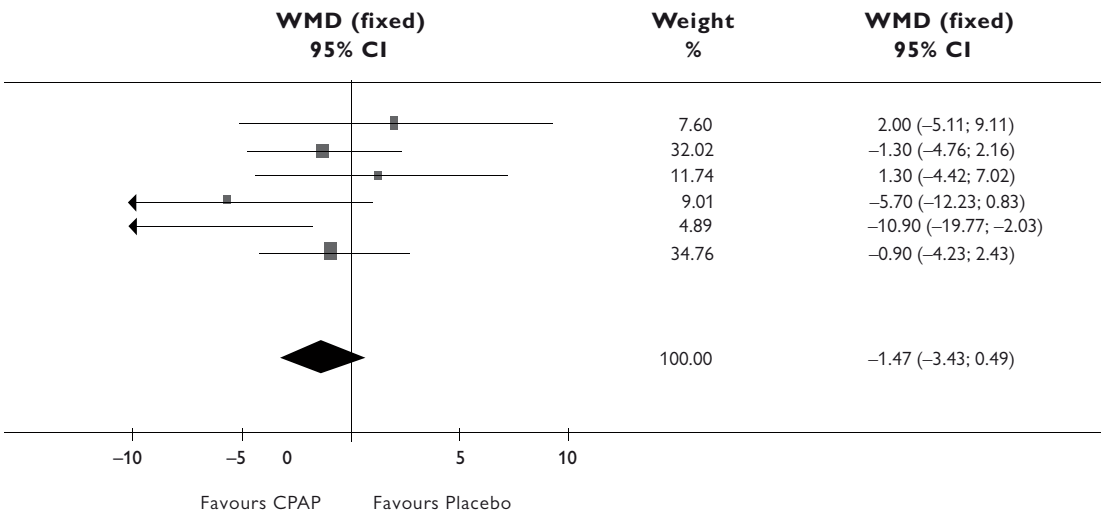
Figure 5.19 *CPAP, effect on SF-36 vitality.*

Review: Obstructive sleep apnoea syndrome
Comparison: 01 CPAP vs Placebo/conservative
Outcome: 07 24 hour, Systolic blood pressure

Study or sub-category	CPAP N	CPAP Mean (SD)	Placebo N	Placebo Mean (SD)
Barbé 2001 [43]	29	124.00 (11.00)	25	122.00 (15.00)
Faccenda 2001 [39]	68	126.90 (10.70)	68	128.20 (9.90)
Barnes 2002 [44]	27	130.30 (9.80)	29	129.00 (12.00)
Pepperell 2002 [46]	48	130.20 (14.60)	47	135.90 (17.70)
Becker 2003 [47]	16	126.40 (14.30)	16	137.30 (11.10)
Barnes 2004 [49]	89	127.30 (11.30)	90	128.20 (11.40)
Total (95% CI)	277		275	
Test for heterogeneity: Chi2=7.89, df=5 (p=0.16), I2=36.6%				
Test for overall effect: Z=1.47 (p=0.14)				

Figure 5.20 *CPAP, effect on 24-hour systolic blood pressure.*


WMD (random)
95% CI
Weight
%
WMD (random)
95% CI
19.42
12.00 (1.97; 22.03)
21.84
22.10 (14.73; 29.47)
15.75
1.00 (–13.07; 15.07)
19.68
0.40 (–9.35; 10.15)
23.32
2.70 (–2.84; 8.24)
100.00
8.02 (–0.98; 17.02)
–100
–50
0
50
100
Favours Placebo
Favours CPAP


WMD (fixed)
95% CI
Weight
%
WMD (fixed)
95% CI
7.60
2.00 (–5.11; 9.11)
32.02
–1.30 (–4.76; 2.16)
11.74
1.30 (–4.42; 7.02)
9.01
–5.70 (–12.23; 0.83)
4.89
–10.90 (–19.77; –2.03)
34.76
–0.90 (–4.23; 2.43)
100.00
–1.47 (–3.43; 0.49)
–10
–5
0
5
10
Favours CPAP
Favours Placebo

Review: Obstructive sleep apnoea
Comparison: 13 CPAP vs Placebo/conservative
Outcome: 08 24, Diastolic blood pressure

Study or sub-category	CPAP N	CPAP Mean (SD)	Placebo N	Placebo Mean (SD)
Barbé 2001 [43]	29	79.00 (5.00)	25	77.00 (10.00)
Faccenda 2001 [39]	68	77.80 (8.20)	68	79.20 (7.40)
Barnes 2002 [44]	27	81.00 (7.20)	29	78.70 (15.30)
Pepperell 2002 [46]	48	82.70 (9.20)	47	85.90 (8.50)
Becker 2003 [47]	16	73.10 (10.50)	16	82.10 (9.10)
Barnes 2004 [49]	89	76.70 (7.50)	90	77.30 (6.60)
Total (95% CI)	277		275	

Test for heterogeneity: Chi2=9.92, df=5 (p=0.08), I2=49.6%
Test for overall effect: Z=1.17 (p=0.24)

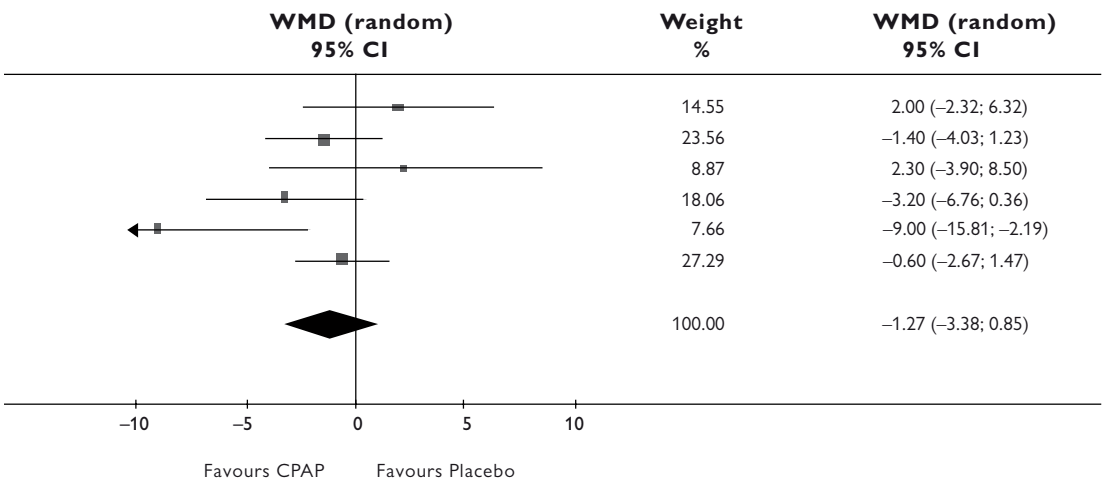
Figure 5.21 *CPAP, effect on 24-hour diastolic blood pressure.*

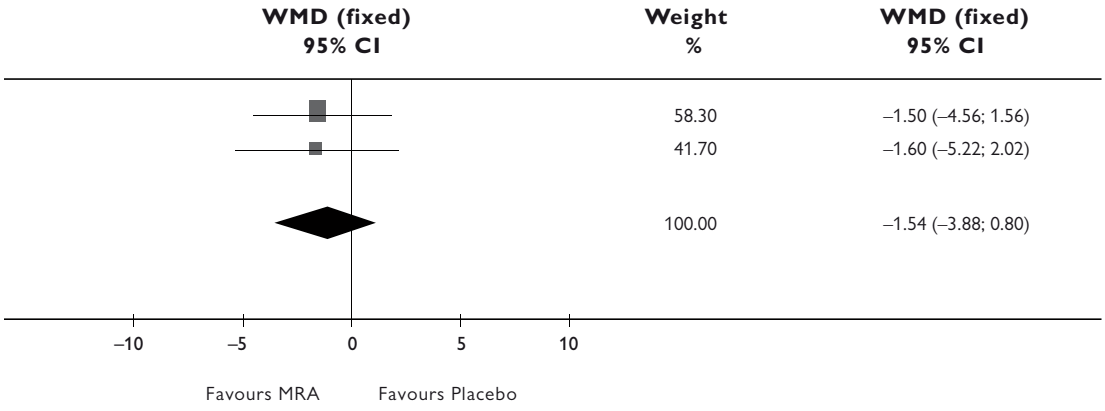
Review: Obstructive sleep apnoea syndrome
Comparison: 02 Mandibular repositioning appliance (MRA) vs Placebo
Oucome: 07 24 hour, Systolic blood pressure

Study or sub-category	MRA N	MRA Mean (SD)	Placebo N	Placebo Mean (SD)
Barnes 2004 [49]	85	126.70 (9.20)	90	128.20 (11.40)
Gotsopoulos 2004 [52]	61	125.30 (10.20)	61	126.90 (10.20)
Total (95% CI)	146		151	

Test for heterogeneity: Chi2=0.00, df=1 (p=0.97), I2=0%
Test for overall effect: Z=1.29 (p=0.20)

Figure 5.22 *Mandibular repositioning appliance (MRA), effect on 24-hour systolic blood pressure.*

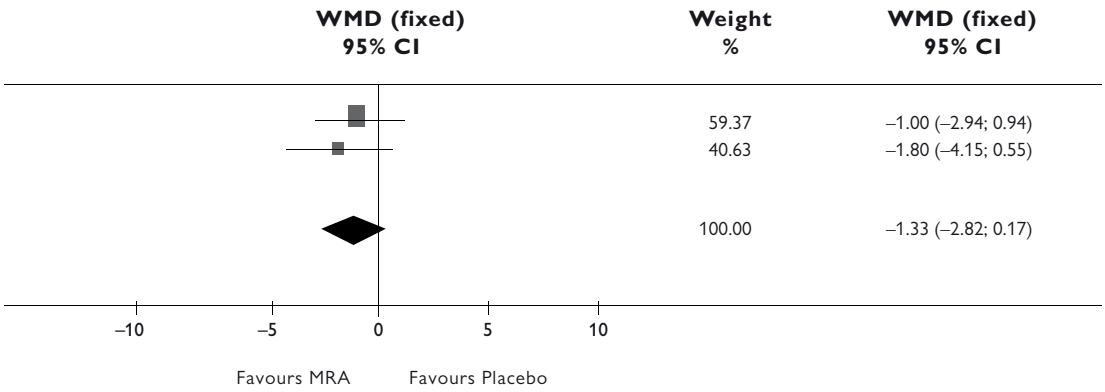

WMD (random)
95% CI
Weight
%
WMD (random)
95% CI
14.55
2.00 (–2.32; 6.32)
23.56
–1.40 (–4.03; 1.23)
8.87
2.30 (–3.90; 8.50)
18.06
–3.20 (–6.76; 0.36)
7.66
–9.00 (–15.81; –2.19)
27.29
–0.60 (–2.67; 1.47)
100.00
–1.27 (–3.38; 0.85)
–10
–5
0
5
10
Favours CPAP
Favours Placebo


WMD (fixed)
95% CI
Weight
%
WMD (fixed)
95% CI
58.30
–1.50 (–4.56; 1.56)
41.70
–1.60 (–5.22; 2.02)
100.00
–1.54 (–3.88; 0.80)
–10
–5
0
5
10
Favours MRA
Favours Placebo

Review: Obstructive sleep apnoea syndrome
Comparison: 02 Mandibular repositioning appliance (MRA) vs Placebo
Oucome: 08 24 hour, Systolic blood pressure

Study or sub-category	MRA N	MRA Mean (SD)	Placebo N	Placebo Mean (SD)
Barnes 2004 [49]	85	76.30 (6.50)	90	77.30 (6.60)
Gotsopoulos 2004 [52]	61	76.20 (7.00)	61	78.00 (6.20)
Total (95% CI)	146		151	
Test for heterogeneity: Chi2=0.27, df=1 (p=0.61), I^2=0%				
Test for overall effect: Z=1.74 (p=0.08)				

Figure 5.23 *Mandibular repositioning appliance (MRA), effect on 24-hour diastolic blood pressure.*


WMD (fixed)
95% CI
Weight
%
WMD (fixed)
95% CI
59.37
–1.00 (–2.94; 0.94)
40.63
–1.80 (–4.15; 0.55)
100.00
–1.33 (–2.82; 0.17)
–10
–5
0
5
10
Favours MRA
Favours Placebo

Compliance with CPAP

Conclusion

- Tolerance and compliance with CPAP are good. About 70% of patients still use it after 1–4 years for a mean of 5.3 (range 4.4–6.2) hours per night (Evidence Grade 2), provided that patients and their CPAP equipments are seen by physicians shortly after treatment starts, followed by individual intervals, but always at least once a year.

Baseline data

Ten studies fulfilled the criteria for compliance with CPAP. One study was of high quality, 6 were of medium quality and 3 were of low quality. A total of 5 971 patients were followed. Men accounted for 84–91% of the populations. Mean age varied from 50 to 59. Mean BMI was 30–35 kg/sq m. Mean AHI was 31–53. Fixed CPAP was used in all studies and had a mean pressure of 8–11 cm [61–65].

Results

Tolerance and compliance with CPAP in studies of medium and high quality

In studies of medium and high quality, a mean of 9% (range 5–18%) immediately refused to test or to take CPAP at home after one night [63,65–68]. Of patients who were prescribed CPAP, a mean of 74% (range 61–87%) used it after 1–4 years, corresponding to 69% (range 50–74%) in an intention-to-treat analysis (Table 5.13). These patients used CPAP during a mean of 5.2 (range 4.4–6.2) hours per night, according to objective measurements. One study reported that 76% of patients on CPAP used it more than 25 hours/week, another that 77% used it more than 21 hours/week, and a third that 73% used it more than 21 hours/week [63,68,72]. The reasons for quitting CPAP treatment were

death in up to 6% of patients, lack of improvement, discomfort, choosing another treatment or no longer suffering from the disease.

A thorough follow-up of patients and CPAP equipment was performed in 5 of the 7 studies [63,64,66,68,72]. A physician saw patients within 2 weeks to 3 months after onset of CPAP and then individually, but always at least once a year. Patients had additional phone support if problems occurred. One study phoned them after two weeks of treatment. The effect of treatment on symptoms was addressed and difficulties using CPAP were taken care off at follow-up. Patients in one study had a less comprehensive follow-up, the first visit coming after 9 months [67]. A mean of 27% (range 24–31%) of the patients did not tolerate CPAP at titration or had stopped using the device in studies with vigorous follow-up, as opposed to 50% in the study with a less comprehensive programme.

Predictors of compliance

A favourable subjective effect on daytime sleepiness and the AHI predicted good compliance with CPAP [62,65,68]. Other predictors of good compliance were good compliance during the first three months of treatment, daytime sleepiness and obesity. Tolerance of nasal masks was related to good compliance, while inconvenience, nasal dryness, air leakage and complaints of a noisy machine were related to poorer compliance [62,63,65,69,70].

Table 5.13 *Compliance with CPAP at follow-up.*

Time at follow-up	n	Still using CPAP*, %	Hours/ night**	Author, year, reference	Quality
12 months	209	68	5.0±2.3	Popescu 2001 [68]	High
12 months	1 103	84		McArdle 1999 [63]	Medium
19±7 months	193	95	6.5±3	Pépin 1995 [61]	Low
22 (12–36) months	1 103	77	5.6 (3.8–7)	McArdle 1999 [63]	Medium
30 (3–70) months	151	71		Lojander 1999 [71]	Medium
30 (25–35) months	149	61	4.4±2.4	Grote 2000 [67]	Medium
32 (6–66) months	325	77	4.7±2.4	Noseda 1997 [72]	Medium
40±20 months	227	74	6.2±2.7	Lacassagne 2000 [66]	Medium
43±20 months	108	85		Hollandt 2003 [65]	Medium
48 months	1 103	68		McArdle 1999 [63]	Medium
72 months	227	74		Lacassagne 2000 [66]	Medium

* Of patients being prescribed CPAP for home use.
** According to time counters of CPAP.

Adverse effects of CPAP

Conclusion

- Mild to moderate discomfort – pain at the bridge of the nose, skin problems, air leaks and disturbing noise from the CPAP machine – from the CPAP mask are common adverse effects of CPAP (Evidence Grade 2). Mild nasal adverse effects such as rhinitis are also common (Evidence Grade 3).

Baseline data

Ten studies investigated the adverse effects of CPA. Only 1 study was prospective [73] and 1 was part of an RCT [48]. Men represented 75–94% of the populations. Mean age varied between 46 and 59. Mean BMI was 29–35 kg/sq m. Mean AHI was 20–53. A total of 4 434 patients were followed. The observation period varied from 2 months to 2.5 years. Studies were published between 1995 and 2003. Two studies distinguished mild from severe symptoms [74,75].

Results

Mild to moderate discomfort related to the mask – pain at the bridge of the nose, skin problems, air leaks or disturbing noise from the CPAP machine – were common (Table 5.14). Almost 50% of patients and partners complained of noisy machines in studies published during the 1990s, but that declined to 16% of patients and 7% of patients in a 2004 study that used modern, more silent machines [76].

One prospective study of medium quality that included 51 patients reported that rhinitis increased from 37% to 57% p=0.013 and sneeze from 53% to 75% p=0.013 [73]. Another study of medium quality reported mild nasal adverse effects in 38% of patients [48]. No increase in nasal symptoms were found in a third study of medium quality [71]. The dry nose and mouth and nasal stuffiness that were common before CPAP did not increase with treatment [71,73]. Nasal bleeding was reported by 5 authors. One study that compared bleeding with baseline data did not find any significant increase [73]. Nasal congestion or drippy nose occurred in 30% (16–57%) of patients on CPAP, sneeze in 44% (29–75%), red eyes or pain in the eyes from mask leaks in 20% (3–31%), claustrophobia in 5% (4–5%), and aerophagia, bloating or flatulence in 0–37%. However, these symptoms were also common before CPAP was started, and the scientific evidence that they were adverse effects of CPAP is insufficient. Only reversible and adverse effects were found.

Table 5.14 *Adverse effects of CPAP.*

	Frequency Mean, range	Severe problems	Evidence Grade	References
Mask discomfort	42% (32–53%)	1–5%	2	Kalan 1999 [70] Hohenhaus-Beer 1995 [77] Engleman 1996 [74] Verse 1999 [78] Hui 2001 [75] Masa 2004 [76]
Nasal bridge pain/ skin problems	39% (23–52%)	4%	2	Pépin 1995 [61] Kalan 1999 [70] Lojander 1999 [64] Hohenhaus-Beer 1995 [77] Hui 2001 [75] Masa 2004 [76]
Mild nasal side effects	38–57%		3	Brander 1999 [73] Woodson 2003 [48]
Air leak	52% (20–73%)	<1%	3	Pépin 1995 [61] Kalan 1999 [70] Lojander 1999 [64] Engleman 1996 [74]
Noisy CPAP*	32% (15–45%)	2%	2	Pépin 1995 [61] Meslier 1998 [62] Kalan 1999 [70] Hohenhaus-Beer 1995 [77] Engleman 1996 [74] Masa 2004 [76]
Partner complaints of noise	36% (7–50%)		3	Pépin 1995 [61] Meslier 1998 [62] Kalan 1999 [70] Hohenhaus-Beer 1995 [77] Masa 2004 [76]

* Noise from the CPAP machine was less of a problem after more silent devices were introduced.

Systematic reviews of auto-CPAP compared to fixed CPAP

Conclusion

- Auto-CPAP utilises a lower mean pressure than fixed CPAP, but the effect on daytime sleepiness, apnoea reduction and compliance is the same (Evidence Grade 1).

Baseline data

Four systematic reviews that compared auto-CPAP with fixed CPAP were identified (Table 5.15). A review by the American Academy of Sleep Medicine included 22 studies [19], a Canadian HTA report identified 24 studies on treatment outcomes [27], a 2004 Cochrane report with a last amendment in September 2003 included 13 studies [3], and a 2004 meta-analysis by Ayas et al was based on 9 studies [28]. The reviews contained a total of 49 different studies. Another 2 studies from 2004 were identified but did not affect the results and conclusions of the 4 reviews [79,80]. We decided to do a review of reviews, given that the prior reviews were of high quality and their results did not differ from either one another or the 2 studies published after the last review.

Results

CPAP pressure is significantly lower during auto-CPAP than fixed CPAP (Table 5.15) [3,19,27,28]. This difference had little effect on outcomes. All reviews reported that there was no difference in reduction of apnoea frequency (AHI) or subjective sleepiness between auto-CPAP and fixed CPAP measured with the ESS [3,19,27,28]. There was no difference in the arousal index or sleep architecture [19,27]. Compliance did not differ between auto-CPAP and fixed CPAP [3,19,27,28]. However, the studies were characterised by high machine usage in the control groups and low withdrawal rates, making it less likely that any compliance benefit could be demonstrated [3]. It is feasible that auto-CPAP increases usage by 15–20 minutes and that this effect is limited to a subgroup of patients who struggle to accept fixed CPAP or require high pressure [3]. Most participants preferred auto-CPAP to fixed CPAP when that distinction was measured.

Table 5.15 *Auto-CPAP vs fixed CPAP.*

	Berry 2002 [19]	**Hailey 2003 [27]**	**Haniffa 2004 [3]**	**Ayas 2004 [28]**
Type of study	AASM* review	HTA report	Cochrane report	Meta-analysis
Number of studies	22	24	13	9
Effect on AHI	No difference	No difference	No difference	No difference
Effect on ESS	No difference	No difference	No difference	No difference
Sleep quality	No difference	No difference		
CPAP pressure	Lower with Auto-CPAP	Lower with Auto-CPAP	Lower with Auto-CPAP	Lower, –2.2 (–1.9 to –2.5) cm
Patients preference		Auto-CPAP in 3 of 4 studies	Auto-CPAP in 4 of 5 studies	
Compliance			No difference	No difference
Quality	Medium	Medium	High	High

* American Academy of Sleep Medicine

Two reviews raised potential safety issues for individuals with heart failure, given that they often have central apnoea and Cheyne-Stokes respiration [19,27]. The studies usually excluded people with congestive heart failure or obstructive respiratory disorders. None of the studies included patients with substantial central apnoea at baseline [19,27].

Results concerning the use of one type of machine are not necessarily generalisable to other devices, given that there are several different types of auto-CPAP machines available, all of which differ in terms of method of operation [19,27].

Compliance with mandibular repositioning appliances

Conclusion

- Mandibular repositioning appliances are still used by 76% of patients after 1 year and by 56% after 5 years (Evidence Grade 3).

Background

Compliance was assessed on the basis of questionnaires or personal interviews. Detailed data on how much the device was used are lacking. The end points are used/not used, how many hours per night and how many nights per week the device was used at the time of follow-up, ie, 1 and 5 years.

Results

Five articles met the inclusion criteria for compliance studies. Two medium-quality studies presented follow-up data on partly the same patients after 1 and 5 year [81,82]. Three low-quality studies presented data for up to 5 years [83–85]. Of the patients 54–75% were still using the device after 1 and 5 years. Marklund used a soft elastomer device, and Izci used a hard acrylic device, while the studies by Pantin and Rose did not report the material used. The reasons for not using the device were no effect (15–34%), adverse effects, ie, uncomfortable odontologic problems (16–31%), other treatment (2–13%) and other or unknown reasons (3–22%). Adverse effects were less common in the study that used the soft elastomer device [81].

The included studies that assessed compliance reported that more than 50% of the patients still used the device after 1 year. However, compliance varied from 51% to 76% independent of the length of the observation period.

Table 5.16 *Compliance with mandibular repositioning appliances at follow-up.*

Time at follow-up	n	Still using MRA	Use of the device	Author, year, reference	Quality
7 months (mean)	144	51%	5±2 nights/ week	Izci 2005 [85]	Low
1 year	619	76%	Use/no use	Marklund 2004 [81]	Medium
2 years (mean)	192	54%	Use/no use	Rose 2002 [84]	Low
5 years	132	76%	Use/no use	Pantin 1999 [83]	Low
5.4 years (mean)	423	56%	Use/no use	Marklund 2006 [82]	Medium

MRA = Mandibular repositioning appliance

Adverse effects of mandibular repositioning appliances

Conclusions

- A minor (0.5 mm) reduction of overbite and overjet, measured as means for a group treated with a mandibular repositioning appliance, can be seen after one year follow-up (Evidence Grade 3).

- No increase in symptoms or signs in the masticatory system as a consequence of treatment could be seen in the included studies (Evidence Grade 3).

- Transient pain and discomfort in the teeth, along with hypersalivation, are the most frequent adverse effects (Evidence Grade 3).

Background

Subjective symptoms reported as adverse effects were dry mouth, excessive salivation, pain in the teeth or jaws and a feeling of change or discomfort in occlusion. Clinical signs regarded as adverse effects were changes in occlusion, measured as differences in overbite and overjet as well as loss of occlusal contacts. Symptoms in the masticatory system – such as temporomandibular joint pain or clicking, headache, jaw muscle fatigue or soreness – were also recorded.

Results

One study of high quality and 12 studies of medium quality fulfilled the inclusion criteria. Three studies of medium quality with a relatively short follow-up period of 4 weeks to 4 months found more temporary discomfort in the jaws or teeth in the morning than with placebo devices or CPAP devices [50,56,86]. This was also seen in a study of low quality [51]. In 2 studies of low quality, over 80% of the patients reported some sort of adverse effect, mostly excessive salivation or dry mouth, that they attributed to the device [83,87]. Pain, soreness or other discomfort in the teeth were also common [83,87]. Fritsch and Pantin did not report any comparative baseline data, making it difficult to compare the frequency

of symptoms at follow-up and baseline. Three studies of medium quality [88–90] and 1 case report [91] compared masticatory system symptoms – such as temporomandibular pain or clicking, headache, jaw muscle fatigue or soreness – to baseline data or to a control group without mandibular repositioning appliances. No increase in the incidence of such symptoms could be seen from these studies. There were no differences in reported or registered adverse effects between studies designed to investigate treatment effects [50,51,53–56,86,90] and those that mainly concerned adverse effects. Nor did the severity of the OSAS/snoring diagnosis seem to influence adverse effects.

There seemed to be no difference in the clinical signs of changes in the occlusion after the use of various types of devices: hard, soft, with or without full occlusal coverage. Of 11 studies – 5 of high or medium high quality [88,89,92–94], 5 of low quality [5,82,85,87,95] and 1 case report [96] – that reported on signs of occlusal changes, 10 showed reductions in overjet and overbite. These changes were usually small, less than 1 millimetre, and of no clinical significance. However, some patients appeared to be more at risk for developing larger reductions of vertical and horizontal relations, up to more than 3 millimetres, as seen in 2 cases [96] and 1 long-term follow-up study [94]. In all 12 studies with more than 1 year of follow-up, which included a total of 746 patients, a bilateral open bite was reported in 12 patients, ie, 1.6%. All of these patients used hard acrylic devices. For the different occlusal changes, no relation between the severity of the changes and the grade of protrusion of the mandible could be seen.

None of the studies with less than 5 months of follow-up reported clinical signs of changes in the occlusion. There was no difference in reported occlusal changes between studies with 2 or 4 years of follow-up. One study with 5 years of follow-up showed a more marked change in overjet and overbite of nearly 3 mm [94]. However, one prospective long term study, did not show any further changes in occlusion [82]. According to most of these studies, changes seemed to develop during the first few years of use of the device and then stabilise.

Table 5.17 *Side effects from mandibular repositioning appliances.*

Side effects	Frequency	Evidence grade	Author, year, reference	Quality
Non-structural side effects				
Pain from teeth	26–69%	3	Engleman 2002 [56] Pantin 1999 [83] Gotsopoulos 2002 [50]	Medium Low Medium
Pain from jaws/ joints/muscles	26%	–	Pantin 1999 [83]	Low
Excessive salivation	19–68%	3	Engleman 2002 [56] Fritsch 2001 [87] Johnston 2002 [51] Pantin 1999 [83] Izci 2005 [85] Gotsopoulos 2002 [50]	Medium Low Low Low Low Medium
Dry mouth	26–86%	–	Pantin 1999 [83] Fritsch 2001 [87]	Low Low
Muscle fatigue	3%	–	Fransson 2003 [88]	Medium
Tooth discomfort	59%	–	Fritsch 2001 [87]	Low
Temporary discomfort in the morning	40–50%	3	Johnston 2002 [51] Marklund 2001 [5] Randerath 2002 [86] Tan 2002 [55]	Low Low Medium Medium
Structural side effects				
Changes in overjet	<1 mm	3	Bondemark 2000 [89] Fransson 2003 [88] Fritsch 2001 [87] Marklund 2001 [5] Battagel 2005 [95] Marklund 2006 [82]** Robertson 2003 [92]	Medium Medium Low Low Low Low Medium
Changes in overjet	>1 mm	–	Almeida 2006 [94] Rose 2001 [96] (n=2)	Low Low
Changes in over-bite	<1 mm	3	Bondemark 2000 [89] Fritsch 2001 [87] Marklund 2001 [5] Battagel 2005 [95] Fransson 2004 [93] Marklund 2006 [82]** Robertson 2003 [92]	Medium Low Low Low Medium Low Medium

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Table 5.17 *continued*

Side effects	Frequency	Evidence grade	Author, year, reference	Quality
Changes in over-bite	>1 mm	–	Almeida 2006* [94] Rose 2001 [96] (n=2)	Low Low
Damaged crowns/ fillings	6%	–	Engleman 2002 [56]	Medium
Lateral open bite	14% + 2 cases	–	Fransson 2004 [93] Rose 2001 [96]	Low Medium
Occlusal changes (not defined)	14–33%	–	Pantin 1999 [83] Walker-Engström 2003 [7] Battagel 2005 [95]	Low Medium Low
Apposition of bone in mandibu-lar fossa	1 case	–	Panula 2000 [91]	Low

* ≥5 years follow-up.
** ≥5 years follow-up of earlier study.

Adverse effects of surgery

Conclusions

- The adverse effects of uvulopalatopharyngoplasty (UPPP) due to snoring or obstructive sleep apnoea include serious perioperative and postoperative complications, including death, bleeding and respiratory compromise (Evidence Grade 2). Persistent adverse effects are frequent, and difficulty in swallowing occurs in about 28% of patients (Evidence Grade 2). Voice changes are also common (Evidence Grade 3).

- The adverse effects of uvulopalatoplasty (UPP) and laser-assisted uvulo-palatoplasty (LAUP) due to snoring or obstructive sleep apnoea include serious postoperative complications (Evidence Grade 3). Persistent adverse effects occur in 50–60% of patients and difficulty swallowing in about 26% (Evidence Grade 2). Globus sensation in the throat and voice changes are common (Evidence Grade 3).

Background

We identified 48 studies that addressed the questions concerning the adverse effects of surgery due to snoring and sleep apnoea. There were

28 studies on uvulopalatopharyngoplasty (UPPP), 20 on uvulopalatoplasty (UPP) and laser-assisted uvulopalatoplasty (LAUP), and 9 on temperature-controlled radio frequency tissue volume reduction (TCRAFTA). Acute complications during the perioperative and postoperative period were reported by 27 studies, postoperative pain by 19 studies, difficulty in swallowing by 18 studies, voice problems by 6 studies, velopharyngeal stenosis and insufficiency by 6 studies, dry throat by 5 studies, taste and smell disturbances by 2 studies and breathing disturbances by 2 studies.

Men made up 69–100% of the populations. Mean age varied between 30 and 54. Mean BMI varied between 24 and 33 kg/sq m. Mean AHI varied between 5 and 59 (range 0–89). Data on age, BMI, AHI and daytime sleepiness were lacking in many studies. The observation period varied from 18 hours to 8 years. Information on the follow-up period was lacking in 5 studies.

Two studies were regarded as high quality, 32 as medium quality and 14 as low quality (Table 5.30).

Results

Uvulopalatopharyngoplasty (UPPP)

Perioperative and postoperative complications

Thirty cases of death were reported in 6 studies (Table 5.18). Respiratory compromise, bleeding, intubation difficulties, infections and cardiac arrest were the main causes of death (Table 5.18) [97–102]. A recent study of high quality comprising 3 130 operations reported perioperative death in 7 patients (0.2%) [102].

Serious perioperative and postoperative complications were reported in 0–16% [97,98,100–108]. These complications included respiratory compromise, bleeding, intubation difficulties, re-intubation, emergency tracheostomy, infections and cardiovascular complications. Postoperative pain was reported for 12–14 days [109–112]. Other complications were seroma and squamos papilloma [103,113].

Persistent complications (Table 5.19)

Persistent adverse effects were reported in 14–62% [101,114,115]. Difficulty in swallowing, including nasal regurgitation, was introduced in 13–36% of patients [114,116,117], globus sensation in 40% [115], voice changes in 7–14% [101,114,115], persistent throat dryness in 3–56% [101,118,119], taste disturbances in 7%, smell disturbances in 8% [115], velopharyngeal insufficiency in 3% [114] and velopharyngeal stenosis in occasional patients [120]. Eleven percent regretted the surgery according to one study [116].

Table 5.18 *Deaths in the perioperative and postoperative period.*

Author Year, reference	Operation	Quality	Source population	Death cases	Reasons for death
			N	n	
Esclamado et al 1989 [97]	UPPP	Medium	135	1	Intubation problems
Harmon et al 1989 [98]	UPPP	Medium	132	2	Bleeding (n=1), pulmonary embolism (n=1)
Fairbanks 1990 [99]	UPPP	Low		16	Bleeding (n=1), loss of airway (n=12), unknown (n=3)
Carenfelt et al 1993 [100]	UPPP LAUP	Low	9 000 2 900	3 1*	Cardiac arrest (n=2), bleeding (n=1), infection (n=1)
Haavisto et al 1994 [101]	UPPP	Low	101	1	Breathing difficulties and asystole (n=1)
Lysdahl et al 2000 [121]	LAUP	Medium	256	1	Infection (n=1)
Kezirian et al 2004 [102]	UPPP	High	3 130	7 *	Unknown (n=4), respiratory problems (n=2), cardiac arrest (n=1)

* Probably the same patient who died from an infection 5 days after LAUP.

LAUP = Laser-assisted uvulopalatoplasty; UPPP = Uvulopalatopharyngoplasty

Table 5.19 *Persistent adverse effects of uvulopalatopharyngoplasty (UPPP).*

	Frequency Mean, range	Evidence Grade	Author, year, references
Death	0–1.5%	2	Esclamado 1989, Harmon 1989, Haavisto 1994, Riley 1997, Mickelson 1998, Terris 2002, Osman 2000, Rombaux 2003, Kezirian 2004, Kim 2005 [97,98,101–104,106–108,122]
Persistent side effects	14–62%	3	Grøntved 2000, Hagert 2000 [114,115]
Difficulty in swallowing	28% (13–36%)	2	Grøntved 2000, Hagert 2000, Lysdahl 2002, Jäghagen 2004 [114–117]
Globus sensation	40%	Inconclusive	Hagert 2000 [115]
Voice changes	7–14%	3	Grøntved 2000, Hagert 2000 [114,115]
Smell disturbances	8%	Inconclusive	Hagert 2000 [115]
Taste disturbances	7%	Inconclusive	Hagert 2000 [115]
Velopharyngeal insufficiency	Single cases	Inconclusive	Katsantonis 1987 [120]

Uvulopalatoplasty (UPP) and laser-assisted uvulopalatoplasty (LAUP)

Perioperative and postoperative complications

One death due to septicaemia was reported in one study [100]. Postoperative complications were reported in up to 5%, including postoperative bleeding, local infections and temporal palatal incompetence [6,106,107,123]. Postoperative pain lasted for a mean of 10–18 days [109, 110,119,122,124,125].

Persistent complications (Table 5.20)

Persistent adverse effects were reported in 52–62% [115,117,126]. Difficulty in swallowing, including nasal regurgitation, was introduced in 19–29% of patients [6,115–117,126,127], globus sensation in 17–36% [115,126], voice changes in 6–10%, taste disturbances in 7%, smell disturbances in 8% [115], increased vomiting reflexes in 4% [126] and velopharyngeal stenosis in one patient [119]. Thirteen to twenty-two percent regretted the surgery [116,128].

Table 5.20 *Persistent adverse effects of uvulopalatoplasty (UPP and LAUP).*

	Frequency Mean, range	**Evidence Grade**	**Author, year, reference**
Death	Single case		Carenfelt 1993 [100] Lysdahl 2002 [116]
Persistent side effects	57% (52–62%)	3	Hultcrantz 1999 [126] Hagert 2000 [115] Berger 2003 [119]
Difficulty in swallowing	26% (19–29%)	2	Levring-Jäghagen 1999 [127] Lysdahl 2002 [116] Hultcrantz 1999 [126] Jäghagen 2004 [117] Ferguson 2003 [6] Hagert 2000 [115]
Globus sensation in throat	17–36%	3	Hultcrantz 1999 [126] Hagert 2000 [115]
Voice changes	6–10%	3	Remacle 1999 [109] Hagert 2000 [115]
Smell disturbances	8%	Inconclusive	Hagert 2000 [115]
Taste disturbances	7%	Inconclusive	Hagert 2000 [115]
Velopharyngeal stenosis	Single cases	Inconclusive	Berger 2003 [119]

Temperature-controlled radio frequency tissue volume reduction (TCRAFTA)

Perioperative and postoperative complications

The perioperative and postoperative complications reported were palatal mucosal breakdown or mucosal ulcers in 3–37% of patients [129–133], palatal fistula in 2% [107,132], uvula loss in 2–7% [131,132], haemorrhage in 5% [132], infections [107], transient choking sensation in 28% [129], transient voice change in 11% [129], abnormal sensation in 19% [129], difficulty swallowing in 13% and pain in 19% [129]. Treatment of the tongue in 1 study of 18 patients reported 1 tongue base abscess and 3 patients with severe tongue swellings requiring hospital admission [130]. Another study on treatment of the tongue reported mouth floor oedema in 2 of 30 patients and tongue base abscess in 2 patients [131]. Postoperative pain lasted for 3–7 days [110,122,130]. But 1 randomised controlled trial that followed 48 patients reported no difference in adverse effects ie, pain and acute complications, within 3 weeks of surgery [48]. No long-term follow-up studies on the adverse effects of TCRAFTA were identified.

Table 5.21 *Data extraction. Treatment effect from RCT studies.*

Author Year Reference Country	**1. Nature of control 2. Design 3. Inclusion criteria**	**Baseline characteristics 1. Number randomised 2. Age (mean, SD) 3. Female (%) 4. BMI 5. AHI (mean, SD) 6. ESS (mean, SD) 7. Hypertensive (%) 8. SBP (mean, SD) 9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Ballester et al 1999 [36] Spain	1. Weight reduction 2. Parallel 3. AHI >15 + severe EDS or AHI >30 + mild EDS	1. 105 2. 53±10 3. 12 4. 32±5 5. 56±20 6. 12±5 7. Missing data 8. Missing data 9. Missing data	3 months	0
Barbé et al 2001 [43] Spain	1. Sham CPAP 2. Parallel 3. AHI >30, ESS <10	1. 55 2. 53±15 3. 9 4. 29±5 5. 55±25 6. 7±3 7. 0 8. 124±15 9. 78±11	6 weeks	1
Barnes et al 2002 [44] Australia	1. Placebo pill 2. Cross-over 3. AHI 5–30	1. 42 2. 45.5±10.7 3. 17 4. 30.2±4.8 5. 13±6.3 6. 11.3±5.0 7. 25 8. 130.3±10.5 9. 81.6±7.5	8 weeks	10

End points	CPAP			Placebo/conservative			Quality rating 1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
	N	Mean	SD	N	Mean	SD	
ESS		CPAP			Weight reduction		Medium
NHP (energy)	68	5.6	4.1	37	10.6	6.1	1. 1
	68	12.7	27.2	37	22.2	30.4	2. 0
							3. 1
							4. 0
							5. 0
							6. 2
MSLT		CPAP			Placebo		High
ESS	29	13	5	25	11	5	1. 1
FOSQ	29	8	3	25	8	5	2. 0
SBP	29	108	11	25	110	10	3. 1
DBP	29	124	11	25	122	15	4. 1
	29	79	5	25	77	10	5. 1
							6. 4
MSLT		CPAP			Placebo		Medium
ESS	28	11.5	4.9	32	12.6	5.1	1. 1
SF-36 (vitality)	28	8.9	4.9	32	9.5	5.1	2. 0
FOSQ	28	59.8	19.4	32	59.4	19.0	3. 0
SBP	28	3.45	0.43	31	3.38	0.40	4. 0
DBP	27	130.3	9.8	29	129.0	12.0	5. 1
	27	81.0	7.2	29	78.7	15.3	6. 2

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Table 5.21 *continued*

Author Year Reference Country	**1. Nature of control 2. Design 3. Inclusion criteria**	**Baseline characteristics 1. Number randomised 2. Age (mean, SD) 3. Female (%) 4. BMI 5. AHI (mean, SD) 6. ESS (mean, SD) 7. Hypertensive (%) 8. SBP (mean, SD) 9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Barnes et al 2004 [49] Australia	1. Placebo pill 2. Cross-over 3. AHI 5–30	1. 104 2. 46±9 3. 21 4. 31±5 5. 22±11 6. 10±3 7. 15 8. 126.5±9.4 9. 76.3±7.5	3 months	20
Becker et al 2003 [47] Germany	1. Sham CPAP 2. Parallel 3. AHI >5 + ESS >10	1. 60 2. 53±9 3. 10 4. 33±6 5. 64±22 6. 14±3 7. Missing data 8. Missing data 9. Missing data	2 months	28
Chakravorty et al 2002 [45] United Kingdom	1. Lifestyle 2. Parallel 3. AHI >15	1. 71 2. 50±11 3. Missing data 4. 37±12 5. 47±25 6. 15±5 7. Missing data 8. Missing data 9. Missing data	3 months	18

End points	CPAP			Placebo/conservative			Quality rating 1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
	N	Mean	SD	N	Mean	SD	
AHI		CPAP			Placebo		Medium
MWT	89	4.8	4.7	90	20.3	10.4	1. 1
ESS	89	30.0	8.5	90	28.0	8.5	2. 0
FOSQ	89	9.2	3.8	90	10.2	3.8	3. 0
SF-36 (vitality)	89	3.3	0.9	90	3.3	0.9	4. 0
SBP	88	58.7	18.2	88	56.0	19.3	5. 1
DBP	89	127.3	11.3	90	128.2	11.4	6. 2
	89	76.7	7.5	90	77.3	6.6	
AHI		CPAP			Placebo		Medium
ESS	16	3.4	3.1	16	33.4	29.2	1. 1
SBP	16	5.1	3.8	16	8.9	5.0	2. 1
DBP	16	126.4	14.3	16	137.3	11.1	3. 1
	16	73.1	10.5	16	82.1	9.1	4. 0
							5. 0
							6. 3
AHI		CPAP			Conservative		Medium
ESS	32	8	28	21	34	21	1. 1
	32	8	6.4	21	11	5	2. 0
							3. 1
							4. 0
							5. 1
							6. 3

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Table 5.21 *continued*

Author **Year** **Reference** **Country**	**1. Nature of control** **2. Design** **3. Inclusion criteria**	**Baseline characteristics** **1. Number randomised** **2. Age (mean, SD)** **3. Female (%)** **4. BMI** **5. AHI (mean, SD)** **6. ESS (mean, SD)** **7. Hypertensive (%)** **8. SBP (mean, SD)** **9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Engleman et al 1994 [33] United Kingdom	1. Placebo pill 2. Cross-over 3. AHI >5	1. 35 2. 49±8 3. 19 4. 33±9 5. Median: 28 6. Missing data 7. Missing data 8. Missing data 9. Missing data	4 weeks	3
Engleman et al 1998 [34] United Kingdom	1. Placebo pill 2. Cross-over 3. AHI >15	1. 23 2. 47±12 3. 9 4. 30±7 5. 43±37 6. 12±4 7. Missing data 8. Missing data 9. Missing data	4 weeks	1
Engleman et al 1999 [37] United Kingdom	1. Placebo pill 2. Cross-over 3. AHI 5–15	1. 37 2. 44±8 3. 38 4. 30±5 5. 10±3 6. 13±3 7. Missing data 8. Missing data 9. Missing data	4 weeks	3

End points	CPAP			Placebo/conservative			Quality rating 1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
	N	Mean	SD	N	Mean	SD	
MSLT	CPAP			Placebo			Medium
	32	7.2	4.0	32	6.1	4.0	1. 1 2. 0 3. 0 4. 0 5. 1 6. 2
MSLT ESS	CPAP			Placebo			Medium
	23 23	9.2 6	3.9 3	23 23	6.8 12	4.3 4	1. 1 2. 0 3. 0 4. 0 5. 1 6. 2
MWT ESS SF-36 (vitality)	CPAP			Placebo			Medium
	34 34 34	16.2 8 58	10.6 4 19	34 34 34	14.4 11 46	8.5 4 23	1. 1 2. 0 3. 0 4. 0 5. 1 6. 2

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Table 5.21 *continued*

Author Year Reference Country	**1. Nature of control 2. Design 3. Inclusion criteria**	**Baseline characteristics 1. Number randomised 2. Age (mean, SD) 3. Female (%) 4. BMI 5. AHI (mean, SD) 6. ESS (mean, SD) 7. Hypertensive (%) 8. SBP (mean, SD) 9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Faccenda et al 2001 [39] United Kingdom	1. Placebo pill 2. Cross-over 3. AHI >15	1. 71 2. Median: 50 3. 17 4. 30±5 5. Median: 35 6. Median: 15 7. Missing data 8. Missing data 9. Missing data	4 weeks	3
Jenkinson et al 1999 [38] United Kingdom	1. Sham CPAP 2. Parallel 3. ODI 4 >10 + ESS >10	1. 107 2. Median: 49 3. 0 4. 35±6 5. Median ODI-4: 30.8 6. Median: 16.5 7. Missing data 8. Missing data 9. Missing data	4 weeks	6
McArdle et al 2001 [40] United Kingdom	1. Placebo pill 2. Cross-over 3. PSG AHI >15 or Non-PSG AHI >30 ESS from letter to authors	1. 23 2. 52±11 3. 8 4. 31±5 5. Median: 42 6. Median: 14 7. Missing data 8. Missing data 9. Missing data	4 weeks	1

End points	CPAP			Placebo/conservative			Quality rating 1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
	N	Mean	SD	N	Mean	SD	
ESS		CPAP			Placebo		Medium
FOSQ							
SBP	68	10.1	5.8	68	12.5	6.6	1. 1
DBP	68	111.3	17.0	68	100.6	16.0	2. 0
	68	126.9	10.7	68	128.2	9.9	3. 0
	68	77.8	8.2	68	79.2	7.4	4. 0 5. 1 6. 2
MWT		CPAP			Placebo		High
ESS							
SF-36 (vitality)	52	30.4	10.0	49	23.9	10.7	1. 1
	52	7.5	4.5	49	12.3	4.8	2. 1
	52	73.0	17.0	49	50.9	20.5	3. 1 4. 1 5. 1 6. 5
ESS		CPAP			Placebo		High
	22	8	4.5	22	12.1	4.7	1. 1 2. 1 3. 1 4. 0 5. 1 6. 4

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Table 5.21 *continued*

Author Year Reference Country	**1. Nature of control 2. Design 3. Inclusion criteria**	**Baseline characteristics 1. Number randomised 2. Age (mean, SD) 3. Female (%) 4. BMI 5. AHI (mean, SD) 6. ESS (mean, SD) 7. Hypertensive (%) 8. SBP (mean, SD) 9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Monasterio et al 2001 [41] Spain	1. Conservative 2. Parallel 3. AHI 10–30	1. 142 2. 54±9 3. 14 4. 29±4 5. 20±6 6. 13±5 7. Missing data 8. Missing data 9. Missing data	6 months	17
Montserrat et al 2001 [42] Spain	1. Sham CPAP 2. Parallel 3. AHI >10 + EDS	1. 47 2. 54±10 3. 9 4. 31±6 5. 54±19 6. 15±7 7. Missing data 8. Missing data 9. Missing data	6 weeks	2
Pepperell et al 2002 [46] United Kingdom	1. Sham CPAP 2. Parallel 3. ODI4 >10 + ESS >9	1. 118 2. 50±10 3. 0 4. 35±7 5. ODI4: 37±20 6. 16±4 7. 19 8. 134±2 9. 85±1	4 weeks	23

End points	CPAP			Placebo/conservative			Quality rating 1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
	N	Mean	SD	N	Mean	SD	
AHI	**CPAP**			**Conservative**			Medium
MSLT	66	6	8	59	17	10	
ESS	20	10	5	20	11	5	1. 1
FOSQ	66	9.6	5.5	59	11.8	5.2	2. 0
	66	106	20	59	102	21	3. 1 4. 0 5. 1 6. 3
ESS	**CPAP**			**Placebo**			High
FOSQ	23	6.7	3.3	22	14.6	5.1	
SF-36	23	109.4	12.5	22	100.7	20.6	1. 1
(vitality)	23	69.4	27.3	22	68.4	20.5	2. 1 3. 1 4. 0 5. 1 6. 4
SBP	**CPAP**			**Placebo**			High
DBP	48	130.2	14.6	47	135.9	17.7	
	48	82.7	9.2	47	85.9	8.5	1. 1 2. 1 3. 1 4. 1 5. 1 6. 5

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Table 5.21 *continued*

Author Year Reference Country	**1. Nature of control 2. Design 3. Inclusion criteria**	**Baseline characteristics 1. Number randomised 2. Age (mean, SD) 3. Female (%) 4. BMI 5. AHI (mean, SD) 6. ESS (mean, SD) 7. Hypertensive (%) 8. SBP (mean, SD) 9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Redline et al 1998 [35] USA	1. Weight reduction and nasal dilators 2. Parallel 3. AHI 5–30 Ads in the area	1. 111 2. 49±10 3. 48 4. 33±7 5. 13.3±10 6. 10±5 7. Missing data 8. Missing data 9. Missing data	8 weeks	14
Woodson et al 2003 [48] USA	1. Sham TCRAFTA 2. Parallel design 3. AHI 10–30	1. 60 2. 49±8 3. 28 4. 29±4 5. 18±9 6. 12±4 7. Missing data 8. Missing data 9. Missing data	8 weeks	16
Barnes et al 2004 [49] Australia	1. Placebo pill 2. Cross-over 3. AHI 5–30	1. 104 2. 46±9 3. 21 4. 31±5 5. 22±11 6. 10±3 7. 15 8. 126.5±9.4 9. 76.3±7.5	3 months	24

End points	CPAP			Placebo/conservative			Quality rating 1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
	N	Mean	SD	N	Mean	SD	
AHI	**CPAP**			**Placebo**			High
MSLT	51	4.7	7.2	46	9.8	9.3	1. 1
ESS	51	10.4	4.8	46	10.3	5.0	2. 0
	51	8.9	4.3	46	10.2	5.6	3. 1
							4. 1
							5. 1
							6. 4
AHI	**CPAP**			**Placebo**			High
ESS	19	4.6	2.7	25	13.6	7.8	1. 1
FOSQ	19	10.3	5.0	25	10.6	3.5	2. 1
	19	17.5	2.6	25	17.2	2.1	3. 1
							4. 0
							5. 1
							6. 4
AHI	**MRA**			**Placebo**			Medium
MWT	85	14.0	10.1	90	20.3	10.4	1. 1
ESS	85	29.6	8.3	90	28.0	8.5	2. 0
FOSQ	85	9.2	3.7	90	10.2	3.8	3. 0
SF-36 (vitality)	85	3.3	0.9	90	3.3	0.9	4. 0
SBP	86	56.6	21.1	88	56.0	19.3	5. 1
DBP	85	126.7	9.2	90	128.2	11.4	6. 2
	85	76.3	6.5	90	77.3	6.6	

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Table 5.21 *continued*

Author Year Reference Country	**1. Nature of control 2. Design 3. Inclusion criteria**	**Baseline characteristics 1. Number randomised 2. Age (mean, SD) 3. Female (%) 4. BMI 5. AHI (mean, SD) 6. ESS (mean, SD) 7. Hypertensive (%) 8. SBP (mean, SD) 9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Gotsopoulos et al 2002 [50] Australia	1. Sham MRA 2. Cross-over 3. RDI >110	1. 85 2. 48±11 3. 19 4. 29±5 5. 27±17 6. 11±5 7. Missing data 8. Missing data 9. Missing data	4 weeks	12
Gotsopoulos et al 2004 [52] Australia	1. Sham MRA 2. Cross-over 3. AHI >10 AHI not used since same patients as in Gotsopoulos 2002 [50]	1. 67 2. 48±11 3. 21 4. 29±5 5. 27±15 6. Missing data 7. 39 8. 127.3±10.6 9. 77.7±7.4	4 weeks	6
Johnston et al 2002 [51] Ireland	1. Sham MRA 2. Cross-over 3. ODI4 >10	1. 21 2. 55.1±6.9 3. 19 4. 31.6±5.9 5. 31.9±21.2 6. 14±6 7. Missing data 8. Missing data 9. Missing data	4–6 weeks	1

End points	CPAP			Placebo/conservative			Quality rating 1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
	N	Mean	SD	N	Mean	SD	
AHI	**MRA**			**Placebo**			Medium
MSLT	73	12	17	73	25	17	1. 1
ESS	73	10.3	4.3	73	9.1	4.3	2. 0
	73	7	8.5	73	9	8.5	3. 0
							4. 1
							5. 1
							6. 3
SBP	**MRA**			**Placebo**			High
DBP	61	125.3	10.2	61	126.9	10.2	1. 1
	61	76.2	7.0	61	78.0	6.2	2. 1
							3. 0
							4. 1
							5. 1
							6. 4
AHI	**MRA**			**Placebo**			Medium
ESS	20	22.9	22.8	20	37.7	24.9	1. 1
	18	11.6	6.7	18	12.6	6.3	2. 0
							3. 0
							4. 0
							5. 1
							6. 2

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Table 5.21 *continued*

Author Year Reference Country	**1. Nature of control 2. Design 3. Inclusion criteria**	**Baseline characteristics 1. Number randomised 2. Age (mean, SD) 3. Female (%) 4. BMI 5. AHI (mean, SD) 6. ESS (mean, SD) 7. Hypertensive (%) 8. SBP (mean, SD) 9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Engleman et al 2002 [56] United Kingdom	1. MRA vs CPAP 2. Cross-over 3. AHI >5 + ESS >8	1. 51 2. 46±9 3. 25 4. 29±4 5. 31±26 6. 14±4 7. Missing data 8. Missing data 9. Missing data	8 weeks	3
Ferguson et al 1996 [53] Canada	1. MRA vs CPAP 2. Cross-over 3. AHI 15–50	1. 27 2. 46±11 3. 11 4. 30±5 5. 25±9 6. Missing data 7. Missing data 8. Missing data 9. Missing data	4 months	2
Ferguson et al 1997 [54] Canada	1. MRA vs CPAP 2. Cross-over 3. AHI 15–55	1. 24 2. 44±11 3. 21 4. 32±8 5. 27±12 6. 11±3 7. Missing data 8. Missing data 9. Missing data	4 months	4

End points	CPAP			Placebo/conservative			Quality rating 1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
	N	Mean	SD	N	Mean	SD	
AHI	**CPAP**			**MRA**			Medium
MWT	48	8	6	48	15	16	1. 1
ESS	48	24	12	48	22	12	2. 0
FOSQ	48	8	5	48	12	5	3. 0
	48	14	2	48	13	3	4. 0 5. 1 6. 2
AHI	**CPAP**			**MRA**			Medium
	25	3.6	1.7	25	9.7	7.3	1. 1 2. 0 3. 0 4. 0 5. 1 6. 2
AHI	**CPAP**			**MRA**			Medium
ESS	20	4.0	2.2	20	14.2	14.7	1. 1
	20	5.1	3.3	20	4.7	2.6	2. 0 3. 0 4. 0 5. 1 6. 2

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Table 5.21 *continued*

Author Year Reference Country	**1. Nature of control 2. Design 3. Inclusion criteria**	**Baseline characteristics 1. Number randomised 2. Age (mean, SD) 3. Female (%) 4. BMI 5. AHI (mean, SD) 6. ESS (mean, SD) 7. Hypertensive (%) 8. SBP (mean, SD) 9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Tan et al 2002 [55] United Kingdom	1. MRA vs CPAP 2. Cross-over 3. AHI 10–50	1. 24 2. 51±10 3. 17 4. 32±7 5. 22±10 6. 13±5 7. Missing data 8. Missing data 9. Missing data	2 months	0
Ferguson et al 2003 [6] Canada	1. No treatment 2. Parallel 3. AHI 10–27	1. 46 2. 45±8 3. 24 4. 32±5 5. 17±4 6. 10±4 7. Missing data 8. Missing data 9. Missing data	7 months	1
Larossa et al 2004 [57] Spain	1. LAUP vs sham LAUP + placebo pill 2. Parallel 3. AHI <30	1. 28 2. 44±7 3. 0 4. 27±3 5. 15±13 6. 11±5 7. Missing data 8. Missing data 9. Missing data	3 months	3

End points	CPAP			Placebo/conservative			Quality rating
	N	Mean	SD	N	Mean	SD	1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
AHI		**CPAP**			**MRA**		Medium
ESS	24	3.1	2.8	24	8.0	10.9	1. 1
	24	8.1	4.1	24	9.0	5.1	2. 0 3. 0 4. 0 5. 1 6. 2
AHI		**LAUP**			**No treatment**		Medium
ESS	21	14.7	7.5	24	22.7	15.2	1. 1
	21	9.3	3.8	24	10.8	9.3	2. 0 3. 1 4. 0 5. 1 6. 3
AHI		**LAUP**			**Placebo**		Medium
ESS	13	15.1	17.5	12	11.5	10.7	1. 1
	13	9.6	3.8	12	10.5	5.4	2. 0 3. 1 4. 0 5. 1 6. 3

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Table 5.21 *continued*

Author Year Reference Country	**1. Nature of control 2. Design 3. Inclusion criteria**	**Baseline characteristics 1. Number randomised 2. Age (mean, SD) 3. Female (%) 4. BMI 5. AHI (mean, SD) 6. ESS (mean, SD) 7. Hypertensive (%) 8. SBP (mean, SD) 9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Woodson et al 2003 [48] USA	1. Sham TCRAFTA 2. Parallel design 3. AHI 10–30	1. 60 2. 48±9 3. 20 4. 28±4 5. 18±9 6. 12±4 7. Missing data 8. Missing data 9. Missing data	8 weeks	12
Wilhelmsson et al 1999 [58] Sweden	1. UPPP vs MRA 2. Parallel 3. AI 5–25	1. 95 2. 50 3. 0 4. 27 5. 19±9 6. Missing data 7. Missing data 8. Missing data 9. Missing data	1 year	15
Cahali et al 2004 [59] Brazil	1. Lateral pharyngo-plasty (LAUP) vs UPPP 2. Parallel 3. AHI >10, failed CPAP	1. 29 2. Missing data 3. Missing data 4. 29±5 5. 39±22 6. 14±12 7. Missing data 8. Missing data 9. Missing data	8 months	2

End points	CPAP			Placebo/conservative			Quality rating 1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
	N	Mean	SD	N	Mean	SD	
AHI	**TCRAFTA**			**Placebo**			High
ESS	23	16.8	13,8	25	13.6	7.8	1. 1
FOSQ	23	9.8	3.9	25	10.6	3.5	2. 1
	23	17.7	2.0	25	17.2	2.1	3. 1 4. 1 5. 1 6. 5
AHI	**UPPP**			**MRA**			High
	43	10.4	9.3	37	5.9	9.0	1. 1 2. 1 3. 1 4. 0 5. 1 6. 4 No ITT. 8 drop-outs in MRA were not studied at follow-up
AHI	**Lateral pharyngoplasty**			**UPPP**			Medium
	15	15.5	10.4	12	30.0	21.6	1. 1 2. 0 3. 1 4. 0 5. 1 6. 3

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Table 5.21 *continued*

Author Year Reference Country	**1. Nature of control 2. Design 3. Inclusion criteria**	**Baseline characteristics 1. Number randomised 2. Age (mean, SD) 3. Female (%) 4. BMI 5. AHI (mean, SD) 6. ESS (mean, SD) 7. Hypertensive (%) 8. SBP (mean, SD) 9. DBP (mean, SD)**	**Follow-up time**	**Number lost to follow-up**
Puhan et al 2006 [60] Switzerland	1. Waiting list for didgeridoo 2. Parallel 3. Snoring + AHI 15–30 age >18	1. 25 2. 48.6±7.4 3. 16 4. 25.8±3.4 5. 21.2±4.7 6. 11.5±4.8 7. Missing data 8. Missing data 9. Missing data	4 months	0

AHI = Apnoea-hypopnoea index; CPAP = Continuous positive airways pressure; DBP = Diastolic blood pressure; EDS = Exessive day time sleepiness; ESS = Epworth sleepiness scale; FOSQ = Functional outcome of sleep questionnaire; LAUP = Laser-assisted uvulopalatoplasty; MRA = Mandibular repositioning appliance; MSLT = Multiple sleep latency test;

End points	CPAP			Placebo/conservative			Quality rating 1. RCT? 2. Concealed allocation? 3. Patients blinded? 4. Investigators blinded? 5. Withdrawals described? 6. Sum of 1–5
	N	Mean	SD	N	Mean	SD	
AHI	Didgeridoo			No treatment			Medium
ESS	14	11.6	8.1	11	15.4	9.8	1. 1
SF-36 (vitality)	14	7.4	2.3	11	9.6	6.0	2. 0
	14	48.6	15.2	11	53.0	11.1	3. 1 4. 0 5. 1 6. 3

MWT = Maintenance of wakefulness test; NHP = Nottingham health profile; ODI = Oxygen desaturation index; PSG = Polysomnography; SBP = Systolic blood pressure; SF-36 = Short form 36; TCRAFTA = Temperature-controlled radio frequency tissue volume ablation; UPPP = Uvulopalatopharyngoplasty

Table 5.22 *Excluded studies. Treatment effect from CPAP, oral appliances and operations.*

Reason for exclusion	References
Follow-up shorter than 4 weeks	[134–151]
Do not include any endpoint of interest for this review	[71,136,152–154]
Effect of blood pressure on selected and healthy patients without hypertension	[155]
Low quality	[86]
Only baseline data	[156]
Less than 20 patients	[122,136,143,151,157–160]
Studies on selected patients with heart failure who did not seek medical attention for a recording, and without any symptoms of sleep apnea syndrome	[161,162]
Compare one mandibular repositioning appliance with another	[7,8,84]
Before and after study, no RCT	[163–169]

RCT = Randomised controlled trial

Table 5.23 *Excluded studies. Treatment effect from pacemakers and sleep positions.*

Reason for exclusion	References
Less than 20 patients	[170–173]
Follow-up shorter than 4 weeks	[174,175]

Table 5.24 *Excluded studies. Treatment effect from pharmacological drugs.*

Author, year, reference	n<20	Follow-up <4 weeks	Not the ESS, MSLT or MWT
Sex hormones			
Collop, 1994 [176]	X	X	X
Cook, 1989 [177]	X	X	X
Keefe, 1999 [178]	X	X	X
Liu, 2003 [179]	X	X	–
Ventilatory stimulants			
Espinoza, 1987 [180]	X	X	X
Mulloy, 1992 [181]	X	–	X
Oberndorfer, 2000 [182]	–	X	X
Hein, 2000 [183]	X	X	X
Guilleminault, 1983 [184]	–	X	X

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Table 5.24 *continued*

Author, year, reference	n<20	Follow-up <4 weeks	Not the ESS, MSLT or MWT
Anti-depressants			
Brownell, 1982 [185]	X	–	X
Brownell, 1983 [186]	X	–	X
Stepanski, 1988 [187]	X	X	X
Whyte, 1988 [188]	X	X	X
Hanzel, 1991 [189]	X	X	X
Berry, 1999 [190]	X	X	X
Kraiczi, 1999 [191]	X	–	X
Anxiolytic drugs			
Mendelson, 1991 [192]	X	X	X
Berry, 1995 [193]	X	X	X
Camacho, 1995 [194]	X	X	X
Cirignotta, 1988 [195]	X	X	X
Hoijer, 1994 [196]	X	X	X
Steroids			
Craig, 1998 [197]	–	X	–
Kiely, 2004 [198]	X	–	X
Immunosuppressive			
Vgontzas, 2004 [199]	X	–	–
Anti-hypertensive			
Mayer, 1990 [200]	X	X	X
Issa, 1992 [201]	X	X	X
Opoid antagonists			
Suratt, 1986 [202]	X	X	X
Acetylcholinesterase inhibitor			
Hanzel, 1991 [189]	X	–	X
Hedner, 2003 [258]	X	X	X
Glutamate antagonist			
Hedner, 1996 [203]	X	X	X
Seretonin (5HT3) receptorantagonists			
Stradling, 2003 [204]	X	X	X
Rasche, 1998 [205]	–	X	X
NMDA antagonist			
Torvaldsson, 2005 [206]	X	X	X
Nicotine tooth patch			
Zevin, 2003 [207]	X	X	–

ESS = Epworth sleepiness scale; MSLT = Multiple sleep latency test;
MWT = Maintenance of wakefulness test

Table 5.25 *Data extraction. Compliance to CPAP.*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**Design** **Inclusion criteria**	**% women** **Age** **BMI** **AHI** **ESS**
Pépin et al 1995 [61] France	1. 193 2. – 3. 19±7 months	Consecutive patients receiving CPAP 1983–1991 in two centres. AHI >10	15% 59±12 years 32±7 kg/m^2 53±25 Missing data
Noseda et al 1997 [72] Belgium	1. 325 2. – 3. Median: 2.7 (0.5–5.5) years	Patients on CPAP from 1991 to 1995. AHI >20	11% 52±10 years 34± 5 57±27 Missing data
Meslier et al 1998 [62] France	1. 3 225 2. 5 339 3. (0.5–>4 years)	Questionnaire to all registered patients in 28 centres who had used CPAP >6 months	13% 59±11 years Missing data Missing data Missing data
Kalan et al 1999 [70] United Kingdom	1. 301 2. 354 3. (0.5–11 years)	Questionnaire to all patients treated with CPAP for >6 months during 1989–1998	10% 54±11 years 75% of the patients were obese with a mean BMI of 32 (24–41) kg/m^2 Missing data Missing data
Lojander et al 1999 [64] Finland	1. 151 2. 194 3. Median: 30 (3–70) months	Consecutive patients on CPAP 1990–1995. Questionnaire	15% 55 (31–76) years 34 (17–54) kg/m^2 ODI-4: 41 (4–108)
McArdle et al 1999 [63] United Kingdom	1. 1 155 2. 1 211 3. 22 months (inter-quartile range 12–36)	Consecutive patients who had received CPAP 1986–1997	14% 50 (43–58) years 30 (27–35) kg/m^2 31 (18–53) 12 (8–16)

	Type of device Pressure	Compliance	Follow-up	Quality	Comments
	Fixed CPAP 11±2 cm 33% used humidifiers	95% still used CPAP mean use: 6.5±3 hours (time counter)	To a chest physician every 6 months. Telephone when needed	Low	
	CPAP n=311 BiPAP n=10 Auto-CPAP n=4	77% used CPAP 4.7±2.4 (0.0–8.6) hours/night (time counters). 73% used CPAP >21 hours/ week	After 4–6 weeks, then on individual basis	Medium	Patients stopped CPAP because doctors did not allow them to continue or because of intolerance
	12 different CPAP 9.9±2.4 cm 18% used humidifiers	100% had used it for >6 months mean use: 6.6±2.3 hours/night, 89% every night and 73% every night and the whole night. 78% used it >1 year	Missing data	Low	Predictor for success: effect on snoring, EDS and good tolerance to mask. Selected and not consecutive patients
	Fixed CPAP Missing data	No mean time of follow-up given. 97% used CPAP during 7.8±4 hours/night self reported use. 83% of patients used CPAP every night	Once a year. Telephone when needed	Low	Lower compliance when dryness nose, leakage, noisy machine. Selected and not consecutive patients
	Fixed CPAP 11 (4–20) cm	71% still using CPAP. 79% of them used CPAP >5 nights, >4 hours/night self reported	3 to 4 times a year to both a doctor and a nurse	Medium	Only self reported data on use/hour
	Fixed CPAP 8 (7–10) cm	4.5% refused home CPAP at titration. 77% used it at 22 months 5.6 (3.8–7) hours/night (time counter). Of these, 76% used it >25 hours/ week. 84% used CPAP after 1 year and 68% after 4 years	Telephone by a nurse after 2 weeks. Clinical follow-up within 3 months. Then individually but always once a year	Medium	CPAP free of charge. Success: Male gender, age <50, ESS >10, BMI >30, CPAP >8, arousals >32, good compliance at start. Death, intolerance, other treatment or cure were reasons for non-compliance

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Table 5.25 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**Design** **Inclusion criteria**	**% women** **Age** **BMI** **AHI** **ESS**
Grothe et al 2000 [67] Sweden	1. 149 2. 149 3. 30 (25–35) months	Consecutive patients trying CPAP during 1994	16% Questionnaire 57±12 30±5.1 33.2 Missing data
Lacassagne et al 2000 [66] France	1. 248 2. 248 3. 39.5±20.4 months	Prospective Consecutive patients evaluating CPAP 1990–1995	10% 57±11 years 33.4±7.27 37.7±22.4
Popescu et al 2001 [68] United Kingdom	1. 187 2. 209 3. 1 year	Prospective Patients who had been offered a CPAP a least one year before June 1995–June 1998	9% 51.0±10.6 years 34.6±7.7 kg/m^2 38.1±22.9 15 (11–18)
Hollandt et al 2003 [65] Germany	1. 108 2. 109 3. 43±25 (0.8–109) months	Prospective Consecutive patients receiving CPAP 1992–1997	Missing data 54±9.7 years 32±6 kg/m^2 47±19 15.4±4.7

AHI = Apnoea-hypopnoea index; BMI = Body mass index; CPAP= Continuous positive airway pressure; EDS = Excessive daytime sleepiness; ESS = Epworth sleepiness scale; ITT = Intention-to-treat

	Type of device Pressure	Compliance	Follow-up	Quality	Comments
	Fixed CPAP 8.5 (2.4) cm	27 (18%) rejected CPAP directly after trial. 74/122 (61%) of patients prescribed CPAP used it after 30 months (ITT 50%). Information from time counters in 47/74: 4.4±2.4 hours/day	Patients were contacted at 2 weeks. Follow-up at 9, 18, 30 months	Medium	
	Fixed CPAP 8.6±1.6 cm	9.2% refused CPAP at start. At 39.5±20.4 months 76% (ITT 69%) continued with CPAP use 6.2±2.7 hours/day. 16% quit CPAP, 6% dead	After 1 month then after 3 months and then every 6 months	Medium	No difference in clinical parameters of patients stopped use CPAP and compliant patients
	Fixed CPAP Auto-CPAP titration	8 (6.2%) did not take CPAP home. One year 128/187 68,5% with a mean use of 5.0±2.4 hours/night. 76.6% used it >21 hours/week (time counter)	After 2 weeks then after 3–6 months and then annually	High	First a 2 weeks loan then 2 weeks without CPAP then CPAP again. Good compliance: high BMI, male, high AHI, good effect on AHI, ESS, feeling better with CPAP
	Fixed CPAP 9±3 cm	6 (5.5%) refused CPAP after the first night. 43±25 months: 87 (85%) (ITT 81%) used CPAP. 47% used it ≥5 hours/night	Missing data	Medium	EDS and ESS predicted success. Inconvenience and lack of improvement predicted failure

Table 5.26 *Data extraction. Side effects from CPAP.*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**Design** **Inclusion criteria**	**% women** **Age** **BMI** **AHI** **ESS**
Hohenhaus-Beer et al 1995 [77] Germany	1. 87 2. 104 3. 9.3 months	Questionnaire to 104 subjects on CPAP with AHI >10 Unclear whether consecutive patients	15% 54.9±9.1 29.8±5.5 kg/m^2 Missing data Missing data
Pépin et al 1995 [61] France	1. 193 2. – 3. 19±7 months	Questionnaire to consecutive patients receiving CPAP 1983–1991 in two centres. AHI >10	15% 59±12 years 32±7 kg/m^2 53±25 Missing data
Engleman et al 1996 [74] United Kingdom	1. 215 2. 253 3. 21 (0.5–97) months	Questionnaire to all patients who had received CPAP before 1994 and used it for >2 weeks. AHI >5 + symptoms of EDS	10% 53±10 years Missing data 47±38 15±6
Meslier et al 1998 [62] France	1. 3 225 2. 5 339 3. >6 months (0.5–>4 years), 78% >1 year	Questionnaire to all registered patients in 28 centres who had used CPAP >6 months	13% 59±11 years Missing data Missing data Missing data
Brander et al 1999 [73] Finland	1. 49 2. 52 3. 6 months	Prospective Consecutive patients on CPAP	24% 54±7 years 35±6 kg/m^2 ODI-4: 43±19 Missing data

	Type of device Pressure	Side effects	Quality Comments
	Fixed CPAP Missing data 20 patients used humidifiers	Mask discomfort 53%, pain nasal bridge/lip 33%, noisy CPAP 40%, noisy CPAP for partner 36%, transport problems with CPAP 7%, sexual disturbance 11%, dry mouth 44%, nasal stuffiness 27%, eye pain 14%, chest pain 11%, dry nose/mouth among subjects without humidifiers	Medium for device. Low for other side effects
	Fixed nCPAP 11±2 cm 33% used humidifiers	Pain bridge nose 30%, air leaks 20%, dry nose/mouth 65%, sneeze and nasal drip 35%, nasal congestion 25%, nose bleeding 4%, sinusitis 5%, noisy CPAP 34%, partner complains of noisy CPAP 50%, CPAP too cumbersome 20%. More side effects due to silicone mask than too individually moulded masks	Low
	Fixed nCPAP Missing data	% problem/% severe problem: Nasal stuffiness 64/4, mask leak 63/<1, dry throat 62/1, cold air stream 45/2, mask rubbing 41/1, noise 41/2, bloating/flatulence 37/<1, red/sore eyes 31/1, nose bleedings 10/0, chest wheeze 21/<1, difficulty exhaling 18/1	Medium for device. Low for other side effects
	12 different CPAP 9.9±2.4 cm 18% used humidifiers	Dry mouth/throat 52%, noisy CPAP disturb partner 47%, nasal congestion 26%, nasal soreness 27%, drippy nose 24%, red eyes 28%, too noisy CPAP 15%	Medium for device. Low for other side effects
	Fixed CPAP 11±3 cm	Before: 33% chronic rhinitis. 41% had had a sinusitis. Before %–after %: Rhinorrhea: 37%–57% p=0.013 Sneeze: 53%–75% p=0.013 Nasal stuffiness: 45–55% ns Mucus in throat: 51–57% ns Dry nose: 75–70% ns Dry mouth/throat: 74–75% ns Blocked ears: 18–19% ns Nose bleeds: 10–15% ns	Medium

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Table 5.26 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**Design** **Inclusion criteria**	**% women** **Age** **BMI** **AHI** **ESS**
Kalan et al 1999 [70] United Kingdom	1. 301 2. 354 3. ≥6 months (0.5–11 years)	Questionnaire to all patients treated with CPAP for >6 months during 1989–1998	10% 54±11 years 75% of the patients were obese with a mean BMI of 32 (24–41) kg/m^2 Missing data Missing data
Lojander et al 1999 [64] Finland	1. 151 2. 194 3. 30 (3–70) months	Questionnaire Consecutive patients on CPAP during 1990–1995	15% 55 (31–76) years 34 (17–54) kg/m^2 ODI-4: 41 (4–108)
Verse et al 1999 [78] Germany	1. 80 2. 92 3. 28±21 months	Questionnaire to patients receiving CPAP during 1990–1997 and still using CPAP	6% 56.5±9.3 years 30.2±5.1 kg/m^2 47.9 (range 13–86) Missing data
Hui et al 2001 [75] China	1. 112 2. 112 3. 3 months	Consecutive patients receiving CPAP 1997–1998. AHI >10 and EDS	10% 45.6±11.2 years 29.3±5.2 kg/m^2 48±24 12.9±4.0
Mason 2002 [208] USA	1. 1 2. 1	Case report	0 57
Woodson et al 2003 [48] USA	1. 21 2. 28 3. 8 weeks	RCT. AHI 10–30, BMI <34	25% 49±9.2 years 29±3.7 20±9.9 13±5.0

	Type of device Pressure	Side effects	Quality Comments
	Fixed CPAP Missing data	Air leak 73%, mask discomfort 43%, sore eyes 34%, pain nasal bridge 52%, dry nose 46%, dry mouth 70%, rhinorrea 35%, nasal congest 43%, epistaxis 0.9%, blood stained mucus 17%, sinusitis 0.4%, noisy CPAP 45%, allergic phenomena from silicon masks 27%, sneezing 29%, aerophagia leading to bloating and flatulence 0.4%, partners complain of CPAP 39%. No life threatening symptoms	Low Selected and not consecutive patients
	Fixed CPAP 11 (4–20) cm	Before: chronic rhinitis 24%, chronic sinusitis 9%, nasal stuffiness 46–38%, dry throat 51–46%, sneezing 36–35%, rhinorrea 21–28%, dry nose 39–46% all non significant changes. Dry nose, sneeze more common at pressure >11 cm than below. After: pain or skin problems from mask 50%, mouth leak 44%, air leak to eyes 50%, air swallowing 27%, difficult exhaling 29%, suffocation 26%. More mouth leak and air swallowing among non users	Medium
	Fixed nCPAP 6.8±1.2 cm 6/92 used humidifiers	Sleep disturbances 71%, dry mouth 48%, dry nose 46%, mask discomfort 41%, nasal crusts 39%, hearing loss 26%, nose bleedings 19%, rhinorrea 16%, conjunctivitis 15%, sinusitis 6%, claustrophobia 5%	Low Selected patients tolerating CPAP, not consecutive
	Regular CPAP 10.4±2.3 cm Auto-CPAP titration	% overall/% severe problem: inconvenience 70/7, nasal block/dry 46/9, mask discomfort 32/4, sore nasal bridge 46/4, embarrassed 26/0, sleep disrupt by CPAP 33/5, less intimacy with partner 22/3	Medium for device, low for other side effects
		Localized gingival recession on the labial of upper tooth, second frontal	Low
	Constant CPAP Mean 8 cm	Most CPAP subjects experienced at least one side effect but none were serious. Nasal 8 (38%), sleep 9 (43%), inconvenience 7 (33%), air mechanics 7 (33%), skin or eyes 8 (38%), subjects affected 20 (95%)	Medium

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Table 5.26 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**Design** **Inclusion criteria**	**% women** **Age** **BMI** **AHI** **ESS**
Masa et al 2004 [76] Spain	1. 315 2. 466 3. 12 weeks	Consecutive patients with severe OSA from 10 centres requiring CPAP with AHI ≥30, ESS ≥12	11% 51.7 years 33.5 kg/m^2 62.7 15.7

AHI = Apnoea-hypopnoea index; BMI = Body mass index; CPAP= Continuous positive airway pressure; EDS = Excessive daytime sleepiness; ESS = Epworth sleepiness scale; ITT = Intention-to-treat; nCPAP = Nasal continuous positive airway pressure; ODI = Oxygen desaturation index; OSA = Obstructive sleep apnoea; RCT = Randomised controlled trial

Table 5.27 *Excluded studies. Side effects of and compliance with CPAP.*

Reason for exclusion	**References**
Less than 100 patients (compliance)	[74,209–223]
Shorter follow-up than 1 year (compliance)	[135,209,211–213,216,220,223–228]
No data on compliance or side effects	[45,213,228–235]
No data on compliance for the whole cohort	[236–238]

	Type of device Pressure	Side effects	Quality Comments
	Missing data 8.8 cm	Skin abrasion 23%, rhinitis 19%, conjunctivitis 3%, oral dryness 21%, mask intolerance 5%, chest discomfort 2%, aerophagia 3%, noise 16%, headache 4%, claustrophobia 4%, smothering sensation 3%, insomnia 9%, difficult exhaling 2%, bed partner intolerance 7%, want to continue with CPAP 96%	Medium for device, low for other side effects

Table 5.28 *Data extraction. Side effects of and compliance with mandibular repositioning appliances.*

Author **Year** **Reference** **Country**	**Number of patients followed up** **Eligible**	**Design** **Inclusion criteria**	**% women** **Age** **BMI**
Pantin et al 1999 [83] Australia	132 (questionn-aire), 106 (clinical examination) 191	Retrospective Snoring with or without OSA	10% 47.5 Missing data
Tegelberg et al 1999 [90] Sweden	67 (30 MRA, 37 UPPP) 95	RCT Mild to moderate OSA	Same study as Wilhelmsson 1999 [58]
Bondemark et al 2000 [89] Sweden	32 32	Prospective follow-up. Habitual snoring or obstructive apnoea	28% 54 (43–80) Missing data
Panula et al 2000 [91] Finland	1 case	Case report Snoring without OSA	1 woman 56 27
Fritsch et al 2001 [87] Switzerland	22	Prospective follow-up. OSA	Missing data Missing data Missing data

	Type of device	Compliance at	Side effects at	Quality Comments
	Material of device not reported, approximately 75% of max protrusion	5 years: 32 patients (24%) did not use the device. Reasons for non-use: no effect 8%, side effects 7.5%, other treatment 3%, other reason 5.5%	5 years: 107 (81%) patients reported side effects, excessive salivation 30%, dry mouth 26%, TMJ pain 26%, dental pain 26%, myofacial pain 25%, occlusal changes 12% (14% at clinical exam)	Low No comparative data on subjective symptoms at baseline
	Hard acrylic, full occlusal coverage except incisors, 50% of max protrusion	4 years: 62% used the splint, mean 6.1 nights/week	4 years: No significant difference in occlusion or TMD symptoms between MRA group and UPPP group	Medium Technical failures of the device: Fractures of Adam's clasps 5/180 (3%), 1 case of fracture of lingual bar, 2 cases of acrylic fractures
	Hard acrylic device, full occlusal coverage, 50–70% of max protrusion	2 years: All patients used the device 6–8 hours/night, 5–7 nights/week	2 years: Overjet −0.4 mm, overbite −0.1 mm compared to baseline. No changes in TMD symptoms	Medium
	Hard acrylic, full occlusal coverage, protruded position: mandibular incisors 1–2 mm anterior maxillary incisors	3 years: Device used 7–8 hours every night	3 years: Lateral open bite bilaterally. Apposition of bone in mandibular fossa seen on radiographs. No subjective discomfort	Low Case report
	Hard acrylic device, full occlusal coverage. No data on protrusion	≤30 months: All patients used the device	≤30 months: 86% reported dry mouth, 59% tooth discomfort, 55% hypersalivation. <1 mm reduction of overjet and overbite	Low No comparative data on subjective symptoms at baseline

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Table 5.28 *continued*

Author **Year** **Reference** **Country**	**Number of patients followed up** **Eligible**	**Design** **Inclusion criteria**	**% women** **Age** **BMI**
Marklund et al 2001 [5] Sweden	92 (75 used the device >50% of the nights, 17 did not)	Retrospective OSA or snoring	15% 53 (25–70) Missing data
Rose et al 2001 [96] Germany	2 cases	Case report OSA	Case 1: 1 woman 61 year, BMI 25.6 Case 2: 1 male 53 year, BMI 24.3
Engleman et al 2002 [56] United Kingdom	48 51	RCT, cross-over (MRA vs CPAP). AHI ≥5 + ≥2 symptoms	25 46 (18–70) Missing data
Gotsopoulos et al 2002 [50] Australia	73 85	RCT, cross-over (MRA vs placebo device). OSA, RDI ≥10 and ≥2 symptoms	19% 48 (±11) 29 (±4.7)

	Type of device	Compliance at	Side effects at	Quality Comments
	Soft elastomer device (47 patients), hard acrylic (28 patients). 6 mm protrusion and 10 mm vertical	Not reported	2.5 years: Overjet −0.4 mm, overbite −0.4 mm, significant changes compared to non-users. No subjective changes in 37/69 patients, changes in the morning 28/69, permanent change 3/69, "don't know" 1/69	Low No separate analysis for hard and soft splints, respectively
	Hard acrylic, full occlusal coverage in mandible, premolar and molar regions in maxilla. Individual protrusion	Case 1: 2.8 years: 6–7 hours each night. Case 2: 2.3 years: compliance not reported	Case 1, 2.8 years: Overbite reduced 3.8 mm, overjet 3.1 mm. Lateral open bite bilaterally. Case 2, 2.3 years: Overbite reduced 2.3 mm, overjet 2.8 mm. Lateral open bite bilaterally	Low Case reports
	1. Soft elastomer device, full occlusal coverage 2. Hard acrylic device, no occlusal coverage in front. No data on protrusion	6 weeks: 79% used the device ≥3 hours/night	6 weeks: 69% reported pain from teeth, jaws or gums, 19% excessive salivation, 6% dental crown damaged	Medium Short follow-up. Adverse events frequency and severity comparable with CPAP treatment
	Hard acrylic, full occlusal coverage. No data on protrusion. Placebo device only in maxilla	4 weeks: 6.7 h/night for both test and placebo device	4 weeks: Significantly more for test device, jaw discomfort, tooth tenderness, excessive salivation. No data on frequency	Medium Short follow-up

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Table 5.28 *continued*

Author **Year** **Reference** **Country**	**Number of patients followed up** **Eligible**	**Design** **Inclusion criteria**	**% women** **Age** **BMI**
Johnston et al 2002 [51] Ireland	20 21	RCT, cross-over (MRA vs placebo device). OSA, ≥10 desaturations (≥4% fall in SaO_2	19% 55 (35–64) 31.6 (21.1–43.8)
Randerath et al 2002 [86] Germany	20	RCT, cross-over (MRA vs CPAP). OSA, AHI 5–30	20% 56.5 (±10.2) 31.2 (±6.4)
Rose et al 2002 [239] Germany	192	Retrospective OSA	12% 54.4 (26–80) 27.5 (19–41.5)
Tan et al 2002 [55] United Kingdom	21 24	RCT, cross-over (MRA vs CPAP). AHI 10–49	16% 51 (±10.1) 32 (±6.8)
Fransson et al 2003 [240] Sweden	65 77	Prospective follow-up. OSA or snoring	18 55 (31–73) 29.2
Robertson et al 2003 [92] New Zealand	100	Prospective OSA with or without habitual snoring	13% 49 years men, 51 years women Missing data

	Type of device	Compliance at	Side effects at	Quality Comments
	Soft elastomer device, 75% of max protrusion. Placebo device only in maxilla	4–6 weeks: >4 hours/night 79%, ≥6 nights/week 68%. No data on placebo device	4–6 weeks: Excessive salivation 68%, temporary occlusal changes in the morning 44%, temporary TMJ discomfort in the morning 42%, 1 patient during the day. No data on placebo device	Low Short follow-up
	Soft elastomer, full occlusal coverage, adjustable telescopic guide rods, 75% of max protrusion	6 weeks: >8 hours/night 33% MRA, 9% CPAP (ns), ≥5 nights/week 100% MRA and CPAP	6 weeks: Temporary discomfort in the mouth or TMJ 40% MRA, 0% CPAP, pressure on the face 10% MRA, 40% CPAP	Medium Short follow-up
	Device model not stated, 4–8 mm protrusion	Mean 22.7 months: 105 patients (54.4%) used the device	Not reported	Low
	14 patients soft device, modified Silensor, buccal connectors 10 patients soft one-piece device	2 months: 17/21 patients preferred MRA. 4/21 patients preferred CPAP	2 months: Temporary jaw discomfort in the morning 50%. 1 patient did not tolerate the device	Medium
	Hard acrylic device with full occlusal coverage, 75% of max protrusion	2 years: 71% (55 of 77) used the device every night, 5 several times/week	2 years: Overjet –0.5 mm, overbite –0.8 mm compared to baseline. 9 patients lateral open bite, 2 patients muscle fatigue. No other subjective symptoms	Medium
	Hard acrylic, full occlusal coverage, 75% of max protrusion	Not reported	2 years (20 patients), 30 months (20 patients) reduced overjet and overbite	Medium Small, unpredictable changes

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Table 5.28 *continued*

Author Year Reference Country	Number of patients followed up Eligible	Design Inclusion criteria	% women Age BMI
Walker-Engström et al 2003 [7] Sweden	32 45	Before–after regarding side effects. AI >5, <25	Missing data Missing data 26
Gotsopoulos et al 2004 [52] Australia	61 67	RCT, cross-over (MRA vs placebo device). Blinded assessor. OSA, RDI ≥10 and ≥2 symptoms	19% 48 (±11) 29 (±4.7)
Marklund et al 2004 [81] Sweden	619 630	Prospective follow-up. Snoring or mild to moderate OSA	29% 51 (25–74) years men 55 (30–75) years women 28 (19–42)

AHI = Apnoea-hypopnoea index; AI = Apnoea index; BMI = Body mass index; CHF = Congestive heart failure; CPAP = Continuous positive airway pressure; MRA = Mandibular repositioning appliance;

Table 5.29 *Excluded studies. Side effects and compliance with oral appliances.*

Reason for exclusion	References
Central sleep apnoea, not OSA or snoring	[241]
No usable data on compliance or side effects	[53,54]
Only cephalometric measures	[242,243]
Same study as Fransson 2002 [243]	[240]
Experimental study	[244]
Same study as Tegelberg 1999 [90], Walker-Engström 2003 [7]. No additional data on side effects	[245]
No mandibular repositioning appliance	[246]
No data on side effects, same study as Tegelberg 1999 [90] and Walker-Engström 2003 [7]	[58]

OSA = Obstructive sleep apnoea

	Type of device	Compliance at	Side effects at	Quality Comments
	Hard acrylic, no data on occlusal coverage 50% of maximal protrusion	4 years: 28 still using device (62%)	4 years: 4/27 (1 missing data) minor occlusal changes, 1/27 obvious occlusal changes	Medium
	Hard acrylic, full occlusal coverage. Protrusion 7±2 mm Placebo device only in maxilla	4 weeks: 6.8±0.1 hours for test and 6.9±0.1 hours for placebo device. 97%±1% of nights	No data on side effects	Probably same patients as in Gotsopoulos 2002?
	Soft elastomer device or hard acrylic. 4–6 mm protrusion, ≥5 mm vertical	1 year: 148 patients (24%) did not use the device. Reasons for non-use: uncomfortable 14%, no effect 3%, odontologic problem 2%, other treatment 2%, other unknown reason 3%	See "Compliance". See also Marklund 2001 [5] for clinical side effects (same patients?)	Medium for compliance. Low for side effects

OSA = Obstructive sleep apnoea; RCT = Randomised control trial;
RDI = Respiratory disturbance index; TMD = Temporomandibular dysfunction;
UPPP = Uvulopalatopharyngoplasty

Table 5.30 *Data extraction. Adverse effects of surgery for obstructive sleep apnoea and snoring.*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**1. Design** **2. Data collection** **3. Inclusion criteria**	**1. % women** **2. Age** **3. BMI** **4. AHI** **5. ESS** **6. % with OSA**
Katsantonis et al 1987 [120] USA	1. 85 2. – 3. 6 weeks–6 months	Retrospective of patients operated May 1982–July 1985	1. Missing data 2. Missing data 3. Missing data 4. Missing data 5. Missing data 6. Missing data
Esclamado et al 1989 [97] USA	1. 135 2. – 3. Within 24 hours	Retrospective review of patients operated 1983–1987 because of OSAS	1. 6 2. 50±11 3. Missing data 4. 59±25 5. Missing data 6. 100?
Harmon et al 1989 [98] USA	1. 132 2. – 3. Peri- and post-operative period	Consecutive patients operated 1981–1987	1. 20 2. 19–70 3. Missing data 4. Missing data 5. Missing data 6. 4.5
Fairbanks 1990 [99] USA	1. 72 centres 2. – 3. 8 years	Retrospective	1. Missing data 2. Missing data 3. Missing data 4. Missing data 5. Missing data 6. Missing data
Zohar et al 1991 [247] Israel	1. 71 2. – 3. 20–24 months	Retrospective on consecutive patients operated because of snoring or OSA during 1983–1988	1. Missing data 2. 44 (25–68) 3. Missing data 4. Missing data 5. Missing data 6. Missing data
Grøntved et al 1992 [248] Denmark	1. 21 2. – 3. Postoperative period		1. 20 2. Missing data 3. 30±4 4. Missing data 5. Missing data 6. Missing data
Carenfelt et al 1993 [100] Sweden	1. 9 000 (UPPP), 2 700 (LAUP) 2. – 3. –	Retrospective Questionnaire to 37 ear-nose-throat departments	1. Missing data 2. Missing data 3. Missing data 4. Missing data 5. Missing data 6. Missing data

	Type of operation	Side effects	Quality Comments
	UPPP	3 (4%) severe nasopharyngeal stenosis. 1 (1%) velopharyngeal insufficiency	Low
	UPPP	Perioperative: Airway obstruction after extubation 5%, failed intubation 5%, severe postoperative haemorrhage 2%, postoperative arrhythmia 1%. 1 died during intubation	Medium
	UPPP 4 tracheostomy, 1 tracheostomy + tonsillectomy. 1 septoplasty	Deaths: 1 died the day after op due to haemorrhage. 1 died on day 21 from pulmonary embolism. Severe bleedings 1,5%, pneumonia, emergency tracheostomy after extubation 1.5%, intubation problems 5%, rhinolalia 1.5%	Medium
	UPPP	16 fatalities were reported. 1 because of haemorrhage and 12 due to loss of airway. 8 near fatalities. 46 nasopharyngeal stenosis and 42 palatal incompetence	Low
	UPPP ± antibiotics	10 days: Pain 100%, hyper nasality 100%, dysphagia 97%, bleeding 4%, local infection 4%. 20–24 months: Nasal reflux 3%, nasal reflux over a tap 15%	Low
	UPPP	33 severe pain, 38% moderate pain. Pain during 1–3 weeks	Medium
	UPPP LAUP	UPPP: 3 deaths (2 cardiac arrest, 1 bleeding). 16 acute complications (severe bleeding or re-intubation) (<0.5%). 20 late complications. LAUP: 1 death in septicaemia. 3 late complications. Prolonged discomfort when swallowing in >10% irrespective of operation method used	Low

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Table 5.30 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**1. Design** **2. Data collection** **3. Inclusion criteria**	**1. % women** **2. Age** **3. BMI** **4. AHI** **5. ESS** **6. % with OSA**
Stepnick 1993 [249] USA	1. 1 2. – 3. 18 months	Case report	A 38-year-old black man
Haavisto et al 1994 [101] Finland	1. 100 (postoperative), 90 (long-term) 2. 101 3. 1 year	Retrospective review on consecutive patients operated for snoring or OSA during 1989–1990	1. 10 2. 47 (24–73) 3. Missing data 4. Missing data 5. Missing data 6. Missing data
Dickson et al 1996 [124] USA	1. 220 2. – 3. –	Patients operated April 1994–Dec 1994	1. 16 2. Missing data 3. Missing data 4. Missing data 5. Missing data 6. 33
Walker et al 1996 [123] USA	1. 275 2. – 3. 6 weeks–18 months	Consecutive patients operated July 1993–Dec 1994 Questionnaire on bleeding, velopharyngeal insufficiency, pain, speech	1. 19 2. 49.9 years 3. Missing data 4. Missing data 5. Missing data 6. Missing data
Ikeda et al 1997 [125] Japan	1. 30 2. 30 3. –	Missing data 1994–1995 Consecutive operated snoring and mild OSA	1. Missing data 2. 50 (30–70) 3. 24±4 4. Missing data 5. Missing data 6. Missing data 7. Non with moderate or severe OSA
Riley et al 1997 [103] USA	1. 182 2. 182 3. Postoperative during hospital stay	Prospective on consecutive patients. Review of risk management protocol	1. 114 2. 48.2±11.2 3. 30.3±6.7 4. 42.3±30.6 5. Missing data 6. 100

	Type of operation	Side effects	Quality Comments
	UPPP	Nasopharyngeal stenosis. He had an almost total obstruction at the level of the palate. Unable to breath through the nose. Problems eating. He had undergone several operation to correct the stenosis	Low
	UPPP	Immediate postoperatively: Early postoperative complications 25%. 57% postoperative complication. Dead 1 (1%), severe bleedings 4 (4%), severe airway problems 5 (5%). After a year: Pharyngeal regurgitation when eating 24%, pharyngeal dryness 31%, difficulty swallowing 10%, speech difficulties 7%, loss of taste 2%, breathing difficulties 5%	Low
	LAUP	Postoperative period. Mild 34% (sore throat for one week). Moderate 45% (sore throat with only liquids for 7–10 days). Severe 21% (no liquids for 2 weeks)	Medium
	LAUP	26 complications = 3.45% were postoperative haemorrhage 2.12%, local infections 0.53%, temporal palatal incompetence 0.53%, temporary loss of taste 0.27%. No case of hyper nasal speech, permanent palatal incompetence, nasopharyngeal stenosis, airway compromise or death	Medium
	LAUP	Peri- and postoperative: Slight pain 30%, moderate pain 20%, severe pain 23%. No troublesome bleeding and no asphyxia after operation	Medium
	Different op for OSAS. Total 210 operations. UPPP (n=169)	During hospital stay postoperatively: Haemorrhage 1.9%, infections 2.4%, seroma 1.4%, arrhythmia 1.9%, unstable angina 0.5%, death 0	Medium

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Table 5.30 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**1. Design** **2. Data collection** **3. Inclusion criteria**	**1. % women** **2. Age** **3. BMI** **4. AHI** **5. ESS** **6. % with OSA**
Isberg et al 1998 [250] Sweden	1. 79 2. 91 3. >2 years	Consecutive patients operated 1991–1993 Questionnaire	1. Missing data 2. Missing data 3. Missing data 4. Missing data 5. Missing data 6. Missing data
Mickelson et al 1998 [104] USA	1. 347 2. – 3. Postoperative period	Retrospective review of consecutive patients operated 1987–1996	1. Missing data 2. 45±11 3. 33±6 4. 52±35 5. Missing data 6. Missing data
O'Reilly et al 1998 [118] United Kingdom	1. 52 2. 63 3. <18 months	Questionnaire to patients operated during preceding 18 months ie March 1993–June 1994	1. 2 2. 40 3. Missing data 4. Missing data 5. Missing data 6. Missing data
Pinczower 1998 [251] USA	1. 60 2. – 3. 2–3 months	Consecutive operated 1994. Volunteer information and questioned	1. Missing data 2. Missing data 3. Missing data 4. Missing data 5. Missing data 6. Missing data
Terris et al 1998 [105] USA	1. 109 2. 109 3. Peri- and post-operative	Retrospective on consecutive patients operated for snoring or OSA from 1991–1996	1. 12 2. 45±10 3. 29±6 4. 38±12 5. Missing data 6. All?
Hultcrantz et al 1999 [126] Sweden	1. 55 (at 1 year), 48 (at 5 year) 2. 55 3. 1 and 5 years	Questionnaire to 55 consecutive patients operated	1. 7% 2. Mean 48 years 3. Mean 26 kg/m^2 4. Missing data 5. Missing data 6. 35

	Type of operation	Side effects	Quality Comments
	LAUP	21/79 patients (27%) reported persistent dysphagia. Such as choking at meals 17 (21%), need to concentrate during meals 6 (8%), nasal regurgitation 4 (5%), globus sensation 4 (5%), food stuck in throat 3 (4%), deficient control of bolus in mouth 2 (3%), difficulty initiating swallowing 1 (1%)	Low
	UPPP with or without associate procedures for OSA ie nasal surgery, tracheostomy etc	Postoperative period: 3 severe and 2 minor respiratory problems, 1 bleeding + chest pain, 2 severe epistaxis, 1 tracheostomy bleeding, 1 bleeding from tonsils and 4 other complications	Medium
	UPPP (laser) (n=19) UPPP (n=16) UPP (knife) (n=17)	All patients experienced pain and 31 had it after 2 months. Drinking problems after 2 months 13%, dryness in throat 42%, food sticking = globus 50%	Low
	LAUP	15 (25%) reported globus sensation. 5 having severe globus and 10 mild globus. Insensitive area on the anterior palatal mucosa was related to globus sensation	Low
	UPPP sometimes combined with other surgery for OSA	Peri- and postoperatively. No deaths. 39 complications. Major complications in 8% of patients and minor in 19%. Bleeding, airway obstruction and postoperative hypertension most common. 4 (3.2%) bleedings after discharge from hospital	Medium
	UPP	56% reported side effects. After one year had 27% swallowing problems, 8% velopharyngeal insufficiency and 4% increased vomiting reflexes. After 5 years: 27 (56%) side effects from LAUP, swallowing problems 19%, velopharyngeal insufficiency 4% and vomiting reflex 4% Telephone contact with author	Medium

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Table 5.30 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**1. Design** **2. Data collection** **3. Inclusion criteria**	**1. % women** **2. Age** **3. BMI** **4. AHI** **5. ESS** **6. % with OSA**
Levring-Jäghagen et al 1999 [127] Sweden	68	1. 76 2. – 3. >6 months + >1 year Consecutive patients operated with UPP 1989–1993. Postal questionnaire	1. 13 2. 48 (26–65) years 3. 26 (21–34) kg/m^2 4. Missing data 5. Missing data 6. Missing data
Remacle et al 1999 [109] Belgium	1. 89? 2. 89 3. 17 (1–37) months	Prospective Consecutive during April 1994–May 1997	1. 21 2. 52 (23–77) 3. Missing data 4. Missing data 5. Missing data 6. 17
Virtaniemi et al 1999 [112] Finland	1. 53 2. 53 3. 24 hours	Prospective VAS Consecutive patients operated	UPPP or tonsillectomy 1. 6% and 45% 2. 45±3 and 32±7 3. 27±3 and 25±4 4. ODI: 16±20 5. Missing data 6. Missing data
Andsberg et al 2000 [111] Sweden	1. 22 2. 22 3. 8 years	Prospective on consecutive patients. Questionnaire	1. 5 2. 50 (37–73) years 3. Missing data 4. AI: 35 (5–89) 5. Missing data 6. 100
Brosch et al 2000 [252] Germany	1. 12 2. 12 3. 9 (6–15) months	Prospective Spectral analysis of voice	1. 0 2. 43 (32–61) years 3. 25 (23–33) kg/m^2 4. Missing data 5. 8.5 (3–16) 6. 42
Boudewyns et al 2000 [132] Belgium	1. 44 2. 103 3. 8 weeks	Prospective Inspection, PSG, questionnaire	1. 14 2. 43.7±10.9 years 3. 26.6±3.2 kg/m^2 4. 5.1±4.3 5. 8.0±5.0 6. Missing data

	Type of operation	Side effects	Quality Comments
	UPP performed with steel scalpel	After 1 year. Dysphagia reported by 29%. It included coughing at meals, nasal regurgitation, food stuck in throat. Deviant swallowing pattern observed in 12/17 patients studied videoradiographically	Medium
	LAUP (n=43) UPPP (n=46)	Pain (0–10): LAUP during 14±6 days, max 8.4. UPPP during 12±9 days max 8.0. Voice changes: LAUP 8%, UPPP 25%. Voice changes lasted in average one year. Postoperative bleeding LAUP 3%. Severe dysphagia LAUP 3%	Medium
	UPPP (n≈31) Tonsillectomy (n=22)	Postoperative pain during 24 hours especially during swallowing was common especially for patients operated with UPPP	Medium
	UPPP + midline glossectomy	All patients had postoperative pain during 2 weeks. At 11 months: 42% inconvenience from tongue, 18% increased secretion in throat and unpleasant smell or taste. At 98 months had 23% postoperative complications and 1 case with problems of swallowing	Low
	UPPP	Increase in fundamental frequency of 10 Hz of 5 vowels	Medium
	TCRAFTA	Mucosal erosion 15.6%, palatal fistula 1 (2.3%), uvula loss 1 (2.3%), excessive swelling 1 (2.3%), haemorrhage 2 (4.5%). Only little pain	Medium

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Table 5.30 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**1. Design** **2. Data collection** **3. Inclusion criteria**	**1. % women** **2. Age** **3. BMI** **4. AHI** **5. ESS** **6. % with OSA**
Grøntved et al 2000 [114] Denmark	1. 69 2. – 3. 27 (12–48) months	Prospective Consecutive patients operated with UPPP 1991–1994. Questionnaire	1. 16 2. 49 (22–82) 3. 26 (18–34) 4. Missing data 5. Missing data 6. 32
Hagert et al 2000 [115] Sweden	1. 415 2. 457 3. 3.3 (1.5–8) years	Retrospective consecutive	1. 17 2. 50±11 3. Missing data 4. Missing data 5. Missing data 6. 27%
Osman et al 2000 [106] United Kingdom	1. 47 2. 47 3. Postoperative	Prospective Snorers and OSA with AHI <20	1. 13 2. 49 (27–71) 3. 28 (23–38) 4. Missing data 5. Missing data 6. Missing data
Troell et al 2000 [110] USA	1. 41 2. – 3. –	Prospective Snoring and mild SDB. RDI <15, BMI <32	1. Missing data 2. 18–65 years 3. Missing data 4. Missing data 5. Missing data 6. Missing data
Bäck et al 2001 [253] Finland	1. 21 2. 16 3. 2 weeks	Prospective Snorers with ODI-4% <15, and daytime sleepiness	1. 0 2. Median: 44 (35–55) years 3. Median BMI: 26.9 (22.7–32.3) kg/m^2, Median ODI: 4% 4. 0.8 (0–7.3) 5. Missing data 6. 43

	Type of operation	Side effects	Quality Comments
	UPPP	Mean 27 months (range 12–48): Complaints of operation 29%, generally dissatisfied 14%, nasal regurgitation 13%, pharyngeal hypersecretion 10%, swallowing problems 9%, speech disturbances 7%, dryness 3%, rhinolalia 3%, serious complications 3%	Medium
	UPPP (n=292) LAUP (n=121)	2–8 years postoperative: 255 (62%) experience side effects. UPPP: Taste 21 (7%), smell 22 (8%), voice 41 (14%), globus 116 (40%), regurgitation 101 (35%). LAUP: Taste 8 (7%), smell 10 (8%), voice 12 (10%), globus 44 (36%), regurgitation 38 (31%). Side effects were the same for LAUP and UPPP and was not affected by OSA or snoring as a diagnosis except for globus which was more common in OSA patients. Author was contacted for questions	Medium
	UPPP (n=18) LAUP (n=29)	Pain was common among both operations. LAUP: 1 severe anaesthetic problem UPPP: 1 severe infection, 3 bleedings, 3 temporal velopalatal insufficiency	Medium
	LAUP (n=10) UPPP (n=9) TCRAFTA (n=22)	Mean days of pain: LAUP: 14 days, UPPP: 14 days and TCRAFTA 3 days	Medium
	TCRAFTA soft palate	14 mucosal blanching	Medium

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Table 5.30 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**1. Design** **2. Data collection** **3. Inclusion criteria**	**1. % women** **2. Age** **3. BMI** **4. AHI** **5. ESS** **6. % with OSA**
Pazos et al 2001 [131] USA	1. 30 (51 operations) 2. 30 3. 4 weeks	Retrospective on consecutive patients operated with radio-frequency. Medical charts	1. Missing data 2. 46 (range 9–81) 3. Missing data 4. Missing data 5. Missing data 6. Missing data
Haraldsson et al 2002 [133] Sweden	1. 16 2. – 3. 2 months	Prospective Missing data BMI <30, AHI/ODI <15	1. 31 2. 49.4±10.4 3. 26.2±2.0 4. ODI: 4.0 ±3.4 5. 11.4±5.0 6. Missing data
Lysdahl et al 2002 [116] Sweden	1. 61 (UPPP), 60 (LUPP) 2. 75 (UPPP), 75 (LUPP) 3. 5–8 years	Prospective consecutive. Questionnaire 75 UPPP and 75 LUPP patients	*UPPP:* 1. 18 2. 45 (10.6) years 3. 27.9 (5.4) kg/m^2 4. Missing data 5. Missing data 6. Missing data *LAUP:* 1. 15 2. 48.1 (8.8) years 3. 26.0 (4.0) kg/m^2 4. Missing data 5. Missing data 6. Missing data
Stuck et al 2002 [130] Germany	1. 18 2. 20 3. Perioperative	Prospective AHI >15, BMI <35, age 18–65	1. 20 2. 49±8 3. 29±3 4. 32±14 5. Missing data 6. 100
Terris et al 2002 [122] USA	1. 17 2. 20 3. 16 weeks	Prospective AHI <20, age >18 BMI <40	1. Missing data 2. 50.3±10.3 3. 27.5±3.5 4. 6.1±5.0 5. 7.1±4.4 6. Missing data

	Type of operation	Side effects	Quality Comments
	TCRAFTA 26 operations on the palate and 25 on the tongue	Within 4 weeks: Palatal mucosal breakdown in 11 cases (37%), uvular slough in 2 cases (7%), mouth floor oedema in 2 cases, tongue abscess in 2 cases	Medium
	TCRAFTA soft palate	No effect on speech according to nasal-oral radio meter and trained listener. Ulceration in 2 patients, sustained blanching first week 3 patients, 1 TMJ disk luxation	Medium
	UPPP LAUP	Follow-up at 5–8 years postoperatively UPPP: Swallowing disturbances 35 (57%), persistent swallowing disturbances 22 (36)%, regretted operation 7 (11%). LAUP: Swallowing disturbances 40 (67%), persistent swallowing disturbances 16 (27%), regretted operation 8 (13%)	Medium
	TCRAFTA	Postoperative period: Severe infection in tongue base (5%), Severe tongue swellings requiring hospital admission (15%). Pain for a mean of 3.5±2.8 days	Medium
	TCRAFTA (=10) LAUP (n=7)	Pain: TCRAFTA 7±4.4 days LAUP 15±4.5 days LAUP patients had more difficulty swallowing than patients in TCRAFTA group	Medium

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Table 5.30 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**1. Design** **2. Data collection** **3. Inclusion criteria**	**1. % women** **2. Age** **3. BMI** **4. AHI** **5. ESS** **6. % with OSA**
Walker-Engstrom et al 2002 [254] Sweden	1. 40 2. 43 3. 4 years	RCT Missing data Male, AI 5–25, Age 20–65	1. 0 2. 50 years 3. 27 kg/m^2 4. 19±9 5. Missing data 6. 100
Berger et al 2003 [119] Israel	1. 25 (LAUP), 24 (UPPP) 3. 12.2±9.9 month 2. –	Prospective questions Subject operated with LAUP	1. 12 2. 49.6 (9.8) years 3. 27.5 (3.2) kg/m^2 4. 25 (14) 5. Missing data 6. Missing data
Ferguson et al 2003 [6] Canada	1. 45 2. 46 3. 7.2±5.9 months	RCT Missing data AHI 10–25	1. 24 2. 45±8 years 3. 32±5 kg/m^2 4. 17±4 5. 10±4 6. 100
Gessler et al 2003 [255] USA	1. 130 2. – 3. 18 hours	Retrospective on patients operated 1995–1998	1. 1.5 2. 36 (20–77) 3. Missing data 4. 40 (7–87) 5. Missing data 6. 100
Rombaux et al 2003 [107] Belgium	1. 49 2. – 3. 6 weeks	Prospective. Disturb snoring BMI <32	1. 18 2. 40 3. 26 4. 9 (0–19) 5. Missing data 6. Missing data (no sleep apnoea investigations)

	Type of operation	Side effects	Quality Comments
	UPPP	4 years: Pronounced complaints of nasopharyngeal regurgitation of fluid by 8%. Difficulty swallowing in 10%	Low
	LAUP (n=24) UPPP (n=24)	LAUP results: Postoperative pain during 9.7 (3.8) days. Away from work during 9.7 (3.8) days. Persistent throat dryness or itching in 12 patients (48%). Velopharyngeal stenosis which was later operated in one patient (4%). No deaths No data on UPPP complications	Medium
	LAUP (n=21)	17 (81%) reported sever severe pain despite analgesia. 4 subjects (19%) had persistent difficulty swallowing at follow-up. 4 subjects (19%) experienced mild bleedings, 5 reported moderate to severe bleedings of which one (5%) required medical attention	Medium
	UPPP	8/130 patients (6.2%) had desaturations <90%. Letter from author saying that there were no death cases, no cardiovascular complications, no infections requiring antibiotic therapy, no post-extubation pulmonary oedema	Low Short follow-up period
	UPPP (n=17) LAUP (n=15) TCRAFTA (n=17)	Early UPPP: infection 18%, bleeding 6%, post pillar narrowing 23%, wound dehiscence 23%. LAUP: infection 7%, post pillar narrowing 20%. TCRAFTA: infection 6%, velopharyngeal fistula 6%. Days of pain: UPPP 21, LAUP 15, TCRAFTA 6. 6 weeks UPPP: globus 23%, voice change 12% pharyngeal reflux 12%, pharyngeal dryness 12%. LAUP: globus 13%, voice change 27%. TCRAFTA: globus 6%, voice change 6%	Medium

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Table 5.30 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**1. Design** **2. Data collection** **3. Inclusion criteria**	**1. % women** **2. Age** **3. BMI** **4. AHI** **5. ESS** **6. % with OSA**
Said et al 2003 [129] USA	1. 39 2. 50 3. 14 (3–26) months	Retrospective on consecutive patients operated April 1998–July 2000. Telephone interview at 3–26 months after operation	1. 10 2. 54.1 (8.6) 3. 28.1 (5.3) 4. 16.9 (17.8) 5. Missing data 6. Missing data
Stuck et al 2003 [256] Germany	1. 322 2. – 3. –	Retrospective on consecutive patients during 1998–2002. Medical charts	1. 20 2. 47.7±10.7 years 3. 27.7±3.6 kg/m^2 4. 20.5±18.5 5. Missing data 6. Missing data
Woodson et al 2003 [48] USA	1. 48 2. 60 3. 3 weeks	RCT Missing data AHI 10–30, BMI <34	1. 20 2. 48±9 years 3. 28±4 kg/m^2 4. 18±9 5. 12±5 6. 100
Jäghagen et al 2004 [117] Sweden	1. 42 2. 46 3. 1 year	Prospective Questionnaire and x-rays	1. 9 2. 46 (27–74) years 3. 26 (21–34) kg/m^2 4. 8 (0–40) 5. Missing data 6. Missing data
Kezirian et al 2004 [102] USA	1. 3 130 2. 3 130 3. 30 days	Prospective Department of veterans affairs register	1. 3 2. 49.8±10.8 3. Missing data 4. Missing data 5. Missing data 6. Missing data

	Type of operation	Side effects	Quality Comments
	TCRAFTA	Reversible within 1 month after operation. Subjective palatal swelling 72%, choking sensation 28%, palatal ulcer 3%, transient voice change 11%, thick mucus 11%, abnormal sensation 19%, dysphagia 13%, moderate to severe pain 15%	Medium
	TCRAFTA	2.4% of operations had short term side effects. Ulcerations on tongue or soft palate 1%, severe dysphagia requiring hospital admission 1%, palsy of hypoglossal nerve 0.3%, tongue abscess 0.3%	Low Only charts and no specific questionnaire
	TCRAFTA (n=23) Sham operation (n=25)	Pain and swallowing increased mildly 1 week after treatment of both the placebo and TCRAFTA groups and remained to baseline by 3 weeks after op with no difference between groups	Medium
	UPPP (n=20) UPP (n=22)	7/42 patients reported dysphagia before operation one of reported worsening after operation and 2 lesser symptoms. 10/35 (29%) patients acquired dysphagia after the operation. Ie an increase from 17% of dysphagia before operation to 40% one year after the operation. The same with both surgical methods. Preoperative video radiography did not predict dysphagia after operation Answer from author reporting side effects of UPPP and UPP in separate	High
	UPPP	Serious side effects after one month: Death 0.2% (n=7). Serious non-fatal complications including re-intubation, emergency tracheostomy, haemorrhage, cardiovascular complications 1.5% (n=47)	High

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Table 5.30 *continued*

Author **Year** **Reference** **Country**	**1. Number of patients followed up** **2. Eligible** **3. Time follow**	**1. Design** **2. Data collection** **3. Inclusion criteria**	**1. % women** **2. Age** **3. BMI** **4. AHI** **5. ESS** **6. % with OSA**
Larrosa et al 2004 [57] Spain	1. 25 2. 28 3. 3 months	RCT Missing data Snoring, male sex, age 30–60, BMI 25–30, AHI <30	1. 0 2. 44±7 years 3. 27±3 kg/m^2 4. 15±3 5. 11±5 6. Missing data
Madani 2004 [257] USA	1. 5 600? 2. 5 600? 3. ≥2 years	Retrospective on cosec patients from 1993–2003 with snoring or nasal congestion, BMI <30	1. 11 2. 19–76 3. 27 4. Missing data 5. 11.4 6. Missing data
Kim et al 2005 [108] South Korea	1. 90 2. 153 3. –	Retrospective review of 153 patients operated 1997–2003	1. 4 2. 44.3±9.2 3. 27.9±2.9 4. 53.3±27.8 5. Missing data 6. 100

AHI = Aponea-hypoponea index; BMI = Body mass index; ESS = Epworth sleepiness scale; LAUP = Laser-assisted uvulopalatoplasty; ODI = Oxygen desaturation index; OSA = Obstructive sleep apnoea; OSAS = Obstructive sleep apnoea syndrome; TMJ = Temporo-mandibular joint; UPP = Uvulopalatoplasty; UPPP = Uvulopalatopharyngoplasty; VAS = Visual analogue scale

	Type of operation	Side effects	Quality Comments
	LAUP (n=13) Sham operation (n=12)	Postoperative pain in 100% of cases during 8–19 days. Minimal complaints in control group. Minor bleeding in one patient after 24 hour controlled by electrocautery in the office	Medium
	LAUP (including radiofrequency in 40%)	Perioperative bleeding 9.5%, deaths 0%, delayed bleedings 0.2%, local infection following nasal radioablation 12%	Low No sleep apnoea recordings. 1 private centre. 1 author
	UPPP	Peri- and postoperative period during 2 weeks from operation. Complications 19 (21%) included bleeding, respiratory complications and postoperative ECG changes. 3 severe bleeding complications	Medium

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6. Ethical Aspects

Conclusions

This chapter deals with ethical questions in a general sense. A systematic literature review has not been performed. Ethical issues arise in discussing diagnostic questions, treatment alternatives and research on obstructive sleep apnoea syndrome (OSAS). This is no different from other conditions. Ethical questions can be raised from different points of view. The patient, the professional, the healthcare system (including the financier) and the community all have different agendas. They may both raise and value the issue differently. The principles of respect for autonomy, beneficence, nonmaleficience and fairness or justice – which are often applied when addressing ethical questions in health care – are highly relevant to OSAS as well.

Diagnostic issues

Because OSAS consists of a combination of subjective symptoms and objective findings, diagnostic accuracy may vary depending on the perspective. There is an obvious risk of a slippery slope when diagnosing. From the patient's perspective, it may be reasonable to be rather generous with a diagnosis as long as there is an effective treatment method that is not accompanied by frequent or severe adverse effects and does not consume excessive patient or community resources. From a professional perspective, there may be financial gains to be had by diagnosing a patient with OSAS, given that it can lead to a demand for professional help in the form of surgery, a device or continuous follow-up and advice. Because OSAS is often associated with snoring, a bed partner's perspective may influence willingness to obtain a diagnosis and suggestions for therapy. The frequent apnoeas that the partner may observe can also induce fear and anxiety, motivating the patient to obtain a diagnosis. In these cases as well, the patient's perspective and outcome are the most important.

From a community point of view, it is important that the same criteria are used so that the opportunity for equal, high-quality treatment can be assured throughout the healthcare system. The community is also interested in proper resource allocation. Thus, Bayesian reasoning should be used when allocating resources for diagnostic measures, given that treatment is justified only for relieving symptoms or improving the prognosis. The principle of justice is relevant when discussing resource allocation. The concept of nonmaleficience also comes into play. A diagnostic tool for OSAS needs to have a likelihood ratio (low LR–) that indicates true disease, considering that some of the treatment alternatives either are associated with poor efficacy and high risk or are cumbersome and have adverse effects.

Treatment issues

The risk/benefit ratio is the most important treatment issue. There is no justification from any perspective for using a method that has questionable efficacy and high risk. Only in patients who face a high risk without treatment is a therapy associated with severe adverse effects indicated. Such patients have to be properly informed so that they can genuinely consent to a procedure, such as surgery, over which they have no control. To treat certain patient groups with perceived risk factors or to treat OSAS in order to reduce the risk of other conditions, such as hypertension or coronary heart disease, must also be based on evidence of the effect on patient outcome, not simply on co-variations. Modalities vary in terms of the demands they place on the patient, the medical profession and the community. Lifestyle changes require the patient to be fully cooperative, whereas practitioners must have the required skills and be able to communicate. The community is normally not subject to specific demands with respect to lifestyle changes, but the risk of traffic accidents in subjects with nocturnal apnoeas regardless of daytime sleepiness may oppose the interests of the patient against those of the community [1]. The interests of the community may differ among various patient categories. Professional drivers or pilots may face stricter standards than those who operate vehicles on personal business only. But because any driver is in a position to injure other people, the argument can be made that the same rules should apply to everyone.

The use of medication, oral appliances or CPAP devices demands co-operation by the patient, correct prescription by the practitioner and sometimes professional follow-up. When it comes to OSAS, countries vary in terms of financial coverage for these treatment modalities. Norwegian patients pay for mandibular advancement devices, whereas the other Nordic countries subsidise the devices by 35–85%. CPAP devices are distributed free of charge in Denmark, Finland and Norway and 50% of Sweden's counties, whereas Icelandic patients have to pay either for the device or a monthly fee. Such differences may explain some of the observed variations in practice. The criteria for a diagnosis of OSAS and a free oral appliance also vary from country to country. The normal values for the apnoea-hypopnoea index (AHI) are probably lower in women than men. Thus, a diagnosis of OSAS based on equal AHI criteria may lead to discriminatory fees.

There is no evidence that surgery has any effect on OSAS. Uvulopalatopharyngoplasty and uvulopalatoplasty are associated with severe risks and demands on county finances. Nevertheless, such surgery is covered by the counties, and patients are treated outside a protocol or registry.

From a community point of view, cost-effectiveness is a major issue. Treatments that are inherently inefficacious have low cost-effectiveness even if inexpensive. It is difficult to compare treatment effects on OSAS and those associated with other conditions and therapies. In order to detect small differences, large samples have to be studied. OSAS studies are generally small in sample size. Only when the effect is truly patient-related, is based on symptom changes and has a high level of significance can it be argued that the effect is clinically relevant.

Research

Studies on any condition are most often designed to answer questions of efficacy rather than adverse effects. Even if adverse effects are generally defined and quantified, their frequency is too low for the study to provide definite answers. The exception is studies that are stopped prematurely due to risks. But there has been no registry so far covering all studies that have been started in a certain area, and there has been no obligation

to report to any authority concerning an unfavourable study on a surgical method or device. Furthermore, studies with an expected or actual unfavourable outcome are not published to the same extent as those with favourable outcomes. It is probable that there are studies on OSAS that remain unpublished. Because most studies concerning obstructive sleep apnoea are exclusively or overwhelmingly on men, it is difficult to draw any conclusions about women.

One of the research problems in the area of OSAS has been the question of blindness of the evaluator [2]. Only two studies on sham operations have been performed, and one oral appliance has been studied using blind evaluators and focusing specifically on adverse effects. This review found no evidence of the efficacy of surgery but concluded that – like all such procedures – it is associated with risks, including death. Careful consideration may have to be given to both the selection of subjects and surgical techniques when discussing or planning studies on surgery in OSAS patients.

Surrogate endpoints are often the main outcome measure for all treatment modalities. Surrogate endpoints carry a risk of false interpretation. The best example is studies on antiarrhythmic treatment after acute myocardial infarction, for which the use of the surrogate endpoint (reduction of the number of PVCs) was associated with increased mortality rates. Reduction of the AHI is often used in OSAS instead of hard endpoints, such as morbidity, mortality or symptoms relevant to the patient.

While it may be unlikely that CPAP devices or oral appliances are associated with severe complications, they can certainly cause adverse effects. It is uncertain whether the studies have been of sufficient duration and completeness of follow-up to properly answer such questions.

Most RCTs have been approved by ethics committees, but few studies have included a discussion of the ethical aspects of the studied treatment or diagnostic tool.

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7. Future Research

Treatment of sleep apnoea started in 1981, but there were no randomised controlled trials until 1994. A huge number of patients worldwide have been treated for obstructive sleep apnoea using CPAP, a number of different oral appliances, a variety of surgical procedures, recommendations of lifestyle changes, weight loss, sleeping in the lateral position, etc. Nevertheless, there is limited or insufficient evidence for many of the above treatment modalities. We strongly suggest that treatment trials be performed before a particular modality is prescribed for a patient. The CPAP equipment, oral appliances and surgical modalities used in such studies need to be standardised.

In the Nordic countries, we identified only one centre at which a randomised controlled trial that met the present inclusion criteria had been performed. Multicenter randomised controlled trials will be needed to achieve adequate power. The Nordic joint project may be a starting point for such studies. That will make it easier to better generalise the findings.

When it comes to CPAP treatment, there is a need for large, long-term studies with the endpoints of traffic accidents, cardiovascular morbidity and mortality. Studies that include patients with cardiovascular disease and hypertension are of interest. Studies on the best regimen for follow-up are important for examining optimal resource utilisation. There is also a need for studies on quality of life and health economics. Whether CPAP treatment influences pulmonary function in patients with OSAS accompanied or unaccompanied by pulmonary disease may also be of interest.

Although there were only a few randomised controlled studies on mandibular advancement appliances, it is probably the most common treatment modality – at least in Sweden. The plethora of different devices, protrusions, openings and follow-up programmes also poses a problem. Large randomised controlled trials with patient-related outcomes are

needed, as well as studies concerning the effect on traffic accidents, morbidity and mortality.

If surgery for obstructive sleep apnoea or snoring is to be considered in the future, controlled trials on efficacy and long-term follow-up for adverse effects are necessary. Large tonsils are also considered to be a risk factor for sleep apnoea, but no controlled trial on tonsillectomy was identified. Nasal surgery is common among sleep apnoea patients. Some researchers argue that it is not possible to perform sham surgery. However, we suggest conservative treatment and delayed surgery in a control group. A registry with an adequate follow-up date would also improve our knowledge about the effect of such procedures.

Overweight and smoking are possible risk factors for sleep apnoea, but no randomised controlled trials concerning weight reduction programmes, bariatric surgery or smoking cessation were identified. The effects of lifestyle changes, including weight reduction and smoking cessation, in randomised controlled trials are therefore important.

The co-variation between cardiovascular disease and obstructive sleep apnoea syndromes need to be further studied. The pathophysiologic mechanisms still remain unclear, and there is a need for pathophysiologic studies on both obstructive and central sleep apnoea in relation to cardiovascular disease.

Sleep apnoea was identified as a traffic risk regardless of daytime sleepiness. That was based on only a few case-control studies, and no prospective study was identified concerning traffic accidents. Many drivers, including professionals, have risk factors for sleep apnoea. Traffic accidents are a huge problem for the community worldwide and there is an urgent need for studies in this field.

Thousands of patients are investigated each year in the Nordic countries. Nevertheless, we identified no study that validated simplified sleep apnoea recordings against home polysomnography. There is also a need for large studies on the day-to-day variability of polysomnography and measures of daytime sleepiness. Normal values for the apnoea-hypopnoea index are needed, as well as the identification of such values adjusted for age and gender.

Appendix **Nordic Survey**

On diagnosing and managing obstructive sleep apnoea syndrome in the Nordic Countries

The assessment project included a survey of primary and specialist care clinical practices in the Nordic countries in 2003. The survey was conducted as a postal questionnaire and focused on adults.

Questionnaires

A Nordic working group designed five different one-page questionnaires (sections A–E), which were specifically planned so that answering them would take as little time as possible. The original English questions were translated into the Nordic languages, except in Norway, where English questionnaires were sent to specialist clinics.

The questionnaire on diagnosing OSAS (section A) considered the numbers of evaluations, which assessments were included in a primary evaluation, and how many evaluations were made at home. The diagnostic centres were also asked to approximate the percentage of evaluated patients that were referred for diverse treatments.

The questionnaire sections B, C and D surveyed three treatment options: nasal continuous positive airway pressure (CPAP), surgery and mandibular advancement devices. The surgical options were divided into uvulopalatopharyngoplasty (UPPP), uvulopalatoplasty and laser-assisted uvulopalatoplasty (UPP, LAUP), radiosurgery of soft palate/tongue base (RFTA), nasal surgery or other (to be specified). In addition to evaluating the numbers of patients treated, the questions dealt with indications, contra-indications, outcome and cost of treatment and patient follow-up.

The questionnaire for primary care physicians (section E) evaluated the numbers of patients seen for snoring and OSAS and how many had been

referred for specialist care. The primary care physicians were also asked whether they would consider reporting patients with OSAS and subsequent daytime sleepiness for evaluation and possible withdrawal of their driving license and whether they believed that OSAS plays a role in the onset of a number of mainly cardiovascular diseases eg hypertension.

Sampling of data

The questionnaires were sent out in each country to 200 (in Iceland 68) randomly selected primary care physicians and to all specialist centres which were thought to treat patients with OSAS in 2003. In Finland the survey was conducted in October 2004 and supplemented by telephone calls in January–February in 2005.

Several experts were consulted in each country to assure that all specialist centres were found. In Denmark the questionnaires were sent to all specialist clinics and private hospitals according to a hospital classification system ("Sygehusklassifikationssystem"). In Finland the special clinics were identified from the web pages of all central and university hospitals. In Iceland all clinics treating sleep apnoea patients were contacted and they all responded. In Norway all medical, ear, nose and throat (ENT) and neurological departments and all neurophysiology laboratories were contacted. Pulmonary departments do not exist in Norway any more, as pulmonary medicine has been integrated to internal medicine. Three large hospitals did not respond posing a probable data loss of a few hundred patients in Norway. In Sweden, all specialist centres were contacted and all responded.

The dentists were selected from a register ("Bevægelsesregistret") in Denmark. In Finland the dentist's questionnaire and also the questionnaire section C was sent to all mouth and teeth clinics in central and university hospitals after consulting three dental specialists. In Iceland there is only one dentist with a contract, and he responded. In Norway all specialists in mandibular surgery and all dentists specialised in mandibular orthopaedics were contacted. Sweden used a stratified sample and contacted only clinics that make 10 or more mandibular advancement devices per year. All these clinics responded.

The general practitioners were selected from a register ("Bevægelses-registret") in Denmark. In Finland 200 general practitioners were randomly selected from the health centre and occupational health practitioner's address register in The Finnish Medical Association. In Iceland the sample of general practitioners was created as follows: Half of all primary health care centres were chosen randomly from a telephone catalogue. The doctor on duty was contacted and asked to present the questions to his colleges who were working that week and the number of doctors was recorded (n = 68). Then the questionnaires were sent by fax and 52 GPs responded. In Sweden, 200 questionnaires were sent to randomly selected GPs and 105 of these responded.

In all countries, at least one reminder to those not responding was sent out a few weeks later. Local HTA agencies carried out the surveys except in Island (no HTA agency) where the university hospital took care of the task.

Results

The response rates for specialist clinics and private hospitals for the sent questionnaires are shown in Table 1.

Diagnostic evaluations

The centres performing diagnostic tests in the Nordic countries were most often hospital-based specialist departments ranging from ENT clinics to various laboratory specialities (clinical physiology, clinical neurophysiology) (Table 2). In Denmark the greatest numbers of diagnostic tests were done by ENT, neurology, anaesthesia, and clinical physiology departments. In the other countries ENT, pulmonary, and laboratory specialists did most of the diagnostic recordings.

According to the survey 5041 diagnostic evaluations for sleep apnoea were performed in Denmark (33 centres) in 2003 (Table 3). The corresponding numbers for Finland (55 centres), Iceland (5 centres), Norway (39 centres) and, Sweden (51 centres) were 13 589, 973, 13 554, and 33 685

respectively. There were 35 centres in the Nordic countries which reported doing less than 52 diagnostic evaluations in 2003.

In most countries in the mean 70% or more of the reported diagnostic tests were primary evaluations (Table 3). In Sweden this percentage was 62%. Fifty-three to eighty-eight percent of diagnostic recording were simplified sleep apnoea evaluations (Table 4). In Iceland all diagnostic recording were overnight polysomnographies with EEG. In both Norway and Sweden some centres used pulse oximetry alone as a diagnostic test. In Denmark and Finland pulse oximetry alone was hardly used at all. Of the simplified recordings most clinics included air flow and respiratory movements in addition to oximetry, but only few clinics used static charge sensitive bed recordings (Table 5). About half of the recordings also included other measurements, most commonly position and snoring signals.

All centres in Iceland regularly used questionnaires when diagnosing OSAS (Table 6). In Finland and Sweden 90% and in Norway and Denmark 60–70% used questionnaires. About half of diagnostic recordings were performed in the patient's home in Iceland and Norway. Most home recordings were done in Denmark (83%) and Sweden (69%), and least in Finland (36%). Seventy to 100% of those undergoing a primary evaluation for sleep apnoea also met a physician who asked about symptoms and 70 to 100% received mouth and throat examination.

A great deal of variation was found regarding patients with OSAS were referred to following the primary evaluation regardless of the number of patients being treated in the clinic (Tables 7A, 7B and 7C). Nasal CPAP seemed to be the most popular treatment in all countries and in all clinic sizes, but after that Finland and Norway favoured surgery and Sweden mandibular advancement devices. In Sweden the second most favourite treatment choice was dental treatment.

CPAP treatment

Varying specialist departments started CPAP treatments (Table 8). The most striking difference between medical specialities was seen in Denmark, where mainly neurology and anaesthesia departments took care of CPAP and Finland, where pulmonary specialists took care of almost all patients. In Iceland one centre took care of all CPAP treatments, but in Denmark, Finland, Norway, and Sweden 28, 31, 29, and 43 centres did so. The prevalence and incidence of CPAP treatments in 2003 are shown in Table 9. Altogether there were 38 centres which reported less than 55 CPAP treatments. Except for Sweden and Iceland, patients received CPAP devices, masks etc free of charge (Table 10). In Iceland a moderate monthly fee was charged. In Sweden the clinics reported 2 698 patients paying for either CPAP devices, masks/nasal inserts or a monthly fee or a combination of these.

Both symptoms and AHI were most often used as indications when deciding to treat patients with CPAP, except in Iceland where indications were decided on a case-by-case basis (Table 11). There were no differences in indications for CPAP treatment when we compared departments starting either less than 100 or more than 100 CPAP treatments in 2003. In the mean half of all the centres starting CPAP treatments did not have any contraindications for this therapy (Table 12). Most of the contraindications, when present, were related to the patient's non-compliance or other illnesses. The appropriate CPAP pressure was most often titrated during the night with an automatic device (Table 13). In Denmark 11, in Sweden 5 and in Norway 9 centres only gave their patients automatic CPAP devices and thus no titration was needed. Most centres routinely called patients for follow-up visits, after a couple of months following initiation of therapy and thereafter yearly (Table 14).

Surgery

There were a total of 108 centres reporting that they operated on OSAS and snoring in the Nordic countries in 2003 (Table 15). The most common operating specialities were divided between the countries as follows:

In Denmark (13 centres) anaesthesia, ENT, maxillofacial surgery and; in Finland (41 centres) ENT, maxillofacial surgery; in Iceland (3 centre) ENT; in Norway (20 centres) mostly ENT; and in Sweden (31 centres) ENT departments. According to the survey in Denmark 188 patients were operated on OSAS and snoring, and the corresponding numbers for Finland, Iceland, Norway, and Sweden were 1 785, 237, 2 760 and 745 (Table 16). Not all of these operations were preceded by a sleep apnoea investigation, but it is not possible to decide whether these were just nasal operations on snoring.

In 2003 only one fifth of the centres in the Nordic countries reported that they performed more than 55 operations on OSAS and snoring. The most common surgical procedure differed between the countries and within the countries when surgery was performed in clinics with different patient volumes (Tables 17A and 17B). In Iceland the biggest proportion of operations were nasal, with some palatal operations. In Denmark the greatest percentage of the operations were palatal, nasal operations being in the minority. In Finland and particularly in Norway radiosurgery or soft palate/tongue base was used. In Sweden, with few operations, uvulopalatopharyngoplasty was still common. Maxillofacial surgery for OSAS and snoring was performed either in small numbers (63 in Finland) or not at all.

Symptoms together with AHI were the most common indications used to make the operative decision (Table 18). In many centres, particularly in Finland, no fixed indications were used and the decision was always made case-by-case. In Sweden, one third of centres reported that they had no contra-indications to surgery, in the other countries this was the case only in a few centres (Table 19). In Norway most centres used AHI (upper limit, from 15 to 40/hour) as a contra-indication. In the Nordic countries the other most common contra-indications were a high body mass index (>30–32 kg/m^2) or the patient not being a good surgical candidate.

Most clinics performed less than 52 operations in 2003, except ten clinics in Norway and seven clinics in Finland (Tables 20A and 20B). In all clinics in Finland and Iceland only one third of operations were followed-up by a sleep study, but in Sweden the number was 82%, and in the two

other countries it varied from 40 to 50%. Circa one third of all operations did not result in an optimal or desired outcome in 2003. Except for Denmark, all countries reported that there had been deaths in connection with sleep apnoea operations (Table 21).

Mandibular advancement devices

A lot of variation between the countries was reported in offering mandibular advancement devices (MAD) for sleep apnoea (Table 22). In Iceland 1, in Denmark 2, in Norway 3, in Finland 15, and in Sweden 51 dentists or dental departments reported that they installed MADs for OSAS or snoring. Correspondingly the numbers of devices installed varied: Denmark 52, Finland 517, Iceland 93, and Norway 12. According to official Swedish statistics 6 775 MADs were installed in Sweden. Assuming that 53% of the MADs were subsided the total number of MADs in use is 12 800. Almost all decisions to prescribe MADs for snoring were preceded by a sleep apnoea study (Table 23). All dentists used individually designed MADs. In Norway, the total cost for the device is paid by the patient, while in the other Nordic countries approximately 35 to 66% of the MADs were paid or subsidized by public funds. The treatment costs varied greatly (160–700 euros), if the patients paid out-of-pocket (Table 24).

In Denmark and Sweden the majority of patients, and in Norway all patients receiving MADS were followed up by a sleep apnoea evaluation. In Finland and Iceland the corresponding numbers were 55% and 20%. Except for a few dentists, all regularly checked patients after a MAD had been prescribed (Table 24). In Finland two thirds of dentists reported that they had the main medical responsibility for the patient after dental treatment, in the other countries the referring department was responsible in the minority of cases (Table 25). In the mean the treatment outcome was reported not to be optimal in 18–50% of cases with this form of therapy (Table 24).

Primary care physicians

The response rate varied from 56% in Norway to 76% in Iceland. The number of OSA patients seen per year by the Nordic general practitioners varied. In all Nordic countries, majority of the general practitioners had seen 1–4 or 5–9 sleep apnoea or snoring patients in 2003 (Table 26). In practice all GPs had an opportunity to refer patients when they suspected sleep apnoea (Table 27) and most had referred 1–4 patients (Table 28).

The Nordic countries have restrictions on motor vehicle driving for these persons, while in Finland the physicians are obligated to declare on this due to a new legislation in 2004. Physicians are set to administer these restrictions. The general practitioners' willingness to report persons with sleepy OSA patients to the relevant authorities for possible withdrawal of their driving license varied greatly between the countries (Table 29). While only about one third of the Norwegian doctors said they would report their patients, nearly all Finnish doctors would do so, the other countries taking intermediate positions. A variation was detected also their ideas whether OSA played a possible role in traffic accidents, onset of hypertension and cardiovascular complications (Table 30).

Table 1 *Response rates (%) of all sent questionnaires (A – diagnosis, B – CPAP treatment and C – surgical treatment) by specialist clinics and private hospitals.*

	Denmark	Finland	Iceland	Norway	Sweden
Anaesthesiology and other	89	–	–	–	–
Clinical physiology and neurophysiology	64	97	100	–	100
Ear, nose and throat	93	71	100	86	100
Mouth and teeth	80	81	–	–	–
Neurology	85	100	–	69	–
Pulmonary	100	92	100	97	100
Private	100	75	100	–	100

A. Diagnosing OSAS

Table 2 *Number and type of departments offering diagnostic evaluations of sleep apnoea.*

	Denmark	Finland	Iceland	Norway	Sweden
Anaesthesiology	16	–	–	–	–
Clinical physiology and neurophysiology	1	13	–	–	21
Ear, nose and throat	3	9	–	14	21
Mouth and teeth	4	–	–	–	–
Neurology	9	4	–	6	–
Pulmonary	0	26	3	16	8
Private	0	3	2	3	1
Total	33	55	5	39	51
Number of clinics doing more than 52 evaluations in 2003	25	43	3	31	45

Table 3 *Diagnostic sleep apnoea evaluations in 2003.*

	Denmark	Finland	Iceland	Norway	Sweden
Total number of evaluations	5 041	13 589	973	13 554	33 685
Primary evaluations (% of all evaluations)	79	71	87	71	62
Primary evaluations per 10 000 inhabitants	9.1	22.6	38.4	26.6	29.1

Table 4 *Type of primary evaluation methods (number of cases).*

	Denmark	Finland	Iceland	Norway	Sweden
Primary evaluations	3 997	9 651	848	9 668	21 316
Polysomnography with EEG (night)	433	762	0	2 383	478
Polysomnography with EEG (day)	72	2	0	22	18
Simplified sleep apnoea evaluation	2 934	8 847	848	630	18 904
Pulse oximetry alone	40	40	0	618	1 915

Table 5 *Type of recordings included in a simplified evaluation of those using simplified recordings (number of clinics).*

	Denmark n=23	Finland n=51	Iceland n=5	Norway n=24	Sweden n=47
Air flow	20	45	5	23	46
Respiratory movements	20	48	5	21	20
Oximetry	21	50	5	24	47
Static charge sensitive bed	5	20	–	4	6

Table 6 *Details of diagnostic evaluation practices (mean percentages).*

	Denmark n=33	Finland n=53	Iceland n=5	Norway n=37	Sweden n=50
Clinics using questionnaires	70	89	100	63	90
Home evaluations	83	36	50	52	69
Patients undergoing primary evaluations for sleep apnoea meeting a physician who asked about the symptoms	97	73	100	87	84
Patients receiving mouth and throat examinations	92	82	100	77	74

Table 7A *Patients evaluated in 2003 referred for the following treatment/s, if any (mean percentages). Clinics performing less than 100 evaluations.*

	Denmark n=9	Finland n=10	Iceland n=2	Norway n=12	Sweden n=4
CPAP	57	46	40	53	41
Surgery	7	25	1	16	3
Dental/orthodontic treatment	2	3	1	7	20
Other treatments (diet, etc)	20	5	58	30	16

Table 7B *Patients evaluated in 2003 referred for the following treatment/s, if any (mean percentages). Clinics performing 100–500 evaluations.*

	Denmark n=30	Finland n=37	Iceland n=5	Norway n=36	Sweden n=39
CPAP	57	37	37	47	34
Surgery	7	16	2	25	6
Dental/orthodontic treatment	3	6	7	6	26
Other treatments (diet, etc)	16	12	53	23	6

Table 7C *Patients evaluated in 2003 referred for the following treatment/s, if any (mean percentages). Clinics performing more than 500 evaluations.*

	Denmark n=2	Finland n=6	Iceland n=0	Norway n=2	Sweden n=8
CPAP	43	41	–	35	35
Surgery	10	8	–	33	5
Dental/orthodontic treatment	8	7	–	2	5
Other treatments (diet, etc)	15	27	–	20	43

B. Treatment with CPAP

Table 8 *Number and type of departments offering CPAP treatments for sleep apnoea.*

	Denmark	Finland	Iceland	Norway	Sweden
Anaesthesiology	14	–	–	–	–
Clinical physiology and neurophysiology	0	–	–	1	12
Ear, nose and throat	3	1	–	10	14
Mouth and teeth	3	–	–	–	–
Neurology	8	1	–	2	–
Pulmonary	0	28	1	16	17
Private	0	1	–	–	–
Total	**29**	**31**	**1**	**28**	**43**

Table 9 *Number of patients receiving CPAP or BiPAP for snoring/sleep apnoea syndrome in 2003.*

	Denmark	Finland	Iceland	Norway	Sweden
Number of new CPAP treatments started	No data	About 1 900	448	4 031	5 730
Total number of patients on CPAP	2 328	10 572	1658	No data	17 700
Number of clinics treating more than 52 patients in 2003 with CPAP	16	27	1	13	34

Table 10 *Direct costs of the CPAP treatment to the patient, if any (number of clinics).*

	Denmark	Finland	Iceland	Norway	Sweden
Patients receive CPAP devices, masks, etc free of charge	28	30	0	27	25
Patients pay for CPAP devices	1	1	0	0	10
Patients pay for masks/ nasal inserts	1	1	0	0	10
Patients pay a monthly/ annual fee	0	1	1	0	9

Table 11 *Indications for CPAP treatment (number of clinics).*

	Denmark	Finland	Iceland	Norway	Sweden
No fixed indications, determined on a case-by-case basis	0	2	1	1	6
Mainly AHI	2	4	0	0	5
Symptoms and AHI	19	25	0	27	2
Mainly symptoms	1	0	0	0	3
Other, including clinics reporting several indications	7	0	0	0	1

Table 12 *Contraindications for CPAP treatment (number of clinics).*

	Denmark	Finland	Iceland	Norway	Sweden
No contraindications	17	16	1	15	22
AHI limits (lower or upper)	1	3	0	3	10
Other	10	12	0	4	10

Table 13 *Titration of appropriate CPAP pressure (number of clinics).*

	Denmark	Finland	Iceland	Norway	Sweden
Pressure adjustment during the night	1	1	1	4	3
Daytime titration followed by night checks	2	0	0	0	5
Patients receive usual CPAP after titration of suitable pressure by AutoCPAP	9	27	0	13	6
Titration not needed, patients are prescribed AutoCPAP	11	0	0	5	9
Other method	2	3	0	0	0
Several of the above mentioned options	4	0	0	5	20

Table 14 *Follow-up of CPAP patients (number of clinics).*

	Denmark	Finland	Iceland	Norway	Sweden
No routine follow-up	2	0	0	0	2
First follow-up visit taking place within 1 week to 6 months	25	30	1	27	29
Patients are also called for annual check-ups	14	22	0	0	26

C. Surgical treatment

Table 15 *Number and type of departments offering surgical treatments for sleep apnoea.*

	Denmark	Finland	Iceland	Norway	Sweden
Anaesthesiology	8	–	–	–	–
Clinical physiology and neurophysiology	0	–	–	–	4
Ear, nose and throat	1	27	3	17	24
Mouth and teeth	2	12	0	–	–
Neurology	2	–	–	–	–
Pulmonary	0	–	–	–	3
Private	–	2	–	3	–
Total	**13**	**41**	**3**	**20**	**31**

Table 16 *Operations during 2003 for snoring or sleep apnoea.*

	Denmark	Finland	Iceland	Norway	Sweden
Total number of operations reported	188	1 785	237	2 760	745
Operations per 10 000 inhabitants >15 years old	0.4	4.2	10.7	7.6	1.0
Mean percentage of operations performed without a preceding sleep apnoea investigation	0	9	18	6	1

Table 17A *Different types of operations performed in clinics performing more than 52 operations in 2003 (mean percentages).*

	Denmark n=1	Finland n=7	Iceland n=3	Norway n=10	Sweden n=1
Uvulopalatopharyngoplasty	50	14	3	19	34
Uvulopalatoplasty or laser-assisted uvuloplasty	0	16	38	13	50
Radiosurgery of soft palate/ tongue base	20	37	0	56	13
Nasal surgery	10	20	58	13	2
Other	20	13	0	3	1

Table 17B *Different types of operations performed in clinics performing less than 52 operations in 2003 (mean percentages). Thirty-eight percentages of clinics performed less than 10 operations.*

	Denmark n=10	Finland n=34	Iceland n=0	Norway n=8	Sweden n=30
Uvulopalatopharyngoplasty	32	17	–	6	39
Uvulopalatoplasty or laser-assisted uvuloplasty	15	16	–	29	21
Radiosurgery of soft palate/ tongue base	14	12	–	32	9
Nasal surgery	15	16	–	24	17
Other	14	34	–	1	11

Table 18 *Indications for surgical treatment (number of clinics).*

	Denmark	Finland	Iceland	Norway	Sweden
No fixed indications, determined on a case-by-case basis	1	14	3	4	7
Mainly AHI	0	0	0	0	0
Symptoms and AHI	6	14	0	12	14
Mainly symptoms	0	4	0	4	6
Other, including clinics reporting several indications	4	8	0	0	4

Table 19 *Contraindications for surgical treatment (number of clinics).*

	Denmark	Finland	Iceland	Norway	Sweden
No contraindications	1	3	1	2	9
Only AHI limits (lower or upper)	1	1	0	14	3
Other	8	35	2	5	18

Table 20A *Details of surgical treatment practices. Clinics performing less than 52 operations.*

	Denmark n=10	Finland n=34	Iceland n=0	Norway n=8	Sweden n=30
Mean percentage of patients followed up after surgical treatment	44	34	0	39	82
Mean percentage of operations not yielding the intended/optimum result based on the physicians' judgement	33	27	0	33	33

Table 20B *Details of surgical treatment practices. Clinics performing more than 52 operations.*

	Denmark n=1	Finland n=7	Iceland n=3	Norway n=10	Sweden n=1
Mean percentage of patients followed up after surgical treatment	100	6	32	40	80
Mean percentage of operations not yielding the intended/optimum result based on the physicians' judgement	10	20	13	21	20

Table 21 *Clinics reporting deaths.*

	Denmark	Finland	Iceland	Norway	Sweden
Number of clinics reporting deaths have ever been associated with surgery for sleep apnoea	0	3	1	1	2

D. Mandibular advancement devices

Table 22 *Response rate and number of dental clinics offering mandibular advancement devices.*

	Denmark	Finland	Iceland	Norway	Sweden
Response rate	86	81	100	23	100*
Number of dental clinics treating OSAS patients	2	15	1	3	51*

* Sweden used a stratified sample of clinics that made 10 or more mandibular advancement devices per year.

Table 23 *Details of mandibular advancement devices prescribed for snoring or sleep apnoea patients during 2003.*

	Denmark	Finland	Iceland	Norway	Sweden
Total number of mandibular advancement devices prescribed	52	517	93	12	12 800**
Mandibular advancement devices prescribed per 10 000 inhabitants >15 years old	0.11	1.2	4.2	0.03	17.5
Mean percentage of mandibular advancement devices installed performed without a preceding sleep apnoea investigation	5.8	3.4	0	1	1
Number of clinics treating more than 52 patients in 2003 with mandibular advancement devices	0	2	1	0	21

** An estimate based on official statistics assuming that 53% of devices were subsided of a total amount of 6 775 devices in 2003.

Table 24 *Details of mandibular advancement device practices for OSAS and snoring patients (mean percentages).*

	Denmark	Finland	Iceland	Norway	Sweden
Devices were subsidized by public funds	47	35	66	0	53
"Out-of-pocket" costs for patients without public subsidies (€)	292	160	100	534	700
Patients receiving devices followed up by sleep apnoea evaluation	95	55	20	100	73
Prescribed devices not yielding the intended/optimum result based on the dentists' judgement	39	30	?	50	18

Table 25 *Follow-up practices with mandibular advancement devices.*

	Denmark n=2	Finland n=15	Iceland n=1	Norway n=3	Sweden n=51
Number of dental clinics which have the main responsibility of the mandibular advancement device treatment	1	10	0	0	5

E. General practitioners (n = 200, except for Iceland n = 68)

Table 26 *Number of consultations for snoring or sleep apnoea in 2003 (percentage).*

Response rate (%)	Denmark 56*	Finland 64	Iceland 76	Norway 56	Sweden 61
No patients	4	5	8	1	2
1–4 patients	52	26	29	24	45
5–9 patients	38	39	37	41	35
10–19 patients	5	20	17	24	13
More than 19 patients	2	11	10	10	4

* In Denmark 28 GPs responded that they did not treat sleep apnoea patients.

Table 27 *Potentiality to refer patients with suspected sleep apnoea (percentage).*

	Denmark	Finland	Iceland	Norway	Sweden
Yes	97	100	100	99	98

Table 28 *Number of referrals for snoring or sleep apnoea in 2003 (percentage).*

	Denmark	Finland	Iceland	Norway	Sweden
No patients	7	8	14	2	5
1–4 patients	80	63	64	50	70
5–9 patients	11	20	17	36	19
10–19 patients	2	6	4	8	6
More than 19 patients	0	3	2	3	0

Table 29 *Willingness to report for evaluation and possible drivers' license withdrawal for patients with sleep apnoea and subsequent daytime sleepiness (percentage).*

	Denmark	Finland	Iceland	Norway	Sweden
Yes	65	91	54	30	63

Table 30 *Do you believe that sleep apnoea syndrome plays a role in the onset of the following conditions (percentage yes).*

	Denmark	Finland	Iceland	Norway	Sweden
Hypertension	69	85	89	72	91
Stroke	71	88	75	66	81
Angina pectoris	57	86	75	52	79
Myocardial infarction	56	81	73	57	84
Cardiac arrhythmia during sleep	78	93	90	74	91
Traffic accidents	84	94	89	77	95