

Recent Advances in the Obstructive Sleep Apnoea/Hypopnoea Syndrome

N J Douglas,**MD, FRCP, FRCPE*

Introduction

The past decade has seen a rapid increase in the number of patients being referred for investigation for the obstructive sleep apnoea/hypopnoea syndrome (OSAHS). Indeed, in many centres, possible OSAHS is now the most common respiratory referral and OSAHS is the most common outpatient respiratory diagnosis. OSAHS is extremely rewarding to treat as the patient benefit can be enormous. It is important that all physicians are familiar with OSAHS as missing the diagnosis can be catastrophic, as OSAHS patients are as dangerous on the road as drunk drivers. This review will highlight recent advances in our understanding of OSAHS.

Epidemiology

The best definition of OSAHS is the occurrence of at least five 10-second breathing pauses (apnoeas) or hypopnoeas (near apnoeas) per hour of sleep in association with sleepiness or at least two other major symptoms, including difficulty concentrating, unrefreshing nocturnal sleep or nocturia¹ (Table I). There are now numerous studies indicating that the frequency of OSAHS in the Western population lies between 0.3% and 4%^{2,3} and is the same order in the oriental population.⁴ However, it is important to distinguish between OSAHS – which is the combination of irregular breathing during sleep with symptoms, usually sleepiness – and isolated irregular breathing during sleep without symptoms. Recent studies show there are many non-sleepy individuals with irregular breathing during sleep^{3,5} but it is not yet clear whether these individuals suffer consequences of this irregular breathing but are unaware of them.

Associated Conditions

Road Accidents

Individuals with OSAHS are dangerous drivers with a 2- to 12-fold risk of being involved in road accidents.⁶⁻⁹ Studies on driving simulators show patients with OSAHS are not only much worse than age, gender and driving experience matched controls, but also that SAHS patients

Table I: Symptoms of obstructive sleep apnoea/hypopnoea syndrome (OSAHS)

Sleepiness
Difficulty concentrating
Daytime fatigue
Unrefreshing sleep
Nocturnal choking
Nocturia
Depression
Decreased libido
<u>Partner's report</u>
Snoring
Apnoeas
Restless sleep
Irritability

when sober drove worse than the normal subjects when legally drunk.¹⁰ Recent evidence shows that accident rates return to the normal range with continuous positive airway pressure (CPAP) therapy.¹¹

Hypertension

There are now unequivocal data indicating that sleep apnoea causes hypertension. Data from animal studies¹² indicate that recurrent apnoeas during sleep result in sustained daytime hypertension with a blood pressure elevation of the order of 16 mm Hg. Daytime hypertension did not result from a similar frequency of awakenings at night due to noises, and thus it seems likely that a combination of hypoxaemia and arousal are required for sustained hypertension to result.¹²⁻¹⁴

Epidemiological evidence of an association between OSAHS and hypertension has been difficult to evaluate because of the existence of confounders such as obesity and smoking which could have led to the apparent association. However, more recent data indicates that hypertension is independent of the known confounders.¹⁵⁻¹⁸ These data indicate an odds ratio of between 1.4 and 2.9 of being hypertensive if one has irregular breathing during sleep. In addition, studies in OSAHS populations have also strongly suggested an association between OSAHS and

* Professor of Respiratory & Sleep Medicine
The University of Edinburgh
Scotland, United Kingdom

Address for Correspondence: Professor Neil J Douglas, Department of Medicine, Royal Infirmary, Edinburgh EH3 9YW, Scotland, UK.
E-mail: n.j.douglas@ed.ac.uk

hypertension independent of confounders^{19,20} and the same is true in hypertensive populations.²¹

A careful case control study with scrupulous matching of OSAHS patients with controls for age, body mass index (BMI), alcohol, smoking, hypertension and drug history showed increased blood pressure in OSAHS patients compared to controls.²²

Perhaps, the most convincing evidence, however, comes from intervention studies. We have shown in a placebo control trial that CPAP reduces diastolic blood pressure by 1.4 mm Hg when all patients' data are analysed on an intention to treat basis.²³ While relatively unimpressive, this global figure hides the fact that some patients did not use their CPAP at all and the blood pressure reduction was greater in those who did.²³ Because of the animal data, we examined an a priori group of patients who had significant nocturnal hypoxaemia, and they showed 4 mm Hg falls in systolic and 5 mm Hg falls in diastolic blood pressure.²³ These data have since been confirmed²⁴ and extended to show that the blood pressure changes are also greater in a small subgroup of patients who were known to be hypertensive.

Thus, there are clear data indicating that OSAHS is associated with a blood pressure rise and that this rise is greater in those with nocturnal hypoxaemia.

Cardiac Disease

There is no clear evidence that OSAHS is causally associated with significant cardiac arrhythmias²⁵ or with myocardial infarction.²⁶ Inadequately controlled non-randomised studies have suggested there may be increased vascular risk in untreated OSAHS.^{27,28} Population data which suggest that there may be an association between ischaemic heart disease and OSAHS²⁹ in fact showed no significant association, if allowance was made for confounders. There were, therefore, no adequate data showing an association with OSAHS and heart disease. However, that is not the same as saying there is evidence of no additional risk, and the clear association between OSAHS and hypertension strongly suggests that there is a real increased risk of cardiac disease in OSAHS.

Stroke

More than half of patients with stroke have irregular breathing during sleep in the early recovery period.^{30,31} The frequency is particularly high in older patients with severe stroke. However, the value of treating this irregular breathing in stroke patients is not yet clear. Early studies have suggested that many patients with irregular breathing during sleep after stroke will decline CPAP therapy and there is no evidence that CPAP has a major effect on outcomes, even in those who accept treatment.³² There are numerous studies

being conducted in this area which should clarify the role of CPAP.

Pre-eclampsia

Snoring is much more common in pregnant than non-pregnant women³³ and both pre-eclampsia and foetal growth retardation are more common in snoring than non-snoring mothers.³³ Recent studies have indicated that women with pre-eclampsia have repeated episodes of upper airway narrowing during sleep which may be improved with CPAP therapy, and that CPAP can reduce their nocturnal blood pressure.³⁴ Recent studies have indicated that upper airway size is decreased in pregnancy, probably due to a decrease in the functional residual capacity due to mass displacement of the diaphragm, and that upper airway size is further narrowed in pre-eclampsia, probably due to oedema.³⁵ Further studies are required to clarify the importance of upper airway narrowing in pre-eclampsia.

Sudden Infant Death Syndrome (SIDS)

An increased frequency of unexplained infant deaths has been reported in families of OSAHS patients.^{36,37} SIDS victims have back-set jaws which predispose to upper airway narrowing,³⁸ a similar abnormality to that seen in obstructive sleep apnoea.³⁹ Further studies are required to clarify whether some cases of SIDS represent upper airway obstruction during sleep with immature arousal responses.

Predispositions to OSAHS

While it has been recognised for decades that obesity predisposes to OSAHS, recent studies have emphasised that this may not be as important as first thought, particularly in the Chinese population.⁴ Even in Caucasians, only around 50% of patients with OSAHS are obese, where this is defined as a BMI of >30 kg/m². In thinner patients with OSAHS, facial structure is important.⁴⁰ Familial back-settings of the mandible and maxilla are major risk factors for OSAHS³⁹ and this is almost certainly genetically determined.

Diagnosis

OSAHS is best defined as the combination of daytime sleepiness or two other major symptoms, usually impaired concentration, unrefreshing sleep or nocturia¹ with at least 5 apnoeas or hypopnoeas/hour of sleep. This is a conservative interpretation of the recent American Sleep Disorders Association recommendation.⁴¹ There are clear data from intervention studies indicating improvement in patients with as few as 5 to 15 respiratory events/hour.⁴²⁻⁴⁵ However, there is need for further work to clarify the threshold frequency and severity gradings for respiratory events during sleep as there are data indicating that both the driving and blood pressure risks do not occur until much higher levels of severity.^{11,23}

OSAHS can be diagnosed in many patients by simplified recordings performed in the home.⁴⁶ Polysomnography is also a useful technique for diagnosing OSAHS but is less cost effective and, I believe, its use should be restricted to patients with non-diagnostic home studies or for patients in whom for geographical or medical reasons an in-patient sleep study is required.

Treatment

The obstructive sleep apnoea/hypopnoea syndrome is one of the most satisfying conditions in Internal Medicine to treat, as this can literally transform the patient's life.

General Measures

All patients who are overweight should be given advice on weight reduction. Patients should also be advised to avoid evening alcohol, when appropriate.

Continuous Positive Airway Pressure Therapy

Despite earlier challenges,⁴⁷ there is now unequivocal evidence from randomised controlled trials that CPAP is an effective form of therapy for symptoms, sleepiness, sleep, cognitive function, quality of life, mood, driving performance and blood pressure.^{23,48-53} These data apply to symptomatic patients with more than 15 apnoeas and hypopnoeas/hour of sleep and, in this group, CPAP is undoubtedly the first choice treatment. The situation is more confused in symptomatic patients with mild OSAHS (5 to 15 events/hour) in whom all studies agree that CPAP produces symptomatic improvement⁴²⁻⁴⁵ but the improvements in sleepiness and cognition were patchy. In addition, patients with mild sleep apnoea tend to use their CPAP relatively poorly with half stopping therapy by 3 years.⁵⁴ Thus, the value of treating these mild patients with CPAP on a regular basis is questionable. Asymptomatic individuals who have frequent irregular breathing have not been shown to benefit from CPAP therapy,⁵⁵ either in terms of improvement in unrecognised sleepiness or in blood pressure.

CPAP therapy is relatively obtrusive and it is important that patients receive adequate education and optimal mask fitting prior to overnight CPAP pressure titration and readily accessible support and trouble-shooting once they take CPAP home. Such measures have been shown to improve CPAP usage and outcomes.⁵⁶ Sleepy patients with severe sleep apnoea tend to use CPAP well, with over 90% still using CPAP at 5 years.⁵² However, patients with few symptoms tend to abandon CPAP more readily as the inconvenience of CPAP appears to outweigh the benefits. In these patients, alternative therapies should be sought.

The main side effect of CPAP is nasal drying and stuffiness which can be reduced by using heated humidifiers.⁵⁷ Mask discomfort is common and close

supervision from CPAP nurses is important to ensure good fit and avoid excessive tightening of the straps.

Mandibular Repositioning Splints (MRS)

Mandibular repositioning splints are designed to keep the lower jaw protruded during sleep, thus preventing the tongue falling back and narrowing the throat. A randomised placebo controlled trial has shown that they improve sleepiness, snoring and apnoeas and hypopnoeas during sleep.⁵⁸ However, recent evidence indicates that the benefit from MRS devices is significantly less than that obtained with CPAP in the same patients.⁵⁹ MRS devices can cause problems of excessive salivation, mouth discomfort, crown displacement and temporo-mandibular joint discomfort. There are no adequate studies indicating the best design or how these side effects should be minimised. There are some concerns that use of MRSs may be low, but more data on this are required.

Pharyngeal Surgery

There are no randomised controlled trials showing benefit from uvulopalato-pharyngoplasty, which was the most common used operation in OSAHS. There is evidence that UPPP can occasionally be associated with perioperative death and certainly with significant perioperative morbidity,⁶⁰ and that UPPP can be detrimental if the patient subsequently requires CPAP therapy.⁶¹ Thus, because of lack of evidence of benefit and evidence of harm, uvulopalato-pharyngoplasty is not advised in OSAHS patients, whether this is carried out by conventional techniques or by laser (LAUP) or by any other modification. Similarly, radio-frequency volume reduction of the palate or tongue cannot be advised at present.

Mandibular Maxillary Osteotomy (MMO)

MMO has been shown in a controlled trial to be as effective as CPAP in normalising breathing pattern overnight and improving both symptoms and daytime vigilance.⁶² However, more data are required from more centres and further information on follow-up decades after surgery.

Other Forms of Therapy

There is no evidence that upper airway muscle pacing is of benefit. Similarly, despite trials of a large number of agents, no clinically useful drug has as yet been found.

Cost-benefit Analysis

Patients with undiagnosed OSAHS are heavy users of healthcare, costing around twice that of age and gender matched controls.^{63,64} Treatment with CPAP has been reported to reduce these costs with evidence of decreased hospitalisations due to cardiovascular or pulmonary

disease⁶⁵ and decreased hospital stays following road accidents.⁶⁶ Indeed, recent studies suggest that CPAP therapy results in a 12-fold cost saving in terms of road accidents alone.⁶⁷

Conclusion

The obstructive sleep apnoea/hypopnoea syndrome is a common disorder which is readily diagnosed and highly effectively treated. All physicians must take an adequate sleep history on all patients that they see. Until this is done, cases of OSAHS will be missed with significant consequences for the quality of life of the patient and for other road users.

Further Reading

Douglas N J. Clinicians' Guide to Sleep Medicine. Arnold, London 2002; ISBN 0340742054.

REFERENCES

- Whyte K F, Allen M B, Jeffrey A A, Gould G A, Douglas N J. Clinical features of the sleep apnoea/hypopnoea syndrome. *Q J Med* 1989; 72:659-66.
- Stradling J R, Crosby J H. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. *Thorax* 1991; 46:85-90.
- Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328:1230-5.
- Ip M S, Lam B, Laufer I J, Tsang K W, Chung K F, Mok Y W, et al. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. *Chest* 2001; 119:62-9.
- Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med* 2001; 163:685-9.
- George C F, Nickerson P W, Hanly P J, Millar T W, Kryger M H. Sleep apnoea patients have more automobile accidents. *Lancet* 1987; 2:447.
- Haraldsson P O, Carenfelt C, Diderichsen F, Nygren A, Tingvall C. Clinical symptoms of sleep apnea syndrome and automobile accidents. *ORL J Otorhinolaryngol Relat Spec* 1990; 52:57-62.
- Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. *N Engl J Med* 1999; 340:847-51.
- Young T, Blustein J, Finn L, Palta M. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep* 1997; 20:608-13.
- George C F, Boudreau A C, Smiley A. Simulated driving performance in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1996; 154:175-81.
- George C F. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. *Thorax* 2001; 56:508-12.
- Brooks D, Horner R L, Kozar L F, Render-Teixeira C L, Phillipson E A. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Invest* 1997; 99:106-9.
- Bao G, Metreveli N, Fletcher E C. Acute and chronic blood pressure response to recurrent acoustic arousal in rats. *Am J Hypertens* 1999; 12:504-10.
- Fletcher E C, Lesske J, Qian W, Miller C C 3, Unger T. Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. *Hypertension* 1992; 19:555-61.
- Hla K M, Young T B, Bidwell T, Palta M, Skatrud J B, Dempsey J. Sleep apnea and hypertension. A population-based study. *Ann Intern Med* 1994; 120:382-8.
- Bixler E O, Vgontzas A N, Lin H M, Ten Have T, Leiby B E, Vela-Bueno A, et al. Association of hypertension and sleep-disordered breathing. *Arch Intern Med* 2000; 160:2289-95.
- Nieto F J, Young T B, Lind B K, Shahar E, Samet J M, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 2000; 283:1829-36.
- Peppard P E, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; 342:1378-84.
- Grote L, Ploch T, Heitmann J, Knaack L, Penzel T, Peter J H. Sleep-related breathing disorder is an independent risk factor for systemic hypertension. *Am J Respir Crit Care Med* 1999; 160:1875-82.
- Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *BMJ* 2000; 320:479-82.
- Worsnop C J, Naughton M T, Barter C E, Morgan T O, Anderson A I, Pierce R J. The prevalence of obstructive sleep apnea in hypertensives. *Am J Respir Crit Care Med* 1998; 157:111-5.
- Davies C W, Crosby J H, Mullins R L, Barbour C, Davies R J, Stradling J R. Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. *Thorax* 2000; 55:736-40.
- Faccenda J F, Mackay T W, Boon N A, Douglas N J. Randomized Placebo-controlled Trial of Continuous Positive Airway Pressure on Blood Pressure in the Sleep Apnea-Hypopnea Syndrome. *Am J Respir Crit Care Med* 2001; 163:344-8.
- Pepperell J C, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling J R, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 2002; 359:204-10.
- Flemons W W, Remmers J E, Gillis A M. Sleep apnea and cardiac arrhythmias. Is there a relationship? *Am Rev Respir Dis* 1993; 148:618-21.
- Hung J, Whitford E G, Parsons R W, Hillman D R. Association of sleep apnoea with myocardial infarction in men. *Lancet* 1990; 336:261-4.
- Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients. Mortality. *Chest* 1988; 94:1200-4.
- Partinen M, Guilleminault C. Daytime sleepiness and vascular morbidity at seven-year follow-up in obstructive sleep apnea patients. *Chest* 1990; 97:27-32.
- Shahar E, Whitney C W, Redline S, Lee E T, Newman A B, Javier N F, et al. Sleep-disordered Breathing and Cardiovascular Disease. Cross-sectional results of the sleep heart health study. *Am J Respir Crit Care Med* 2001; 163:19-25.
- Bassetti C, Aldrich M S. Sleep apnea in acute cerebrovascular diseases: final report on 128 patients. *Sleep* 1999; 22:217-23.
- Parra O, Arboix A, Bechich S, Garcia-Eroles L, Montserrat J M, Lopez J A, et al. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. *Am J Respir Crit Care Med* 2000; 161:375-80.
- Sandberg O, Franklin K A, Bucht G, Eriksson S, Gustafson Y. Nasal continuous positive airway pressure in stroke patients with sleep apnoea: a randomized treatment study. *Eur Respir J* 2001; 18:630-4.
- Franklin K A, Holmgren P A, Jonsson F, Poromaa N, Stenlund H, Svanborg E. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. *Chest* 2000; 117:137-41.
- Edwards N, Blyton D M, Kirjavainen T, Kesby G J, Sullivan C E. Nasal continuous positive airway pressure reduces sleep-induced blood pressure

- increments in preeclampsia. *Am J Respir Crit Care Med* 2000; 162: 252-7.
35. Douglas N J. Systematic review of the efficacy of nasal CPAP. *Thorax* 1998; 53:414-5.
 36. Mathur R, Douglas N J. Relation between sudden infant death syndrome and adult sleep apnoea/hypopnoea syndrome. *Lancet* 1994; 344: 819-20.
 37. Tishler P V, Redline S, Ferrette V, Hans M G, Altose M D. The association of sudden unexpected infant death with obstructive sleep apnea. *Am J Respir Crit Care Med* 1996; 153:1857-63.
 38. Rees K, Wright A, Keeling J W, Douglas N J. Facial structure in the sudden infant death syndrome: case-control study. *BMJ* 1998; 317: 179-80.
 39. Mathur R, Douglas N J. Family studies in patients with the sleep apnea-hypopnea syndrome. *Ann Intern Med* 1995; 122:174-8.
 40. Ferguson K A, Ono T, Lowe A A, Ryan C F, Fleetham J A. The relationship between obesity and craniofacial structure in obstructive sleep apnea. *Chest* 1995; 108:375-81.
 41. American Sleep Disorders Association. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; 22:667-89.
 42. Engleman H M, Kingshott R N, Wraith P K, Mackay T W, Deary I J, Douglas N J. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999; 159:461-7.
 43. Engleman H M, Martin S E, Deary I J, Douglas N J. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. *Thorax* 1997; 52:114-9.
 44. Monasterio C, Vidal S, Duran J, Ferrer M, Carmona C, Barbe F, et al. Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med* 2001; 164: 939-43.
 45. Barnes M, Houston D, Worsnop C J, Neill A M, Mykityn I J, Kay A, et al. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. *Am J Respir Crit Care Med* 2002; 165:773-80.
 46. Whittle A T, Finch S P, Mortimore I L, Mackay T W, Douglas N J. Use of home sleep studies for diagnosis of the sleep apnoea/hypopnoea syndrome. *Thorax* 1997; 52:1068-73.
 47. Wright J, Johns R, Watt I, Melville A, Sheldon T. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. *BMJ* 1997; 314:851-60.
 48. Engleman H M, Martin S E, Deary I J, Douglas N J. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. *Lancet* 1994; 343:572-5.
 49. Engleman H M, Martin S E, Kingshott R N, Mackay T W, Deary I J, Douglas N J. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. *Thorax* 1998; 53:341-5.
 50. Jenkinson C, Davies R J, Mullins R, Stradling J R. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. *Lancet* 1999; 353:2100-5.
 51. Ballester E, Badia J R, Hernandez L, Carrasco E, de Pablo J, Fornas C, et al. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999; 159:495-501.
 52. McArdle N, Douglas N J. Effect of continuous positive airway pressure on sleep architecture in the sleep apnea-hypopnea syndrome. A randomized controlled trial. *Am J Respir Crit Care Med* 2001; 164: 1459-63.
 53. Hack M, Davies R J, Mullins R, Choi S J, Ramdassingh-Dow S, Jenkinson C, et al. Randomised prospective parallel trial of therapeutic versus subtherapeutic nasal continuous positive airway pressure on simulated steering performance in patients with obstructive sleep apnoea. *Thorax* 2000; 55:224-31.
 54. McArdle N, Devereux G, Heidarnejad H, Engleman H M, Mackay T W, Douglas N J. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999; 159:1108-14.
 55. Barbe F, Mayoralas L R, Duran J, Masa J F, Maimo A, Montserrat J M, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. a randomized, controlled trial. *Ann Intern Med* 2001; 134:1015-23.
 56. Hoy C J, Vennelle M, Kingshott R N, Engleman H M, Douglas N J. Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome? *Am J Respir Crit Care Med* 1999; 159:1096-100.
 57. Massie C A, Hart R W, Perez K, Richards G N. Effects of humidification on nasal symptoms and compliance in sleep apnea patients using continuous positive airway pressure. *Chest* 1999; 116:403-8.
 58. Mehta A, Qian J, Petocz P, Darendeliler M, Cistulli P. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. *Am J Respir Crit Care Med* 2001; 163:1457-61.
 59. Engleman H M, McDonald J P, Graham D, Lello G E, Kingshott R N, Coleman E L, et al. A randomized crossover trial of continuous positive airway pressure and mandibular repositioning splint treatments for the sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 2002; 165:855-9.
 60. Sher A E, Schechtman K B, Piccirillo J F. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep* 1996; 19:156-77.
 61. Mortimore I L, Bradley P A, Murray J A, Douglas N J. Uvulopalatopharyngoplasty may compromise nasal CPAP therapy in sleep apnea syndrome. *Am J Respir Crit Care Med* 1996; 154:1759-62.
 62. Conradt R, Hochban W, Brandenburg U, Heitmann J, Peter J H. Long-term follow-up after surgical treatment of obstructive sleep apnoea by maxillomandibular advancement. *Eur Respir J* 1997; 10:123-8.
 63. Kryger M H, Roos L, Delaive K, Walld R, Horrocks J. Utilization of health care services in patients with severe obstructive sleep apnea. *Sleep* 1996; 19:S111-6.
 64. Kapur V, Blough D K, Sandblom R E, Hert R, de Maine J B, Sullivan S D, et al. The medical cost of undiagnosed sleep apnea. *Sleep* 1999; 22:749-55.
 65. Peker Y, Hedner J, Johansson A, Bende M. Reduced hospitalization with cardiovascular and pulmonary disease in obstructive sleep apnea patients on nasal CPAP treatment. *Sleep* 1997; 20:645-53.
 66. Krieger J, Meslier N, Lebrun T, Levy P, Phillip-Joet F, Saily J C, et al. Accidents in obstructive sleep apnea patients treated with nasal continuous positive airway pressure: a prospective study. The Working Group ANTADIR, Paris and CRESGE, Lille, France. Association Nationale de Traitement a Domicile des Insuffisants Respiratoires. *Chest* 1997; 112:1561-6.
 67. Douglas N J, George C F. Treating sleep apnoea is cost effective. *Thorax* 2002; 57:93.