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Treatment Options for Sleep Apnoea

Ronald R. Grunstein,[1] *Jan Hedner*[2] and *Ludger Grote*[2]

1 Centre for Respiratory Failure and Sleep Disorders, Royal Prince Alfred Hospital and University of Sydney, and Sleep Disorder Service, St Vincent's Clinic, Sydney, Australia
2 Department of Clinical Pharmacology, Sahlgrens Hospital, Gothenburg, Sweden

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Abstract

Sleep apnoea (SA) is a common sleep disorder affecting 4 to 25% of the adult population. The most common form, obstructive SA, is characterised by recurrent upper airway obstruction during sleep associated with sleep disruption and hypoxaemia. There is increasing evidence that SA leads to impaired vigilance, quality of life, driving accidents and probably represents a vascular disease risk factor. Currently, the most effective treatments are aimed at increasing upper airway space by either air pressure [(continuous positive airway pressure (CPAP)], upper airway surgery or oral appliances. CPAP is the main treatment modality for moderate to severe SA but noncompliance approaches 50% in clinic populations. A number of pharmacological agents have been used in SA but at this stage, none are indicated in moderate to severe SA.

"Laugh and the whole world laughs with you; snore and you snore alone"

Anthony Burgess, British author.

1. What Is Sleep Apnoea?

Sleep apnoea (SA) forms part of a spectrum of conditions linked by the loss of a normal pattern of breathing during sleep. At one end of this spectrum are individuals who snore (perhaps only intermittently) and have little or no disruption of sleep, so called 'simple snorers'. At the other end of the spectrum are patients with severe gas exchange disturbances in sleep with secondary awake respiratory failure. The spectrum of breathing disorder relevant for therapeutic assessment usually starts with individuals who snore heavily disturbing their partners. Over 30% of these heavy snorers have some degree of upper airway obstruction in sleep resulting in partial (hypopnea) or complete (apnoea) pauses in breathing. In practical terms, individuals with repeated hypopneas or apnoeas are labelled as having 'SA'.

Simple snorers exhibit vibration of the palate and adjacent tissue as the airway narrows during sleep (fig. 1). In SA, there is more marked narrowing or even total airway occlusion. There are 2 types of SA – the more common obstructive SA, where repeated interruption of airflow during sleep is associated with futile respiratory efforts, and central SA, where there are no real efforts to breathe (see section 2). Often both forms coexist in the same patient. With cessation or reduction of airflow, progressive hypoxaemia develops. Apneic events are typically terminated by arousal and upper airway patency is re-established. Arousals may result from activation of chemoreceptors, sensation of increasing respiratory effort or local sensory reflexes in the upper airway. In the typical patient with SA, after a few deep breaths (often loud snores), the cycle of events is repeated as often as 200 to 600 times per night. As a result of recurrent arousals, sleep is dramatically fragmented with loss of normal sleep architecture. This, in turn, results in loss of vigilance or even severe sleepiness during the day. In extreme cases, there are patients with severe respiratory failure in sleep ('hypoventilation') and some respiratory failure awake.

2. Pathophysiology

2.1 Obstructive Sleep Apnoea

Upper airway closure occurs when the pharyngeal intraluminal pressure (suction pressure applied to upper airway in inspiration) exceeds the forces that dilate the pharynx.[1] Therefore, in most cases of SA, 2 sets of opposing forces and anatomical components determine the state of the upper airway in sleep. The anatomical components are airway size and the physical properties of the pharyngeal walls; the forces include muscle tone/function, tissue weight and intraluminal (suction) pressure. In turn, muscle tone and suction pressure are influenced by sleep stage and relative respiratory drive to the diaphragm versus the upper airway dilator muscle. Most studies report that patients with SA have reduced upper airway dimensions.[2] In a patient with reduced upper airway size, greater suc-

tion pressure is generated in inspiration. In the awake state, there is reflex compensation by increased upper airway dilator muscle activity, normalising airflow resistance.[3] However, during sleep, upper airway muscle activity falls, particularly in the genioglossus, resulting in airway occlusion in patients with SA.[4]

Apart from upper airway motor defects, there may be defects in sensory mechanisms that normally protect the upper airway from closure.[5] In patients with SA, clinical and histopathological changes have been identified that suggest that chronic airway vibration from snoring and repeated occlusion may produce a defect in sensory control. Obesity also increases the likelihood of upper airway collapse presumably secondary to increased lateral airway fat pad size as well as chest and abdominal loading of the respiratory system in sleep. In some cases, obesity will cause obesity-hypoventilation syndrome (OHS, formerly Pickwickian syndrome). Patients with OHS are characterised by profound hypoxaemia during sleep, particularly REM sleep, and awake respiratory failure with elevated carbon dioxide levels.

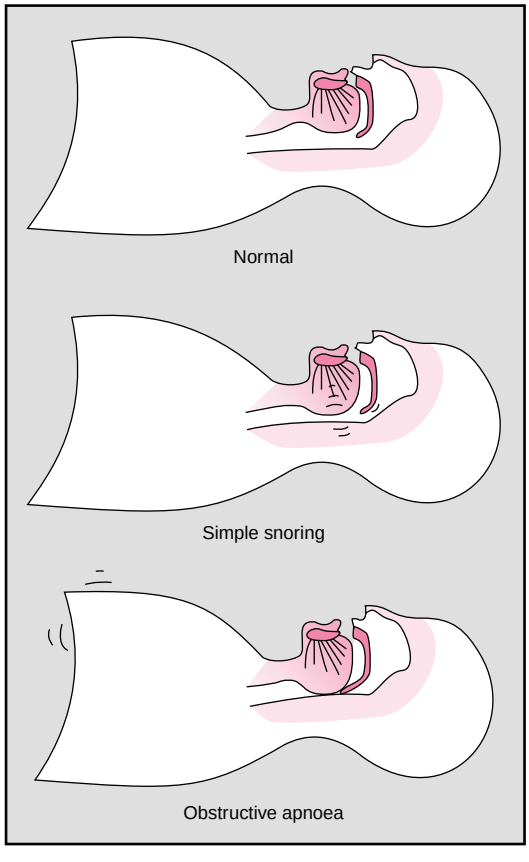

Fig. 1. Illustration of upper airway changes with simple snoring and obstructive apnoea. In simple snoring there is some narrowing of airway during sleep compared with normals but in obstructive sleep apnoea, complete closure occurs.

2.2 Central Apnoea

The term 'central apnoea' refers to a form of apnoea where breathing effort is not detected, in contrast to obstructive apnoea where breathing efforts are often vigorous. It is important to differentiate 'central apnoeas' which tend to occur in patients with awake hypercapnia and reduced respiratory drive (hypoventilation syndromes) from central apnoeas classically occurring as part of the periodic breathing in patients with cardiac failure or stroke,[6] so-called Cheyne-Stokes breathing. Sporadic central apnoeas may also occur in patients with obstructive SA. The aetiology of central apnoea in the nonhypoventilating patient [i.e. normal CO_2 tension (pCO_2) awake] is complex, involving interplay between respiratory control (often, heightened chemoreceptor drive to hypoxia and hypercapnia) and upper airway narrowing.[6] Central apnoea with normal awake pCO_2 is very rare in patients who do not have cardiac failure or stroke.

2.3 Implications for Therapy

The therapeutic implications of SA pathophysiology are listed in table I.

3. Clinical Epidemiology

The dominant symptoms associated with SA are listed in table II. Sleepiness may be severe leading to sleep 'attacks' while driving ('active sleepiness') or may manifest itself as a constant struggle to stay awake during monotonous tasks with sleep

Table I. Possible therapeutic approaches in sleep apnoea based on pathophysiology

Approach	Examples
Widening upper airway space	Nasal CPAP
	Upper airway surgery
	Oral appliances
	Anti-obesity agents
Increasing upper airway muscle activity in sleep	Electrical pacemaker ?Serotinergic agents
Modulating respiratory control	Carbon dioxide
	Triazolam
Reducing REM sleep	Tricyclic antidepressants
	Clonidine
Minimising hypoxaemia or neuroprotection	Oxygen ?Sabeluzole
Sleepiness reduction	Stimulants
	Modafinil
Suppressing arousals	Hypnosedatives

CPAP = continuous positive airway pressure.

occurring immediately on having a rest ('passive sleepiness'). The patient is often unaware of the condition and treatment is sought by spouse, bed partner or other family members. Clinical impression as a method of detection of SA is associated with a surprisingly poor specificity and sensitivity.[7] Symptoms such as daytime sleepiness are common in the general community and may be secondary to lack of sleep, medications or other sleep disorders. Snoring may also be underestimated because the partner is not present at interview or the patient lives alone.[7]

3.1 Prevalence and Correlates of Sleep Apnoea

SA is very common. Approximately 9% of female and 24% of male middle-aged public servants have more than 5 apnoeas per hour of sleep, and using a cut-off of 15 apnoeas and hypopnoeas per hour, 4% of women and 9% of men had SA.[8] Upwards of 80% of middle-aged men snore and 25% of heavy snorers have SA.[9]

All epidemiological investigations have consistently shown that obesity, especially central obesity, is strongly associated with adult sleep disordered breathing.[10] In Sweden, over 50% of obese men and one-third of obese women report habitual loud snoring compared with 15.5% of men in the general population.[11] Studies based only on questionnaires also underestimate the prevalence of SA. SA is about 2 to 3 times more common in men, particularly in younger age groups. This is explained by the higher and earlier prevalence of central obesity in men although it is possible that the upper airway in women is less prone to occlusion in sleep.[12] The exact relationship between SA and age is unclear. SA is more common in middle-aged males than younger patients. It also appears more common in infants and children compared with adolescents and young adults. SA may be less prevalent in elderly patients and it has been speculated that this is evidence for a deleterious effect of SA on mortality.

SA also aggregates in families.[13] Individuals with familial retrognathia or brachycepahlic appearance are very prone to upper airway narrowing in sleep. Approximately 40 to 50% of variance in apneic activity can be attributed to familial factors. This, in turn, has been linked to a familial association between SA and sudden infant death syndrome. Other important related factors include race, where there appears to be higher prevalence

Table II. Symptoms of sleep apnoea

Sleep related
Heavy snoring
Witnessed apnoeas
Choking, gasping, nocturnal panic
Upper airway symptoms: dry mouth, sore throat, mucus production, chronic cough
Chest discomfort, palpitations
Nocturia (secondary to excessive nocturnal urinary output)
Gastro-oesophageal reflux
Daytime symptoms
Excessive daytime sleepiness
Morning headaches
Fatigue
Poor memory and concentration
Impaired mood
Upper airway symptoms: dry mouth, sore throat, mucus production, chronic cough
Chest discomfort, palpitations

in young African Americans, Mexican Americans, and urbanised Polynesians, possibly related to predisposition to central obesity.[7]

Although acute alcohol ingestion worsens snoring and SA, it is controversial whether lifetime alcohol consumption may be a risk factor for the development of SA. Current but not past smoking may be a dose-dependent risk factor for SA.[14] Apart from obesity, conditions causing narrowing of the upper airway will promote the development of SA. These include fixed upper airway lesions (e.g. nasal obstruction, enlarged tonsils), macroglossia (acromegaly, amyloid, hypothyroidism) or neurological conditions impairing upper airway muscle tone. For example, 60% of patients with acromegaly have some degree of SA.[15]

3.2 Measuring Sleep Apnoea

Unfortunately, there is no agreed definition of SA. As outlined in section 1, there is a spectrum of disease and no particular cut off point where normality ends and disease begins. In some ways this is not unlike disease cut-offs for hypercholesterolaemia or diabetes mellitus where definitions change as research accumulates on the impact of having a fasting blood sugar or cholesterol level above or below a certain point. With respect to SA, much of this type of longitudinal information is lacking because of the expense of detailed prospective sleep investigation of large community populations and the availability of effective treatment, such as nasal continuous positive airway pressure (CPAP).

In the past, most researchers used a working definition of 5 apnoeas per hour of sleep (apnoea index >5) to define SA. However this is an arbitrary cut-off which allowed researchers to communicate in a common 'language'. As SA is increasingly recognised as a common disorder, such definitions are being reconsidered because airflow cessation may be incomplete. Indeed it may be that, for different complications of SA, different measurements may be important. For example, the important measurement index for daytime sleepiness may be some measure of arousals and sleep fragmentation, while for hypertension the magnitude of the blood pressure (BP) changes during apnoea and arousal may be more important.

Other researchers have emphasised the importance of considering symptoms rather than only measurement of abnormal breathing during sleep. The term 'sleep apnoea syndrome' (SAS) has been used to describe individuals with objective evidence of SA and symptoms. The prevalence of SAS (apnoea/hypopnoea index >5 and marked daytime sleepiness) is 4% in men and 2% in women.[8] However, there are problems with this approach as sleepiness is common in the community and not always attributable to SAS even in those with abnormal breathing events. Sleep loss/deprivation is a common feature of modern lifestyle and the resulting daytime sleepiness may be coincidental to coexisting mild forms of SA.

Under ideal circumstances, a full sleep study is the most appropriate investigation for assessing SA but this is expensive. If current epidemiological surveys are matched by outcome data, full sleep studies may need to be minimised by using limited respiratory monitoring. However large trials of the cost benefit and reliability of home monitoring of patients with SA have not been performed. It is also important to differentiate 'screening' of asymptomatic individuals from patients who present with symptoms. Based on current knowledge, there is no justification to routinely screen for SA as we do for high cholesterol or hypertension. However, patients presenting with sleepiness or other apparent complications of SA, may justify investigation.

4. Sequelae of Sleep Apnoea

4.1 Cardiovascular

Patients with SA clearly have acute cardiovascular changes as an immediate consequence of their breathing disturbance. However, it is more controversial whether these acute changes lead to chronic disturbances in cardiovascular function or an increased incidence of vascular end-points.[16]

4.1.1 Acute Effects

Obstructive apnoeas are accompanied by profound haemodynamic changes including increases

in systemic and pulmonary arterial BP. With progressive apnoea, there is worsening hypoxaemia, increasing pleural pressure swings, bradycardia (and possibly bradyarrhythmias), heightened sympathetic nerve activity (SNA) and an overall rise in BP (fig. 2). With arousal and resumption of ventilation, oxygen saturation returns to normal. There are marked increases in heart rate and BP may rise to levels ranging from 200 to 300mm Hg. SNA increases, but this appears to be rapidly interrupted prior to the post-apnoea peak in BP. There is a fall in stroke volume during apnoea, particularly at apnoea termination. Therefore, the combination of a fall in stroke volume and rise in BP suggests a substantial increase in total peripheral resistance.

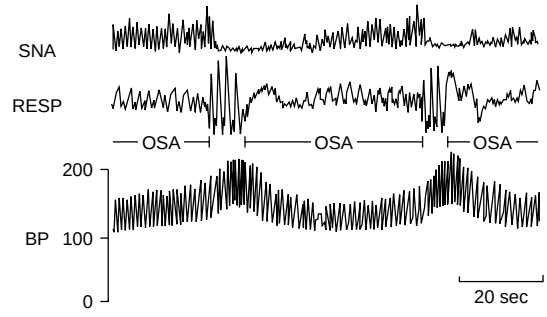

Fig. 2. Changes in sympathetic nerve activity (SNA), respiratory effort (RESP) and blood pressure (BP) during long obstructive apnoeic episodes (OSA). BP and SNA increase as the episode progresses with a surge at apnoea termination.

4.1.2 Chronic Effects

In experimental models of sleep apnoea, 'exposed' animals clearly develop a reversible elevation of mean arterial pressure.[17,18] Patients with SA are characterised by markedly elevated sympathetic nerve traffic in the awake state and a potent pressor response to eucapnic hypoxia compared with controls.[19] This pressor response is related to disease severity and likely to be the result of exposure of the cardiovascular system to intermittent hypoxia during sleep. Patients with SA have increased left ventricular mass (measured using echocardiography) compared with patients without SA with similar daytime BP values.[20] Some workers have suggested SA may produce idiopathic dilated cardiomyopathy which reverses with nasal CPAP therapy.[21] Pulmonary hypertension may occur in the absence of lung disease.[22] SA is a common finding in clinic patients with hypertension, but this may be due to shared confounding factors such as central obesity and increasing age. A number of more recent studies have strongly suggested that SA is a risk factor for hypertension independent of obesity.[23,24]

The advent of nasal CPAP has prevented large studies investigating the natural history of untreated severe SA. However, in certain sleep disorder centres established in the 1970s, long term data is available suggesting that mortality risk is increased in untreated SA.[25] A number of groups have reported an increased risk of myocardial infarction and stroke in SA.[26-28] Interestingly, long term hospitalisation with a cardiorespiratory diagnosis was markedly reduced in CPAP-treated patients.[29] The ongoing multicentre Sleep Heart Health study in the US may assist in the future in determining the influence of SA on health outcome.[30]

4.2 Psycho-Social Effects

Sleepiness in SA is predominantly related to repetitive arousal and sleep fragmentation, but a direct effect of hypoxaemia is possible. SA is also characterised by a range of excessive daytime sleepiness from simply increased sleep time in a previously short sleeper to virtual obtundation. Sleepiness may lead to both impaired work performance[11] and driving.[31] Although poor performance in simulation tasks may be overcome by greater vigilance in the real-life situation, data from a number of centres demonstrate a higher actual accident rate in patients with SA compared with controls. Treatment with nasal CPAP dramatically improves daytime sleepiness and even driving simulator performance.[31] Patients with SA also demonstrate decrements in performance in higher level cognitive testing including impaired memory. Quality of life (QoL) is also impaired. Data from the Swedish Obese Subjects study[11]

indicates that in equally obese men and women, a history of SA is associated with impaired work performance, increased sick leave and a much higher divorce rate.

5. Nonpharmacological Treatment

5.1 Conservative Therapy/Lifestyle Factors

Some studies have suggested that reduction of smoking and alcohol consumption will lead to reduced self-reported snoring and reverse mild SA.[32] Avoiding sleep deprivation may be important as sleep loss may reduce upper airway tone and respiratory drive.[33] A number of studies have demonstrated a reduction in SA severity after bodyweight loss, either through caloric restriction or bariatric surgery. However, most of these studies report short term results and are uncontrolled. Another approach is to try and minimise sleep time spent in the supine position as there a number of patients, in whom SA is positional.

5.2 Devices

5.2.1 Nasal Continuous Positive Airway Pressure

Until the early 1980s, tracheostomy was the main form of treatment available for patients with SA and was usually performed on patients with severe symptomatic disease with cardiorespiratory failure. The advent of nasal CPAP in 1981 revolutionised the management of SA and allowed a wider range of patients to be treated.[34] CPAP is generated by a electro-mechanical blower which delivers airflow via wide-bore tubing to a nasal mask with a fixed expiratory resistance. Adjustment of flow allows a varying pressure to be generated at the nares. The therapeutic pressure is usually determined by a sleep study when pressure is increased steadily during sleep until apnoea, snoring, hypoxaemia and associated arousals are eliminated. When the correct pressure is set, there is often a 'rebound' of deep sleep. It is important to stress that CPAP is not a cure for SA. Cessation of treatment will lead to a recurrence of sleep-disordered breathing and accompanying symptoms, although with regular CPAP use there is a decrease in the underlying level of SA severity.[35]

A number of randomised studies comparing CPAP with oral placebo, 'sham' CPAP or conservative treatment demonstrate positive outcomes with reduction in sleepiness and improvement in QOL.[36,37] However, it is important to note that these trials are, in effect, unblinded and not controlled in the same sense as therapeutic drug trials. Nasal CPAP is hard to 'blind' and even 'sham' CPAP machines with lower delivered pressure may be obvious to patients. Nevertheless, the compelling positive outcomes of these randomised studies and over 15 years of 'before and after' studies make nasal CPAP the gold standard therapy of moderate to severe degrees of SA.

Unlike some medications, detailed compliance studies are possible with nasal CPAP. The latest CPAP devices are now configured so that it is possible to detect the length of time that CPAP masks are actually on the patient. Studies using such devices show that CPAP compliance is variable and up to 50% of patients prescribed CPAP have difficulty with compliance.[35] Problems affecting compliance with nasal CPAP include a sense of claustrophobia, mask air leaks, nasal congestion and dryness of the mouth and throat (usually associated with mask or mouth airleaks), and the inconvenience or non-acceptance of using a machine. Patient compliance is higher in patients with a greater degree of symptoms irrespective of the underlying degree of SA and also in patients receiving close support and education. Over the past few years, there have been an increasing number of technological advances in CPAP design with better fitting and sealing masks, built in humidification to reduce nasal adverse effects, and smaller, quieter motors. Recently, CPAP machines have been developed with special inbuilt sensors that automatically adjust to provide the lowest pressure needed to keep the upper airway patent.[38] It would be expected that these changes will improve compliance to some extent, although interestingly the actual pressure level set on the CPAP device is unrelated to compliance.[39] However, despite these technical

advances, there will always be a significant proportion of patients with SA who will reject CPAP therapy.

Devices that allow variation between the set inspiratory and expiratory pressures, known as bilevel positive airway pressure, were originally introduced to improve compliance in CPAP users.[40] Although this compliance-improving role is unproven, this form of positive airway pressure therapy has been used increasingly in the management of severe respiratory failure in sleep, such as OHS and other hypoventilation syndromes.

5.2.2 Mandibular Advancement Splints

A more recent approach has been the development of oral appliances which aim to create more airway space in sleep by forward movement of the mandible, tongue or both.[41] Reasonable results have been described for mild to moderate SA in before and after studies. Controlled data is becoming available which support further larger and more detailed studies of these devices. Adverse effects include jaw discomfort, excessive salivation and sore teeth. Long term effects on tempero-mandibular joint function are unavailable. Compliance is difficult to measure.

5.2.3 Upper Airway Electrical Pacemaker

A challenging therapeutic concept is the use of electrical pacing to increase upper airway dilator tone when the airway is occluding.[42] Although there has been some promising animal data, long term function of these complex devices and their efficacy is currently unavailable.

5.3 Surgery

5.3.1 Tracheostomy

Prior to the introduction of nasal CPAP as a treatment for SA, tracheostomy was the only effective therapeutic modality. Tracheostomy is only currently indicated in patients with severe SA who have been unable to comply with CPAP or related therapies. Tracheostomy can produce significant morbidity and may be a problem in the morbidly obese fat-necked individual. However, with skilful minimalist surgery and close follow-up, tracheostomy may be a therapeutic option in some patients.

5.3.2 Facial Reconstructive Surgery

Many patients with SA have abnormalities in facial structure on cephalometry and correction of such factors by maxillofacial surgery (mandibular advancement, maxillo-mandibular surgery) may lead to cure in SA. However, the correlation of mechanical characteristics of the pharyngeal airway with cephalometry is only indirect and, moreover, such surgery is expensive, potentially requiring several operative procedures. Exact selection criteria are not available for this form of surgery, although it would appear to be inappropriate for obese patients.[43] Some younger patients may opt for this surgery in the future to avoid long term use of nasal CPAP.

5.3.3 Uvulopalatopharyngoplasty

Uvulopalatopharyngoplasty (UPPP) was developed for the treatment of heavy snoring in Japan in the early 1950s and involves a careful removal of uvula and part of the soft palate.[44] Despite early enthusiasm, the operation has never lived up to its promise as a 'cure' for SA.[45] Accumulated data from many studies over the past decade suggests caution in performing this form of surgery for SA. There are no preoperative tests which satisfactorily predict the response to surgery. There is a significant morbidity and even, mortality.[46] Excessive removal of palatal tissue will lead to velopharyngeal incompetence and nasal regurgitation and speech changes, although these adverse effects are less with more experience with UPPP. Many studies report particularly poor results in obese patients. However, meaningful outcome data are lacking. There may be a 'placebo' effect in UPPP and in some cases of mild SA, the improvement may reflect night-to-night variability. There are no large trials of UPPP controlled by conservative therapy, oral placebo or other modalities.[47] Recently, there has been great enthusiasm for UPPP performed with a surgical laser or radiofrequency ablation aiming at stiffening or shrinking palatal tissue rather than complete removal. No well designed

studies show any advantage of these techniques over conventional UPPP.

6. Pharmacological Treatment

6.1 Introduction

Considering the clear limitations of nasal CPAP and other currently available treatment modalities for patients with SA, the extraordinarily high prevalence of sleep apnoea and the profound impact of SA on daytime performance and cardiovascular function, it is surprising that there have been few systematic attempts to identify drug treatments for SA. To date, no drug has proven to have a short term efficacy comparable with CPAP in large clinical trials.

There are number of issues pertinent to developing drug treatment of SA. Firstly, there is no absolute consensus on the best way of measuring the severity of sleep apnoea and its complications and, in addition, at the milder end of the disease spectrum, factors such as night-to-night variability may affect measurement of treatment efficacy. Secondly, different pathophysiological subtypes of SA may exist and these subtypes may be selectively suitable for pharmacological treatment. For example, there are minimal data on the neurotransmitters involved in upper airway control. Although upper airway obstruction may be the end mechanism of disease, this in turn may be produced by reduction in one neurotransmitter or excess of another. Thirdly, there are no established animal models of SA useful for drug development. Finally, it may be important to develop disease-specific outcome measures in QoL and daytime symptoms in these patients with mild disease. These measurements are crucial because, as discussed in section 3.1, up to 15 to 20% of adults have mild degrees of SA, a situation which has been described as a serious potential public health problem.[48]

6.2 Obstructive Sleep Apnoea

6.2.1 Tricyclic Antidepressants

The first trials suggesting a beneficial effect of the nonsedating tricyclic antidepressant protriptyline on SA were published in the early 1970s.[49] The efficacy of protriptyline is highly variable depending on the type of outcome variable measured and the study population. A daily dosage of 2.5 to 30mg administered over 2 to 24 weeks has been shown to result in a 5 to 75% reduction in SA events in patients with OSA.[50-52] However, although dramatic effects have been described in single patients, most trials have included fewer than 10 patients, often in nonplacebo-controlled designs. Moreover, protriptyline is well known to reduce REM sleep, a sleep stage which is commonly associated with increased apnoeas in patients with SA. Thus, reduction of REM sleep may account for the overnight apnoea reducing effect of protriptyline.[50] This sleep stage altering effects of certain drugs is an important consideration in clinical drug studies in sleep apnoea.

In addition, the improvement of symptoms associated with daytime somnolence suggests that effects other than reduction of apnoeas may be of importance. For instance, masked or coexisting depression is not uncommon in patients with OSA and it is possible that at least part of the protriptyline effect in this context may be explained by its antidepressive properties. In addition, the treatment effect may be due to a REM sleep restriction, which has been suggested to reduce daytime hypersomnolence in patients without SA.[53]

Protriptyline is also not unique amongst tricyclic antidepressants in therapy of SA. Imipramine, which is a less selective noradrenaline reuptake inhibitor, was found in 2 uncontrolled studies,[54,55] to exert similar effects to protriptyline. One report has suggested the response may be even greater in central SA.[8]

The mode of action of these agents is not really known. There is also a need for larger, controlled and prospective trials to confirm the effects of tricyclic agents in OSA. Such trials could also lead to a better identification of subgroups of patients that are particularly good responders to therapy. For instance, it is possible that tricyclic antidepressants are more useful in patients with highly REM-dependent OSA. Furthermore, patients with mild

sleep apnoea and coexisting depression may constitute a specific target group. Finally, the use of tricyclic agents in OSA is constrained by relatively frequent adverse effects including bladder atonia and impotence in men. Thus, female patients with SA may constitute the preferable target group for treatment.

6.2.2 Serotonergic Agents

The considerable interest in serotonergic agents and OSA derives from an early trial of the serotonin (5-hydroxytryptamine; 5-HT) precursor tryptophan which was found to induce a moderate reduction of obstructive apnoea.[56] The subsequent development of selective serotonin reuptake inhibitors (SSRIs) has provided new tools for investigation in this field. An approximately 40% reduction of apnoea/hypopnea index, mainly during non-REM (NREM) sleep, was reported in a nonblind trial of fluoxetine.[57] The effect was comparable with that of protriptyline although fluoxetine treatment was associated with significantly fewer adverse effects. The SSRI paroxetine produced an approximately 20% response on respiratory disturbance index (RDI) during NREM sleep in a double-blind controlled study.[58]

Interest in serotonergic drugs has also been stimulated by studies of central serotinergic transmission in certain animal experimental models of SA. Stimulation of 5-HT_2 receptors in the cat brain stem facilitated hypoglossal nerve activity with a potentially beneficial effect on upper airway patency in cats.[59] Reciprocally, in the English bulldog, inhibition of 5-HT_2 receptors led to a diminution of upper airway muscle activity.[60] Interestingly, paroxetine has been reported to reduce the frequency of apnoeas more than hypopnoeas.[58] The unchanged hypopnea frequency probably represents a balance between a shift from complete to partial airway occlusion episodes (increasing hypopnea frequency) and resolution of some hypopneas. This would support an improvement of upper airway stability in response to a stimulation of serotonin transmission. It remains unknown whether this effect is attributable to a specific subpopulation of serotonergic receptors and if the treatment effect may be enhanced with the introduction of specific serotonin subreceptor agonists. This may be resolved by future trials directed towards exploring the efficacy of such compounds.

At present it appears as if serotonergic agents would be preferable to tricyclic agents by virtue of an approximately similar efficacy, but fewer adverse effects. Serotonergic agents appear to have a reasonable effect on SA during NREM sleep and to be less effective during REM. However, because of a limited overall efficacy and the lack of long term data, general treatment in OSA by these agents is not warranted unless treatment with nonpharmacological modalities like CPAP is unsuccessful.

6.2.3 Sex Steroids

The epidemiological preponderance of SA in men versus women and increased prevalence in post- versus premenopausal women has suggested a protective effect of sex steroids against SA. Moreover, awake genioglossus electromyogram activity is lower in post- compared with premenopausal women, and estrogen and progesterone replacement in postmenopausal women resulted in a significant increase of muscle activity.[61] Despite this, hormone replacement therapy in postmenopausal women,[62] use of anti-androgens in men[63] or administration of medroxyprogesterone (MPG) to male patients[64,65] with SA have proved disappointing with no reduction in apnoeic events during sleep.

In contrast, MPG appears to have a beneficial effect in breathing disorders associated with daytime hypercapnia. The ventilatory stimulant effect of MPG has been well documented in different animal models.[66,67] Hypercapnia in patients with the 'Pickwickian syndrome' (in reality patients with OHS) was reduced and recurred after withdrawal of MPG treatment.[68] This beneficial effect, which has been repeated in other studies of patients with obesity and hypercapnia, appears to have an extended duration in women.[69] It also implies that MPG may be successfully used in hypercapnic conditions and in particular those associated with nocturnal hypoventilation. The potential adverse effects of MPG, which clearly limit its applicability

in SA, include impotence, breast discomfort, hirsutism, alopecia and thromboembolic disease. However, ongoing and future trials in specific subgroups of patients with hypercapnic ventilatory failure may help to identify target groups for treatment. At present, the only role for MPG is in the management of patients with SA with awake respiratory failure and noncompliance with CPAP or pressure support ventilation.

6.2.4 Theophylline

Theophylline is a ventilatory stimulant which blocks the ventilatory depressant action of adenosine. Diaphragm contractility is increased by theophylline, but the effect on upper airway muscle function is uncertain. Theophylline has been widely used in patients with SA. Although an overall improvement in SA by up to 40%,[70,71] has been reported, other studies have found no effect.[72,73] Most of these studies were not placebo-controlled and data on sleep quality were not presented. A subsequent long term follow-up study has also demonstrated that any potentially beneficial effect is lost with time in the majority of patients.[70] In a placebo-controlled trial of theophylline in patients with OSA[74] there was a significant reduction in obstructive events during sleep (-29%), but sleep quality was significantly worsened by theophylline. Theophylline has a prominent influence on sleep structure, with increased frequency of arousals, as well as increased amount and latency of sleep stage 1. Consequently, daytime sleepiness may be increased.[75] Because of all these limitations, theophylline has no place in the routine treatment of patients with OSA.

6.2.5 Antihypertensive Agents

As discussed in section 4, systemic hypertension is common in patients with OSA and antihypertensive drug therapy is therefore also common. Pharmacologically-induced BP elevation in a dog model was found to cause increased upper airway collapsibility.[76] In contrast, experimentally induced nocturnal BP increases in humans were found not to induce upper airway collapse during NREM sleep.[77] Using a model attempting to simulate SA in the rat, other workers have shown that hydralazine-induced BP reduction was accompanied by a decrease in SA activity.[78]

Some studies have examined the effect of antihypertensive agents on patients with SA. Both the ACE inhibitor cilazapril and the β-blocker metoprolol reduced apnoea-hypopnoea frequency by approximately 30%.[79] The α_2 adrenergic agonist, clonidine reduced REM sleep-related OSA activity in 6 out of 8 patients, while no effects were seen in NREM sleep.[80] Similar beneficial effects on SA have also been described for calcium antagonists.[81,82] However, there are data suggesting that antihypertensive treatment may also increase SA.[81,80] Therefore, the effect of antihypertensive agents on SA remains unclear. Although the decline in SA may be associated with BP reduction it is possibly directly related to a direct effect of the drug itself. It is also unclear whether any effect persists with long term treatment.

6.2.6 Medical Gases: Oxygen and Carbon Dioxide

Low flow oxygen reduces hypoxaemia during sleep in patients with SA to a mild extent without any clinically significant impact on symptoms and frequency of apneic events.[83] Higher oxygen flows lengthen the duration of apnoeas and decrease tonic genioglossal muscle electrical activity.[84] Extended nocturnal low flow oxygen administration for 30 days caused a modest reduction in nocturnal apnoea and an increase in daytime pCO_2, but no change in sensitivity to chemical ventilatory stimuli during daytime or in daytime symptoms.[83] The beneficial effect of oxygen may have been related to an increased ventilatory drive caused by elevated pCO_2 levels. Inhalation of 3% CO_2 during sleep markedly increased upper airway inspiratory muscle activity and reduced SA by approximately 80%.[84] However, the effect of CO_2 on sleep quality has not been thoroughly investigated and there are methodological problems associated with stabilising the CO_2 level throughout the night which severely hampers the applicability of this treatment modality.

6.2.7 Other Pharmacological Approaches

A number of other pharmacological approaches have been attempted in OSA. For instance, nicotine applied as a chewing gum[85] or via a transdermal delivery system[86] was found to slightly reduce SA. However, nicotine also disturbs sleep and has gastrointestinal adverse effects limiting usefulness. The benzodiazepine antagonist flumazenil was used in a small study of 10 patients with SA in which there were no significant effects on SA and sleep structure.[87] A putative glutamate antagonist, sabeluzole, was found to reduce hypoxaemic events in a plasma concentration dependent manner in patients with OSA.[88] In this double-blind controlled trial, the subjective effects were relatively modest. The vigilance promoter, modafinil improved alertness and complaints of sleepiness in a recent pilot study in patients with SA without changes in respiratory parameters.[89] There are also no data on the usefulness of nasal sprays or other agents aiming to reduce upper airway inflammation. Finally, despite the increasing interest in anti-obesity agents, there have been no well designed studies of any of these drugs in patients with SA.

6.2.8 Treatment of Sleep Apnoea in Endocrine Disorders

As discussed in section 3.1, the prevalence of SA is increased in acromegaly and hypothyroidism. In acromegaly, treatment with the somatostatin analogue, octreotide reduces central apnoea and to a less extent, OSA. This effect is not directly related to the degree of growth hormone suppression.[90] The efficacy of thyroxine in treating SA in patients with hypothyroidism is controversial, particularly if there is coexisting obesity.[91-94] The degree of myxoedematous involvement in the upper airway may also impact on treatment. In these endocrine disorders, it is important to follow-up therapy to ensure effective treatment of SA.

6.3 Central Sleep Apnoea

6.3.1 Acetazolamide

Acetazolamide induces a metabolic acidosis which stimulates respiratory drive. The beneficial effects in patients with central SA are well documented. An approximately 70% reduction of central apnoeas along with improvement of daytime symptoms was demonstrated after one week of therapy.[95] Other more recent studies have demonstrated extended effects of acetazolamide. The reduction of central apnoea activity (approximately 70%) remained after 1 month of therapy, while there was no effect on obstructed breathing events.[96] Another long term study demonstrating a persistent effect on central apnoeas up to 6 months after discontinuation of therapy has led to the suggestion that acetazolamide induces a long lasting resetting of the CO_2 response threshold.[97] However, the clinical use is limited because of potential adverse effects of acetazolamide treatment like electrolyte changes, precipitation of calcium phosphate salts in alkaline urine and paraesthesias.

6.3.2 Theophylline

There is recent interesting data suggesting a favourable effect of theophylline in central apnoea associated with congestive heart failure. In a placebo-controlled trial of 15 patients with compensated heart failure there was an approximately 60% reduction of central apnoeas per hour of sleep after theophylline compared with approximately 20% reduction after placebo.[98] The degree of concomitant intermittent hypoxia was also reduced, whereas the right and left ventricular ejection fraction did not change. Interestingly, cardiac output has been described to increase after theophylline and it remains to be clarified whether the main effect on central apnoeas is explained by respiratory stimulant properties or the positive inotropic effect of the drug. Further studies focusing on the effect of theophylline on mortality and QoL would be useful in these patients.

6.3.3 Other Treatments

Presently available treatment modalities in cardiac failure associated central SA include supplemental oxygen and CPAP therapy.[99] The value of CPAP in this group is strongly supported by studies from one group and multicentre studies are ongoing. Other workers have previously reported benefit from short acting benzodiazepines which may act by suppressing the degree of respiratory drive

which contributes to this Cheyne-Stokes pattern of central apnoea.[100]

7. Conclusion

To date, there is no highly effective pharmacological treatment in SA. However, the limitations of existing therapeutic modalities are triggering an intense search for possible candidate drugs. The lack of adequate animal models and incomplete understanding of the pathophysiology of SA imposes limitations on the process of rational drug development. It is possible that future developments in SA drug therapy may result from chance observations during drug therapy of other disorders. No drug has shown a reduction in SA by more than 50% in controlled studies. However, in comparison with existing treatment modalities such as CPAP or surgery this may be an acceptable treatment goal, providing compliance with therapy is high. In fact, the absolute efficacy of surgery does not exceed 50% and decreases with time and the overall compliance with nasal CPAP is most likely lower than 50% of sleep time.

There is a great lack of outcome data after drug therapy in SA. In fact, a consensus on optimal outcome variables to be used in therapeutic trials in patients with OSA has not been reached. Should this be related to subjective well-being, reduction of an elevated cardiovascular risk, reduction of SA or simply polysomnographically assessed sleep? With the clarification of these issues we are likely to increase the possibilities of identifying effective pharmacological treatments for SA in the future.

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Correspondence and offprints: Dr *Ronald R. Grunstein*, Centre for Respiratory Failure and Sleep Disorders, Ward E9, Royal Prince Alfred Hospital, Camperdown 2050, Sydney, Australia.
E-mail: rrg@mail.med.usyd.edu.au