LEADING ARTICLE

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Pharmacotherapies for Obstructive Sleep Apnoea
Where Are We Now?

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Abstract

Obstructive sleep apnoea (OSA) is common, causes considerable morbidity and probably contributes to mortality particularly through associated cardiovascular disease. The physical therapy of continuous positive airway pressure (CPAP) is extremely effective in the majority of patients but most patients would prefer an alternative. Intuitively, OSA should be amenable to pharmacotherapy. The upper airway of affected individuals can be narrowed but is patent during wakefulness. Collapse of the airway during sleep occurs when negative intra-luminal pressure generated by inspiratory effort exceeds the tone of the upper airway dilators. This mismatch may be in part due to respiratory drive instability but the state-dependent fall in drive to the airway dilator muscles is the biggest factor in most patients.

Various drugs have been investigated as treatment for OSA. Acetazolamide, theophylline, nicotine, opioid antagonists and medroxyprogesterone have been used to increase respiratory drive. Clonidine has been tested with the aim of reducing rapid eye movement sleep when OSA is often most severe. Various antidepressants have been used to suppress rapid eye movement sleep and to preferentially activate the upper airway dilators. The drug trials have often been of poor design and none has included more than a few patients. Most of the drugs have been found to be ineffective and those that have worked for some patients (acetazolamide and protriptyline) have produced intolerable adverse effects.

There have been recent advances in the understanding of the neurotransmitters involved in the control of sleep and the upper airway motor neurones, offering the possibility of novel approaches to the drug treatment of OSA for those patients who cannot tolerate or do not benefit from CPAP. It seems likely that a better understanding of the mechanisms of OSA in individual patients and tailoring of drug therapy will be the way forward.

1. Obstructive Sleep Apnoea (OSA)

Obstructive sleep apnoea (OSA) is characterised by intermittent closure of the upper airway during sleep leading to repetitive episodes of asphyxia. Continued respiratory efforts against the closed airway produce increasingly negative intra-thoracic pressure swings. Cardiac output is impaired with bradycardia and a fall in arterial blood pressure. The apnoeas usually resolve with an arousal from sleep, which is associated with a burst of sympathetic activity, tachycardia and a surge in arterial blood

pressure. There is often a fall in arterial oxygen saturation and in some cases the level may not recover between apnoeas. Partial obstruction of the airway or a fall in respiration without a complete cessation (hypopnoea) may also lead to an arousal from sleep. One measure of the severity of OSA is the frequency of events during sleep. The minimal diagnostic frequency is an apnoea/hypopnoea index (AHI) of >5 per hour,[1] treatment is more often initiated when AHI is >15 and in severe OSA the index may be >60 per hour.

The forces tending to close the airway are dependent on its shape and size. Patients with retrognathia, macroglossia and tonsillar hypertrophy may have a smaller airway, which is more likely to close. OSA is strongly associated with obesity (figure 1) and, in particular, neck circumference.[2] It has been estimated that a neck circumference of >48cm corresponds to a 20-fold increase in risk of OSA.[3] Sleeping position is important in some OSA patients. The airway is more likely to close when lying supine and less so in a lateral or upright position. The static closing forces interact with dynamic forces produced by airflow through the airway and negative pressure generated by the inspiratory muscles, in particular the diaphragm.

Fig. 1. The archetypal patient with obstructive sleep apnoea (OSA) is overweight, male and in late middle age. Increasing neck circumference is associated with an increased risk of OSA.

Dilating muscles at various levels in the upper airway oppose the forces tending to close it. These include the muscles of the palate and the genioglossus, which pulls the tongue forward and stabilises the airway. The tone in these muscles falls during sleep compared with wakefulness and reaches a nadir in rapid eye movement (REM) sleep[4] when apnoeas may be most pronounced (figure 2). One mechanism increasing the likelihood of OSA in obese patients is an increase in the flow requirement through the airway during sleep, related to smaller oxygen reserves and increased metabolism compared with non-obese individuals.[5] Instability in respiratory drive may exacerbate OSA by producing periodic respiratory effort.[6] There is evidence that the vibration of snoring leads to damage to the afferent limb of the reflex arc that compensates for changes in airway pressure.[7] Tone in the effector muscles may be lowered temporarily by sedating medication including alcohol,[8] and it is possible that permanent damage may be caused by the physical trauma of snoring on the muscle fibres and the afferent nerves.[7]

The prevalence of sleep disordered breathing, which incorporates the diagnosis of OSA, has been estimated in a number of studies in different countries. It has been estimated to be about 4% in middle-aged men in the US[9] and around 6% in the UK and Australia.[10,11] Among women, the prevalence is between two to six times lower than in men.[9-11] Postmenopausal women are up to four times more likely to have OSA than pre-menopausal women. In population studies the increased risk is less for postmenopausal women on hormone replacement therapy (HRT).[12] OSA is almost always associated with snoring. Symptoms include unrefreshing sleep, daytime somnolence, low mood, poor concentration and reduced libido, and those experiencing OSA are often concerned about the impact of their nocturnal behaviour on their partners.[13] There can be a considerable reduction in health status as measured, for example, by the generic SF-36 Questionnaire.[14]

OSA is probably an independent risk factor for cardiovascular mortality, including strokes and congestive cardiac failure,[15] but this has been difficult

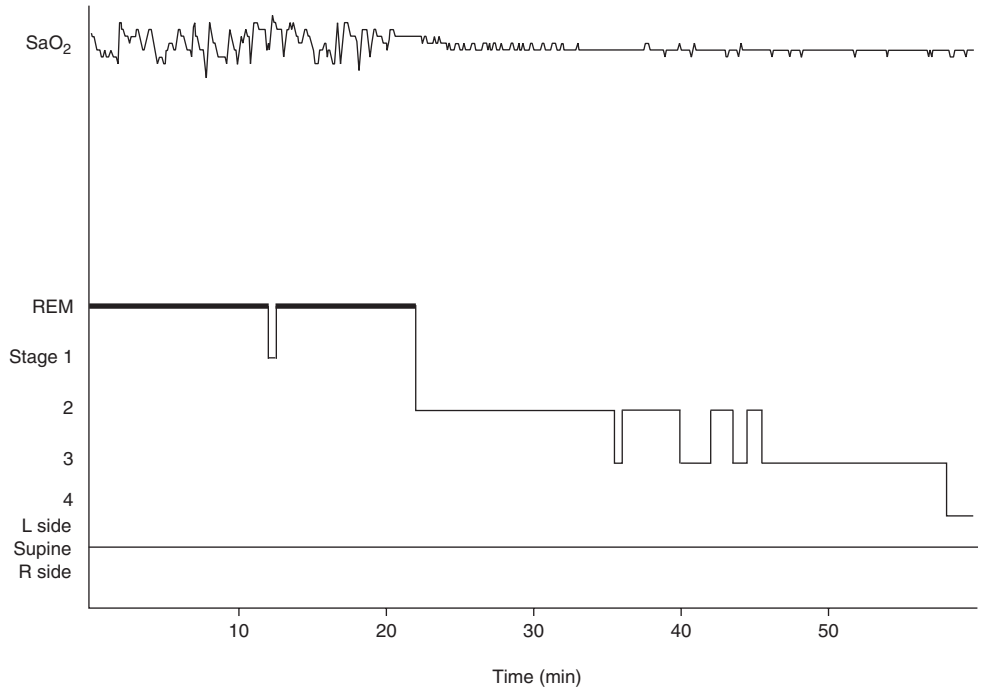

Fig. 2. Obstructive sleep apnoea (OSA) may be worst in or limited to rapid eye movement (REM) sleep. Voluntary muscle tone is at a nadir during REM sleep and the output from the hypoglossal nerve to genioglossus falls particularly in this sleep stage. In this patient, the oxygen desaturation events were due to OSA and only occurred during REM sleep. **L** = left; **R** = right; **SaO_2** = oxygen saturation.

to prove. The risk factors of male gender, obesity, hypertension, insulin resistance and abnormal lipids tend to aggregate in individuals with OSA. The challenge has been to differentiate and quantify the relative risks of these various potential factors in the development of cardiovascular disease. It is nonetheless an important endeavour as OSA is so common that a small reduction in any associated risk could lead to a clinically valuable fall in the rate of cardiovascular disease.

There are several theoretical mechanisms through which OSA could produce cardiovascular disease. The mechanism that has attracted the most attention is the proposal that OSA causes hypertension. In dogs it has been shown that the combination of arousals from sleep and hypoxia can produce daytime hypertension where sleep disruption alone does not.[16] There are several population studies that show associations between OSA and hypertension.[17-19] In the Sleep Heart Health Study, for example, there were increases in systolic and diastolic blood pressure, and the incidence of hypertension (defined by the use of antihypertensives, or systolic blood pressure ≥140mm Hg or diastolic blood pressure ≥90mm Hg) in patients with OSA.[17] When adjusted for age, sex, racial group, obesity, alcohol and tobacco usage, OSA with AHI ≥30 compared with <1.5 per hour of sleep gave an odds ratio of 1.3 (95% CI 1.03, 1.83) for the presence of hypertension.

As a consequence of disturbed nocturnal sleep, individuals with OSA may have difficulty performing complex motor tasks as shown in studies on driving simulators.[20] There is evidence that this translates into an increased number of road traffic accidents. In one series, drivers with OSA were three times more likely to have had a motor vehicle collision than controls and one-third had been involved in an accident in a 3-year period before treatment was offered.[21] In severe cases, usually associated with both obesity and chronic lung disease, OSA can lead to ventilatory failure and treat-

ment with nasal intermittent positive pressure ventilation may be life saving.[22]

Irrespective of the debate around cardiovascular risk and OSA there are clear indications for therapy in patients with symptoms. The most frequently used treatment is continuous positive airway pressure (CPAP). This has been shown to be highly effective in the majority of patients and some of the evidence is discussed in the following section (section 2). It is likely that the success of CPAP has suppressed interest in the pharmacological treatment of OSA. Early drug studies were often poorly constructed,[23] but the negative results have probably discouraged further enquiry along similar lines. As discussed in this section, the relative contributions to the severity of OSA of fixed airway abnormality, changes in airway tone, sleep state, sleeping position and ventilatory instability are different between patients. CPAP, or in severe cases more complex non-invasive ventilatory support,[22] can treat patients irrespective of the underlying mechanism so long as it is tolerated. In contrast, drug therapy will probably need to be better matched to the underlying mechanism. In none of the studies of medication to date has any stratification been attempted along these lines.[23]

2. Continuous Positive Airway Pressure (CPAP) as the Current Treatment of Choice

It is instructive to examine the evidence for the use of CPAP in the treatment of OSA as this provides a benchmark against which to compare the effectiveness of any drug treatment. CPAP was first described as a treatment for sleep apnoea in 1981.[24] It is delivered via a well-fitted mask usually applied to the nose but occasionally including the mouth (figure 3). The mask is attached to a pump that generates continuous pressure that is adjusted for the individual patient. The device acts as a pneumatic splint keeping the airway from closing, thus, preventing apnoeas and hypopnoeas and subsequent arousals.

In a randomised trial, CPAP was compared with sub-therapeutic CPAP set at 1 cmH_2O as a placebo

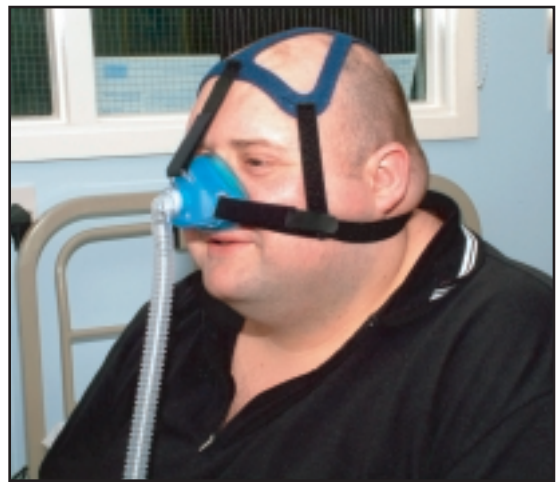

Fig. 3. Continuous positive airway pressure (CPAP) machine and nasal mask. The mask is held in place by head straps and most patients adapt well to wearing it during sleep.

control.[25] The patients' perceived level of sleepiness fell, as did objective measures of sleep propensity. In a case-controlled series, improvement in quality of life measured on several dimensions was demonstrated with very large effect sizes.[26] Interventional studies have shown that treating OSA can reduce arterial hypertension. In an extension of the study described above,[25] 24-hour mean arterial blood pressure rose by 0.8mm Hg over 1 month in patients on sub-therapeutic CPAP, whereas in the treatment group there was a fall of 2.5mm Hg. This difference was highly significant and the falls were greatest among patients with a higher starting level for blood pressure and for those already receiving antihypertensive medication.[27] In a case-controlled series, CPAP was seen to decrease the risk of driving accidents from three times normal to the background population rate.[21]

CPAP treatment is only effective if it is used. Uptake rates of around 75% have been reported in some study populations,[28] but other authors have recorded far lower acceptance and it has been claimed that CPAP fails more people than it treats because of poor tolerance of the equipment.[29] The physical inconvenience of the mask and pump means that given the choice some patients prefer a less effective treatment such as a mandibular ad-

vancement splint.[30] In other individuals daytime somnolence persists despite apparently effective treatment of nocturnal apnoeas and good compliance with CPAP.[31] There are individuals with severe OSA who are asymptomatic and present to medical attention with snoring. They are much less likely to comply with CPAP but may still need treatment to reduce the risk of cardiovascular morbidity.[32] Drug therapy may have a role in each of these circumstances.

3. Previously Proposed Drug Treatments for OSA

A number of classes of drug have been suggested as possible treatments for OSA. The gender difference in incidence for OSA has prompted trials of progestogens and estrogens. Attempts have been made to alter ventilatory drive using, for example, acetazolamide and theophylline. Since sleep apnoea is often most frequent and the apnoeas most prolonged in REM sleep, drugs have been given to change the sleep architecture and specifically suppress REM sleep. Unfortunately, most of the studies aiming to measure the effectiveness of drug treatments have involved only a few patients and have often been uncontrolled or nonblind. Even otherwise well constructed studies have been of short duration. Some of the more robust data are reviewed in this section.

3.1 Sex Hormones

OSA is less common in women than in men. Among women, OSA is more common after than before the menopause, while in population studies HRT seems to be protective.[12] Progestogens are known to increase ventilatory drive.[33] It has been argued that medroxyprogesterone not only increases respiratory drive but better matches diaphragmatic and upper airway tone. This has been demonstrated in decerebrate cats, although this may not accurately model the human situation.[34] For all these reasons medroxyprogesterone has been trialled as a treatment for OSA.[35,36] In an early study it was shown that medroxyprogesterone could reduce the frequency of sleep-disordered breathing events but the patients had apnoeas that were, in the main, central and not obstructive in origin.[35] Central apnoeas are caused by a failure of ventilatory drive and would be expected to improve on treatment with respiratory stimulants. There has been just one well designed, double-blind, crossover trial in patients with OSA and this showed that medroxyprogesterone had no positive effects.[36]

It is possible that OSA is more common in men than women not because progesterone is protective but because testosterone increases the risk of developing sleep apnoea. There are, for example, case reports of testosterone-induced sleep apnoea in women[37] and testosterone can worsen OSA in men.[38,39] Changing testosterone levels does not offer itself immediately as a therapeutic manoeuvre. There are adverse effects on sexual function but more importantly decreasing the testosterone level may not improve OSA. Testosterone levels are already reduced in patients with OSA probably as a result of the disruption of normal sleep architecture.[40] It is not clear that further reducing the levels would be an effective therapy. In the controlled study into the effectiveness of medroxyprogesterone discussed in the previous paragraph, all of the patients were male.[36] The testosterone level fell with the administration of medroxyprogesterone but there was no improvement in sleep-disordered breathing. From the current evidence there may be a benefit from medroxyprogesterone in patients with predominantly central apnoeas but it cannot be recommended for the treatment of OSA. Manipulating testosterone levels does not seem likely to be beneficial.

3.2 Acetazolamide

Other drugs that affect ventilatory drive have been tried in the treatment of OSA. Acetazolamide inhibits carbonic anhydrase, producing a metabolic acidosis and an increase in respiratory drive. In uncontrolled studies it has been shown to improve symptoms in patients with central sleep apnoea,[41] and to reduce the apnoea frequency in patients with OSA but only by about one-quarter.[42] In a randomised, controlled trial, acetazolamide did reduce the

AHI of ten patients with OSA.[43] The AHI was approximately halved from 50 per hour to 26 per hour ($p < 0.03$) [figure 4a]. However, there was no change in the frequency of arousals from sleep or in total sleep time. Patients felt no more rested after the treatment and there was no improvement in their subjective experience of daytime somnolence. Acetazolamide was offered as long-term treatment for three of the ten patients but only one was able to continue with the drug. The others developed adverse effects causing withdrawal; intolerable paraesthesia in one case and nocturnal enuresis in the other. From these data acetazolamide is unlikely to be of benefit to patients with OSA.

3.3 Theophylline

Theophylline has a respiratory stimulant effect that seems at least in part to be central in origin.[46] It has been hypothesised that it might affect upper airway tone and there is evidence that aminophylline (theophylline combined with ethylenediamine) improves diaphragmatic contractility.[47] There have been several uncontrolled trials and two placebo-controlled studies, one each with theophylline[48] and aminophylline.[49] In the case of theophylline, 12 patients were studied and no difference was found for AHI between treatment and placebo. There was a decrease in the number of arterial desaturations overnight on the treatment. However, the majority of this apparent improvement was due to a reduction in the total sleep time, which fell by more than an hour on the active treatment night. In the study of aminophylline there was a 24% decrease in the time overnight spent asleep on the active drug compared with placebo.[49] There was no improvement in apnoea frequency. A more recent study has compared theophylline with CPAP.[50] There was a reduction in the number of respiratory events overnight with theophylline but CPAP was much more effective, and again patients treated with theophylline had a shorter total sleep time. At present there is no evidence to support the use of theophylline in the treatment of OSA.

3.4 Opioid Antagonists

There is evidence for an increased level of some opioids in the cerebrospinal fluid of people with OSA.[51] These levels fell in six patients who were successfully treated surgically for their OSA.[51] In a single night study of ten obese patients with OSA the opioid antagonist naloxone was compared with a saline infusion.[52] With the naloxone infusion the maximal fall in oxygen saturation was smaller, as were the number of desaturations per hour, but only by 25%. Sleep staging was not available for all patients but REM sleep decreased by 80% in those in whom it was measured. Doxapram acts as a respiratory stimulant both peripherally at the carotid body and centrally at the respiratory centre. It antagonises the respiratory suppression caused by opioids but not their analgesic effects. In a study of just four patients doxapram infusion was compared with placebo as a treatment for OSA.[53] The duration of apnoeas was decreased but the number of desaturations per hour was unchanged and the proportion of time spent asleep did not improve. In view of the short half-lives and need for intravenous administration, these agents are not practical for the treatment of OSA. The minor improvements in respiratory indices that have been found suggest that the contribution of elevated opioid levels to the severity of OSA is, at most, slight.

3.5 Nicotine

Cigarette smoking may be a risk factor for OSA but there is contradictory evidence and at present the data are inadequate to settle the question.[54] Nicotine increases respiratory drive through direct effects on respiratory neurones in the medulla and also affects hypoglossal nerve output.[55] It has been proposed that the effect of nicotine is greater on airway stability than respiratory drive and it has been proposed as a treatment for OSA.[56] In a study of eight people with OSA, five of whom were or had been smokers, nicotine gum reduced the number of apnoeas in the first 2 hours of sleep with a fall in AHI from 85 to 49 in the first hour.[56] There was no apparent change in sleep structure but the definition of arousal required a 25 second body movement and

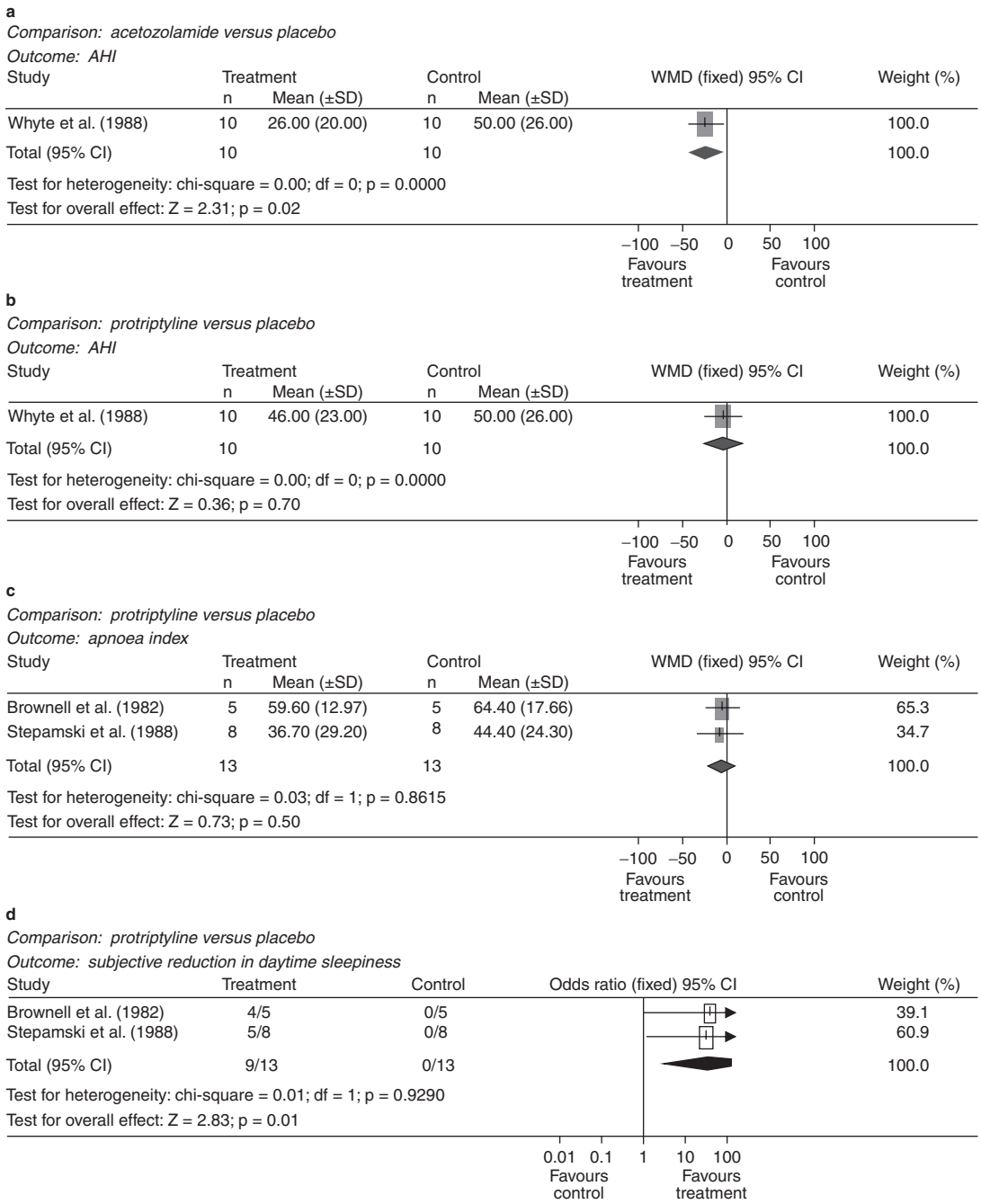

Fig. 4. Graphical representation of results from the Cochrane review of drug treatments for obstructive sleep apnoea (reproduced from Smith et al.,[23] with permission). (**a**) Acetazolamide vs placebo: effect on apnoea hypopnoea index (AHI) [per hour] expressed as weighted mean difference (WMD);[43] (**b**) protriptyline vs placebo: effect on AHI (per hour) expressed as WMD;[43] (**c**) protriptyline vs placebo: effect on apnoea index (per hour) expressed as WMD;[44,45] (**d**) protriptyline vs placebo: effect on subjective feelings of sleepiness expressed as odds ratio of benefit.[44,45] **df** = degrees of freedom; **n** = number of patients.

there may have been a greater change in less prolonged arousals. In a randomised controlled trial, 20 (ten female) nonsmoking snorers were administered transdermal nicotine or placebo.[57] The intensity of snoring was decreased by the active treatment but the number of apnoeas was not. In this study, sleep quality deteriorated with nicotine; initial latency to sleep increased from 7 to 18 minutes and total sleep time decreased by 33 minutes. Many of the patients had marked gastrointestinal adverse effects. The risk of creating nicotine addiction would be a major disincentive to using it as a treatment for OSA and the data are not available to support efficacy. Other nicotinic agonists might have a role but there are no data available to date.

3.6 Antihypertensive Agents

There have been studies to establish the best drug treatment of hypertension in patients with OSA.[58] There is some evidence that antihypertensives may not only effect blood pressure control but also reduce apnoea frequency, although the mechanisms are obscure. In a randomised, placebo-controlled study the β-adrenergic antagonist metoprolol and the ACE inhibitor cilazapril were both shown to reduce apnoea frequency by about one-third.[59] Changes in sleep quality and daytime symptoms were not reported. A nonblinded study of cilazapril showed similar results.[60] There are well designed and reported studies that show no useful effect of antihypertensives on OSA. In a randomised study cilazapril was compared with placebo in 54 hypertensive men with moderately severe to severe OSA.[61] Blood pressure was reduced and there was a minor reduction in OSA during non-REM but not REM sleep. Another study randomised 40 patients with hypertension and OSA to treatment with two of five agents (balanced incomplete block design) to compare the effects of atenolol 50mg, amlodipine 5mg, enalapril 20mg, hydrochlorothiazide 25mg and losartan 50mg given in once-daily oral doses on blood pressure.[58] Atenolol was most effective in reducing blood pressure while none of the drugs was found to reduce OSA severity or improve daytime well being. In a third study, celiprolol, another β-adrenergic antagonist, did not reduce OSA severity.[62] There is remaining doubt about the effectiveness of antihypertensives in reducing OSA severity, but there is no evidence to suggest that they lead to a deterioration and so treatment of hypertension can be recommended in OSA patients and atenolol is probably the drug of choice.

3.7 Clonidine

Attempts have been made to reduce the incidence of sleep-disordered breathing and sleep apnoea by reducing the proportion of REM sleep. Drugs with this action include clonidine and tricyclic antidepressants. Clonidine has been shown to suppress REM sleep[63] and there has been one placebo-controlled study of its effects on OSA.[64] In this study of just eight patients there was no overall improvement in the AHI compared with placebo and, although there was a statistically significant increase in the mean lowest oxygen saturation, this was not clinically important. REM sleep was completely suppressed in only two of the patients and there may have been dose administration issues. In patients where REM sleep was not suppressed, the AHI in REM sleep was paradoxically increased. There was no effect on apnoea frequency during non-REM sleep. There was no improvement in daytime symptoms after treatment with clonidine. The complex outcome of this study remains interesting but it does not suggest that clonidine will be an effective treatment for OSA.

3.8 Tricyclic Antidepressants

The tricyclic antidepressants suppress REM sleep and protriptyline has been recommended as a treatment for OSA.[65] There have been three randomised, controlled trials involving a total of 23 patients comparing protriptyline with placebo.[43-45] No difference was found in the frequency of apnoeas overnight or any other measure of a respiratory disturbance including oxygenation levels during sleep between active and placebo treatments (figures 4b and 4c). REM sleep was significantly reduced in just one of the studies.[44] Participants frequently reported adverse effects including dry

mouth, urinary hesitance, impotence and visual disturbance. In one study, long-term follow-up was offered: only three of five patients agreed to participate and one of these then developed urinary retention.[44] Daytime sleepiness was not measured objectively in any of these studies but, in two,[44,45] there were improvements in subjective measures of daytime sleepiness (figure 4d). Since there had been no change in AHI it seems likely that this represents a nonspecific alerting effective of the protriptyline.

Protriptyline was first proposed as a treatment for OSA because of its effects on REM sleep. However, it has also been shown to increase upper airway respiratory motor activity. In a study of decerebrate cats both hypoglossal and recurrent laryngeal nerve activity was consistently increased after protriptyline administration, while phrenic nerve activity was not altered.[66] As described in the previous paragraph, protriptyline has not been shown to be effective as a treatment of OSA but there are more promising results from other antidepressants, in particular the selective serotonin reuptake inhibitors (SSRIs), fluoxetine and paroxetine.

4. Serotonin and the Upper Airway

Individuals with OSA at night have a patent airway during wakefulness. Compared with healthy individuals, the activity of genioglossus may be increased during wakefulness to keep the airway open combating the abnormal collapsibility or narrowing of the airway.[67] During sleep the airway tone drops intermittently which can lead to airway occlusion.[3] In recent years there have been several advances in the understanding of the neuropharmacology of these sleep-dependant changes in airway tone.[68] Glycine produces the generalised atonia of postural muscles in REM sleep through postsynaptic receptors on the motor neurones.[69] This does not seem to be the most important mechanism for the airway dilators, rather it seems that there is a withdrawal of excitatory inputs which is more marked for tonic activity than phasic respiratory activity.[70]

Although it is not the only airway dilator implicated in the development of OSA, genioglossus has been most studied. The motor traffic to genioglossus in the hypoglossal nerve decreases from wake to non-REM sleep to a nadir in REM sleep, which is reflected in the increase in frequency and severity of apnoeas seen in many patients with OSA. The hypoglossal nerve is depolarised by serotonin *in vivo*.[71] There is tonic serotonergic input to the hypoglossal motor neurones from the medullary raphe that decreases from wakefulness to non-REM to a minimum in REM sleep.[72]

If serotonin is applied directly to the hypoglossal nucleus in unrestrained rats there is an increase in tonic activity for as long as the serotonin is delivered.[73] There are difficulties when trying to extrapolate this finding to a possible treatment for OSA in humans. Serotonin does not cross the blood-brain barrier so serotonin itself is not a candidate treatment. In different sites and in different animal models, serotonin has been shown to decrease rather than increase genioglossus activity presumably through auto-regulatory mechanisms acting at presynaptic receptors.[74] Similarly, the serotonin antagonist ondansetron might be expected to increase the frequency of obstructive apnoeas, but in adult bulldogs at least it can produce a decrease in the severity of sleep-disordered breathing.[75] There has been one study of ondansetron in humans with OSA but this failed to show any effect.[76] This may be because the dose administered was much lower than that used in the dog studies or that the mechanism of OSA is different in bulldogs. Finally, even when serotonin is applied directly to the hypoglossal nucleus there are still sleep-related changes in the phasic genioglossus activity showing that serotonin is not the only transmitter involved.[73]

To date, there have been no human studies of serotonin agonists for OSA. However, there are data on SSRIs. Paroxetine has been shown to increase genioglossus activity in healthy volunteers during wakefulness.[77] The serotonergic medullary raphe nuclei are most active during awake time and inhibiting serotonin reuptake would be expected to produce a large effect at this time. During sleep, and in particular REM sleep, these neurones are far less active and since there are lower levels of serotonin

released, preventing reuptake is likely to be a less effective strategy. In one study fluoxetine was compared to protriptyline in the treatment of OSA.[78] There was no placebo limb but fluoxetine was more effective than protriptyline in controlling apnoeas producing a reduction in the AHI from 57 to 34 per hour. There was no effect on the AHI during REM sleep. In a study of paroxetine in patients with OSA, there was only a modest improvement in the apnoea frequency overall from 25 to 18 per hour.[79] There was a 35% drop in the number of apnoeas in non-REM sleep but no change in the frequency in REM. There was no reduction in the extent or severity of daytime symptoms attributed to OSA. Serotonin agonists, should they be developed, might be more effective than the reuptake inhibitors since in theory at least they may be able to increase tone in the airway dilators even in REM sleep.

5. Outstanding Questions About Drugs Aimed at Raising Airway Dilator Tone

Increasing motor output using drugs such as serotonin agonists may be effective in patients with OSA because they have an abnormally low airway tone during sleep. However, many patients with OSA probably have increased rather than reduced airway muscle tone at least in the daytime.[67] Attempts to increase drive to the airway dilators at night could lead to muscle fatigue and a paradoxical deterioration. An analogy can be made with attempts to increase the output of the diaphragm in patients with ventilatory failure due to chronic obstructive pulmonary disease. Increasing respiratory drive with doxapram seems to increase the death rate compared with resting the respiratory muscles with non-invasive ventilation.[80] After fatiguing exercise it is possible to increase diaphragm output by stimulating the phrenic nerve electrically[81] and it is suggested that there is a central controller that down-regulates voluntary effort to reduce the risk from fatigue. In OSA, CPAP acts to splint open the airway reducing the work required of the airway dilators. To date, attempts to increase the tone in the upper airway pharmacologically have met with limited success but the theoretical risk of fatigue should be borne in mind.

There is another subgroup of patients with OSA for whom drug therapy may well be ineffective. These individuals have a patent airway during wakefulness because they are upright not merely because they are awake. Some only develop apnoeas when supine (figure 5) and may experience airway obstruction in wakefulness in this position. Increasing airway tone during sleep to daytime levels may not resolve the apnoeas if they are supine. In contrast, careful positioning in sleep can reduce AHI and may be as effective as CPAP in improving symptoms even if it is not as effective in eliminating apnoeas.[82]

6. Drug Therapy for OSA in Metabolic and Endocrine Disorders

Weight reduction can increase upper airway cross-sectional area[83] and, in some individuals, OSA may be cured.[84] Drugs have a limited role in the management of obesity as adjuncts to diet and exercise. Orlistat prevents fat absorption, and consequent adverse effects include fatty stools, faecal urgency and malabsorption of fat-soluble vitamins. It can produce modest weight loss (2–5 kg/year over placebo). Current research into its benefits only extends to 1 year of treatment.[85] Sibutramine inhibits reuptake of noradrenaline, serotonin and, to a lesser extent, dopamine. It promotes a feeling of satiety through increasing the actions of noradrenaline and serotonin on CNS α- and β_1-adrenoceptors and can produce similar degrees of weight loss to orlistat. It should be used with caution in OSA as it can cause hypertension.[86,87]

Hypothyroidism is often cited as a risk factor for OSA[32] but the strength of the association is perhaps weaker than was once thought. Studies of patients with OSA have shown that about 3% have thyroid dysfunction.[88,89] In a small study, just two of 20 patients with hypothyroidism had clinically significant OSA.[89] Treatment with thyroxine may improve OSA[90] but not always.[91] Weight loss may be a beneficial effect of thyroxine replacement but OSA can improve before weight loss has oc-

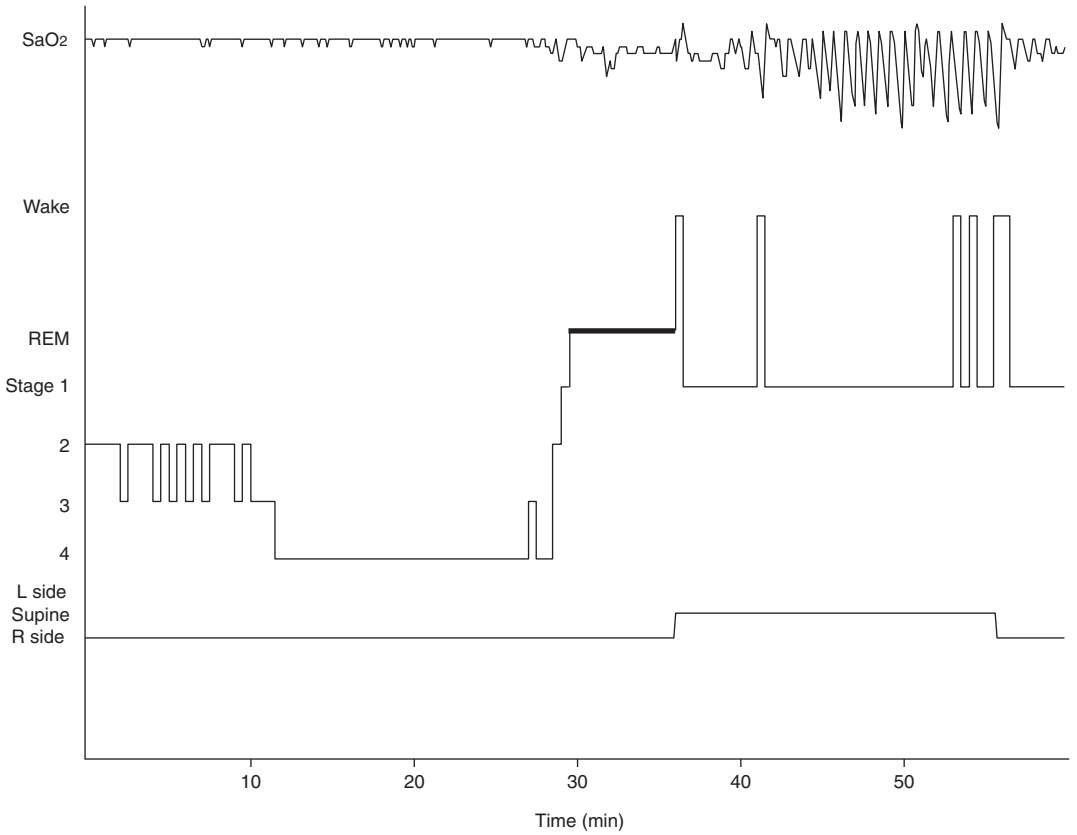

Fig. 5. Positional obstructive sleep apnoea (OSA). In some people, OSA only develops when they are supine. Careful positioning during sleep may improve overnight respiration and daytime symptoms. **L** = left; **R** = right; **REM** = rapid eye movement sleep; **SaO_2** = oxygen saturation.

curred.[92] It has been argued that this is because of increased ventilatory drive with preferential activation of the upper airway dilators compared with the diaphragm.[92] Acromegaly is thought to predispose patients to OSA through the development of craniofacial abnormalities, macroglossia and thickening of laryngeal tissues.[93] Again, there may be an effect on airway tone or respiratory drive as normalisation of growth hormone levels can result in improvement in the OSA despite the persistence of anatomical abnormalities.[94,95]

7. Persisting Daytime Sleepiness on CPAP Treatment

A further role for drug therapy in OSA is in the treatment of persistent sleepiness in patients using CPAP. Even when abnormal respiratory events during sleep are normalised by CPAP therapy, daytime somnolence may remain an intrusive symptom. It is important in such individuals to review the original diagnosis and consider alternative or coexisting reasons for sleepiness. If no other remediable cause is identified, then wakefulness-promoting drugs can be considered. Amphetamines improve daytime alertness in patients with OSA,[31] but they have considerable drawbacks including abuse potential and cardiovascular adverse effects.

Modafinil is a more recently developed wake-promoting agent, chemically unrelated to amphetamines, which acts on specific areas in the anterior hypothalamus. Its exact mechanism of action is not yet known but there is evidence that it reduces

persistent sleepiness in patients complying with CPAP therapy.[96] It is generally well tolerated, with mild-to-moderate headache being the most frequently experienced adverse effect.[96] There are no reports of serious cardiovascular adverse effects or of a withdrawal syndrome on cessation of treatment. Modafinil is licensed in the UK for persisting sleepiness in patients using CPAP for OSA. In the US, New Zealand and Australia it is only currently licensed to treat sleepiness associated with narcolepsy. There is concern that its use may reduce compliance with CPAP and leave patients open to the cardiovascular risks of OSA. This was not demonstrated in two published clinical series[96,97] but in one study there was a decrease in CPAP usage amounting to a mean of 12 minutes each night.[98] This is unlikely to be of clinical significance, but it must be remembered that these patients were under close observation in the setting of a trial and compliance may slip in patients who are less well monitored. A broader debate exists around whether patients who cannot tolerate CPAP should be given modafinil to control daytime symptoms.[99] The long-term effects of this are unknown and this course is not recommended at present.

8. Conclusions

Intuitively, OSA should be amenable to drug treatment in at least a proportion of patients with the condition. Currently, the treatment of choice is CPAP and this has been shown to be effective in controlling apnoeas at night irrespective of sleep stage, reversing daytime symptoms, reducing hypertension associated with apnoeas and the increased risk of car accidents through sleepiness. The track record for pharmacotherapy is poor by comparison. Thyroxine replacement, and treatment of acromegly and obesity, all have a role for a limited number of patients. In selected individuals who tolerate CPAP but do not feel improvement in the daytime, modafinil can be a useful adjunct assuming other causes for daytime sleepiness have been excluded.

Attempts to treat OSA directly with medication have to date been disappointing. Acetazolamide reduces the frequency of apnoeas at night but has unacceptable adverse effects. Other drugs given in the hope of increasing respiratory drive have been shown to decrease sleep quality. Antihypertensives may have a small impact on AHI, but this is not a consistent finding and there seems to be little impact on symptoms. SSRIs may reduce the apnoea frequency overall but are ineffective during REM sleep when apnoeas are often most pronounced. They have not been shown to improve daytime symptoms or reverse the long-term risks of OSA. Serotonin agonists may have more to offer but as yet there are no published studies of their efficacy. Theoretical problems exist including auto-regulation of hypoglossal nerve output through presynaptic receptors, which may paradoxically worsen apnoeas when activated by serotonin. Position-dependent OSA may not respond to increased airway tone. The possibility of unopposed hypoglossal activity leading to airway dilator fatigue has not so far been addressed.

For the present, CPAP remains the treatment of choice for OSA. With developments in the understanding of the neuropharmacology of the upper airway it is to be hoped that drug treatment will become a realistic alternative at least in some subgroups of the population with OSA. Large scale studies of suitable duration will be needed to prove efficacy. It is also likely that it will be necessary to better understand the particular factors influencing severity in individual patients to better target those likely to benefit from any particular agent.

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