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Adult obstructive sleep apnoea

Amy S. Jordan, PhD, **David G. McSharry, MB**, and **Prof. Atul Malhotra, MD**
University of Melbourne, Melbourne, VIC, Australia (A S Jordan PhD); Institute for Breathing and Sleep, Melbourne, VIC, Australia (A S Jordan); Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA (D G McSharry MB, Prof A Malhotra MD); and Letterkenny General Hospital, County Donegal, Ireland (D G McSharry)

Abstract

Obstructive sleep apnoea is an increasingly common disorder of repeated upper airway collapse during sleep, which leads to oxygen desaturation and disrupted sleep. Symptoms include snoring, witnessed apnoeas, and sleepiness. Pathogenesis varies; predisposing factors include small upper airway lumen, unstable respiratory control, low arousal threshold, small lung volume, and dysfunctional upper airway dilator muscles. Risk factors include obesity, male sex, age, menopause, fluid retention, adenotonsillar hypertrophy, and smoking. Obstructive sleep apnoea causes sleepiness, road traffic accidents, and probably systemic hypertension. It has also been linked to myocardial infarction, congestive heart failure, stroke, and diabetes mellitus though not definitively. Continuous positive airway pressure is the treatment of choice, with adherence of 60–70%. Bi-level positive airway pressure or adaptive servo-ventilation can be used for patients who are intolerant to continuous positive airway pressure. Other treatments include dental devices, surgery, and weight loss.

Introduction

Obstructive sleep apnoea is a common disorder of repetitive pharyngeal collapse during sleep.[1] Pharyngeal collapse could be complete (causing apnoea) or partial (causing hypopnoea). Disturbances in gas exchange lead to oxygen desaturation, hypercapnia, and sleep fragmentation, which contribute to the consequences of obstructive sleep apnoea—eg, cardiovascular, metabolic, and neurocognitive effects. Although several treatments exist, they are often either poorly tolerated or only partially alleviate abnormalities. Thus, improvement of patient adherence to existing treatments and development of new treatments (or combinations of treatments) are needed. In view of the obesity pandemic, the propensity for pharyngeal collapse and therefore the number of cases of obstructive sleep apnoea are likely to rise.

The landmark study investigating the prevalence of obstructive sleep apnoea was the 1993 Wisconsin Sleep Cohort Study.[2] This study reported that the prevalence of obstructive sleep apnoea—defined as more than five apnoeas or hypopnoeas per h of sleep plus excessive daytime sleepiness—was 4% in middle-aged men and 2% in middle-aged women (age 30–60 years). Subsequent studies suggest that prevalence in high-income countries is higher

Correspondence to: Dr Amy S Jordan, Melbourne School of Psychological Sciences, The University of Melbourne, Parkville, VIC 3010, Australia, ajordan@unimelb.edu.au.

Conflicts of interest

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than previously reported (10% in women and 20% in men),[3,4] perhaps a result of worsening obesity and improving technology over time.[5] Obstructive sleep apnoea is a global health problem; Brazil and several Asian countries have the same, if not higher, prevalence as high-income countries, despite less overall obesity.[6,7]

Diagnosis and definitions

Patients with obstructive sleep apnoea report snoring, witnessed apnoeas, waking up with a choking sensation, and excessive sleepiness.[1] Other common symptoms are non-restorative sleep, difficulty initiating or maintaining sleep, fatigue or tiredness, and morning headache.[8] Indicators include a family history of the disease or physical attributes suggestive of obstructive sleep apnoea—eg, a small oropharyngeal airway or markers of obesity (eg, large neck circumference).[9]

The best test for obstructive sleep apnoea is overnight polysomnography in a laboratory with the primary outcome measure of apnoea–hypopnoea index (number of apnoeas plus hypopnoeas per h of sleep). This test involves concurrent monitoring of both sleep and respiration (figures 1, 2). To monitor sleep–wake state, electroencephalogram, left and right electro-oculogram, and chin electromyogram are recorded. The respiratory recordings should include: respiratory effort measurement (eg, respiratory inductance plethysmography bands placed around the thorax and abdomen), airflow monitoring by nasal air pressure and thermal air sensor, and arterial oxygen saturation. Electromyography of the anterior tibialis is also often done to assess limb movements that might alter sleep stage or respiration and body position is monitored because of the position-specific nature of obstructive sleep apnoea in many patients (figure 1).

Table 1 shows the characteristics of each stage of sleep and arousals, and table 2 shows the criteria for respiratory events. Several definitions of hypopnoea exist and can lead to different values for apnoea–hypopnoea index between laboratories. Ruehland and colleagues[10] showed that apnoea–hypopnoea index could be reckoned as 25·1, 8·3, or 14·9 using three different criteria. Definitions of respiratory event are based on consensus,[11] although different criteria are used around the world. Variability of definitions can affect patients (eg, the reported severity can affect eligibility for government-funded treatment) and interpretation of research studies. Although standardised definitions might improve consistency and reproducibility,[12] fixed definitions of apnoea–hypopnoea index might also have limitations. Because obstructive sleep apnoea has different effects on different organ systems, one fixed definition is unlikely to predict all negative outcomes. For example, the different consequences of obstructive sleep apnoea are best predicted with different components of the polysomnography (eg, desaturations by 4% or more in pulse oximetry can best predict hypertension,[13] while desaturations of 2% can predict fasting hyperglycaemia,[14,15] and the frequency of arousals can predict impaired memory consolidation[16]). Thus, different definitions of hypopnoea might predict different consequences of obstructive sleep apnoea. Measument of nasal pressure is a recent addition to polysomnography. Because nasal pressure is more sensitive than thermistor for detection of hypopnoeas, the reported apnoea–hypopnoea index (and perhaps the normal range) increases accordingly. Thus, doctors should be aware that subtle differences between laboratories might have a major effect on the reported apnoea–hypopnoea index.

Although polysomnography is usually definitive, the procedure is cumbersome, expensive, and time consuming. Thus, home diagnosis and management has been increasingly investigated. Randomised controlled trials[17–20] have shown that home-based diagnosis and treatment are no worse than laboratory diagnosis and treatment for some patients. All major studies excluded potentially complicated patients (eg, those with lung disease, heart failure,

or neuromuscular disease), emphasising that home testing is not appropriate for all patients. However, for some patients, carefully designed home management procedures can provide timely and cost-effective management of obstructive sleep apnoea.[17] Ongoing studies focusing on clinical outcomes will help to define optimum management of obstructive sleep apnoea.

Pathophysiology and risk factors

Traditionally, obstructive sleep apnoea was considered to primarily be a problem of upper airway anatomy, where craniofacial structure or body fat decreased the size of the pharyngeal airway lumen, leading to an increased likelihood of pharyngeal collapse.[21] During wakefulness, the airway is held open by the high activity of the numerous upper airway dilator muscles, but after the onset of sleep, when muscle activity is reduced, the airway collapses.[22,23] Although this sequence probably occurs in obstructive sleep apnoea, several other factors also contribute (figure 3).[24] The importance of these non-anatomical and non-neuromuscular factors is shown by patients with apparently normal upper airway anatomy and very responsive or numerous upper airway dilator muscles who still develop obstructive sleep apnoea.[25]

One important variable is the stability of the respiratory control system. When the central respiratory output waxes and wanes, the activity of the upper airway dilator muscles varies accordingly so that periods of low central respiratory drive are associated with low upper airway dilator muscle activity, high airway resistance, and a predisposition to airway collapse.[26,27] Thus, respiratory control instability (also known as high loop gain) is probably a causative factor of obstructive sleep apnoea in some patients.[25,28]

Another potentially important factor is the propensity to arouse from sleep (the arousal threshold).[29] After arousal, most people hyperventilate briefly and if large enough, CO_2 concentration in blood can fall below the chemical apnoea threshold, resulting in a central apnoea.[30] If hypocapnia is mild, respiratory drive is reduced to just below the eupnoeic level when sleep resumes. Because the upper airway dilator muscles also receive respiratory input, hypocapnia reduces the activity of the upper airway dilator muscles and could lead to collapse of the airway. Arousals that halt respiratory events in obstructive sleep apnoea are typically associated with quite large hyperventilation because respiratory drive has risen substantially during the respiratory event,[30] causing hypocapnia in at least some patients. Individuals with low arousal thresholds might also arouse before the dilator muscles are able to reopen the airway. In such cases, delay of arousal with non-myorelaxant sedatives might help to treat the condition if the upper airway muscles are sufficiently responsive to respiratory stimuli to stabilise the airway before arousal.[31] Care must be taken with this approach, because sedatives can prolong respiratory events in some patients (those who cannot re-open the airway without arousal).

Lung volume might also be a causative factor.[32,33] In animals and man, the cross-sectional area of the upper airway increases when lung volume increases (either naturally or with passive increases in functional residual capacity). Conversely, the airway is smaller and collapses more easily when lung volume is small.[34] This relation probably exists because the lower and upper airways are mechanically linked,[35] so that with increased lung volumes, the mediastinal structures are pulled caudally, resulting in stiffening and dilation of the pharyngeal airway. Increased lung volume also probably stabilises the respiratory control system by increasing the stores of O_2 and CO_2 and thus, buffering the blood gases from changes in ventilation.[36] Functional residual capacity falls between waking and sleeping in normal-weight individuals[37] and is therefore presumed to contribute to the sleep-related collapse in obstructive sleep apnoea.[33,38,39] However, even when awake, obesity often

reduces functional residual capacity to residual volume, particularly when in the supine position.[40] Therefore, whether lung volume falls further between wake and sleep in obese patients with obstructive sleep apnoea remains unclear.

Any factors that impair the upper airway anatomy or muscle function—eg, dysfunctional upper airway dilating muscles—will also predispose to obstructive sleep apnoea.[41] The largest and most commonly studied airway dilator muscle is the genioglossus, which constitutes most of the tongue. Adequate contraction of the genioglossus seems to be necessary and sufficient to keep the upper airway open during sleep.[42] Fatigue, neural injury, and myopathy can cause the genioglossus to malfunction in people with obstructive sleep apnoea.[43–45] Pharyngeal sensory impairment might also contribute to collapse of the upper airway.[46,47]

Fluid retention and shift of fluid overnight from the legs to the neck might also affect airway mechanics. Oedema can be especially problematic in states of excess extracellular fluid volume—eg, heart failure, end-stage renal disease, and hypertension.[48] Treatment with diuretics or mechanical methods to redistribute fluid yields some improvement in obstructive sleep apnoea.[49,50] Accumulation of fluid might narrow the pharyngeal airway lumen and could be a therapeutic target for at least some patients.

Being male and obese are major risk factors for obstructive sleep apnoea. Obesity could increase the likelihood of airway collapse by directly affecting the anatomy of upper airway as fat is deposited in surrounding structures.[51] MRI studies suggest that fat is deposited within the tongue, which could impair function of the genioglossus muscle.[52] However, obesity might also increase the risk of obstructive sleep apnoea via effects on lung volumes and therefore stability of respiratory control. How male sex predisposes to obstructive sleep apnoea is less clear.[53] Men tend to gain weight more centrally than do women, and this pattern probably results in men having more fat stored in upper airway structures and the abdomen than do women.[54] However, anatomical studies have shown that men tend to have larger or similar size pharyngeal airway cross-sectional areas than do women, suggesting that differences in fat deposition might not greatly impair airway anatomy. Several studies[53] suggest that the airway is longer in men than in women, independent of body height, which could explain the increased propensity for airway collapse in men. The passive pharyngeal airway collapsing pressure provides an overall measure of the anatomy of the upper airway that accounts for all anatomical measures and their interactions, but it does not account for neuromuscular reflexes.[55,56] The passive pharyngeal airway collapsing pressure is generally higher in men than in women for any given body-mass index, suggesting that generally, anatomical factors predispose men to pharyngeal collapse more than women. Women also have better respiratory load responses than do men (eg, higher minute ventilation during inspiratory resistive loading).[57,58] Finally, the more central fat distribution in men might reduce lung volumes for a given body-mass index.

Age is another major risk factor.[59] Older individuals might have reduced tethering of the upper airway by lung volume because of loss of elastic recoil in the lung. They might also have a more easily collapsible airway caused by loss of collagen or a reduced arousal threshold caused by poorer quality of sleep. Finally, the efficiency of the upper airway dilator muscles might fall with age.[60–62]

Additional risk factors for the development of obstructive sleep apnoea include genetic factors and ethnic origin, which affect craniofacial anatomy, obesity, and perhaps lung volume. Menopause—independent of age and body-mass index—is also a risk factor. Menopause could be related to redistribution of body fat to central regions and loss of lean muscle mass (with a proportionate increase in fat mass). Finally, smoking is also commonly

linked with obstructive sleep apnoea. Although the exact mechanisms of this association are not clear,[4] they might include increased inflammation of the upper airway, nasal stuffiness, reduced airway sensation, and reduced arousal threshold or frequent arousals because of unstable sleep. A more complete understanding of the pathogenesis of obstructive sleep apnoea and its risk factors could lead to new means to treat or prevent the disease.

Consequences

Randomised trials have shown that obstructive sleep apnoea causes sleepiness based on significant improvements in symptoms with continuous positive airway pressure compared with controls.[63] People with obstructive sleep apnoea are more likely to have motor vehicle accidents (perhaps up to seven-times as many as those without the disease[64]). This risk might be mitigated, at least in part, by treatment.[65] Obstructive sleep apnoea also affects quality of life and different aspects of health domains with improvements noted after treatment with continuous positive airway pressure, particularly in adherent patients.[1]

Obstructive sleep apnoea leads to systemic hypertension,[66] as shown by animal studies (showing increased systemic blood pressure with induction of sleep apnoea, which resolves with relief of apnoea),[67] large cross-sectional and longitudinal epidemiological studies,[68,69] and several randomised trials[70] showing that treatment for obstructive sleep apnoea reduces systemic blood pressure. Treatment with continuous positive airway pressure seems to reduce blood pressure, although only by 2–3 mm Hg, and less than the reductions gained by treatment with anti-hypertensive drugs.[71] However, continuous positive airway pressure also improves other symptoms besides hypertension.[72] Results of meta-analyses[70,73] have defined predictors of improvement in blood pressure after continuous positive airway pressure, including adherence, young age, baseline blood pressure (ie, blood pressure can fall greatly in hypertensive patients), daytime sleepiness (ie, larger falls in sleepier patients), and severity of obstructive sleep apnoea. However, proponents of theories on central regulation of blood pressure would argue that large changes in blood pressure are unlikely to occur if continuous positive airway pressure simply reduced vasoconstriction;[74] various counter-regulatory mechanisms (eg, baroreflexes) would stabilise blood pressure, at least in the short term. Nonetheless, some patients given continuous positive airway pressure do have large improvements in blood pressure as well as reductions in surges in nocturnal blood pressure associated with obstructive sleep apnoea. However, this link is still controversial; some studies have shown that the connection between obstructive sleep apnoea and hypertension is weak when covariates are accounted for.[75–77]

The relation between hard cardiovascular outcomes and obstructive sleep apnoea is unproven.[78] Marin and colleagues[79] reported results of a prospective observational cohort study in which severe untreated obstructive sleep apnoea was associated with an increased incidence of both fatal and non-fatal cardiovascular events compared with patients with treated obstructive sleep apnoea and various control groups. Although these data accord with the idea that treatment of obstructive sleep apnoea prevents cardiovascular events, the result might be caused by a treatment bias—ie, patients who adhere to continuous positive airway pressure might also be motivated to adhere to diet and exercise advice and to adhere to drugs.[80] Other epidemiological studies[72,81] have linked obstructive sleep apnoea with myocardial infarction, congestive heart failure, and stroke. Ad-hoc subgroup analyses suggest that obstructive sleep apnoea has a bigger effect on cardiovascular outcomes in young men compared with old men. Asymptomatic patients often do not adhere to treatment and so do not improve much in randomised trials. Several observational studies have assessed the effect of obstructive sleep apnoea on overall mortality and cancer risk, although large, controlled, randomised trials are needed to draw definitive conclusions.[82,83]

No data show that continuous positive airway pressure prevents myocardial infarction, congestive heart failure, or stroke, although this topic is being investigated.[72,78] Among patients with heart failure, continuous positive airway pressure improves cardiac function, although the existing studies are small.[84] To show that obstructive sleep apnoea increases the chance of cardiovascular events, studies in high-risk patients are needed. Assessing changes in surrogate outcome measures or biomarkers might also be informative.[85]

Obstructive sleep apnoea has been linked with diabetes mellitus. Foster and colleagues[5,86] showed that 87% of obese patients with type 2 diabetes had clinically important obstructive sleep apnoea, although because obesity is a common risk factor for both obstructive sleep apnoea and diabetes mellitus, the association could simply be a correlation. Diabetes can lead to neuromyopathy, which might impair reflexes in the upper airway, increasing the likelihood of obstructive sleep apnoea.[1] However, few data support this contention. Furthermore, because of the release of counter-regulatory hormones during obstructive apnoea, glycaemic control might be expected to be worse in patients with diabetes if obstructive sleep apnoea is left untreated.[87,88] However, most data show no major improvement in glycaemic control with treatment of obstructive sleep apnoea.[89] A potential explanation for this finding relates to adherence to continuous positive airway pressure. A study from India[90] showed improvement in metabolic syndrome in a setting where adherence to continuous positive airway pressure was high. Additionally, because standard of care in type 2 diabetes requires fairly good glycaemic control, the incremental benefits of continuous positive airway pressure beyond as a standard treatment might be small. Moreover, the interactions between obstructive sleep apnoea and obesity and their effects on glucose regulation are probably complex.[91,92] Finally, obstructive sleep apnoea and diabetes mellitus could affect vascular function through different pathways,[93,94] therefore treatment of obstructive sleep apnoea could improve vascular outcomes in diabetes. Standard therapeutic targets for diabetes—eg, hypercholesterolaemia, blood pressure, and glycaemic control—have probably been exploited as much as possible, suggesting the need for new therapeutic targets. Efforts are ongoing to assess the effect of continuous positive airway pressure in patients with diabetes.

Randomised controlled trials of continuous positive airway pressure are difficult to do for both ethical and logistical reasons.[22] Symptomatic patients will benefit from continuous positive airway pressure, making long-term assignment to an untreated control group challenging. Conversely, adherence of asymptomatic patients is often poor, reducing any potential benefit of assignment to continuous positive airway pressure.[72,95] Comparative effectiveness research might be feasible, in which two active treatments are compared to one another (eg, continuous positive airway pressure *vs* oral appliance);[96,97] however, definitive data will be difficult to collect until improvements are made in treatment or the identification of patients likely to benefit from continuous positive airway pressure (or combinations of treatment).

Management

Nasal continuous positive airway pressure is the treatment of choice for adults with obstructive sleep apnoea.[98] It was first reported as an effective means of preventing collapse of the pharyngeal airway in 1981.[99] The mechanism of continuous positive airway pressure is debated, but probably involves maintenance of a positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure.[33] Continuous positive airway pressure also increases end-expiratory lung volume, which stabilises the upper airway through caudal traction.[100] The decision to start treatment with continuous positive airway pressure should include a discussion with the patient about the potential alleviation of symptoms and possible cardiovascular protection.[73,95,98] Continuous positive airway

pressure has substantial benefits for some patients and adherence is roughly 60–70%, much the same as adherence to inhalers in patients with asthma, anti-convulsant drugs in those with epilepsy, and maintenance of good glyceamic control in diabetes.[98] It is also highly cost effective when considering its effects on neurocognitive and cardiovascular sequelae.[101]

Patients likely to maintain long-term adherence include those who snore heavily, have severe sleep apnoea, and have substantial excessive daytime sleepiness.[102,103] Because short-term adherence and early perceived benefits are the best predictors of long-term adherence, efforts to optimise adherence are best done before or shortly after starting treatment.

Several points should be considered when managing patients who are struggling to adhere to continuous positive airway pressure (figure 4). First, intensive support can be beneficial according to some studies.[104] Education and support can improve adherence: patients who understand the benefits of treatment and who are helped to troubleshoot difficulties are likely to respond favourably. Second, some patients have nasal difficulties that limit their ability to tolerate nasal treatment with continuous positive airway pressure. Nasal decongestants and heated humidification can be beneficial for such patients. In rare cases, nasal surgery can improve adherence. Third, although randomised trials have not shown one type of mask to be better than another, some patients prefer a full face mask to a nasal mask, while others prefer a nasal pillow device. Fourth, some patients respond to hypnotherapy if they develop insomnia or frequently wake when using continuous positive airway pressure.[105] Some data support the use of eszopiclone in patients who are starting continuous positive airway pressure. Our clinical experience suggests that consolidating sleep (stabilising or preventing fragmented sleep) can enable adherence so that hypnotherapy is no longer needed once the patient has habituated to the new equipment. Sedatives should be used cautiously in patients with obstructive sleep apnoea.

Several alternative options are available for patients in whom continuous positive airway pressure is unsuccessful. Bi-level positive airway pressure can be used (and might be preferred by some patients who have expiratory pressure discomfort), although randomised trials[106] have shown no major benefit compared with continuous positive airway pressure. Second, expiratory pressure relief strategies—eg, C-Flex (Philips Respironics; Murraysville, PA, USA) or EPR (Resmed; San Diego, CA, USA)—can improve discomfort during expiration in some patients. Most data[107] suggest that such treatment offer no major benefit compared with standard continuous positive airway pressure. Third, auto-titration positive airway pressure has been used to vary pressure on an ad-hoc basis to maintain stable ventilation. Some patients who need different pressures to be applied (eg, based on body posture or sleep stage) might benefit from variable pressure devices that can lower the applied pressure when appropriate. However, most randomised trials[108] have shown no improvement in adherence with auto-titration compared with standard continuous positive airway pressure. Some data[109] suggest that auto-titration positive airway pressure worsens outcomes, seemingly because changes in intrathoracic pressure lead to arousal from sleep and haemodynamic instability. Thus, the data supporting new technologies to improve adherence are not compelling,[110] but occasional benefits are seen in clinical practice.

For patients in whom positive airway pressure is unsuccessful, alternatives include oral devices, upper airway surgery, positional therapy, and other conservative measures. Different oral devices work in different ways but generally they apply pressure to the jaw to prevent retroglossal collapse. Oral devices are preferable to continuous positive airway pressure in some patients, particularly those with mild-to-moderate disease.[111,112] However, the efficacy of oral devices varies and little data on outcomes have been collected.[113–116]

One challenge with such devices is that several visits to a dentist are needed with satisfactory outcome difficult to judge until after 6–9 months of gradual titration. Although the device, plus repeated visits to the dentist, can be costly, oral devices are likely to be cost effective if they successfully treat obstructive sleep apnoea.

Some simple surgeries can be done to the soft palate (somnoplasty, laser-assisted uvulopalatopharyngoplasty), but the resulting improvements in symptoms are generally small at best. Fewer than 50% of patients have major improvements in apnoea–hypopnoea index with uvulopalatopharyngoplasty, therefore many doctors recommend against this procedure. However, because surgical procedures obviate the difficulties of patient adherence, some researchers recommend surgical treatments.[117–120] Aggressive surgeries—eg, maxilla-mandibular advancement—are probably more effective than simple surgeries, but many patients would rather avoid major surgery for obstructive sleep apnoea. Tracheostomy eliminates obstructive sleep apnoea but it can substantially reduce quality of life. Prediction of which patients will respond to a particular procedure is poor at present, although research is ongoing.[121] Experimental surgeries such as hypoglossal nerve stimulation are being studied, but definitive data are not available.[122–124] Thus, further study is needed to define the best treatment for obstructive sleep apnoea.

Conservative measures can also be helpful. Avoidance of depressants including alcohol can be helpful since such substances can worsen symptoms. Sleeping for 7–8 h per night can reduce sleepiness. Avoidance of a supine posture can also help patients whose apnoea is caused by sleep position, although such patients often prefer continuous positive airway pressure to positional treatment.[125] Additionally, positional treatment can be difficult to monitor at home and thus, clinical outcomes are variable. Positional treatment can also be used in combination with other treatments when interventions such as oral devices or surgery give incomplete responses. Weight loss through diet and exercise can also be helpful.[5] Few patients achieve long-term maintenance of reduced bodyweight, but education and support can be helpful. Some data[126] suggest that bodyweight increases after treatment with continuous positive airway pressure, emphasising the need for diet and exercise advice for all patients. Epidemiological data[127] suggest that exercise might have other benefits for obstructive sleep apnoea in addition to weight loss; however, the mechanism of this improvement is unclear. Similarly, neuromuscular exercises are beneficial for some patients,[128] although the data are not definitive.

Sleepiness persists in some patients despite good adherence to continuous positive airway pressure.[129,130] The mechanism underlying this finding is unclear, but might result from consequences of apnoea that are irreversible. Such patients are managed supportively with efforts to improve adherence and sleep duration as much as possible. Several randomised trials have been done to test the usefulness of stimulants such as modafinil to treat residual sleepiness in patients who adhere to continuous positive airway pressure. In most studies, patients benefit from stimulants, although some studies[131] suggest that use of continuous positive airway pressure is compromised. Thus, patient education is important to emphasise that stimulants can provide an adjunctive treatment for sleepiness but do not treat the underlying apnoea: ongoing adherence to continuous positive airway pressure is needed.

Central apnoeas develop in roughly 10% of patients who start treatment with continuous positive airway pressure.[132] These apnoeas are also known as complex apnoea and have been the subject of debate.[133] Although the mechanisms are unclear,[134] various theories have been suggested,[133] including lung stretch reflexes reducing ventilatory motor output, improvement in CO_2 clearance with relief of upper airway obstruction yielding a partial pressure of CO_2 below the chemical apnoea threshold, and reduction of anatomical deadspace by washout of CO_2 from the upper airway. Irrespective of the underlying

mechanism, most results[134] suggest that these central apnoeas resolve spontaneously with ongoing continuous positive airway pressure treatment. Even so, some researchers advocate for the use of new devices—eg, adaptive servo-ventilation—to treat such apnoeas.[135] If breathing normalises spontaneously over time, then the use of expensive new devices might not be justified. Conversely, if a patient's first experience of continuous positive airway pressure treatment is unpleasant (perhaps because of repeated central apnoeas), then long-term adherence to treatment might be poor as a result.[135] Thus, early intervention to treat central apnoeas could improve long-term adherence to positive airway pressure. Treatment-emergent central apnoeas seem to have no effect on outcomes or long-term adherence[133] and thus, efforts at early intervention with new devices have been unsuccessful. As a result treatment-emergent central apnoea can be considered a minor problem.

Prevention

Although many risk factors for obstructive sleep apnoea are fixed, weight loss (though diet and exercise), and avoidance of cigarettes, alcohol, and other myorelaxant drugs can be beneficial.[5,86] Results of a randomised controlled trial[5,86] show that a 10 kg reduction in bodyweight can yield a reduction in apnoea–hypopnoea index of roughly five events per h. Obstructive sleep apnoea resolved in 63% of patients with mild disease, whereas only 13% of patients with severe obstructive sleep apnoea had remission. Although bariatric surgery is highly effective at causing weight loss, long-term elimination of apnoea varies.[136] Several studies[40,137–140] have shown that obstructive sleep apnoea re-emerges or persists after surgical or non-surgical weight loss.

Future directions

Future treatments for obstructive sleep apnoea are likely to be targeted to the cause of disease since the disease occurs for different reasons in different patients (figure 3). For patients with a low arousal threshold, sedatives or hypnotics might be useful, whereas for patients with unstable ventilatory control, oxygen or acetazolamide might improve obstructive sleep apnoea.[28] Palate surgery will probably help patients with anatomical problems at the level of the velopharynx.[141] For patients with upper airway muscle dysfunction, treatments such as hypoglossal nerve stimulation,[122] muscle training exercises,[128] or strategies to increase hypoglossal output might be useful. For patients with multifactorial disease, combination treatment might be necessary. Further research into disease mechanisms should focus on new treatment strategies.[24] Ultimately, drugs might be developed to either block apnoea or attenuate its consequences.

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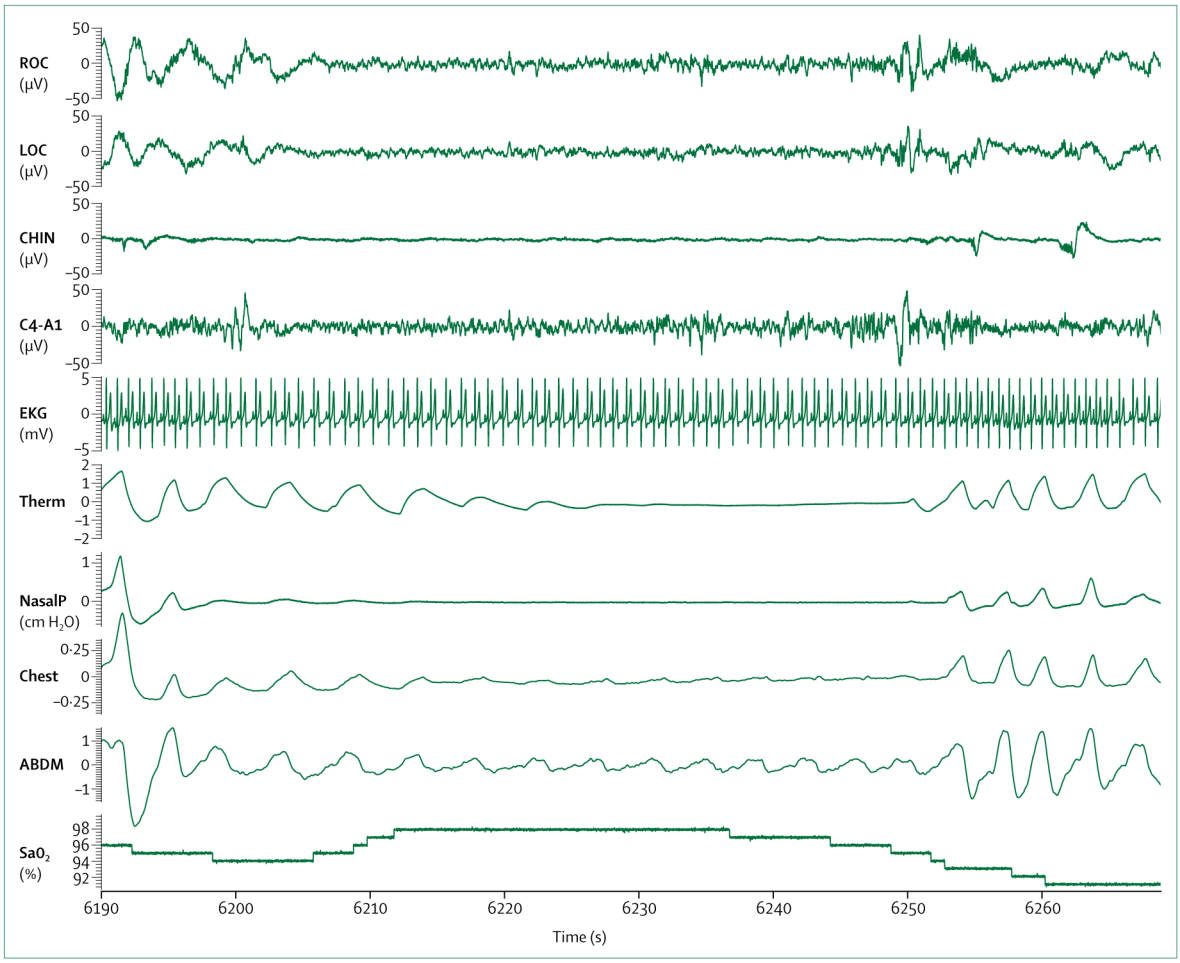
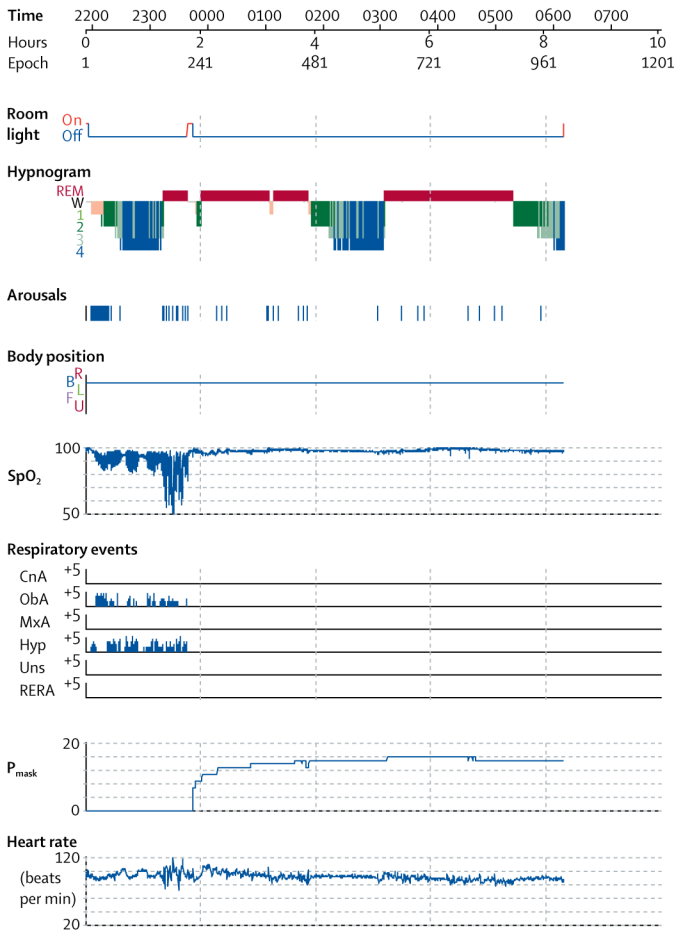


Figure 1. An example of the signals recorded during overnight polysomnography

Shows an obstructive apnoea with cessation of airflow for more than 10 s despite persistent respiratory efforts shown on the chest and abdominal respiratory bands. The apnoea is associated with arterial oxygen desaturation and is terminated by arousal from sleep. C4-A1=electroencephalogram. LOC=left electro-oculogram. ROC=right electro-oculogram. CHIN=chin electromyogram. CHEST=respiratory inductance plethysmography bands placed around the thorax. ABDM=respiratory inductance plethysmography bands placed around the abdomen. P_{Nasal}=airflow monitoring by nasal air pressure. Therm=airflow monitoring by thermal air sensor. SaO_2=arterial oxygen saturation. EKG=electrocardiogram. ABDM=abdomen.



	Baseline	CPAP
Total sleep time (min)	99·0	381·5
Stage 1 (%)	11·1	2·5
Stage 2 (%)	15·2	15·1
Stage 3+4 (%)	14·6	9·6
Stage REM (%)	25·8	62·5
Sleep efficiency (%)	96·1	98·7
Sleep latency (min)	2·5	1·5
REM latency (min)	75·0	6·5
Arousal index (n per h)	22·5	3·1
PLM arousal index (n per h)	0	0
Respiratory summary		
Obstructive apnoeas (n)	86	0
Mixed apnoeas (n)	0	0
Central apnoeas (n)	0	0
Hypopnoea (n)	128	0
AHI (per h)	129·7	0
AHI NREM (n per h)	131·4	0
AHI REM (n per h)	124·7	0
Lowest SaO_2 (%)	49	92
Average SaO_2 (%)	83	97
Desaturations ≥4% TST (n)	171	0
PLM Index (n per h)	0	0

Figure 2. An example summary report from an overnight split night polysomnography

Total time in bed was 489·5 min. Half of the night was diagnostic, half therapeutic. The hypnogram shows sleep stages throughout the night. Shortly before midnight, continuous positive airway pressure was started (P_{mask} increases from 0), which was followed by elimination of respiratory events, normalisation of arterial oxygen saturation, and REM rebound (>2 h of REM). Sleep efficiency is the proportion of time in bed spent asleep after lights out. Sleep latency is the time from lights out until the first epoch of sleep. REM latency is the time from lights out until the first epoch of sleep. An epoch is a time window of 30 s. CnA=central apnoea. ObA=obstructive apnoea. MxA=mixed apnoea. Hyp=hypnoea. Uns=unclear events. RERA=respiratory event related arousal. PLM=periodic limb movement. TST=total sleep time. REM=rapid eye movement. W=awake. NREM=non-rapid eye movement. R=right. B=back. L=left. F=front. U=upright. On the hypnogram, 1, 2, and 3 represent NREM stages 1, 2, and 3.

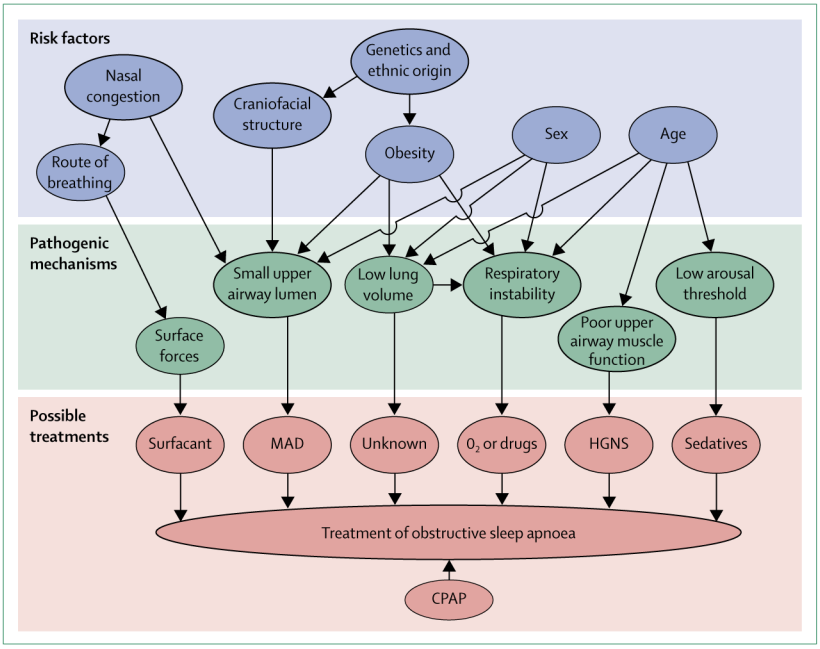


Figure 3. Risk factors, pathogenic mechanisms, and possible treatments for obstructive sleep apnoea

Risk factors for obstructive sleep apnoea probably act through one or more pathogenic mechanisms. One or two of the pathogenic mechanism might predominate in each patient and give rise to the disorder. Although CPAP treats obstructive sleep apnoea irrespective of underlying cause, treatments based on tackling individual pathogenic mechanisms might prove a successful alternative approach—eg, fluid accumulation outside the airway could make the upper airway lumen smaller and might respond to diuretic treatment. CPAP=continuous positive airway pressure. MAD=mandibular advancement device. HGNS=hypoglossal nerve stimulation.

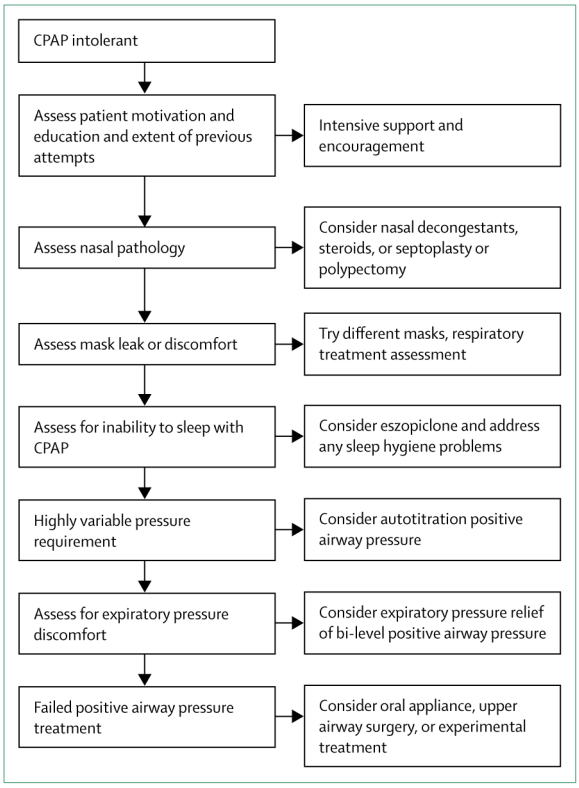


Figure 4. Suggested steps for management of patients struggling with CPAP
CPAP=continuous positive airway pressure.

Table 1

Adult sleep staging and arousal scoring

	EEG characteristics	Relevance to OSA	Normal amounts
Wake	Low voltage, mixed frequency when eyes are open or alert; α activity (8–13 Hz) while relaxed with eyes closed	Typically increased in OSA	15–20% of time in bed
N1	Predominantly low amplitude and relatively fast θ activity (3–7 Hz) accompanied by slow rolling-type eye movements	Typically increased in OSA	4–6%, more in older patients
N2	Sleep spindles (12–14 Hz bursts lasting >0·5 s) and K complexes (large negative EEG wave followed immediately by a slower positive wave) on a background of low voltage, mixed frequency EEG	Typically increased in OSA	50–65%, more in older patients
N3	Slow (<2 Hz), high amplitude (> 75 μV) EEG waves for more than half the epoch	Often absent or reduced in OSA, but associated with improved severity or complete absence of OSA when present	15–20%, less in older patients
REM	Low voltage, mixed frequency EEG with periodic runs of sawtooth waves accompanied by irregular movements of both eyes and low muscle tone	Often absent or reduced in OSA; often accompanied by worsening of respiratory events and more pronounced desaturation than the non-REM stages	15–20%
Arousals	3–15 s return of waking or faster activity in the EEG; concurrent increase in EMG must be recorded in REM sleep	Commonly occur at the end of respiratory events, but also occur spontaneously or as a result of other stimuli (eg, leg movements)	20 per h of sleep

According to AASM scoring manual. REM=rapid eye movement. OSA=obstructive sleep apnoea. EEG=electroencephalogram. EMG=XXXX

Table 2

Adult respiratory event scoring

	Definition
Apnoea	Airflow reduced to less than 10% of baseline for more than 10 s; obstructive if respiratory effort is present, central if no respiratory effort is present
Hypopnoea (recommended definition)	Airflow reduced to less than 30% of baseline for more than 10 s, in association with a 4% oxygen desaturation
Hypopnoea (alternative definition)	Airflow reduced to less than 50% of baseline for more than 10 s, in association with a 3% oxygen desaturation or an arousal from sleep
Respiratory effort related arousal	Sequence of breaths lasting more than 10 s that do not meet the standard hypopnoea definition but that are characterised by high upper-airway resistance (snoring and flattened inspiratory nasal pressure signal) and that terminate in arousal from sleep

According to AASM scoring manual.