A critical review of the treatment options available for obstructive sleep apnoea: an overview of the current literature available on treatment methods for obstructive sleep apnoea and future research directions

Alessandra J. Booth¹,²*, Yasmina Djavadkhani³ and Nathaniel S. Marshall¹,³

¹NHMRC Centre for Research Excellence NeuroSleep, the Centre for Translational Sleep and Circadian Neurobiology, the Woolcock Institute for Medical Research, University of Sydney, 431 Glebe Point Rd, Glebe, Sydney NSW 2037, Australia
²Clinical Sciences Programme, University of Exeter, Heavitree Rd, Exeter, Devon EX1 2LU, England
³Sydney Nursing School, University of Sydney, 88 Mallett St, Camperdown, Sydney NSW 2050, Australia

*Corresponding author: Email: ajb263@icloud.com

Obstructive sleep apnoea (OSA) is a leading yet often undiagnosed cause of daytime sleepiness. It affects between 3 and 7% of the adult population, and the prevalence is expected to increase due to the obesity epidemic and ageing population. OSA is a sleep-related breathing disorder in which the airway completely (apnoea) or partly closes (hypopnea) during sleep at the end of expiration. This can lead to decreases in blood oxygen saturation and sleep fragmentation. Those who suffer with OSA are often unaware of their symptoms. Severe, untreated OSA can have serious implications such as an increased risk of cardiovascular disease, motor vehicle accidents, poor neurocognitive performance and increased mortality. Many patients are prescribed continuous positive airway pressure (CPAP) as a treatment, but compliance with CPAP is often low. We briefly review the diagnosis and prognosis for obstructive sleep apnoea. But the main focus of our review is the critical evaluation of the numerous treatment strategies available for sleep apnoea as a multi-comorbid and multi-factorial condition. We also highlight areas that need further research.

Key words: pharmacotherapy, sleep-disordered breathing, cardiovascular diseases, critical, surgery, mandibular advancement splints

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Introduction

Obstructive sleep apnoea (OSA) is a condition of periodic and recurrent closure of the upper airway at the end of exhalation during sleep (Guilleminault, Tilkian and Dement, 1976). This airway closure can lead to a drop in oxygen saturation levels and fluctuations in blood pressure and heart rate. Patients can experience daytime sleepiness due to fragmented sleep and disturbances in normal sleep architecture.

Clinically, patients often present with snoring and daytime sleepiness. The gold standard diagnostic method for OSA is full overnight polysomnography (PSG) carried out in a sleep laboratory. PSG combines a range of measurements such as heart rate, blood oxygen saturation and EEG-based sleep staging. Other simplified diagnostic techniques using fewer overnight channels do exist, but they often provide less information for differential diagnoses such as REM Behaviour Disorder, Periodic Limb Movement Disorder or Central Sleep
Apnoea which may require a full PSG (Schlosshan and Elliott, 2004). A diagnosis of obstructive sleep apnoea syndrome (OSAS) requires significant daytime sleepiness along with an abnormal apnoea–hypopnoea index (AHI > 5 events per hour of sleep), whereas a diagnosis of OSA only requires an AHI > 5 (AASM, 2001). There may also be a contribution from the potential sleepiness inducing effects of hypoxia and particularly hypercapnia (Zhang et al., 2013; Wang et al., 2014a; Wang, Yee and Rowsell, 2014b).

Daytime sleepiness is often clinically measured using the Epworth Sleepiness Scale (ESS), a numerical questionnaire that asks patients to choose how likely they are to doze while performing different activities. An ESS score of 10 or more (on a scale of 0–24) is suggestive of pathologic somnolence (Johns, 1991). Although intuitive, very severe OSA is not always accompanied by severe daytime sleepiness. Some patients seem quite resistant to the daytime effects of poor sleep and may be very high-functioning individuals despite severe OSA. In addition, daytime sleepiness may have many different causes. This makes daytime sleepiness, as a symptom, neither sensitive nor specific to sleep apnoea (Gottlieb et al., 1999).

The severity of OSA is determined by the numbers of 10 second or greater cessations of breathing per hour (apnoeas) and reductions in airflow per hour (hypopnoeas). An apnoea is a complete closure of the upper airway which can vary from seconds to minutes. A hypopnoea is currently defined as being at least a 30% reduction in airflow combined with a 3% arterial oxygen desaturation levels, or an arousal from sleep (Berry et al., 2012). These combined to form the apnoea–hypopnoea index of a patient. AHI is calculated by dividing the total number of events by the hours of sleep (AASM, 1999; Table 1).

### Prognosis

Patients with untreated OSA have 2.5 times the risk of having an accident while driving (Tregear et al., 2009). The daytime sleepiness can cause them to have an increased reaction time and fall asleep at the wheel, injuring both themselves and others. The poor quality of sleep associated with sleep apnoea might also be the cause of the high rates of depression (Mccall, Harding and O’Donovan, 2006), impaired quality of life, anxiety and poor performance at work seen in patients with OSA. Untreated OSA is also linked to an increase in cardiovascular disease risk (Marin et al., 2005; Chami et al., 2011) and with hypertension (Peppard et al., 2000b), insulin resistance (Aurora and Punjabi, 2013), hyperlipidaemia (Phillips et al., 2011) and metabolic syndrome (Bonsignore et al., 2012). Those with OSA often have co-morbid cardiovascular diseases and are at a six-fold higher risk of having a stroke (Redline et al., 2010) as well as a three- to four-fold higher mortality risk (Young et al., 2008; Punjabi et al., 2009). The most recent longitudinal studies have indicated that some of the excess mortality may come from cancer-related deaths (Nieto et al., 2012; Campos-Rodriguez et al., 2013; Marshall et al., 2014).

### Treatment strategies available for OSA

#### Non-implantable medical devices

**Continuous positive airway pressure**

Continuous positive airway pressure (CPAP) (Sullivan et al., 1981) is the gold standard treatment for OSA. CPAP masks are worn throughout the night and provide a constant pressure to pneumatically splint open the collapsing upper airway open during periods of muscle relaxation (Giles et al., 2006). The pressure required to prevent apnoea varies between individuals and is determined by a personalized overnight titration procedure. This involves increasing CPAP pressure until breathing is normalized in all stages of sleep. Patients with OSA who comply with CPAP treatment have reduced blood pressure (Martinez-Garcia et al., 2013), arterial stiffness (Kartali et al., 2014) and have a lower risk of having a cardiovascular event compared with those with untreated moderate–severe OSA (Marin et al., 2005). While CPAP is a highly efficacious treatment when used correctly, many patients struggle to adapt to it and non-adherence rates are probably at least 50% (Weaver and Grunstein, 2008). Some patients report finding the mask uncomfortable, too invasive or experience claustrophobia (Chasens et al., 2005). Newer CPAP machines that vary the pressure overnight in an effort to increase patient comfort do not increase compliance (Ayas et al., 2004; Bakker and Marshall, 2011). In addition, even in quite sleepy patients with mild OSA, CPAP is not very effective in treating daytime sleepiness (Marshall et al., 2006) and does not improve neurocognitive outcomes in a large proportion of patients, even those with moderate–severe OSA and high compliance (Antic et al., 2011). Despite this, it remains the gold standard treatment for sleepy patients with moderate–severe OSA (Giles et al., 2006).

**Mandibular advancement splints**

The mandibular advancement splint (MAS) is another treatment modality for OSA. It is similar to a mouthguard that is sure to pneumatically splint open the collapsing upper airway. This involves increasing CPAP pressure until breathing is normalized in all stages of sleep. Patients with OSA who comply with CPAP treatment have reduced blood pressure (Marin et al., 2005; Chami et al., 2011) and with hypertension (Peppard et al., 2000b), insulin resistance (Aurora and Punjabi, 2013), hyperlipidaemia (Phillips et al., 2011) and metabolic syndrome (Bonsignore et al., 2012). Those with OSA often have co-morbid cardiovascular diseases and are at a six-fold higher risk of having a stroke (Redline et al., 2010) as well as a three- to four-fold higher mortality risk (Young et al., 2008; Punjabi et al., 2009). The most recent longitudinal studies have indicated that some of the excess mortality may come from cancer-related deaths (Nieto et al., 2012; Campos-Rodriguez et al., 2013; Marshall et al., 2014).

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with mild-to-moderate OSA or for patients with severe OSA who cannot tolerate CPAP (Kushida et al., 2006). MAS has been shown to be effective in reducing AHI by 14 and ESS by just <2 points in a randomized controlled trial (RCT) lasting 4 weeks (Petri et al., 2008). Short-term, RCTs have shown that patients comply with MAS therapy better than CPAP and that patients generally report preferring MAS (Gagnadoux et al., 2009; Phillips et al., 2013). Observational long-term compliance focused studies have suggested that ~64% of patients continue to use MAS regularly (Almeida et al., 2005). Unfortunately, some patients experience MAS-associated side effects such as migration of the lower dentition (Marklund et al., 2001; Hammond et al., 2007) and dry mouth (Fritsch et al., 2001). Patients who comply with MAS have experienced improvements in vascular function (Itzhaki et al., 2007; Trzepizur et al., 2009), blood pressure (Gotsopoulos et al., 2004; Phillips et al., 2013), daytime sleepiness (Gindre et al., 2008) and an increased quality of life (Phillips et al., 2013). Clinical prediction of which patients will benefit from MAS is currently an open line of research (Sutherland et al., 2014), but it is currently used for patients with mild-to-moderate OSA and those who cannot tolerate CPAP (Marklund, Verbraecken and Randerath, 2012).

Surgery

There are a large and increasing number of surgical procedures aimed at directly reducing sleep apnoea severity. Maxillomandibular Advancement (MMA) is probably the most efficacious but least suitable for general use, and uvulopalatopharyngoplasty (UPPP) is one of the oldest, most widely studied and used procedures.

Maxillomandibular advancement

MMA involves surgically repositioning both the upper and lower jaws forward to correct an abnormally small upper airway space caused by a small bony enclosure. By bringing both the upper and lower jaws forward the upper airways are enlarged, thus reducing the likelihood of upper airway collapse (Varghese et al., 2012). MMA is thought to be the most effective surgical treatment for OSA but is often used after other options have been exhausted due to the long recovery time and potential risks of the surgery. MMA is only effective in carefully selected patients with a particular facial phenotype (Aurora et al., 2010) and those without significant comorbidities that may impact surgical risk.

Uvulopalatopharyngoplasty

This procedure is the most common surgery aimed at alleviating OSA and involves removing excess tissue at the back of the throat such as the uvula to create a wider airway (Sundaram, Lim and Lasserson Toby, 2005). This approach has been heavily criticized in recent years as it has marginal efficacy in many cases (Elshaug et al., 2008). The procedure may suffer from large variations both in the hands of different surgeons but also in its efficacy in different patients. For this reason, much like MMA, it should be used sparingly in carefully selected patients (Mackay, Jefferson and Marshall, 2013).

Weight loss

Weight loss is an effective treatment for overweight and obese patients with OSA. This is both because of a reduction in the apnoea–hypnoea index and also because of beneficial effects on other associated cardiometabolic risk factors. In the community-based Wisconsin Sleep Cohort, a 10% decrease in weight has been shown to be associated with a 26% reduction in AHI (Peppard et al., 2000a). Although weight loss reduces OSA severity, it may take a relatively long time to achieve and may not cure OSA. Therefore, weight loss is considered an adjunctive therapy. Weight loss therapy via diet, pharmacotherapy and surgery is increasingly being researched for OSA and may eventually come to replace or join CPAP as the first-line therapy in overweight-obese patients. Indeed in a recent RCT, weight loss alone caused greater improvements in cardiometabolic risk factors than CPAP did (Chirinos et al., 2014).

Weight loss in OSA patients has also been rigorously tested via dietary interventions (Foster et al., 2009; Tuomilehto et al., 2009). It is recommended that patients with OSA who are overweight begin a weight reduction program. Weight gain around the neck is thought to narrow the upper airways due to a build-up of fat around the upper airways. But weight gain inside the abdomen may also play an important physical and indirect cause of OSA. Weight loss may help to reduce a patient’s AHI (Johansson et al., 2009) and also reduce the significant cardiovascular risk that accompanies sleep apnoea. However, as with weight loss programs in all people who are overweight, weight loss in patients with sleep apnoea is not always successful or sustainable. In addition, some patients may lose weight but not experience any improvements in their sleep apnoea.

Bariatric surgery

There are numerous bariatric surgery approaches that can be used to help reduce a patient’s AHI through weight loss. Laparoscopic adjustable gastric band (LAGB) surgery involves placing a device around the stomach that constricts the size of the stomach pouch, therefore reducing the amount of food consumed in one sitting. In a recent trial, OSA patients lost on average 27.8 kg at 2 years with a concomitant reduction in OSA severity after LAGB surgery (Dixon et al., 2012). Compared with conventional weight loss patients (who lost 5.1 kg), LAGB patients lost more weight but their sleep apnoea was not reduced by a greater amount than diet alone (25.5 events and hour vs. 14.0 events, \( p = 0.18 \)). This was caused by an under-powering of the trial caused by an unexpected decline in the effectiveness of weight loss for OSA after patients lost over 10–15 kg. Once patients lost around this amount of weight, their sleep apnoea stopped improving.

Pharmacotherapy for weight loss targeted at sleep apnoea

Sibutramine/Meridia

Sibutramine (marketed in UK as Meridia) has been shown to lower a patient’s respiratory disturbance index during the night as well as ESS score via its weight loss effects (Yee et al., 2013; Biederman et al., 2007). By decreasing weight, sibutramine may also decrease OSA severity. However, the long-term cardiovascular safety of sibutramine is currently under investigation.
2007). However, weight loss was only modest and in 2010 the FDA removed Sibutramine from the market as a high number of cardiovascular events were observed in patients taking the drug (Carlfman, Morrissey and Drazen, 2010; FDA, 2010).

**Orlistat/Xenical**

Orlistat (marketed in UK as Xenical in the higher dose prescriptive form and as Alli in the over-the-counter lower dose form) works by inhibiting gastric and pancreatic lipases and thus reducing dietary fat absorption. It blocks around 30% of fat from being absorbed and should be taken within an hour of eating (Boulghassoul-Pietrzykowska, Franceschelli and Still, 2013). Patients who had Orlistat in randomized clinical trials lost 2.7 kg more than those on the placebo medication (Rucker et al., 2007). The only study we found that looked specifically at the use of Orlistat in patients with OSA was a prospective case series. The use of Orlistat was found to benefit weight loss; however, AHI was not measured before and after the Orlistat trial so it is uncertain whether the weight loss was accompanied by a reduction in AHI or what the true placebo-adjusted weight loss effect might be for OSA patients (Svendsen and Tonstad, 2011).

**Lorcaserin/Belviq**

Lorcaserin marketed as Belviq is indicated to be used in conjunction with a reduced calorie diet and exercise program for chronic weight management. The drug works by activating serotonin receptors in the brain which decreases hunger levels (Halford et al., 2007). In a recent trial, overweight patients with type 2 diabetes mellitus who received a diet and exercise program along with lorcaserin lost 5.8 kg compared with 2.2 kg in the placebo group at 1 year (O’Neil et al., 2012). Caution should be taken when prescribing lorcaserin to patients taking serotonergic drugs due to the risk of serotonin syndrome. There has yet to be any sleep apnoea-specific clinical trials with lorcaserin, so it is uncertain how effective it is at reducing sleep apnoea severity.

**Phentermine and topiramate/Qsymia**

A randomized clinical trial study looking at obese patients who were unable to comply with CPAP prescribed either phentermine with extended release topiramate (marketed as Qsymia) or placebo in conjunction with a weight loss program (recommended indication for overweight patients). Participants allocated to taking phentermine and topiramate lost 10.2% of their body weight compared with the placebo group who lost on average 4.3% (Winslow et al., 2012). The weight loss was also associated with a lowered AHI.

**Pharmacotherapy for OSA that directly treats sleep apnoea rather than through weight loss**

Apart from drug therapy for weight loss, there are also drugs that target the daytime sleepiness or that directly target airway stability.

**Pharmacotherapy for daytime sleepiness**

Wake-promoting drugs can be prescribed to treat the daytime sleepiness associated with OSA rather than the OSA itself; they are a group of drugs that stimulant the central nervous system to promote wakefulness.

Some patients who adhere to CPAP can still experience daytime sleepiness, and the FDA lists an on-label indication for modafinil for this purpose (FDA, 2007). Modafinil, marketed as Provigil (UK/USA), has been shown to increase patient’s daily functioning as assessed by improvements in the Functional Outcomes of Sleep Questionnaire (FOSQ) (Weaver, Chasens and Arora, 2009), it has also been shown to improve a patient’s ability to engage in everyday activities. However, as wake-promoting drugs do not prevent apnoeas, patients who use solely wake promoters to manage their OSA will probably still experience the long-term complications associated with the disease (although this has not been studied yet). Modafinil may also be of effective symptomatic benefit in patients with mild-to-moderate sleep apnoea who do not use mechanical treatment, but this is an off-label indication and has not been tested for a period of longer than 2 weeks (Chapman et al., 2013). The European Medicines Agency recently revoked the OSA indication for modafinil due to concerns about its risk/benefit ratio. The EMA also expressed concerns about the extent of off label use of Modafinil and its abuse potential (EMA, 2011).

**Drugs to treat sleep apnoea airway stability**

Drugs that specifically target the upper airway to effectively improve breathing throughout the night and reduce the severity of apnoeas could have therapeutic benefits for OSA. Patients may be more compliant with treatment if it involves taking a tablet as opposed to using a CPAP machine. Drugs that aim to improve both airway tone and ventilatory drive have been tested in randomized clinical trials (Hedner, Grote and Zou, 2008), but none so far have reliably demonstrated a clinically relevant level of efficacy (Mason, Welsh and Smith, 2013).

**Lifestyle and behavioural modification**

Lifestyle modification is often recommended for those diagnosed with OSA, but there are few studies conducted to quantify the effectiveness of suggestions such as reduction alcohol and positional therapy.

**Reducing alcohol consumption**

As alcohol is a sedative, it causes relaxation of the muscles. Increased relaxation of the upper airway during sleep increases the chances of the airway collapsing even in asymptomatic patients (Mitler et al., 1988). It is therefore recommended that those diagnosed with sleep apnoea reduce their alcohol consumption both for its effect on upper airway stability but also because of its high caloric content. However, the effect of alcohol consumption on AHI in patients with OSA has not been thoroughly investigated.

**Sleep hygiene and positional therapy**

Medical Practitioners may offer advice on improving sleep hygiene such as waking up and going to sleep at the same time.
time each day. It is also recommended that patients avoid exposure to light before bed and get adequate light stimulation in the morning. In patients with OSA, apnoeas tend to occur when the patient is lying on their back (known as the supine position); therefore, it is recommended that patients try to sleep on their side, this can be enforced by the patient attaching a ball into the back of their pyjama top. Current guidelines recommend positional therapy for those with mild positional OSA who cannot tolerate CPAP as it can be a cheap and effective solution for these patients (Oksenberg and Gadoth, 2014); however, it is less effective than CPAP in reducing AHI (Ha, Hirai and Tsoi, 2014). Although lifestyle modification if often recommended for patients with OSA, there is very little evidence quantifying its effectiveness (Shneerson and Wright, 2001).

Conclusion

With the prevalence of OSA increasing due to an ageing population and the obesity epidemic (Peppard et al., 2013), there is a growing need for better treatment options for OSA.

Patients with OSA are often intolerant to the gold standard treatment of CPAP and also the second-line therapy, MAS. Apart from upper airway surgery and weight loss measures, there are few alternative options. Patients with untreated severe OSA are at risk of lowered quality of life as well as the significant co-morbid health issues associated with OSA. In addition to this, the daytime sleepiness associated with sleep apnoea can also lead to work and traffic-related accidents.

With so many patients unable to use CPAP, there has recently been a change in treatment options available. Newer studies focusing on phenotyping patients will allow clinicians to recommend the best suitable treatment for that specific patient. For example, encouraging patients with mild sleep apnoea to engage with a weight loss program to reduce their likelihood of progressing to severe OSA (Tuomilehto et al., 2013).

Future research will investigate a multimodality care strategy for those with OSA to treat night-time and daytime symptoms separately and addressing the multi-morbidities that are often seen with OSA. Pharmaceutical products have thus far been ineffective treatments to directly reduce OSA but because of their potential to be more easily adhered to by patients and their ease of translation into routine practice pharmaceuticals remain an open avenue for research (e.g. clinical trial registration number ACTRN12614000364673).

Further investigation should be done into finding strategies to help overweight patients with OSA to lose weight and in determining the effectiveness of combining different treatment options for OSA in one patient.

Author biography

A.J.B. undertook a research placement at The Woolcock Institute of Medical Research in Sydney, Australia investigating obstructive sleep apnoea in 2013-14. She is graduating in June 2015 with a B.Sc (Hons) in Medical Science from Exeter Medical School. She has an interest in clinical trials and sleep medicine.

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