Review Article

Treatment of obstructive sleep apnoea

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Obstructive sleep apnoea (OSA) is a prevalent disorder with significant co-morbidities. Presently only rarely, treatments for obstructive sleep apnoea are curative. More typically, this is a disease that requires lifelong intervention and commitment from both the patients and healthcare providers. In light of the commitments, there is no uniform approach to treating sleep apnoea. Rather, approach to treatment of OSA should be governed by disease severity, symptoms and health risk and by which approach will work best for in a specific patient. It is equally important to identify and treat contributors to obstructive sleep apnoea severity, including obesity and endocrine disorders. In this sense, treating the patient with obstructive sleep apnoea requires a long-term partnership between patient and sleep medicine healthcare providers. With a strong partnership, obstructive sleep apnoea may be effectively treated in growing numbers of patients.

Key words CPAP - obesity - OSA - sleepiness - treatment

Obstructive sleep apnoea (OSA) impacts negatively the health and well being of tens of millions of individuals worldwide. This disorder is an independent risk factor for hypertension, heart failure, myocardial infarction, stroke and arrhythmias, where severity of sleep apnoea typically predicts risk. OSA may also impair cognitive function, mood, diabetic control, and potentially liver and renal function. Unfortunately, OSA is frequently a challenging chronic disorder for which the most effective therapies require considerable effort and commitment from the patient. Due to significant health consequences of untreated sleep apnoea, like quality of life and the long-term commitment required by the patient, an individualized and flexible treatment plan must be developed based upon the disease severity, the individual, specific treatment goals, the overall health risk for sleep apnoea morbidities, and the likelihood of its success. This, in turn, requires extensive communication within a strong collaboration between physician and patient to develop the most effective individual treatment plan. The first two steps in managing an individual patient with OSA are to decide what to treat and then how to treat. Close collaborative follow up is required to determine how effectively the treatment plan is working. Large-scale studies focusing on individuals with mild to moderate disease can provide the much needed insight into how best to manage the majority of individuals with mild-moderate OSA.

Deciding what to treat

The treatment goal should be to normalize the apnoea hypopnoea index (AHI), but normalizing all levels of AHI in all subsets of patients may not result

in improved health outcomes. Moreover, because the treatment requires a substantial effort on the patient's part, it is of utmost importance to decide first exactly what should be treated.

AHI: In considering the AHI, earlier studies strongly support treating severe obstructive sleep apnoea (AHI >30 events/h)[1-8]. In this subset of patients, treating OSA effectively has been shown to improve both subjective and objective sleepiness[9,10], oxygenation[3,8], some aspects of cognitive function[3,10-12], hypertension[13], significant cardiovascular events and mortality, mood and quality of life[3,14]. Recent studies show extremely high independent odds ratios for cardiovascular mortality in OSA[1,2], where treating OSA effectively dramatically negates the morbidity and mortality risks associated with OSA[1]. Thus, in all patients with AHIs of 30/h or higher, there is substantial evidence from carefully designed randomized controlled trials to support the importance of treating the AHI in severe OSA. However, this group represents 15-20 per cent of all individuals with obstructive sleep apnoea. The vast majority of patients must be examined in greater depth to approximate how significantly OSA might impact on health or quality of life. The Table summarizes components of the treatment decision process to provide individualized assessment of the risks and benefits of treating mild to moderate OSA.

Table. Issues to address to optimize obstructive sleep apnoea therapy

- *Apnoea/hypopnoea index*: Does the patient have severe OSA (>30 apnoeas/hypopnoesa/h?
- *Sleepiness, fatigue, mood and cognitive function*: Are there other causes of sleepiness/fatigue in the patient? Does the sleepiness or fatigue impose risk (driving or work related) or impact negatively of the individual's quality of life?
- *Obesity and overall health status*: Does obesity contribute to the severity of OSA in this individual? If so, what aspects should be addressed: caloric intake, nutritional content and/or activity level/exercise?
- *Underlying endocrine disorders*: Does the clinical history and physical examination suggest hypothyroidism, Cushing's syndrome or acromegaly as a potential contributor to OSA severity?
- *Use of medications that may worsen sleep disordered breathing*: Does the patient use alcohol, sedatives, muscle relaxants, narcotics or testosterone supplementation?
- *Associated disorders*: Cardiovascular - Are there additional cardiovascular risk factors in this individual which represent the highest risk and the most important to target first? Hyperglycaemic control- Does the patient have diabetes or borderline diabetes?

Sleepiness/fatigue: Sleepiness and fatigue are, perhaps, the most common presenting symptoms or signs in OSA[15]. One of the challenges with treating OSA sleepiness is that sleepiness in the general population is high (>15%) and thus, numerous aetiologies for sleepiness/fatigue may be present in a given individual with OSA[16]. A thorough sleep history and physical exam is essential to detect other fixable sources of sleepiness/fatigue to exclude insufficient sleep time, poor sleep hygiene, other primary sleep disorders, medication, illness and conditions. When other causes have been addressed, it is reasonable to treat any individual with sleepiness for OSA, including mild and moderate. A recent meta-analysis examined the effects of continuous positive airway pressure (CPAP) on mild-moderate OSA defined with an AHI between 5 and 30/h[17]. Seven controlled studies qualified for this analysis. Subjective sleepiness was significantly reduced with treating mild-moderate OSA. In contrast, the effects on objective measures, the multiple sleep latency test and the maintenance of wakefulness test were not significantly improved with effectively treating OSA[17]. One of the major health risks of sleepiness/fatigue is drowsy driving related motor vehicle accidents. Mild sleep apnoea (AHI 6-15/h) increases the risk of motor vehicle accidents with an odds ratio 2.6 with the 95 per cent confidence interval between 1.7-3.9 [18]. Even more important, the rate of personal injury is higher for all motor vehicle crashes where the at fault driver has mild OSA[19]. CPAP reduces motor vehicle crash rates in individuals with an AHI >10/h[19]. Whether CPAP therapy reduces motor vehicle accidents in individuals with mild sleep apnoea remains controversial[20], but because treating sleep apnoea improves sleepiness, the decision to treat mild sleep apnoea should be based on sleepiness, at least for now. Thus, individuals with OSA and sleepiness, drowsiness or inattentiveness while driving should first be carefully assessed for all potential causes of sleepiness, then treated for reversible non-OSA causes of sleepiness and reassessed. If sleepiness persists, even individuals with mild or moderate OSA should be treated at least short term to determine whether treated OSA lessens drowsiness and drowsy or inattentive driving. It is important to understand that these assessments of drowsiness, fatigue and motor vehicle crash risk are not exact. So that if there is any doubt, treatment should be tried. At the same time, a number of patients will have residual sleepiness despite therapy and this, too, must be further addressed.

Whether mild or moderate OSA contributes to neurobehavioural impairments, beyond sleepiness and

vigilance, remains controversial, but there are several studies supporting a link. Chervin's group has shown that cognitive impairment is evident in children with mild OSA[21]. That treating OSA in children improves cognitive performance further supports this concept[22]. Similarly, treating OSA in individuals with Alzheimer's disease also improves cognitive performance[23]. Variance in cognitive performance in adults without Alzheimer's is sufficiently high and to date studies of these groups of OSA subjects have not been adequately powered to determine treatment effect. There are several studies in adults to suggest that oxyhaemoglobin desaturation time may be an important variable in determining risk for cognitive dysfunction from OSA[24,25].

Obesity: Obesity is the major risk factor for OSA and this condition is a major health crisis in many developed countries[26]. Addressing obesity should be a priority for every sleep medicine health care provider, and developing an effective realistic weight loss plan for overweight and obese patients with OSA should be a cornerstone in every treatment plan. Obesity is defined by a body mass index > 30 kg/m^2 and overweight is defined as a body mass index 25-30 kg/m^2. The prevalence and severity of OSA rise in parallel with the body mass index[27]. An increase of body weight by 10 per cent over time increases the AHI, on average, by 30 per cent[28]. On the other side, a 10-15 per cent reduction in body weight can reduce the AHI by 50 per cent[29,30]. With too few patients effectively treated to normalize the AHI, weight loss should be considered as an important complementary treatment for OSA. Thus, every effort to lower weight and reduce the AHI for the untreated hours of disease should be made, particularly because this effort is likely to lessen the severity of many OSA co-morbidities. The frontline weight management programme should include current diet assessment, history of previously used weight loss strategies, education about target daily caloric intake, and exercise capacity and expected caloric loss from specific exercise endeavours. For patients who have obesity co-morbidities, including OSA, and have failed dietary behavioural management programmes, bariatric surgery may be considered. These procedures include gastric restriction with or without intestinal bypass. In general the surgeries result in an overall 60 per cent loss of excess body weight with substantial reductions in the AHI in most patients and a resolution of OSA in >80 per cent of patients over time[31]. In summary, in all overweight and obese patients with OSA, the importance of weight loss should be emphasized and discussed carefully upon each patient visit, and every patient should understand how clinically important weight loss is to reduce OSA and its co-morbidities. Finally, it is critical to convey the importance of a healthy diet for all family members, particularly the children, as it is far easier to maintain weight than to lose weight.

Endocrine disorders: There are several endocrine conditions that may present as OSA and at the same time may contribute to OSA and its symptomatology. Thus, all initial evaluations of patients should include consideration of whether the patient has clinical signs and symptoms of hypothyroidism, acromegaly or Cushing's syndrome. Of these conditions, hypothyroidism is the most common (2% of adults), and its presentation can have considerable overlap with OSA symptoms: fatigue, weight gain, myalgias, memory loss, decreased libido, and depressed mood. Signs and symptoms that may also be present in hypothyroidism but are not expected in uncomplicated OSA include hoarseness, facial swelling, weakness, coarse dry hair or skin, hair loss, cold intolerance, non-pitting oedema, low pulse pressure and hyporeflexia with delayed relaxation. In the sleep clinic the prevalence of subclinical hypothyroidism is approximately 11 per cent[32-34]. As a common occurrence with OSA symptomatology overlap there remains a controversy whether all patients should be screened for hypothyroidism. Clearly if any of the more specific hypothyroidism signs or symptoms are present then ordering a blood thyroid stimulating hormone and free thyroxine 4 (TSH and FT4) are warranted. It is important to understand that subclinical hypothyroidism can be identified by blood work with a normal physical exam[35]. Treating clinical hypothyroidism can result in marked improvements in the AHI, particularly if the TSH is very high[35-39], and treating subclinical hypothyroidism appears to improve sleepiness more so than AHI[40]. One important consideration in treating newly diagnosed OSA and hypothyroidism may be the timing of therapies. It is widely accepted that rapid replacement of thyroid hormone can result in cardiovascular stress including ischaemia in untreated OSA patients[36]. It is therefore recommended to treat OSA first with CPAP and to begin thyroid replacement therapy only after CPAP is effectively alleviating apnoeic events[36]. When the patient is euthyroid, careful reassessment of OSA is needed over the next year, as the AHI may fall and the optimal pressure may change as upper airway soft tissues recede.

Acromegaly is defined as excessive growth hormone. OSA is extremely common in patients with acromegaly (>50%)[41,42], but this is an extremely uncommon clinical condition (1 in 25,000 individuals, or 0.0%). Patients with acromegaly may have both central and obstructive sleep-disordered breathing events. Grunstein and colleagues[41] discovered that patients with central sleep apnoea events have higher growth hormone levels and insulin-like growth factor-1 levels, suggesting a link between growth hormone and sleep-state dependent respiratory control. Treatment with a long-acting somatostatin analogue, octreotide improves the AHI whether of not growth hormone levels normalize.

Cushing's disease is the least common of the endocrine disorders that may influence OSA[43]. The prevalence of Cushing's syndrome is 1 in 500,000[44]. Like hypothyroidism there is some overlap in symptomatolgy and signs. Features suggestive of Cushing's syndrome include a fat pad or palpable hump on the mid upper back, facial flushing, thin fragile skin, slowly healing skin, acne in older individuals, bone loss, and truncal purple or pink striae. It is unclear whether treatment of Cushing's improves sleep apnoea, but because treatment is associated with loss of head and neck soft tissue, it is likely that OSA would improve with treatment of Cushing's.

Medications that may worsen OSA: As the lists of available nonprescription and prescription medications rapidly expand, so does the list of medications that can worsen OSA. Alcohol, a frequently self-prescribed mind altering substance has been shown to clearly increase AHI[45-50]. Patients should be diagnosed and treated for OSA on their present alcohol consumption. However, alcohol use should be discouraged and when alcohol ingestion has changed significantly, the OSA severity and treatment should be reassessed. Numerous sedating medications worsen OSA and/or cause central sleep apnoea, particularly clonazepam, quetiapine, methadone, lorazepam, diazepam[51-55]. Testosterone supplementation or replacement therapy is also associated with increasing the AHI and increasing the severity of oxyhaemoglobin desaturations[56-58]. One of the newer medications in rheumatoid arthritis, infiximab, a chimeric monoclonal antibody to TNF-α, has been suggested to worsen OSA, in a case study[59]. Numerous medications promote weight gain, but many of these medications are used to treat serious medical conditions and thus careful discussion with the patient's other physicians is essential to decide upon

whether any medication can be replaced. Because the majority of medications have not been assessed for effects on OSA, it is possible that recent medication changes in a given patient may contribute to worsening of symptoms. It is important to understand the rationale for each medication and to discuss with the physician who prescribed any medication that may worsen OSA, the need for the medication and whether there are alternative medications without effects on OSA. When the medication is clinically needed, a sleep study should be performed on the steady dose followed by reassessment of OSA treatment plans.

Disorders and medical conditions that may be worsened by OSA: There will be patients with mild to moderate OSA who do not have sleepiness, fatigue or cognitive impairments, and the question then comes-do any of these patients need treatment? Presently, this question is incompletely answered by clinical research, but snoring and mild OSA can increase blood pressure, and both conditions are associated with a 10-fold risk in carotid artery atherosclerosis[60]. Mild-moderate OSA is an independent risk factor for type II diabetes[61], and CPAP therapy can improve glycaemic control and insulin resistance[62-65]. Fibromyalgia is associated with OSA and there is a case report of marked improvement with treatment for OSA[66]. Further, carefully controlled, double-blinded clinical trials are needed to determine how aggressively to treat patients with mild-moderate OSA who have no neurobehavioural symptoms but have hypertension, atherosclerosis and/or diabetes.

Deciding how to treat OSA

In addition to addressing weight loss in overweight and obese patients and medications and illnesses that might exacerbate OSA in all patients, subsets of patients will have either severe OSA with or without symptoms or mild-moderate OSA with symptoms or disease interactions for which studies support the concept that lowering the AHI could improve outcomes. There are no widely accepted universally effective therapies for OSA. Treatments that have been proven effective to lower the AHI in subsets of patients include positive airway pressure (PAP) therapy, including continuous PAP (CPAP), positional therapy, oral appliances designed to advance the mandible, several upper airway surgical procedures, and medications.

Positive airway pressure therapy: Of all of the available treatment options, the one that requires the most effort from the patient, PAP, is the most effective therapy for OSA. PAP therapy, predominantly CPAP, has been

shown to reduce the AHI to <5 events/h in almost every patient. In patients with moderate-severe OSA CPAP improves subjective and objective sleepiness[67], cognitive performance[68-71], and cardiovascular outcomes including a moderate effect on hypertension[72], a small effect on ejection fraction in heart failure[73], a reduction in pulmonary hypertension[74-76], a lowering of the incidence of ventricular arrhythmias[77,78], myocardial infarction[1,79,80], cardiac death[1], and reduced need for either coronary bypass surgery or coronary artery stent placement[1,79,80]. Clearly as a therapy with all of these effects in individuals with severe OSA that costs <$700 in the first year and perhaps $200/yr thereafter CPAP is, not only a highly effective therapy, but a remarkably cost-effective treatment, as well. For patients with severe OSA with or without sleepiness, those with mild-moderate OSA with severe sleepiness, and those individuals with high cardiovascular risk, every effort must be made to (i) have the patient understand why CPAP is so important, and (ii) to make CPAP as comfortable, tolerable and used effectively as possible. The patient should understand that positive airway pressure therapy is not an easy therapy for most patients but physician and patient will work together to make the treatment as tolerable and successful as possible. There are several recent studies demonstrating techniques and strategies to improve adherence[81-83]. It is also important to understand that treatment does not end with the PAP prescription, but continued observation of the patient with reassessment of the success of each treatment goal, including weight loss, and continued monitoring of the objective compliance and effectiveness data.

Mandibular advancement devices: For severe obstructive sleep apnoea non positive airway pressure therapies should be considered only after every effort to make CPAP work has been exhausted. For mild-moderate OSA with minimal sleepiness and fatigue, oral appliances may be considered. The oral appliance options are described in excellent detail in another paper in this issue[84]. The mandibular advancement appliances are effective in subsets of patients; oral appliances are easier to use, and self-reported compliance is higher than CPAP compliance[85]. Patients with mild OSA and with a lateral AHI <5/h are more likely to benefit from either oral appliance or positional therapies[86-88].

Surgical options for treating OSA: The primary appeal for a surgical treatment for OSA is the potential to cure OSA. The downsides to surgery are, of course, the operative risk, pain and discomfort without certainty that the procedure will alleviate OSA sufficiently to

circumvent the need for CPAP therapy. The options and details of surgical therapies, typically done in a step-wise fashion from simpler to more involved procedures, and their success rates and complications are presented elsewhere in this issue[89]. In patients contemplating surgical options, it may be beneficial to have them try CPAP for several weeks to understand what is involved with PAP therapy and to understand if treated effectively how much of an impact on daytime cognitive function and sleepiness OSA treatment might have. For those individuals who do go through with the two-phase surgeries, culminating in maxillomandibular advancement, success defined as a reduction in the overall AHI by >50 per cent and an AHI <20 is observed overall in 64 per cent of subjects[90]. Thus, 36 per cent of patients may go through the multiple operations and still have significant OSA. Success defined as an AHI <5/h post-operatively occurs in <15 per cent of patients underging level I surgery only and in 40 per cent of patients undergoing both level I and II procedures[91]. Clearly all patients must understand both the benefits and the probability of success to make the best treatment decision.

Medical therapeutic trials for OSA: Overall, results have been disappointing for pharmacotherapeutic trials in OSA. There is great promise that OSA can be treated pharmacologically in that individuals with OSA are capable of maintaining an open upper airway and normal breathing while awake[88]. No matter what position most patients assume, apnoeas and hypopnoeas occur only during sleep and are rapidly and fully corrected upon arousal. Thus, a neurochemical alteration in respiratory control of the upper airway occurs in sleep. Animal studies suggest that at the level of the upper airway motoneurons two of the changes that likely contribute to pharyngeal collapse in sleep are reduced noradrenergic and nicotinic cholinergic tone and increased muscarinic cholinergic tone[92,93]. However, to date, clinical trials of noradrenergic and nicotinic agents have not been successful in reducing the AHI significantly in subjects with OSA[88]. It is possible that subsets of patients respond, but longer-term trials are needed. Serotonergic drugs have also been assessed for effectiveness in treating OSA. Here, too, sample sizes were too small to examine carefully. There may be subsets of individuals who do improve significantly on selective serotonin reuptake inhibitors[94]. Donepezil lowered the AHI from a mean of 20 to 10/h and lowered the time spent with hypoxaemia in sleep by 70 per cent in subjects with mild to moderate Alzheimer's and mild-moderate OSA[94]. There were parallel improvements in

cognition. Clearly, larger studies in patients with OSA and no cognitive impairment should now be performed assessing the effects across multiple doses and across several nights/dose.

Treating residual daytime sleepiness: As mentioned earlier not all sleepiness in OSA is directly related to OSA. Thus, it is imperative to identify and address all potentially reversible causes of sleepiness in each individual presenting with OSA and sleepiness or fatigue. Once CPAP therapy has been initiated, a next step is to determine whether PAP is effective in alleviating all sleep-disordered breathing and is worn for all sleep. Santamaria and colleagues[82] have published an excellent follow up treatment plan to ensure optimization of CPAP therapy, including treating insufficient sleep and other sleep disorders, depression, nasal symptoms, dryness, desensitization to PAP and verification of correct pressures and optimal mask. When all of these causes and conditions have been fully addressed and sleepiness persists, it is reasonable to use stimulant therapy to increase vigilance and alertness, but it is essential to understand and to convey to the patient that modafinil cannot substitute for CPAP or an oral appliance. A recent study examined the effect of modafinil after CPAP withdrawal on driving performance[95]. As expected driving performance after CPAP withdrawal deteriorated. However, modafinil did not rescue the impaired performance[95]. In regular CPAP users modafinil does improve objective and subjective sleepiness[96], and effects appear to endure[97]. Armodafinil, the R-enantiomer of modafinil, appears equally effective in improving residual sleepiness in CPAP-treated OSA and has a much longer half-life (10-15 h), yet does not appear to interfere with nighttime sleep[98]. Because of the increased cardiovascular risks in patients with OSA, use of amphetamine-based stimulants with a potential added risk for cardiovascular morbidities[99] should be discouraged. In summary, stimulant therapy has a place in treating select patients with refractory sleepiness who are being treated successfully for OSA but only after carefully addressing other causes and ensuring optimal use of PAP therapy.

Conclusions

OSA is a complicated disorder with significant morbidities affecting multiple organ systems. At the same time, for most individuals with OSA, this is a life-long illness that requires significant effort on the part of both the sleep medicine health care delivery team and the patient. Additionally, the treatment options and assessment of effectiveness are complicated, with outcomes rapidly updated. Consequently, specialized treatment centers will play important roles in ensuring excellent health care delivery for patients with OSA. Every patient must have a treatment plan designed specifically in consideration of that individual's underlying illnesses, OSA severity, and treatment targets. This treatment plan should be developed in collaboration with the patient as a realistic, achievable plan. The patient must be continually followed as the disease, its co-morbidities as well as our treatment options are rapidly evolving.

Acknowledgment

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