International Journal of Otorhinolaryngology and Head and Neck Surgery
Paramasivan VK et al. Int J Otorhinolaryngol Head Neck Surg. 2023 Dec;9(12):1011-1018
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937

DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20233594

Review Article

Medical management of obstructive sleep apnea: a review article

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Received: 20 July 2023
Accepted: 17 October 2023

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ABSTRACT

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of complete or partial obstruction of upper airway during sleep. Various pathophysiological phenotypes contributing for the repetitive events of apnea and hypopnea have been identified in the recent studies. Consequently, various new modalities of treatment are being introduced to be implemented either independently or in conjunction with the previously available treatment modalities. This article imparts a thorough knowledge of various modes of treatment available for the non-surgical treatment of OSA. Many studies conducted in the past had emphasized the importance and effectiveness of lots of non-surgical modes of treating OSA. Our article includes a concluding description of all those studies including those on CPAP and myofunctional therapy. Thorough knowledge of both i.e., the pathophysiological phenotypes and available modes of treatment is necessary for the successful treatment of obstructive sleep apnoea. Recent advances, both in terms of causative factors as well as corresponding treatment options, should be laid down in the form of management guidelines as a part of evidence-based medicine.

Keywords: OSA, Medical management, CPAP, Myofunctional therapy

INTRODUCTION

Obstructive sleep apnea (OSA) confers a substancial economic burden on the society, also due to low diagnosis and treatment rate.[1] It is the most common type of sleep-disordered breathing and is characterized by recurrent episodes of upper airway collapse during sleep.[2] It can leads to numerous cardiovascular and metabolic conditions including hypertension, coronary artery disease, stroke, heart failure, type 2 diabetes or nonalcoholic fatty liver disease (NAFLD), leading to substantial morbidity and mortality.[3] The aetiology of OSA is multifactorial, consisting of a complex interplay between anatomic and neuromuscular factors, causing upper airway collapsibility.[4] OSA is recognized to be a heterogeneous disorder with both anatomical (upper airway) and nonanatomical traits. Several components including the upper airway anatomy, effectiveness of the upper airway dilator muscles like the genioglossus, arousal threshold of the individual, and inherent stability of the respiratory control system determine the pathogenesis of OSA.[5] Risk factors for OSA includes male gender, obesity and a variety of craniofacial and oropharyngeal features such as a large neck circumference, retro- or micrognathia, nasal obstruction, enlarged tonsils/adenoids, macroglossia and low-lying soft palate.

Approach to treat sleep apnea depends on the specific type and severity of the OSA. Adult OSA treatment goal choices vary with age, symptoms, positive air pressure (PAP) history and OSA severity. Understanding patient-specific goals is the essential first step in the shared decision-making process when choosing surgical or nonsurgical treatments. Ultimately, goal-focused discussions ensure alignment of priorities and definitions of success between the patient and the provider.[6] Successful and holistic treatment of a patient with OSA

includes reversing all the debilitating symptoms faced by the patient, including the metabolic and oxidative stress. Moreover, recent evidence has shown significant discordance between the levels of AHI used to denote outcomes of therapy and real world clinical outcomes such as QOL, patient perception of disease, cardiovascular measures, disease burden and/or survival.[7] Once the diagnosis is established, the patient should be included in deciding an appropriate treatment strategy that may include positive airway pressure devices, oral appliances, behavioral treatments, surgery, and/or adjunctive treatments. OSA should be approached as a chronic disease requiring long-term, multidisciplinary management. For each treatment option, appropriate outcome measures and long-term follow-up are described.[8]

The medical treatments or approaches can typically improve OSA or resolve it. They aren't cures, but they can reduce apnea to the point where it stops happening or isn't severe enough to cause symptoms. Many treatments should be a part of your daily (or nightly) routine. That can ultimately reduce or even eliminate sleep apnea's effects on your life for as long as you use these treatments.

EDUCATION AND BEHAVIOR

The patient should be educated about the risk factors, natural history and consequences of OSA. Importantly, all patients should be warned about the increased risk of motor vehicle crashes associated with untreated OSA and the potential consequences of driving or operating other dangerous equipment while feeling sleepiness.[9] It was found that rate of motor vehicle crash increases 3 times in patients with untreated OSA as compared to general community.[10] Patients should also be counselled to avoid activities that requires vigilance and alertness if sleepy.

LIFESTYLE MODIFICATION

Lifestyle modifications is indicated for all the patients who have been diagnosed with OSA and a modifiable risk factor have been found in them. Patients who are overweight or obese should be encouraged to lose weight. Patients whose OSA improves or resolves after weight loss should strive to maintain their weight loss since weight gain has been associated with worsening or recurrence of OSA.[11] Obesity being an important risk factor, correlates well with severity of OSA. Waist circumference is considered as a better measure than BMI or neck circumference to predict OSA.

Counselling regarding ongoing diet modification and exercise, as well as referral to a nutritionist, may be beneficial. Nevertheless, longer-term follow-up of several randomized studies suggests that the initial improvement in AHI achieved through weight loss can persist for several years.[13] There is evidence from RCTs to suggest that diet-only, exercise-only, and combined diet and exercise interventions all attenuate OSA severity despite highly variable changes in weight.[14] These weight-independent effects of intervention on OSA severity are likely due to multifactorial mechanisms that may modulate upper airway stability, chemoreceptor sensitivity, visceral adiposity, neuroendocrine control, sleep quality, and other aspects of OSA pathophysiology, which are yet to be discovered.[15]

All patients should be advised that alcohol and certain common medications, such as opioids, may worsen their OSA. All patients with untreated OSA should avoid alcohol prior to sleep, because it can exacerbate OSA, worsen sleepiness, and promote weight gain. Issa et al suggested that increased tendency to develop obstructive apnoea after alcohol is the result of alcohol-induced oropharyngeal muscle hypotonia, while the increased duration of obstructive apnea is the result of alcohol-induced depression of arousal mechanisms.[16]

POSITIONAL THERAPY

Patients with positional OSA should change their sleep position accordingly, although this can be pragmatically challenging. Positional therapy, consisting of a method that keeps the patient in a non-supine position, is an effective secondary therapy or can be a supplement to primary therapies for OSA in patients who have a low AHI in the non-supine versus that in the supine position. Patients who normalize their AHI when they sleep in a non-supine position tend to have less severe OSA, to be less obese, and to be younger.[17] Several commercial devices are available that use vibratory feedback around the chest or neck to restrict supine sleep.[18]

Srijithesh et al found that CPAP has a greater effect on improving AHI compared with positional therapy in positional OSA, while positional therapy was better than inactive control for improving ESS and AHI.[19] Therefore, positional therapy should be considered as an important part of OSA treatment but not generally relied upon as the sole therapy.

NASAL ADHESIVE SPLINTS

These over-the-counter products improve breathing by making it easier for air to travel through your nose. Internal (NoZovent) and external (Breathe Right Strips) nasal dilators are among the few commercial products available for the treatment of OSA. Although nasal dilators have demonstrated improved nasal breathing, they have not shown improvement in OSA outcomes, with the exception of mild improvement in apnea index when internal nasal dilators were used.[20]

ORAL APPLIANCE THERAPY FOR OSA

Oral appliances can benefit carefully selected OSA patients who prefer not to use CPAP or have comprehensive surgeries. Oral appliances improve upper

airway patency during sleep by enlarging the upper airway or by decreasing upper airway collapsibility. Oral appliances can be categorized as tongue retaining devices and mandibular advancement devices (MADs), with the latter being more commonly used. MADs cover the upper and lower teeth and hold the mandible in a forward position with respect to the resting position and can be customizable or over-the-counter.[21] Mandibular advancement device (MAD) therapy has emerged over the last decade as an alternative therapy for OSAHS.[22] Randomised control trials have demonstrated a reduction of the apnoea/hypopnoea index (AHI) to some extent and an improvement of daytime sleepiness with oral appliance therapy.[23]

Although cephalometric evaluation is not always required for patients who will use an oral appliance, appropriately trained professionals should perform these examinations when they are deemed necessary.[22] Oral appliances are appropriate for use in patients with primary snoring who do not respond to or are not appropriate candidates for treatment with behavioral measures such as weight loss or sleep-position change.[22] Intolerance and improper use of the device are potential problems for patients using oral appliances, which require patient effort to use properly. Oral appliances may aggravate temporomandibular joint disease and may cause dental misalignment and discomfort that are unique to each device.[22]

PAP THERAPY

PAP stands for positive airway pressure. Continuous PAP (CPAP) is the most common form of PAP that is used for OSA treatment. PAP devices function as a pneumatic support that allows one to maintain upper airway patency by increasing the upper airway pressure above a 'critical' value (pressure value below which airways collapse).[24]

Nasal CPAP

Nasal continuous positive airway pressure is the treatment of choice for adults with obstructive sleep apnoea.[25] 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.[26] Continuous positive airway pressure also increases end-expiratory lung volume, which stabilises the upper airway through caudal traction.[27]

Continuous positive airway pressure therapy significantly improves subjective and objective measures of sleepiness in patients with OSA across a diverse range of populations.[28] Aloia et al reported that compliant use of CPAP at 3 months was associated with greater improvements in attention, psychomotor speed, executive functioning and nonverbal delayed recall.[29] Antonopoulos et al and Tregear et al in their meta-analytic studies demonstrated a significant protective effect of nCPAP on road traffic accidents in patients of OSA.[30,31]

Martinez-Garcia et al found that among patients with OSA and resistant hypertension, CPAP treatment for 12 weeks compared with control resulted in a decrease in 24-hour mean and diastolic blood pressure and an improvement in the nocturnal blood pressure pattern.[32] Shrihama et al showed that long term (24 months) use of CPAP in both good and poor adhere CPAP users, reduced both systolic and diastolic blood pressure.[33] They found a significant reduction in diastolic blood pressure among patients with good CPAP adherence during the 24-month follow-up period, when compared to the group with poor CPAP adherence. No significant association was found between CPAP adherence and weight loss. Long-term, good CPAP therapy adherence was associated with lower diastolic blood pressure without significant weight loss.[33] Ruzicka et al demonstrated that decrease in blood pressure by treatment with CPAP in patients with diabetes mellitus (DM), chronic kidney disease (CKD) and OSA indicates the contribution of OSA to severity of hypertension in this clinical scenario. Decrease in blood pressure in the absence of changes in sympathetic activity is suggestive of other mechanisms induced by OSA that plays a larger role in the maintenance of hypertension in these patients.[34] Logan et al observed that acute abolition of OSA during stage-2 sleep by CPAP reduces systolic BP and increases baro-reflex sensitivity.[35] Also they observed that CPAP therapy for 2 months was accompanied by reductions in nocturnal, daytime and 24-h systolic BP. These results suggest that in patients with refractory hypertension, treating co-existing OSA with CPAP may reduce both nocturnal and daytime BP.[35] Table given below reviewed the various studies regarding the effect of CPAP on blood pressure of OSA patients, when given and followed up for variable time interval.

Table 1: Review of studies regarding effect of CPAP on bloodpressure of OSA patients.

Name of study	Year of study	Sample size	Significant reduction in systolic blood pressure	Significant reduction in diastolic blood pressure	Duration of follow up
Martinez-Garcia et al	2013	194	-	+	12 weeks
Shrihama et al	2021	918	+	+	2 years
Ruzika et al	2020	13	+	+	6 weeks
Logan et al	2003	11	+	+	8 weeks

Usui et al found that treatment of coexisting OSA by CPAP in heart failure patients lowers daytime muscle sympathetic nerve activity (MSNA), systolic blood pressure and heart rate. Inhibition of increased central sympathetic vasoconstrictor outflow is one mechanism by which nocturnal CPAP reduces awake BP in the HF patients with moderate to severe OSA.[36] Milleron et al in his long-term prospective study, indicated that the treatment of OSA in coronary artery disease patients is associated with a decrease in the occurrence of new cardiovascular events, and an increase in the time to such events.[37]

Chirinos et al observed that adherence to a combined regimen of weight loss and CPAP may result in incremental reduction in insulin resistance and serum triglyceride as well as reductions in blood pressure.[38] Nadeem et al, in their study, analysed that CPAP causes decrease in total cholesterol and LDL, and increase in HDL, when used in the treatment of OSA.[39]

Rotenberg et al found that rate of CPAP adherence remains persistently low. No clinically significant improvement in CPAP adherence was seen even in recent years despite efforts toward behavioral intervention and patient coaching. This low rate of adherence is problematic, and therefore questioned the concept of CPAP as gold-standard of therapy for OSA.[40]

Bilevel PAP

BiPAP or bilevel positive airway pressure, has two fixed preset inspiratory and expiratory pressures. Airway is first opened by higher inspiratory pressure. The machine senses when inspiration is complete and then the pressure is decreased to the fixed expiratory pressure. Ishak et al in their study concluded that in patients with moderate-severe OSA who fail CPAP therapy due to low adherence, BiPAP is well tolerated and achieves sufficient control of sleep-disordered breathing and its symptoms.[41] Schafer et al concluded in their study that patients with OSA resistant to initial CPAP are morbidly obese with impaired awake blood gas values. BiPAP in the control mode is adequate for nocturnal ventilation, and improves awake blood gas values.[42]

Auto PAP

In auto-PAP (APAP) or auto-adjustable positive airway pressure, a lower and upper range of pressure to be delivered is preset. The machine senses whenever there is increased resistance and increases the pressure to overcome resistance and open the airway. Alves et al suggested that APAP should be used primarily as an initial therapeutic strategy for pressure titration. After a few days, switching to CPAP is as effective but also cheaper.[43] Identifying circumstances in which APAP is a definite improvement over CPAP in terms of costs or effects should be the focus of future studies.[44]

Adaptive servo-ventilation

Adaptive servo-ventilation (ASV) machines monitor a person's breathing while they sleep and deliver customized air pressure to stabilize breathing. Main difference between ASV and CPAP machines is that ASV machines deliver air pressure dynamically, adjusting according to person's breathing patterns, whereas CPAP machines deliver a set level of air pressure throughout the night. Sharma et al found in their study that in patients with heart failure and sleep disorder breathing, ASV was more effective than control conditions in reducing the AHI and improving cardiac function and exercise capacity.[45] Pepperell et al in their study, concluded that adaptive servoventilation produces an improvement in excessive daytime sleepiness in patients with Cheyne-Stokes breathing and chronic heart failure. Their study suggested improvement in neurohormonal activation with this treatment.[46]

Expiratory PAP

Expiratory positive airway pressure (EPAP) devices allow the user to inhale with ease, but during expiration, the device's resistance causes the upper airway pressure to become positive during exhalation. The device's effectiveness depends on their resistance and the pressure they generate.[47] The primary difference is that with CPAP, the pressure remains positive during the entire breathing cycle eliminating any potential collapse of the upper airway. With EPAP, the pressure is positive only during the expiration and remains near zero or becomes slightly negative during inspiration, allowing upper airway collapse in some users.[47] The proposed mechanisms of action for the nEPAP devices include (a) increased functional residual capacity (FRC), producing tracheal traction and reducing upper airway collapsibility, or (b) passive dilatation of the upper airway by the expiratory pressure, carrying over into inspiration, or (c) both.[48] Optipillows EPAP mask, Bongo Rx and Theravent are some of commercially available EPAP devices in market.

PHARMACOTHERAPY

A variety of pharmacologic agents have been investigated in randomized trials as primary therapeutic agents or as add-on therapy, for management of OSA. List includes drugs that might act to stimulate respiratory drive directly (e. g., theophylline) or indirectly (e. g., acetazolamide), drugs that reduce upper airway collapsibility (e. g., desipramine), antimuscarinics (e. g., oxybutynin), or noradrenergic agents (e. g., atomoxetine).

Cannabinoids

Carley et al in their study, found the therapeutic potential of cannabinoids in people with OSA. In comparison to placebo, dronabinol was associated with lower AHI, improved self-reported sleepiness, and greater overall treatment satisfaction.[49] However, American academy of

sleep medicine (AASM) prescribes that medical cannabis and/or its synthetic extracts should not be used for the treatment of OSA due to unreliable delivery methods and insufficient evidence of effectiveness, tolerability, and safety.[50]

Sulthiame

Hedner et al in their study on carbonic anhydrase inhibitor sulthiame (STM) in OSA found that STM showed satisfactory safety profile in moderate and/or severe OSA. STM reduced OSA, on average, by more than 20 events/h, one of the strongest reductions reported in drug trial in OSA.[51] Further studies are required before sulthiame can be used routinely in patients with OSA.

Modafinil

The wake-promoting agent modafinil has a beneficial effect on daily life and well-being in patients with excessive sleepiness associated with OSA, shift work disorder or narcolepsy.[52] Modafinil is a well tolerable drug, without adversely affecting cardiovascular parameters or scheduled sleep.[52] Rosenberg et al found that compared with modafinil, the wake-promoting effects of armodafinil persist later in the day. It is for this reason that armodafinil may be a particularly appropriate therapy for patients with persistent excessive sleepiness due to OSA, shift work disorder or narcolepsy.[53]

Anti-depressants

Brownell et al in their double-blind cross over study, found that protriptyline can be effective in patients with sleep apnea when the disorder is not life-threatening.[54] REM reduction during treatment with protriptyline can account for decreased REM apnea time. Similar decreases in REM stage time and REM apnea duration and similar improvement in oxygenation continued after six months of treatment.[54] Hanzel et al in their study, concluded that fluoxetine is beneficial to some, but not all, patients with OSA. Fluoxetine was better tolerated than protriptyline.[55]

Taranto-Montemurro et al in their study on desipramin in OSA, found that reduction AHI driven by improvement in muscle compensation. In OSA patients, noradrenergic stimulation with desipramine improves pharyngeal collapsibility and may be effective treatment in patients with minimal upper airway muscle compensation.[56]

Acetazolamide

Tan et al in their randomised cross over trial, concluded that in highlander with OSA, acetazolamide could reduce blood pressure, improve sleep-disordered breathing and oxygen saturation, and result in improved cognitive performance.[57] Possible mechanisms behind improved blood pressure due to acetazolamide therapy might be acetazolamide-related reduction in the CO_2 to HCO_3^- conversions by inhibiting the synthesis of carbonic anhydrase, resulting in metabolic acidosis and increased minute ventilation.[57] The increased ventilation might increase the oxygen saturation and stabilise the breathing pattern by left shifting the CO_2-ventilation response curve, which, therefore, may prevent periodic breathing. Another pathway might be that acetazolamide inhibits the activity of carbonic anhydrase in renal proximal convoluted tubules.[57] This might result in a diuretic role by reducing H^+ production and Na^+ reabsorption, and increase of excretion of Na^+, water and carbonate. This diuretic effect of acetazolamide could reduce the fluid transfer from the legs to neck by reducing the fluid accumulation from daytime orthostatic gravity and associated sleep-disordered breathing at night.[57] Carbonic anhydrase inhibition may constitute a potential target for drug therapy in patients with sleep apnea and comorbid hypertension.[58]

Atomexetine and oxybutinin

Taranto-Montemurro et al in their another study found that the combination of atomoxetine (norepinephrine reuptake inhibitor) and oxybutynin (antimuscarinic) markedly improved the measures of upper airway collapsibility, increased breathing stability, and slightly reduced the arousal threshold. Patients with relatively lower AHI and less severe upper airway collapsibility had the best chance for OSA resolution with atomoxetine-oxybutinin.[59] Genioglossus responsiveness increased approximately threefold on giving both of the above drugs as combination.[60] But neither atomoxetine nor oxybutynin reduced AHI when the administered separately.[60]

Theophylline

Sleep-disordered breathing episodes are associated with severe nocturnal arterial blood oxyhemoglobin desaturation and excessive arousals. Hu et al concluded that in these patients, oral theophylline therapy may reduce number of episodes of central apnea and hypopnea and duration of arterial oxyhemoglobin desaturation during nocturnal sleep.[61] However, Mulloy et al found sleep quality became significantly worse while giving theophylline to OSA patients. They concluded that theophylline may be beneficial in patients with OSA, but part of improvement is due to the deterioration in the sleep quality.[62]

Intranasal steroids

Kiely et al found that intranasal fluticasone is of benefit to some patients with OSA and rhinitis.[63] Rezaeetalab et al suggested in their study that inhaled corticosteroid might be beneficial in treatment of overlap syndrome.[64] Kheirandish-Gozal et al found that 6-week treatment with intranasal budesonide effectively reduced the severity of mild OSA syndrome and the magnitude of the underlying adenoidal hypertrophy.[65] They found justified, the use of topical steroids as initial therapeutic option in otherwise healthy children with mild OSA.

ORAL NEGATIVE PRESSURE THERAPY

The oral pressure therapy (OPT) consists of a bedside console that connects with flexible tubing to premanufactured polymer mouthpiece. Through the mouthpiece, a pump in console creates oral vacuum in the oral cavity intended to move the soft palate anteriorly to decrease obstruction of the airway during sleep.[66] Farid-Moayer et al demonstrated in their study that in appropriately responsive patients, OPT can improve OSA without need for custom manufacture of an oral device.[66]

MYOFUNCTIONAL THERAPY

In myofunctional therapy, OSA patients are been taught to do daily exercises to strengthen their tongue and throat muscles. Orofacial myofunctional therapy (OMT) consists of isotonic and isometric exercises targeted to oral and oropharyngeal structures, with aim of increasing muscle tone, endurance, and coordinated movements of pharyngeal and parapharyngeal muscles.[67] Camacho et al demonstrated in their meta-analytic study that myofunctional therapy decreases apnea-hypopnea index by approximately 50% in adults and 62% in children. Lowest oxygen saturations, snoring, and sleepiness outcomes improve in adults.[68] Myofunctional therapy could serve as an adjunct to other OSA treatments.[68]

CONCLUSION

OSA is a complex heterogenous disorder, having variable newly emerging pathophysiological phenotypes, contributing to the insight knowledge of efficiency and safety of various available modes of treatment for OSA. It has the probability to affect multiple organs of the body including heart, brain etc. In regards to the same, it is very essential to develop the different and relatively more efficacious methods of treatment in near future, which are capable of treating all the possible phenotypes with whatsoever the severity may be. The treatment modes must be capable of treating, not only the sign and symptoms of OSA but also its complications. For this, multidisciplinary approach and strict implementation of education and behavioural modifications are required and combination of all the discussed modalities forms the basis of holistic approach towards treatment of OSA. Healthy life style changes and side sleeping position along with evidence-based management should be encouraged and guidelines for the management of OSA must be laid down accordingly.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Paramasivan VK, Bhatia JSS, Pandyan K. Medical management of obstructive sleep apnea: a review article. Int J Otorhinolaryngol Head Neck Surg 2023;9:1011-8.