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Review

Therapeutic alternatives with CPAP in obstructive sleep apnea

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Abstract

Obstructive Sleep Apnea (OSA), characterized by airflow cessation (apnea) or reduction (hypopnea) due to repeated pharyngeal obstructions during sleep, causes frequent disruption of sleep and hypoxic events. The condition is linked to many adverse health related consequences, such as neurocognitive and cardiovascular disorders, and metabolic syndrome. OSA is a chronic condition requiring long-term treatment, so treatment using continuous positive airway pressure (CPAP) has become the gold standard in cases of moderate or severe OSA. However, its effectiveness is influenced by patients' adherence. Surgery for OSA or treatment with oral appliances can be successful in selected patients, but for the majority, lifestyle changes such as exercise and dietary control may prove useful. However, exercise training remains under-utilized by many clinicians as an alternative treatment for OSA. Other interventions such as oral appliance (OA), upper way stimulation, and oropharyngeal exercises are used in OSA. Because the benefit of all these techniques is heterogeneous, the major challenge is to associate specific OSA therapies with the maximum efficacy and the best patient compliance.

Keywords : OSA, oral appliance, upper way stimulation, oropharyngeal exercises, pulmonary rehabilitation

Highlights

- ✓ Even though the role of OA is similar to that of CPAP in clinical practice, clinicians may not achieve the abolition of all obstructive events during sleep by means of OA.
- ✓ There is currently an alternative therapy to CPAP or OA for subjects with mild to moderate OSA, consisting in the use of upper airway stimulation devices.

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Introduction

Obstructive sleep apnea is characterized by airflow cessation (apnea) or reduction (hypopnea) due to repeated pharyngeal obstructions during sleep, causing frequent disruption of sleep and hypoxic events. The pathophysiology of OSA varies and includes different underlying mechanisms, such as the effectiveness of the upper airway dilator muscles (genioglossus), the upper airway anatomy, the arousal threshold of the individual, and the inherent stability of the respiratory control system (1). It is well-know that obesity is the most significant risk factor, with other factors such as smoking, alcohol abuse, chronic nasal congestion, male gender, age, and the use of sedative medications playing a significant role in OSA development (2, 3). In addition, OSA is linked to many adverse health-related consequences, such as neurocognitive and cardiovascular disorders, and metabolic syndrome (4, 5, 6). OSA has become a chronic condition which requires long-term treatment, so treatment using continuous positive airway pressure (CPAP) has become the gold standard in cases of moderate or severe OSA, but its effectiveness is influenced by patients' adherence. Surgery for OSA or treatment with oral appliances can be successful in selected patients (4), but for the majority, lifestyle changes such as exercise and dietary control may also prove useful. However, exercise training remains under-utilized by many clinicians as the alternative treatment for OSA (7). Other interventions such as oral appliance (OA), upper way stimulation, and oropharyngeal exercises are used in OSA.

Discussion

Prevalence

OSA has been recognized as a very common pathology in recent years, but it still remains undiagnosed and untreated in many cases. Apnea-hypopnea index (AHI) quantifies both sleep apnea severity and the number of apneal or hypopneal obstructive events per hour of sleep. The prevalence of OSA was found to be 24% in men and 9% in women aged 30-60 years, thus defining OSA as an AHI greater than 5 events/hour in the Wisconsin Sleep Cohort in the United States of America. The values of prevalence worldwide do not vary significantly, thus confirming that OSA is as common in the developing world as in the occidental society (8). In Europe, the prevalence may be even greater, taking into account that modern diagnostic techniques are used. For example, in a Swiss study including over 2,000 subjects with the diagnosis of moderate-severe OSA, the prevalence was 23.4% in females and 49% in males (9).

Risk Factors

The highest risk factor for OSA is obesity, especially central adiposity. According to the worsening pandemic obesity worldwide, the prevalence of OSA is yet increasing. Moreover, obesity may contribute to the development of OSA by affecting the upper airway mechanisms (2). The deposition of fat in the parapharyngeal region can reduce the caliber and promote collapsibility by modifying the shape of the upper airway. Obesity is also responsible for reducing the lung volumes and increasing airflow resistance (10). In the pathogenesis of obesity, a key role is represented by the interaction between OSA and obesity, in part because excessive daytime sleepiness and other symptoms of OSA may accelerate weight gain due to reduced physical activity and energy expenditure. Weight loss is a key measure of therapy for overweight or obese patients with OSA, as it may confer a positive impact on other diseases such as cardiovascular disorders and type 2 diabetes and it may reduce the severity of OSA (8, 11).

There is an age-related increase in the prevalence of OSA. Some mechanisms include changes in the anatomic parapharyngeal structures, parapharyngeal fat deposition, and lengthening of the soft palate (12). It is also well acknowledged that there is a 2 to 3-fold higher prevalence of OSA in men compared to women (8). Men present themselves more often for the clinical assessment for OSA because they have typical symptoms of OSA (loud snoring, witnessed apneas, and excessive daytime sleepiness). This fact is responsible for the underdiagnosed OSA in women, with women more likely presenting with atypical symptoms such as poor energy levels and fatigue (13).

In addition, multiple craniofacial features related to pharyngeal soft tissue or skeletal morphology may predispose to upper airway collapse. Hyoid position, mandibular size, and maxillary height have been associated with an increased risk for OSA. Decreased velopharyngeal area and tonsillar hypertrophy are soft tissue features that have been associated with increased upper airway collapsibility (1).

Smoking is another factor implicated in the development of OSA. The data are controversial, as the effect of nicotine decreases the upper airway resistance with a consequent reduction in the risk of OSA, whereas in case of withdrawal, this resistance would become more important and would cause a greater risk of OSA. Smoking is a well-acknowledged risk factor for respiratory diseases, various neoplasia, and metabolic disorders. Various compounds in cigarette smoke, such as volatile organic compounds, heavy metals, and nicotine are responsible for

the increased oxidative stress and systemic inflammation, with an important role in the occurrence of lipid and glucose metabolic dysfunction and endothelial injury, resulting in the development of cardiovascular, cognitive, and metabolic disorders (14, 15).

Diagnosis

Recognizing and treating OSA is very important in clinical practice. The first step in the diagnosis is a clinical evaluation, which involves a sleep history and a physical examination of the respiratory, cardiovascular, and neurologic systems. The examiner should note symptoms such as snoring, witnessed apneas, nocturnal choking or gasping, and restlessness and excessive sleepiness. The differential diagnosis is made through the general evaluation in order to select the appropriate test(s) and to recognize the associated medical conditions such as obesity, hypertension, stroke, and congestive heart failure. In the diagnosis of OSA, nocturnal polysomnography is the gold standard, but in cases of high suspicion of OSA, nocturnal cardiorespiratory polygraphy is edifying. In the third edition of the International Classification of Sleep Disorders (ICSD-3), OSA is defined as a respiratory disturbance index (RDI) $\geq$ 5 events/hour of sleep in patients who associate typical symptoms of OSA (daytime sleepiness, fatigue or insomnia, unrefreshing sleep, loud snoring, witnessed apneas, awakening with a gasping or choking sensation), or an RDI $\geq$ 15 events/hour of sleep (even in the absence of symptoms) (16).

Comorbidities

A high prevalence of comorbidities in seen in OSA patients (17). There are specific patterns, with men more often affected by diabetes and ischemic hearts disease and women by hypertension and depression (18, 19). Also, OSA is responsible for the development of cardiovascular and cerebrovascular diseases through high sympathetic nervous activity, oxidative stress, systemic inflammation, intermittent hypoxia, systemic hypertension, endothelial cell dysfunction, and accelerated atherosclerosis. Systemic hypertension is the most studied cardiovascular comorbidity in OSA. Respiratory events such as apneas or hypopneas during sleep are followed by hypertensive peaks, so that a variability of blood pressure may occur. Another aspect in these patients is resistant hypertension or incomplete blood pressure control on maximum drug therapy (20). In patients with OSA, atrial fibrillation is very frequent, with CPAP therapy having a protective role (21). Another pathology with a high prevalence in OSA patients with central obesity is metabolic syndrome (MetS), responsible for increasing cardiovascular risk. Recent studies have also shown that OSA is part of the MetS. The intermittent hypoxia and the sleep loss or fragmentation are involved in the pathogenesis of insulin resistance (17). In these conditions, OSA treatment with sufficient adherence (at least 4 hours/night) is required besides the implementation of lifestyle interventions and weight loss programs (22).

The association between OSA and chronic obstructive pulmonary disease (COPD), known as "overlap syndrome" from the early studies (23), has a prevalence of 1.0 to 3.6% in the general population, 8-56% in OSA patients, and 3-66% in COPD patients (24). In COPD patients who have consulted clinicians for pulmonary rehabilitation, a severe form of OSA has been diagnosed in 45% of the cases, with these patients having poor sleep quality and hypoventilation episodes during sleep (17, 25). Moreover, overlapping patients have higher rates of mortality compared to OSA patients, and in this direction there is a protective effect of CPAP treatment (26). These data suggest that a low body mass index (BMI) in patients with COPD protects against OSA, but the upper airway and the systemic inflammation are responsible for increasing the prevalence of OSA in COPD patients (27).

Asthma and OSA are often associated, so asthmatic patients often report symptoms such as daytime sleepiness, poor asthma control, and poor quality of life. In patients with difficult-to-treat asthma, the prevalence of OSA is about 49%. Patients with severe asthma show poor sleep quality and excessive daytime sleepiness. Often, asthmatic patients present hypopneas. It appears that both asthma and OSA play a synergistic role in the upper airway inflammation, in part because the upper airways seem to be smaller in patients with asthma and OSA (17).

Therapeutic Attitudes in OSA

In the last two decades, advances in sleep medicine and the availability of improved diagnostic tools have led to a better recognition and treatment of the disease. The management of patients with OSA requires a multidisciplinary approach, and many treatment options are currently available in order to eliminate the nocturnal apnea events and the intermittent hypoxia. Positive airway pressure (PAP), available since the beginning of the 1980s, provides the most effective and commonly used treatment. PAP devices function as a pneumatic support that maintains upper airway patency by increasing the upper airway pressure above a 'critical' value (the pressure value under which the airways collapse). The device is applied to the patient through a nasal or oronasal mask, overnight or during sleep hours at a set positive pressure. This pressure can vary according to the severity of OSA, so higher

pressures are needed in order to make nocturnal apneas disappear. PAP therapy is indicated in patients with an AHI greater than 15 events/hour of sleep, independently from the presence of comorbidities and severity of symptoms. If the AHI is above 5 and below 15, PAP is indicated in the presence of comorbidities such as hypertension, coronary artery disease, or previous cerebrovascular accidents, or in the presence of other symptoms (i.e., sleepiness, impaired cognition, mood disorders) (28, 29). Alternative options include weight control, mandibular advancement devices, oral appliance, upper airway stimulation, oropharyngeal exercises, and a number of upper airway surgical approaches.

Lifestyle Intervention

As previously shown, obesity is an important risk factor for OSA, and over 70% of patients with OSA suffer from obesity. A strict correlation has recently been established between the body mass index (BMI) and AHI. Weight loss is therefore a main goal in the management of OSA and all patients should be encouraged to control their weight (30).

The term "Mediterranean diet" refers to many common features including the abundant use of olive oil as the main culinary source of fat, plentiful consumption of plant-based foods (e.g. nuts, vegetables, fruits, cereals, grains and vegetables), consumption of fresh and varied fruits, frequent consumption of fish and other seafood, moderate wine consumption with meals, limited meat (mainly poultry) or processed meat intake, and low-to-moderate consumption of processed products (31). Besides this, the Mediterranean diet is characterized by abundant plant foods with antioxidant molecules which have an anti-inflammatory effect. Longer beneficial effects of a moderate-carbohydrate (40%), high-fat (40%) calorie-restricted Mediterranean diet on weight and waist circumference have been demonstrated among individuals with metabolic syndrome or more cardiovascular risk factors. Therefore, a Mediterranean diet seems a promising approach to reduce mechanical loads and thus improve OSA severity, compared to a low-fat, calorie-restricted diet (32, 33).

In a study comparing the Mediterranean diet with a low-carb diet, patients in the Mediterranean diet group had a greater improvement in AHI after 6 months, mainly due to an important reduction of the waist circumference, improved upper airway neuromuscular control, and upper airway muscular capacity (34).

While dietary-induced weight loss is effective in the treatment of OSA, OSA influences weight loss through sleep fragmentation and poor sleep quality, so these mechanisms could have implications for therapeutic approaches. Borel et al. studied this assumption in a group of males with visceral adiposity who underwent a weight loss intervention that included nutritional counselling and moderate physical activity promotion. At one-year follow-up, males with OSA had smaller reductions in waist circumference, in total fat mass and triglycerides, and attenuated improvement in high-density lipoprotein cholesterol compared to males without OSA (35). In a study by Spiegel et al. (36), the variation of leptin and ghrelin levels were correlated with increased sympathetic nervous system activity or cardiac sympathovagal balance due to sleep loss. In addition, the subjects with sleep deprivation self-reported increased hunger, probably due to increased signaling towards reward and pleasure centers of the brain that enhance the hedonic perception of food, which would drive motivation for food seeking and consumption. The obvious implication of these findings is that inadequate sleep resulting from OSA could promote excessive eating, especially with high carbohydrate content, and impair weight loss, but there was no information related to diet prior to undergoing these sleep protocols (36, 37).

Training Programs

Physical activity (PA) has been recognized as a key determinant for good health. PA is defined as any training program resulting in energy expenditure. A PA plan is scheduled, repetitive, structured, and purposive in the sense that it maintains or improves one or more objectives (38). Moreover, several studies have demonstrated that low levels of PA are associated with higher incidence of OSA, obesity, and metabolic syndrome (39, 40). It is possible that patients with OSA are unable to do physical exercises due to excessive daytime sleepiness and fatigue (39). The exercises have multiple effects on OSA, such as improving the severity of OSA, decreasing the severity of central sleep apnea in patients with chronic heart failure and reducing the occurrence of cardiovascular diseases, impaired glucose tolerance, and fatigue (41). The AASM recommends training programs as a treatment option for patients with OSA, given that regular PA reduces the prevalence of OSA (42, 43).

A meta-analysis by Iftikar et al. showed that exercise training has a significant effect on AHI that seems to be independent of the BMI changes. The exercises improve upper airway dilator functions during sleep and another one refers to the possibilities of including PA in the daily routine that seems a reorganization of parapharyngeal fat distribution and diminishes the arousals. Moreover, the improvement in sleep efficiency with exercise is similar to what is typically achieved with CPAP. Likewise, the

effects on daytime sleepiness (as measured by the Epworth Sleepiness Scale) with exercise training is similar to those seen with CPAP (44).

Oral Appliance

Oral appliances (OA) are the second most-used therapy in treating snoring and mild to moderate OSA as a primary therapy or as an alternative in patients who do not tolerate CPAP devices. It involves the application of dental splints in order to maintain the mandible in an advanced position and/or the tongue in a protruded position, in order to prevent upper airway obstruction during sleep. Imaging studies show that the lateral dimension of the velopharyngeal region is increased due to mandibular advancement resulting in an enlarged upper airway space. The lateral tissue movement via connections between the lateral walls and the ramus of the mandible leads to the lateral expansion of the airway space. Also, the mandibular advancement determines an anterior tongue movement. While CPAP and OA therapies are responsible for reducing the upper airway collapse during sleep, they differ in efficacy, cost and side effects. The type of OA device is very important in order to quantify the amount of mandibular advancement responsible for the decrease of AHI (45). The role of adjustable OA devices is to obtain the optimum symptom relief and achieve a significant reduction in the AHI for subjects with a baseline AHI >10 events/hour of sleep (46, 47).

Generally, the treatment effect is determined by the level of advancement, but clinicians must take into consideration the potential side effects. One study by Kato et al. compared 3 levels of advancement (2, 4, and 6 mm), concluding that improvement in overnight oximetry (25%, 48% and 65% of patients showing improvement in desaturation) and in the upper airway closing pressures varies with the degree of advancement (48). In mild to moderate OSA patients, there is no significant difference between the levels of advancement (50% or 75%) in reducing AHI or the proportion of patients successfully treated (49). However, in patients with severe OSA, maximizing the level of advancement by 75% compared to the 50% maximum advancement is important in order to achieve a successful treatment (50).

OA therapy has often been indicated in mild cases of OSA, and the severity of OSA decreases even more with OA in patients with higher baseline AHI, but there is a smaller probability of achieving an AHI < 5 events/hour of sleep. Despite the inferiority of efficacy when compared with CPAP, OA is preferable in patients who do not tolerate CPAP, being very useful in such cases. Lorenzi-Filho demonstrated that when compared to CPAP, OA has the same effectiveness on symptomatology such as excessive daytime sleepiness, quality of life, and the improvement of cardiovascular biomarkers such as endothelial function, blood pressure, and microvascular reactivity (51). In obese patients, while the BMI increases, OA is not so efficient. OA should be considered a potentially complementary therapy in addition to CPAP in order to improve treatment outcomes. Almeida et al. demonstrated that patients who were compliant with CPAP (>4 hours/night) showed improvements in symptomatology (especially excessive daytime sleepiness), even in the nights they were not wearing it by using OA. Patients using OA have an option for a day off CPAP, resulting in less pressure on the teeth by wearing OA. Combination therapies are preferred in order to improve adherence, with a decrease of a specific treatment side effect or burden. In conclusion, the oral appliance is used specifically to decrease snoring in mild, moderate, or severe OSA, preferably intermittently or with CPAP as it is a simple and cost-effective therapy (52).

Upper Airway Stimulation

Unilateral and phasic upper airway stimulation (UAS) stimulates the hypoglossal nerve, resulting in the augmentation of the neural drive, through a device that acts via a cuff electrode connected to an implanted impulse generator that incorporates an effort sensor placed between the intercostal muscles. Only one device is currently approved by the Food and Drug Administration (FDA) in the USA. In this way, the tongue protrudes through a stimulation sequence that can be programmed. The UAS can be turned on by the patient with a programmer and it is used only during the sleep period and can be activated via a patient programmer. By combining the forward movement of the tongue with the mechanical coupling of the soft palate, clinicians can obtain an enlargement of the retro lingual and retro palatal airways (53). The Stimulation Therapy for Apnea Reduction (STAR) improved the oxygen desaturation index by 70% (25.4 to 7.4 events/h), reduced AHI by 68% (29 to 9 events/h), and also had a beneficial effect on decreasing the arousal index. This device can also be used as an additional tool in subjects with moderate to severe OSA because it improves the excessive daytime sleepiness as quantified by the Epworth Sleepiness Scale (ESS) and increases the quality of life as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ). Before proceeding to UAS, OA should be the first recommended procedure. These procedures will improve the hypoglossal nerve mapping and how clinicians might quantify the impact of UAS in anatomy. Studies have shown that UAS is not an option for

morbidly obese patients, but more sophisticated analyses (imaging and/or polysomnography) need to be done. Examining the role of complementary treatments in incomplete responders with targeted surgery, OA, weight loss, or medications needs to be explored (54).

Oropharyngeal Exercises

Considering the role of the dilator muscles of the upper airway in OSA, several studies have investigated the effects of oropharyngeal exercises on OSA severity. Oropharyngeal exercises (Oropharyngeal myotherapy - OMT) are a treatment modality used for patients with orofacial myofunctional disorders, with benefits on the orofacial structures and on the cervical muscles. OMT implies exercises and other strategies capable of increasing sensitivity, proprioception, mobility, coordination, and strength of orofacial structures. At the same time, OMT favors a good performance of respiration, mastication, deglutition, and speech. Guimarães et al. demonstrated that oropharyngeal exercises target soft palate elevation and that they recruit several upper airway muscles, such as the tensor and the levator veli palatini, as well as the muscle fibers of the palatopharyngeal and palatoglossal muscle, tongue repositioning, and training of the mandibular elevation in order to avoid mouth opening during the night (55). One of the goals of training was to increase the tone of the elongated soft palate and uvula, as it is well-known that elongation of this structure is associated with higher rates of obstructive apnea, AHI, and respiratory disturbance index (56). The study included 31 patients with moderate OSA and divided them into two groups: the first group received placebo, and the other group received OMT targeting the lateral pharyngeal wall, the tongue, and the soft palate (55). After three months of exercise training, AHI was reduced by 39% and the lowest oxygen saturation during sleep was elevated. Another recent review demonstrated a 50% reduction of AHI in patients with OMT (57). Also, in cases of a mean baseline ESS score greater than 10, patients showed a significant improvement after OMT, with a mean reduction of six points (58). More recently, Ieto et al. have shown that after 3 months of oropharyngeal exercises, subjects showed a 36% reduction in snoring frequency and a 59% reduction in the overnight power of snoring (59). In addition, another study showed that oropharyngeal exercises cause various effects in the treatment of mild to moderate obstructive sleep apneal syndrome, such as: the significant reduction of the patients' neck circumference, the improvement of symptoms like daytime sleepiness and snoring intensity, the significant improvement in sleep indices minimum oxygen saturation, $SaO2 < 90$ %, sleep efficiency, arousal index, and total sleep time N3 stage of sleep. Although it is not clear how OMT can influence the collapsibility of the upper airway during sleep, it has been speculated that OMT can influence the remodeling of the upper airway. The oropharyngeal exercises are a complex and integrated approach, which is why clinicians cannot quantify the improvement of each exercise. In addition, the exercises must be performed with a specific frequency (two or three times a day) and this may limit the clinical applicability. Therefore, how well patients adhere to oropharyngeal exercises in 'real-world' clinical practice is still unknown (60).

Conclusions

Over the past years, due to the increasing prevalence of OSA, new therapies beyond CPAP have been developed and are now currently available. The first treatment option in selected cases with mild OSA is OA, but new evidence also suggests that OA may be effective in selected moderate to severe OSA cases.

Even though the role of OA is similar to that of CPAP in clinical practice, clinicians may not achieve the abolition of all obstructive events during sleep by means of OA. There is currently an alternative therapy to CPAP or OA for subjects with mild to moderate OSA, consisting in the use of upper airway stimulation devices. The principle of oropharyngeal exercises is repetitive muscle training, with specific gains in the endurance of muscles, tonicity, and coordination that may improve the condition of muscle fatigue in subjects with OSA and act on the equilibrium of contraction between the different muscles that involve the velopharyngeal, oropharyngeal, and hypo pharyngeal segments.

In addition, they can decrease the volume of specific structures and fat in the pharyngeal-dilating muscles, thus also reducing the potential upper airway collapse in apneic subjects. However, these hypotheses have not yet been verified. Because the benefit of all these techniques is heterogeneous, the major challenge is to associate specific OSA therapies with maximum efficacy and optimal patient compliance.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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