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Obstructive Sleep Apnea: A Pathophysiology and Pharmacotherapy Approach

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Abstract

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by complete cessation of upper airflow during sleep, leading to repetitive episodes of desaturations and arousals. The symptoms include excessive daytime somnolence and are associated with a significant cardiovascular morbidity and mortality. The prevalence of OSA is higher in men with an approximate rate of 14 and 5% in women respectively. Typical risk factors for obstructive sleep apnea in the normal adult population are obesity, aging, gender, menopause, ethnicity, genetical predisposition, craniofacial anatomy, smoking, alcohol consumption and some other factors such as REM sleep, surface tension, and impaired sensory processing. Several screening questionnaires can be performed in out-patient settings to identify the patient symptoms. Polysomnography is considered as the gold standard for diagnosis of OSA. Different surgical treatments and devices are readily available for an effective management of this disease. Proper diagnosis and treatment improves not only the quality of life but also relatively decreases patient morbidity and mortality. A multifaceted approach is necessary for an accurate management of the OSA.

Keywords: obstructive sleep apnea, excessive daytime somnolence, obesity, polysomnography, quality of life

1. Introduction

The first clear modern description of obstructive sleep apnea (OSA) was given by Burwell in 1956 in the publication entitled, "Extreme Obesity Associated with Alveolar Hypoventilation:

A Pickwickian Syndrome.” The name came from Charles Dickens’ *The Posthumous Papers of the Pickwick Club* (1837). It is unclear if the patient named Joe with overweight exhibited symptoms of OSA, and it took another decade before Gastaut and colleagues in 1966 recognized OSA in obese patients and noted these nocturnal disturbances to possibly be linked to their daytime somnolence [1].

Obstructive sleep apnea (OSA) is a potentially serious and life-threatening disorder affecting millions of people around the world. It is a sleep-related respiratory condition, characterized by the complete or partial collapse of breathing because of a narrowing or closure of the upper airway during sleep, resulting in intermittent cessations of breathing (apneas) or reductions in airflow (hypopneas) despite ongoing respiratory effort [2]. The symptoms include excessive daytime sleepiness, Mood changes, Fragmented sleep, as well as the decreased health-related quality of life. Patients often complain of snoring, Gasping or choking, frequent nocturnal awakenings, early morning headaches, poor concentration and coordination, anxiety, irritability, and insomnia, yet many patients are unaware of these symptoms and disease onset is insidious [3, 4]. The underlying mechanism of OSA is still under investigation, but it is precisely multifaceted.

The economic burden of OSA is substantial due to its high prevalence and economic costs in the community globally, the profound clinical effects on an individual’s cognitive and general functioning and the increased risk of adverse health complications [2]. Moreover, mounting evidence suggests that OSA can increase the risk of cardiovascular diseases (hypertension, coronary heart failure, stroke etc.), metabolic syndrome, Neurological problems and increased in societal effects such as traffic accidents [3, 5–7].

2. Prevalence of OSA

OSA is a common chronic disorder with an estimated prevalence of 2–4% in general and the disorder was believed to be rising continuously with an approximate rate of 14% in men and 5% in women aged 30–70 years respectively [8–10]. It is higher in patients with obesity; diabetes mellitus type II and other cardiovascular disorders which includes ischemic heart disease, heart failure, cardiac arrhythmias, stroke, atherosclerosis and myocardial infarction [8, 10]. Research on current prevalence (Seventh Joint National Committee) shows that OSA was identified as a secondary cause of Hypertension (HTN) and ranges from 37 to 56%, the prevalence rate of OSA in resistant hypertensive patients were estimated to be 70–83% [11]. Among the pediatric population, the rate affects between 1.2 and 5.7% and it is estimated that 36% of obese children are at high risk of OSA [12]. Since it is reported that more than 85% of patients with OSA symptoms have never been diagnosed clinically [13].

3. Pathophysiology of OSA

The pathogenesis of OSA can be multifactorial, complex and incompletely understood [13, 14]. The changes in upper airway anatomy tissue characteristics and neuromuscular

function, sleep-dependent changes can assume to play the major role between the individuals (Figure 1). Certain factors that may contribute to OSA include obesity, thickened lateral pharyngeal walls, nasal congestion, enlarged uvula, facial malformations, and tonsillar hypertrophy. As the patient falls asleep, the muscle tone of the nasopharynx is reduced during sleep and airways become contracted. These episodes are typically accompanied by repeated oxy-hemoglobin desaturation, oxygen levels in the body start to drop and carbon dioxide levels rise by short micro-arousals by the patient when the airway patency is restored. This causes activation in sympathetic nervous system and contraction of nasopharyngeal tissue, which results in obstruction of the airway. These cyclic episodes continue throughout the night with reduced deep Non-Rapid eye movement sleep (NREM) and Rapid eye movement sleep (REM) [13]. Several studies have confirmed that the airway dilating muscles in OSA patients can no longer resist the negative pressure in airways during inspiration. In severe cases, the respiratory events can occur 50–100 times per hour; each event lasts for about 20–40 s [9]. The severity of OSA is measured by the apnea-hypopnea index (AHI). The frequency of apneas and hypopneas per hour of sleep. Apnea is defined by complete obstruction of the upper airways lasting for at least 10 s (i.e. airflow restriction by more than 90% (according to AASM criteria). Hypopnea is defined as airflow restriction more than 30% (according to AASM criteria)

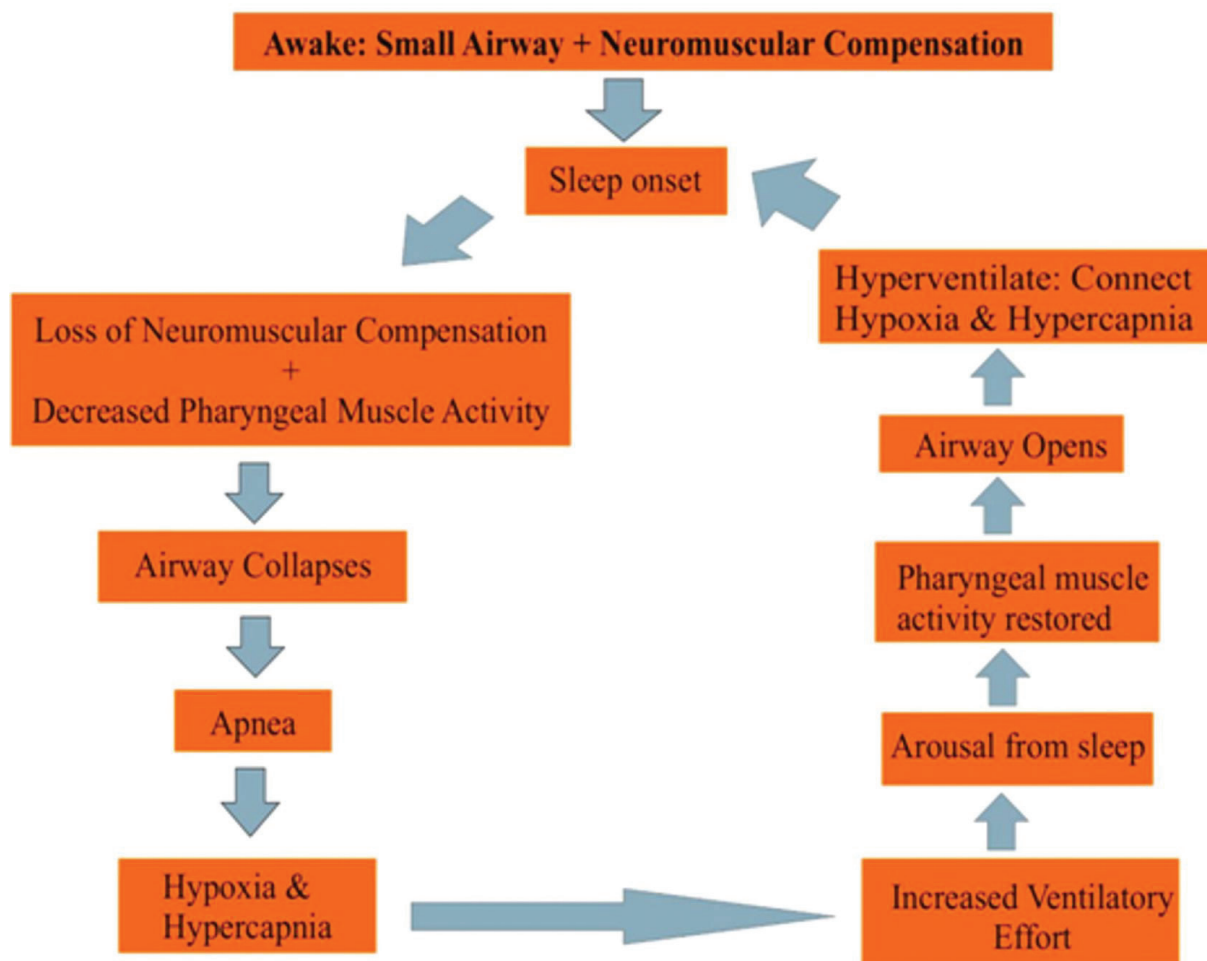


Figure 1. Pathophysiology of OSA.

OSA severity	RDI measurement (events/hr)
Mild OSA	≥ 5
Moderate OSA	≥ 15
Severe OSA	≥ 30

Table 1. OSA severity is defined by the AASM.

lasting for more than 10s. The oxygen desaturation index (ODI) is defined as the number of desaturations per 1 h of monitored sleep when oxygen saturation is reduced as compared to the baseline standard level. The respiratory effort related arousal (RERA) can also be used. RERA is defined as an episode characterized by an increased respiratory effort caused by upper airway airflow reduction resolved with arousal and accompanied in most cases with hypoxemia. The respiratory disturbance index (RDI) is the sum of RERA and AHI [9, 15].

According to the third edition of the International Classification of Sleep Disorders (ICSD-3), obstructive sleep apnea (OSA) is defined as polysomnography derived obstructive respiratory disturbance index (RDI) ≥ 5 events/h associated with typical OSA symptoms, or an obstructive RDI ≥ 15 /h in the absence of clinical OSA symptoms [9]. According to American Academy of sleep medicine (AASM), OSA is commonly divided into three levels of severity as detailed in **Table 1** below.

4. Diagnosis of OSA

The diagnosis of Obstructive sleep apnea starts with thorough history and physical examination to elucidate the signs and symptoms of the syndrome. Common symptoms patients complain of snoring, disturbed sleep, daytime somnolence, decreased libido as well as a history of hypertension, cardiovascular disease, and diabetes. Depending on the nonspecific and other variable features of OSA, its diagnosis based on a clinician's subjective analysis alone may be inaccurate [13]. A number of out-patient screening questionnaires such as Epworth sleepiness scale (ESS), Berlin Questionnaire STOP-BANG questionnaire, Sleep Apnea of Sleep Disorder Questionnaire SA-SDQ, OSA50 questionnaire etc. to help and identify patients with OSA [9, 16, 17]. Advances in sleep medicine and the availability of improved diagnostic tools have led to a better recognition and treatment of the disease. The outpatient examination should be repeated and the patients should be then referred, depending on the result of the follow-up examination, to a sleep laboratory [8].

An overnight polysomnography is considered to be the gold standard for the diagnosis of obstructive sleep apnea (**Figures 1** and **2**). A screening tool is necessary to stratify patients based on their clinical symptoms, their physical examinations, and their risk factors, in order to ascertain patients at high risk and in urgent need of PSG and/or further treatment [18]. The diagnostic PSG was performed using the computerized polysomnographic system including the monitoring of electroencephalogram (EEG), submental and anterior tibial electromyogram (EMG), oxygen saturation (SaO_2), electrocardiogram (ECG), inductance plethysmography

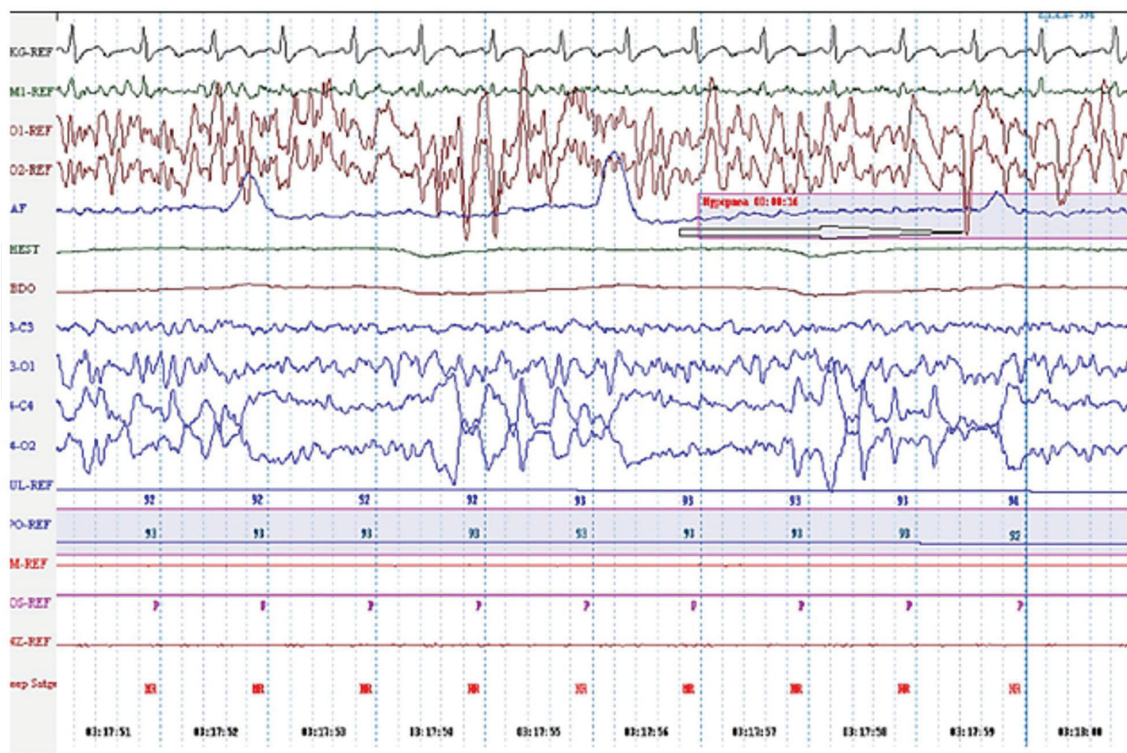


Figure 2. Polysomnography representation of airflow obstruction.



Figure 3. Polysomnography representation of airflow obstruction with desaturation.

of chest walls and abdomen, nasal pressure sensor, and oronasal thermistor. The polysomnographic recording was scored manually by the sleep specialist. The sleep stage scoring and event scoring were done in accordance with the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events [19] (**Figure 3**).

Total obstructive Apnea/hypopnea index (AHI) was calculated as the number of obstructive apneas and hypopneas per hour of total sleep time (TST). The threshold for diagnosis of OSA was set at an AHI ≥ 5 and the severity of OSA was arbitrarily defined by cut-off levels of AHI [20]. Additional diagnostic models for OSA include portable sleep monitors, radiographic studies for anatomic analysis. It is necessary to remember that OSA can occur and progress over short periods of time, and its association with significant morbidity, coupled with the relatively low risk and high reward of therapy, that requires a thorough workup and treatment plan [13].

5. Complications of OSA

Several risk factors have been identified in the development of OSA namely male gender (up to age 65), increasing age, menopause, overweight, truncal obesity reflected by several markers including BMI, neck circumference, and waist-to-hip ratio, craniofacial abnormalities, upper airway anatomy, smoking, alcohol, and genetic predisposition [21]. Obesity is considered as the most important clinical risk factor for the development of OSA. Several studies have shown that more than half of the prevalence of OSA is attributable to excess body weight as opposed to substantial improvement with weight reduction [19]. Fat Deposition around the pharyngeal airway and abdomen may likely to reduce residual capacity function, which would be predicted to reduce lung volume tethering effects on the upper airway [22]. This latter mechanism emphasizes the great importance of central obesity as compared with peripheral obesity since it is the abdomen much more than the thighs that affect upper-airway size. Therefore, obesity has been associated with functional impairment in upper airway muscles [23]. **Figure 4** represents the complications of OSA.

The prevalence of OSA increases with age and the gender differences diminish significantly after menopause [21]. Although several potential mechanisms have been proposed, the explanation for this aging increase in the prevalence of OSA remains unknown. The exact mechanism of OSA was not fully known but, it begins as just loud snoring, then gradually over a period of time cessations of breathing and symptoms of excessive sleepiness develop, and thereafter may remain stable or worsen with weight gain. Numerous studies have attempted to know the cause of the age-related impact on OSA, no definitive conclusions have been reached [22]. Anatomical and pathophysiological susceptibility to OSA appears to increase with age in older people, who had a poorer responsiveness of pharyngeal dilator muscles, the genioglossus negative pressure stimuli appear to deteriorate with aging [23].

Craniofacial anatomy is probably one of the important factors in non-obese cases with OSA. Several soft and hard tissue factors may alter the mechanical properties of the upper airway muscles and increase its propensity to collapse during sleep. Features such as retrognathia, tonsillar hypertrophy, soft palate, inferiorly positioned hyoid bone, maxillary and

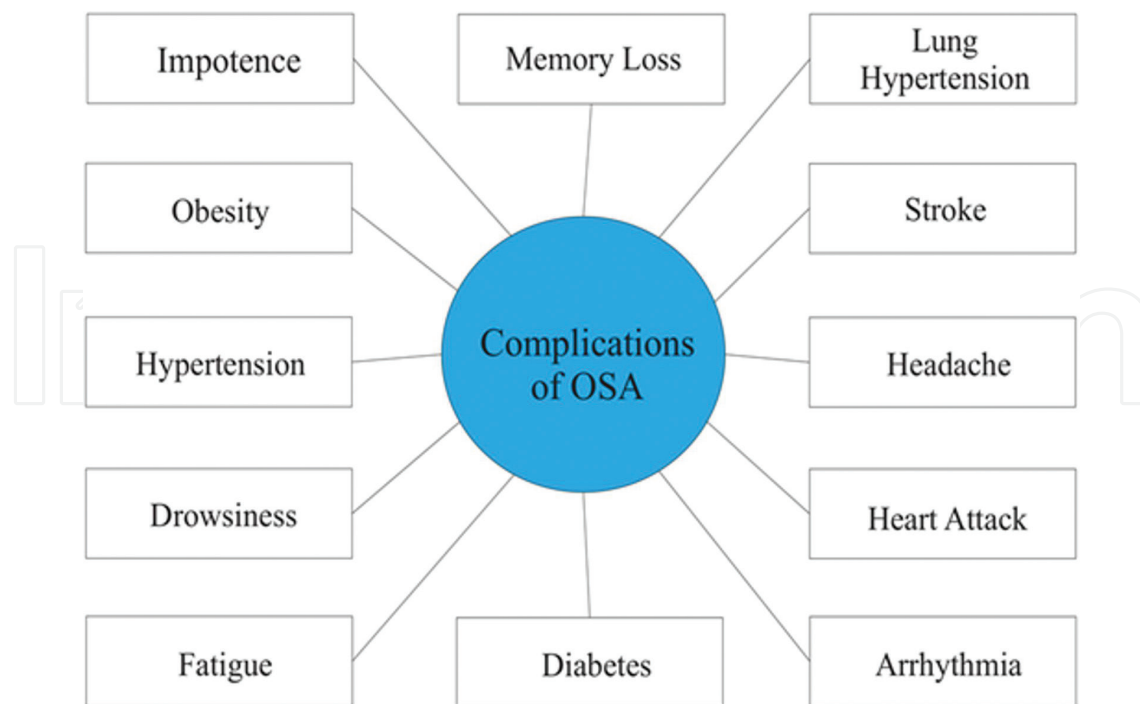


Figure 4. Complications of OSA.

mandibular retroposition, can narrow upper airway dimensions and promote the occurrence of apneas and hypopneas during sleep. Differences in craniofacial structures may alter the risk for obstructive sleep apnea across different racial groups. Therefore, different racial groups are prone to develop obstructive sleep apnea at varying degrees of obesity, clinicians should consider the possibility of this disorder particularly in the presence of clinically detectable craniofacial abnormalities [4]. According to clinic-based studies, the significant gender gap in the prevalence of OSA was reported. Recent population-based studies have confirmed that the prevalence of OSA is higher in men than women. This difference between clinic and epidemiological prevalence suggests several explanations for the gender gap. Firstly, women may not present with a similar symptomatic profile as men (loud snoring, nocturnal snorting or gasping, and witnessed apneas). Women were more likely to present with atypical complaints namely insomnia, depression, fatigue, and lack of energy, less likely to have apnea. The other reasons for this gender disparity are differences in body fat distribution (or other gender-related upper airway anatomy differences), control of ventilation, physiology of the pharyngeal airway dilator muscles activation, and hormonal differences. Therefore, the evidence suggests that women are underdiagnosed and untreated for OSA compared to men [21].

Social factors such as smoking and alcohol consumption are considered as possible risk factors for progression of obstructive symptoms [13]. Epidemiological studies show that current smoking is associated with high prevalence of snoring and obstructive sleep apnea. Smoking can alter the upper airway properties and increase its collapsibility during sleep [4]. Ingestion of alcohol especially at dinner or during the evening relaxes dilator muscles, increases upper airway resistance, and decreases respiratory reflexes, and so it leads to snoring and apnea episodes in susceptible individuals [24].

Familial aggregation of obstructive sleep apnea was first recognized in the 1970s by Strohl and co-workers in a family with several affected individuals. The relative risk of obstructive sleep apnea can be two-four fold higher in first-degree relatives [23]. Genetic factors of obesity, soft tissue characteristics, and craniofacial abnormalities together given the wealth of evidence implicating these factors in the pathogenesis of the disorder. However, the genetic basis of obstructive sleep apnea needs a better attention, the available study reports suggest that inquires about family history can help the clinician to diagnose the disorder early for further treatment [4]. Medications such as muscle relaxants, sedative hypnotics (benzodiazepines and barbiturates), narcotics, opioid analgesics and other central nervous system depressants, preferentially inhibit upper airway muscle activity while also depressing the respiratory centers of the brain [24].

There are several other risk factors associated with OSA namely nasal congestion, pregnancy, menopause, hypothyroidism, diabetes and pregnancy. Available data suggest that OSA is three times higher in patients with insulin resistance than it is in the general population. Hypothyroidism leads to deposition of mucoproteins in the upper airway that causes enlargement of the soft palate, pharyngeal and laryngeal mucous membranes, thereby increasing the propensity for upper airway collapse during sleep. Thus, patients with hypothyroidism may have increased susceptibility to obstructive sleep apnea. Pregnant women also experience higher rates of snoring particularly in the third trimester due to some of the physiologic changes that accompany pregnancy (e.g., higher progesterone levels, decrease in sleep time in the supine position). Thus, early case identification may have implications for maternal and fetal outcomes. Knowledge of risk factors for obstructive sleep apnea is therefore crucial for proper diagnosis and treatment at those with the highest risk [4, 21].

6. Pharmacotherapy of OSA

OSA is a common condition in which nasal and oral airway ceases in spite of continued diaphragmatic efforts and is associated with poor quality of life, increased healthcare-related costs. Numerous efficacious treatments are available, but the patient should not shy away from therapeutic options, and medical practitioners should not hesitate to implement treatment regimens in addressing the problem of OSA. Treatment of OSA depends on the severity, duration, and cause of the patient's symptoms as well as the patient's lifestyle, comorbidities, and overall health [13]. The detailed treatment procedures are discussed below (**Figure 5**):

6.1. Positive airway pressure treatment (PAP)

First-line therapy for most patients with OSA continues the use of PAP especially in patients with greater apnea-hypopnea index score (AHI). PAP devices work as pneumatic support that allows maintaining adequate airway patency above a critical value (pressure value below which the airway collapses). The device is applied to the patient, through a nasal or oronasal mask during sleep in overnight at a required positive pressure. The pressure

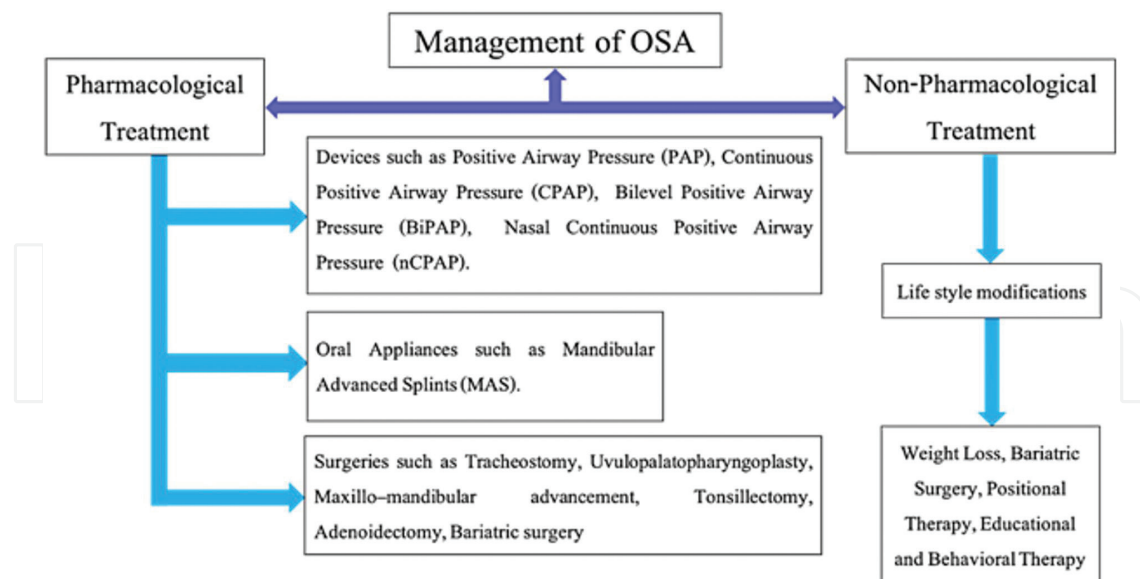


Figure 5. Pharmacotherapy of OSA.

can be varying with the severity of OSA and high pressures are required to avoid apneas during rapid eye movement sleep (REM) in the supine position or in severe obesity cases. However, patient compliance for PAP devices levels average 40–50% due to mask leaks, nasal congestion and sleep disruption. In moderate to severe OSA cases PAP therapy is remains as life-long treatment, many advanced PAP ventilators such as continuous positive airway pressure (CPAP), auto-titrating positive airway pressure (APAP), and bi-level positive airway pressure (BPAP) therapies have been commercialized in order to maintain efficacy and maximal comfort for patients [8, 25].

6.2. Continuous positive airway pressure (CPAP)

CPAP therapy was initially applied as treatment of OSA by Sullivan and colleagues in 1981 [26]. Since its initial description, the device is considered as the gold standard treatment for OSA. The clinical application of this CPAP has deeply modified the course of the disease over the last three decades, offering to thousands of patients the first non-invasive method to control their disorder. Worldwide, CPAP is constantly recommended as the first-choice treatment for patients with moderate to severe OSA. Continuous PAP (CPAP), generally administered through the nose (nCPAP), delivers a single pressure to the posterior pharynx throughout the night and acts as a pneumatic splint that maintains the patency of the upper airway in a dose-dependent fashion. The best pressure for CPAP treatment is typically determined during an in-laboratory attended sleep study. CPAP therapy is indicated in all patients with an AHI greater than 15, independently from the presence of comorbidities, type of work and severity of symptoms; if the AHI is above 5 and below 15, CPAP is indicated in the presence of symptoms (i.e. sleepiness, impaired cognition, mood disorders) or in the presence of hypertension, coronary artery disease or previous cerebrovascular accidents [8, 25, 27].

6.3. Oral appliances

Over the last 10 years, oral appliances have gained increasing recognition as a useful alternative to CPAP for the treatment of patients with mild to moderate OSA and for those who do not tolerate or adhere to CPAP. The most frequently used oral appliances are mandibular advanced splints (MAS). These splints attach to both the upper and lower dental arches in order to advance and retain the mandible in a forward position, further the size of upper airway will be widened particularly in its lateral dimension, and the function of upper airway dilator muscles, particularly the genioglossus, will improve through the protrusion of the jaw during sleep [30]. As the pharyngeal collapsibility is reduced, the risk of apnoeic events will be lowered. Side effects that are more persistent include arthralgia, teeth pain and occlusal changes [8]. Several randomized trials have evaluated the efficacy of MAS versus CPAP in mild to moderate obstructive sleep apnea, treatment with MAS significantly reduces the number of apneas/hypopneas (normalizing nocturnal SaO₂), reduces daytime somnolence, and improves quality of life [28]. It has been demonstrated that the treatment success is achieved in patients with the following characteristics: young people, women, patients with small necks, and milder OSA [29]. Another group of oral appliances includes the orthodontic micro-implants that are connected to the extra-orally anchored mask. Overnight application of these devices significantly reduces the AHI and few studies have shown similar efficacy compared with MAS. This type of implants could be used in patients with few teeth, exaggerated gag reflex, or intolerance for classic MADs [27]. Although its efficacy is still undetermined to recommend the use of these oral appliances in clinical practice [30].

The role of surgery in the management of OSA has been widely explored in an attempt to find a treatment option that could be definitive [6]. A wide variety of procedures are available, many of which are directed at the site of obstruction [2]. Initially, Kuhlo and colleagues in 1969 followed by Lugaresi and colleagues in 1970 were the first to treat OSA effectively (or Pickwickian syndrome) by means of a tracheostomy. By bypassing the upper airway, tracheostomy is purported to be curative for OSA. The surgical procedure is effective at preventing OSA-related arrhythmias, reducing pulmonary artery pressures, and improving hypertension and diabetes in patients with OSA. Unfortunately, tracheostomy has several problems including patient dissatisfaction (e.g., psychosocial aspects), perioperative complications (e.g., wound infection, tissue necrosis, bleeding), recurrent bronchitis, granulation tissue, trachea-innominate fistula formation, and stoma stenosis [31].

6.4. Surgical treatment

The aim of the surgery is to remove the cause of upper airway obstruction and to widen the airway, after a precise detection of the site where the obstruction occurs [8]. The most common sites of obstruction are the oropharyngeal tract (collapse of the retropalatal and retrolingual regions due to macroglossia, low-lying soft palate or enlarged tonsils) and the nose (congestion, polyposis, chronic rhinitis) [32]. Tonsillectomy and adenoidectomy are the most commonly used surgical procedures to treat OSA in children and are highly effective [8]. Uvulopalatopharyngoplasty (UPPP), either conventional or laser assisted (LAPP), is a widely used surgical procedure for the treatment of OSA. This technique consists of the

resection of the uvula, part of the soft palate and tissue excess in the oropharynx, and is usually performed with simultaneous tonsillectomy [31]. The success rate for UPPP alone is 30, 60% along with a tonsillectomy. The common side effects of UPPP surgery include velopharyngeal insufficiency (up to one-third of patients), dry throat and swallowing difficulty [33]. Tracheotomy is the most established surgical treatment for OSA and must be carried out in selected patients with severe OSA for whom all other treatment approaches have failed [34]. Maxillomandibular advancement (MMA) is indeed a highly effective treatment for tracheotomy. In fact, the efficacy of most treatments decreases with age and weight gain. This indicates a major factor determining the recurrence of OSA after surgery [8].

6.5. Weight control and bariatric surgery

Excess body weight and obesity are considered as largest predisposing factors for obstructive sleep apnea (OSA) over 70% of OSA patients have obesity. Population-based studies have documented a strong correlation between body mass index (BMI) and apnea-hypopnea index (AHI). Observational studies on the effects of dietary or surgical weight loss which show that reducing obstructive sleep apnea severity is possible with a decrease in body weight where a significant reduction in AHI score can be seen [4]. In patients with morbid obesity (BMI > 40) bariatric surgery, including gastric bypass and bandage, is presented as the optimal alternative for achieving considerable weight reduction when conservative treatments like CPAP, oral devices, and upper airway surgeries are failed [35]. Evidence has demonstrated, that bariatric surgery is co-adjuvant in the treatment of OSA, effectively reducing severity in up to 75% of cases. But, the remission rate for OSA 2 years after bariatric surgery in relation to the quantity of weight loss is up to 40% [27].

6.6. Educational and behavioral therapies

Educational and behavioral therapies are the first step in approaching patients with OSA, independently from the treatment chosen. Patients should be instructed to avoid risk factors such as tobacco, alcohol consumption (particularly in the evening), using sedatives and hypnotics. The physician main priority is to explain the patients the role that obesity plays in their disorder, and advice to maintain an optimal weight [8]. Another goal of the educational therapy is to help each patient to recognize the need for regular use of nocturnal CPAP. Recent reports suggest that a supportive intervention can significantly increase compliance in patients with moderate to severe OSA [36].

6.7. Positional therapy

Body position during sleep greatly affects the number and severity of obstructive events due to anatomical and physiological mechanisms. The supine position, mainly due to effects of the gravity on the tongue and soft palate position, is generally associated with an increased number of apneas/hypopneas [37]. Postural OSA can take place mainly in patients sleeping in the supine position. If postural OSA is diagnosed with standard criteria, patients can benefit from a positional therapy (PT). The therapy includes “Tennis ball technique” consisting of a tennis ball strapped to the back to discourage supine position, supine alarm

devices and a number of positional pillows. The success rate can be considered by proper selection of patients and post-treatment AHI has to be below 10. However, trials on the long-term effects of PT on important outcomes, such as metabolic and neurocognitive changes, are still needed to be studied [38].

A number of novel therapeutic options for management of obstructive sleep apnea are now under evaluation. The stimulation of upper airway muscles has been considered as a potential approach to prevent obstructive apneas over the years [39]. The Inspire Upper Airway Stimulation is the first system recently approved in patients with moderate to severe OSA, who are intolerant to use CPAP. Trials conducted on patients with moderate to severe OSA intolerant to CPAP showed 68% reduction in the median AHI score with a subjective improvement in daytime sleepiness and quality of life over 12 months of period [40]. Other emerging treatment options are intended for patients with mild disease or as a remedy for simple snoring. Among these nasal expiratory PAP (nEPAP) has recently gained attention [41]. The nEPAP is a disposable adhesive device placed over each nostril in order to increase the airflow resistance during the exhalation with a consequent improvement in the upper airway patency. A study in patients with mild to moderate OSA, nEPAP significantly reduced apneas, snoring, AHI score and improves subjective daytime sleepiness [42]. Therefore, further research is necessary to assess the potential benefits of this evolving technology.

7. Conclusion

Over recent decades, diverse studies have been carried out to improve our understanding of the physiological mechanisms and outcomes of OSA, providing relevant insights into its potential contribution to the development of various treatment alternatives. Although an effective treatment is still unavailable, the combination of several therapeutic strategies to prevent of risk factors, improving sleep disturbance and quality of life should be the focus in patients with OSA. A multidisciplinary approach is needed for a treatment protocol that is able to directly address the etiological processes of the disease in order to reduce its prevalence.

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Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication.

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