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THE THERAPEUTIC MEANS OF OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS)

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Abstract
Obstructive sleep apnea syndrome (OSAS) is one of the most common conditions that occur during sleep. OSAS involves the existence of at least 5 breathing breaks of at least 10 seconds in a sleeping hour.
OSAS etiologic factors are numerous, the most important being the increased body weight of patients (a high percentage of 50% of patients with OSAS with different degrees of obesity), age (OSAS is diagnosed in middle-aged people), craniofacial deformities, multiple pathologies leading to narrowing of the upper airways, gender (is more common in men), genetic causes (more common in black and Hispanic people), alcohol, tobacco, hypnotic and sedative medications.
Symptoms of OSAS are characterized by daytime and night-time symptoms. Of the daytime symptoms, patients frequently report headache and morning fatigue, daytime somnolence, memory impairment and concentration. Of the nocturnal symptoms, the most common symptoms experienced by patients are snoring and repeated episodes of apnea. Patients also report nocturia, polakiuria, decreased libido, symptoms that are often attributed to other pathologies. Due to concentration disturbances and low cognitive performance among patients with OSAS, they will experience a decrease in work capacity, which is reflected by the loss of work, reflected by the decrease in the number of working days.
OSAS treatment is complex, different depending on the severity of the disease and the existing comorbidities of the patient.
Keywords: *obstructive sleep apnea syndrome, PAP.*

Rezumat
Sindromul de apnee în somn forma obstructivă (SASO) este una din afecțiunile cele mai frecvente apărute în timpul somnului. SASO presupune existența într-o oră de somn a cel puțin 5 pauze respiratorii, cu o durată de cel puțin 10 secunde
Factorii etiologici ai SASO sunt numeroși, cei mai importanți fiind greutatea corporală crescută a pacienților (un procent ridicat, de 50% din pacientii cu SASO având diferite grade de obezitate, vârstă (SASO este diagnosticată la persoanele de vârsta medie), deformările cranio –faciale, multiple patologii ce determină îngustarea căilor aeriene superioare, sexul (este mai frecventă la bărbați), cauze genetice (mai frecventă la rasa neagră și hispanici), consumul de alcool, tutun, medicamente de tipul celor hipnotice și sedative.

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Simptomatologia SASO este caracterizată de simptome diurne și nocturne. Dintre simptomele diurne pacienții relatează frecvent cefalee și oboseală matinală, somnolență diurnă, tulburare de memorie și concentrare. Dintre simptomele nocturne, cele mai frecvente simptome manifestate de pacienți sunt sforăitul și episoadele repetate de apnee. De asemenea, pacienții relatează nicturie, polakiurie, scăderea libidoului, simptome care de cele mai multe ori sunt puse pe seama altor patologii. Datorită tulburărilor de concentrare și a performanțelor cognitive scăzute ce apar în rândul pacienților cu SASO, aceștia vor prezenta scăderea capacității de muncă, fapt care se reflectă prin afectarea locului de muncă, reflectat prin scăderea numărului de zile lucrătoare.

Tratamentul SASO este complex, diferit în funcție de severitatea bolii și de comorbiditățile existente ale pacientului.

Cuvinte cheie: *sindromul de apnee în somn forma obstructive, PAP.*

Classification, Etiological Factors and Symptomatology

Obstructive sleep apnea syndrome (OSAS) is one of the most common conditions that occur during sleep. OSAS involves the existence of at least 5 breathing breaks of at least 10 seconds in a sleeping hour. In OSAS, during inspiration there is a critical pressure that exceeds the capacity of the dilated airway muscles, which will lead to the collapse of the upper airways.

The OSAS classification is performed using the HAI (hypopnea-apnea index) that measures the number of breath pauses in one hour, in conjunction with the degree of blood oxygen desaturation. Therefore, if HAI has a value of between 5 - 15, OSAS is classified as being mild, if the HAI has a value between 15 - 30, then OSAS is considered as moderate and a value of the HAI is greater than 30 , it will determine the classification of OSAS as severe[1]. The high prevalence of OSAS in the population attracts an alarm because left untreated; it can lead to multiple complications such as brady-rhythm disorders and tachyarrhythmia disorders, heart failure, stroke, diabetes, dyslipidaemia, neuropsychiatric disorders, even death sudden.

OSAS etiologic factors are numerous, the most important being the increased body weight of patients (a high percentage of 50% of patients with OSAS with different degrees

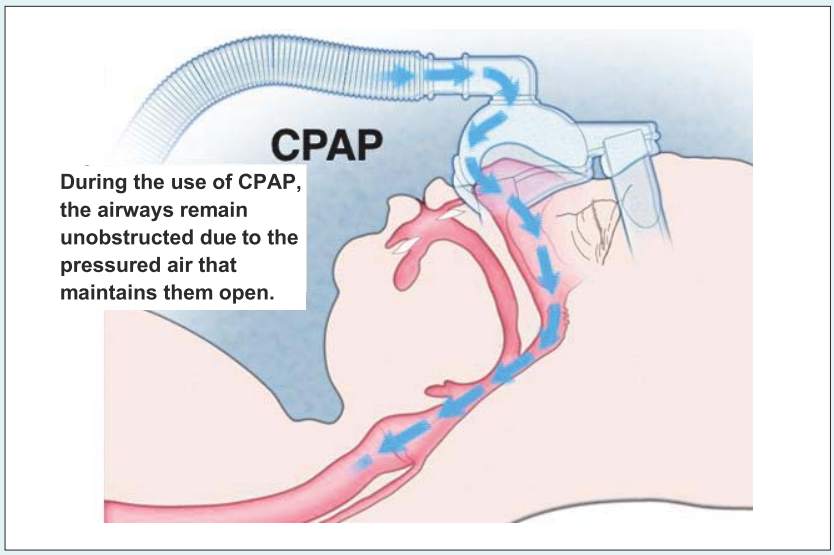

Image 1: *The effect of CPAP on the airways*[15]

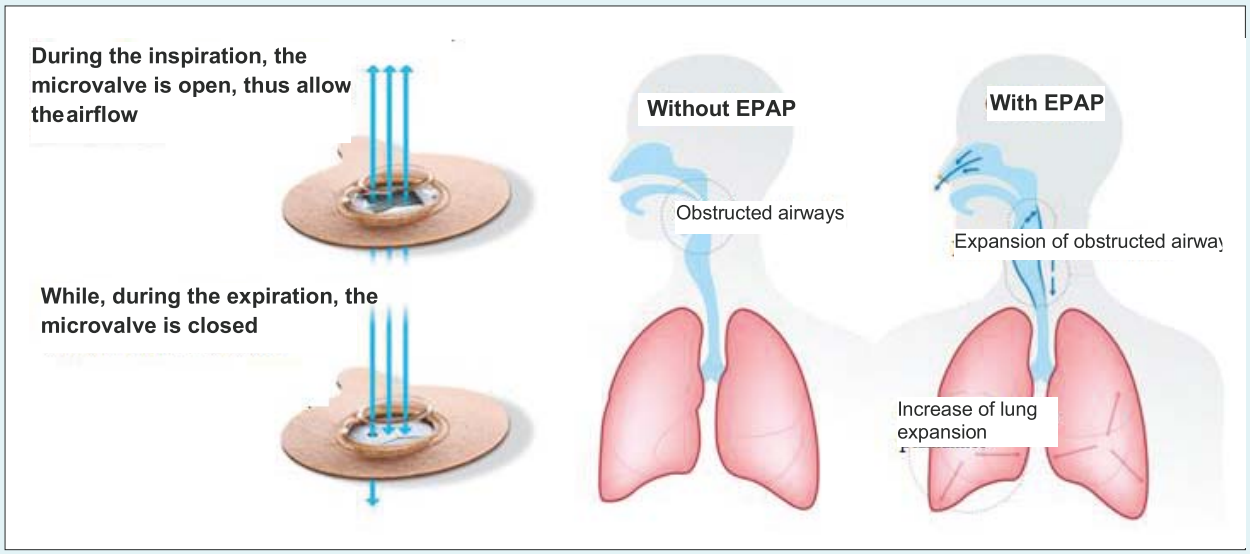

Image 2: *How EPAP works* [25]

of obesity), age (OSAS is diagnosed in middle-aged people), craniofacial deformities, multiple pathologies leading to narrowing of the upper airways, gender (is more common in men), genetic causes (more common in black and Hispanic people), alcohol, tobacco, hypnotic and sedative medications.

OSAS is most commonly determined by the reduction in size of the upper airways due to numerous causes such as macroglossia, amygdala hypertrophy, deviated nasal septum, craniofacial abnormalities, existence of fat deposits on the neck[2]. Also, a number of systemic diseases are mentioned, such as acromegaly, myxoedema, mucopolysaccharidosis, neoplastic diseases that cause infiltration of soft tissue in the neck, thus contributing to the narrowing of the airways, which increases their resistance, later resulting in their collapse[3].

The upper airways are kept open by the action of several muscles in the throat, which

have a role in the propulsion of the hyoid bone, but also in the modulation of airway resistance during sleep [4]. The neck dilator muscle that was most investigated is the genioglossus muscle, its structural modifications being described using Remmers electromyography in 1978. In this regard, it was demonstrated that at the beginning of apnea the activity of this muscle is low and then the micro-awakenings, which denote the end of the apneic episode, increase the tone of the dilator muscle of the throat, thereby restoring the permeability of the airways[5,6].

Symptoms of OSAS are characterized by daytime and night-time symptoms. Of the daytime symptoms, patients frequently report headache and morning fatigue, daytime somnolence, memory impairment and concentration. Of the nocturnal symptoms, the most common symptoms experienced by patients are snoring and repeated episodes of apnea. Patients also report nocturia, polakiuria, decreased libido, symptoms that are often attributed to other pathologies.

Due to concentration disturbances and low cognitive performance among patients with OSAS, they will experience a decrease in work capacity, which is reflected by the loss of work, reflected by the decrease in the number of working days. Also, through increased daytime sleepiness, which reduces patients' alertness, studies have highlighted the high number of road accidents caused by patients affected by OSAS. In this respect, in England, 20% of road accidents are caused by patients with OSAS[7], especially those who are in an advanced state of the disorder. Since OSAS is an autoimmune condition[8], its diagnosis and treatment should be as prompt as possible to prevent the development of its complications[9], while also contributing to the major reduction of road accidents[10,11].

Therapeutic options of obstructive sleep apnea syndrome (OSAS)

OSAS treatment is complex, different depending on the severity of the disease and the existing comorbidities of the patient. The standard treatment option is to use PAP. Along with this, surgical interventions in the ENT sphere and the use of mandibular prostheses can be used. At the same time, adjuvant measures are necessary such as weight loss, rules on sleep hygiene, smoking avoidance, alcohol consumption avoidance, and hypnotic, sedative drugs.

1. PAP Therapy: The golden treatment of OSAS, the PAP therapy, was introduced in 1971 in the USA[12]. This implies the supply of positive air pressure (PAP) with the help of a device, thereby causing upper airway to be maintained open[13,14].

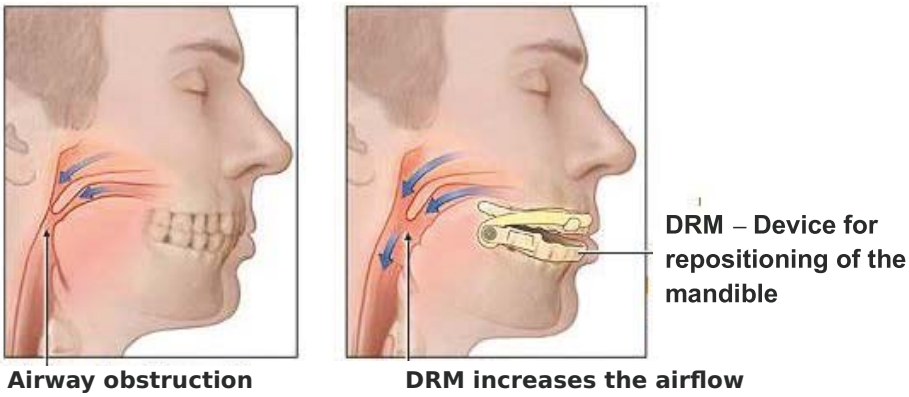

Image 1: *The effect of CPAP on the airways*[15]

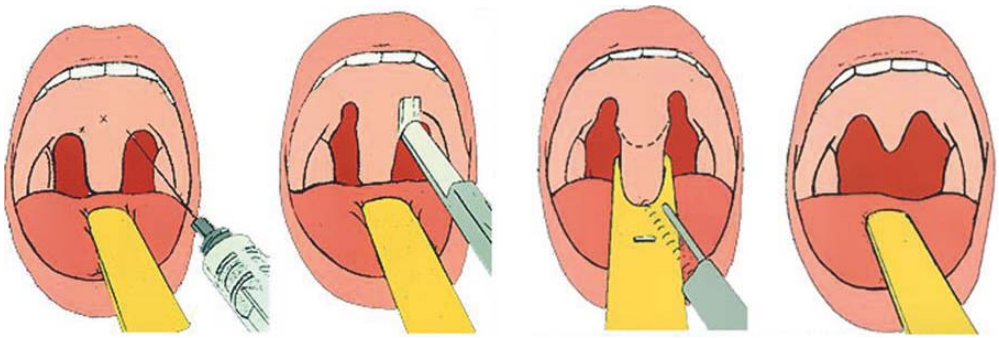

Image 4: *Opening of the airways by using UPPP* [62]

Depending on the mode of supply of pressure there are several types of devices: CPAP, with which the pressure is supplied continuously, Auto-PAP, the pressure being determined by auto-titrating and BiPaP, which uses two pressures, one with a high value, being represented by inspiratory pressure and lower pressure, representing expiratory pressure[16,14].

Auto-PAP provides different positive pressure, gradually being monitored by pressure sensors at the chest level, unlike CPAP that provides the same pressure during sleep[17]. Thus, patients under treatment with the Auto-PAP device, by receiving pressures of about 2.2 cm H_2O smaller than those using CPAP, have a better compliance to the treatment, having a record of the average hours recorded per night of PAP using increased by 0.2 hours/ night[18,19,20].

EPAP (nasal expiratory positive airway pressure) is another treatment alternative for patients who do not tolerate CPAP[21], being particularly recommended for patients with mild and moderate OSAS[22], while CPAP is recommended for patients with moderate and severe OSAS form[23,24] and rarely for mild OSAS form[16].

PAP treatment results in improvement of OSAS by decreasing the number of apnea

episodes, hypoxemia correction, decrease in snoring, slight decrease of blood pressure (by 3.3–3.4 mmHg)[26,13], decrease in daytime sleepiness[27,28], alongside the increase in the quality of life[16, 20, 28, 24]. The use of PAP for 3 months led to a decrease in insulin resistance[29, 30] improvement in pro-coagulant status[31] and of inflammatory changes[32], increased survival rate of patients by reducing the risk of recurrence of atrial fibrillation[33, 35], removal of sinus bradycardia[32], improvement of left ventricular dysfunction after 1 year of PAP use[36], all of which led to an increase in the patients' quality of life, prevention of disease complications, along with a lower rate of hospitalization[37]. Cerebral MRI in OSAS patients revealed grey matter decrease in the hippocampus, left parietal lobe, right anterior and parietal gyrus, but using CPAP for 3 months and for longer than 6 hours/ day was found to increase the grey matter at the level of the hippocampus and frontal lobe, these being clinically manifested by improvements in memory, in attention, executive and constructive function, and improved sleep[38,39].

Although PAP is the optimal OSAS treatment, a percentage of 5-50% of patients discontinues treatment or refuses its use in the first week of use. In order to increase patients' compliance with PAP treatment, it is necessary to have specialized medical staff, both at the beginning of the treatment and throughout its use, to explain and monitor the occurrence of possible adverse complications of the PAP device, along with the psychological support for the patients[40, 41]. In this respect, it has been demonstrated that close monitoring of patients with OSAS has led to an increase in patient compliance with this type of treatment[42], increasing by about 35 minutes/ night the PAP device hours of use[43].

As side effects that may occur during PAP treatment we mention: claustrophobia[42, 40], gingival bleeding[44], nasal ulceration, sneezing[24], nasal mucosal dryness, eye and face irritation, rhinorrhea[45].

2. Mandibular prostheses: Another OSAS treatment is represented by mandibular prostheses. They play a role in stabilizing the jaw and the hyaline bone, positioning the mandible to the front, thus preventing their posterior movement when the patients adopt the supine position[46, 47, 16]. They determine the increase in the diameter of the CAS, predominantly in the velopharyngeal, determining especially in width, compared to the anterior-posterior diameter[48], thus preventing the collapse of the upper airways[16,49,50,51].

Mandibular prostheses are recommended for patients with moderate or mild OSAS, not recommended for patients with severe OSAS or with heart disease[50]. They have a role in

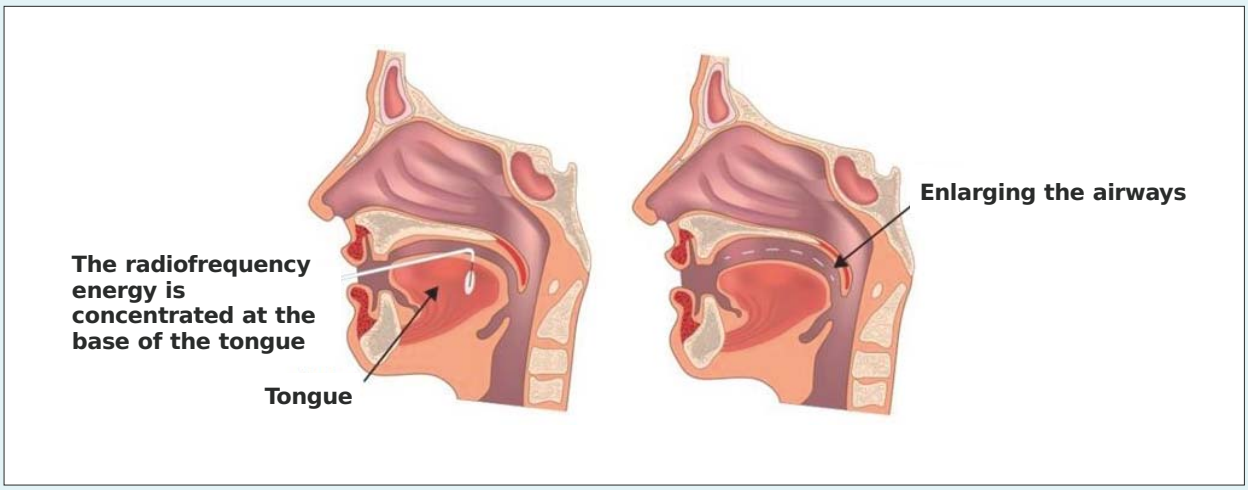

Image 5: *Radio frequency ablation for the treatment of OSAS (radiofrequency energy at the base of the tongue)* [70]

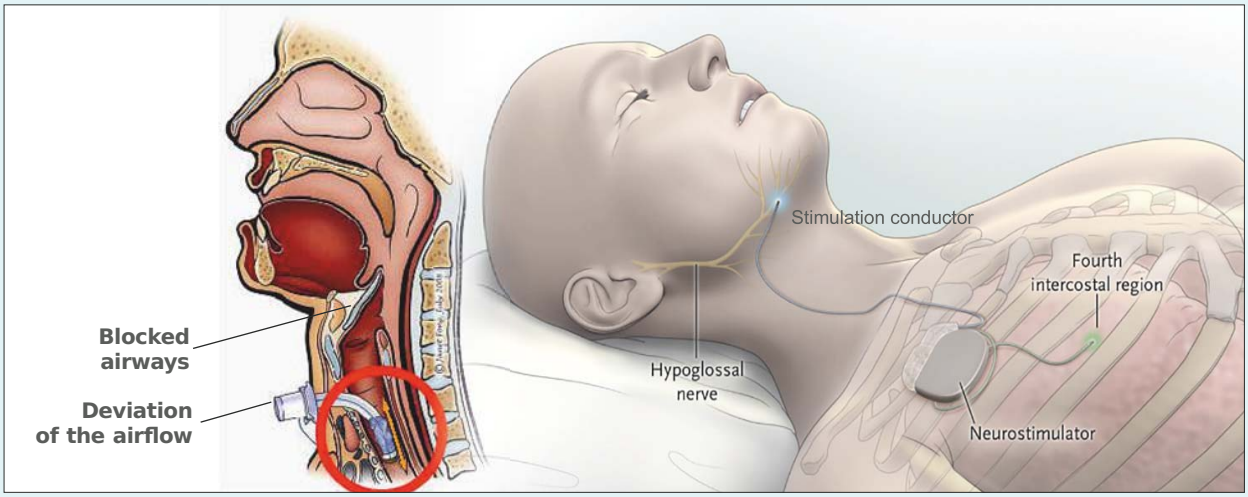

Image 6: *Tracheostomy as a treatment method for OSAS*[71]
Image 7: *Neuro-stimulation as treatment method for OSAS* [76]

reducing snoring[52], but also its intensity by approximately 3dB, reducing the daytime sleepiness[53], decreasing the HAI. By providing the mandible advance with every 2 mm, a HAI decrease of approximately 20% is obtained, but starting with the mandibular uptake by 50%, side effects are noticed to appear[54, 55] such as mandibular pain, hyper salivation, dental pain[50], impaired temporomandibular joint[56].

The use of mandibular prostheses initially involves consulting the dentist for the detection of diseases such as enantiosis, periodontitis, temporomandibular joint disorders[49,50] which contraindicate their use, and subsequently during treatment it is necessary to have dental medical check-ups periodic at 6 and 12 months thereafter.

3. Surgical interventions: *The OSAS diagnosis also involves conducting an ENT consultation to detect the causes of obstruction of the upper airways. The most frequent surgical interventions in the ENT area are uvulopalatopharyngeoplasty, septoplasty, polypectomy, tonsillectomy, diminishing the base of the tongue, reduction of the nasal cortex hypertrophy.*

Uvulopalatopharynoplasty (UPPP) reduces

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the HAI by 50%[57], reduces daytime sleepiness, reduces snoring[58], thereby causing improvement in sleep disturbance and clinical symptomatology of patients with OSAS. It involves the excision of the uvula and the back of the palate, thus increasing the retropalatin space[59]. Possible postoperative complications are the occurrence of hemorrhage, dysphagia, velopalatine insufficiency, dry mouth, nasopharyngeal stenosis[60]. Along with classical UPPP, the laser UPPP can also be performed by performing palatine and uvula laser incisions[61] with effectiveness on the HAI, resulting even in its normalization in 19% of patients with OSAS, along with snoring.

Clinical trials have demonstrated the superior therapeutic efficacy of simultaneous application of multiple surgical techniques in the upper airways[63], these being especially applied in advanced stages of the disease[64]. Thus, UPPP may be associated with tonsillectomy or radiofrequency ablation applied at the base of the tongue, but also associated with genioglossus muscle suspension, resulting in significant improvements in patient symptomatology, reduction of snoring in 75% of patients, decrease in daytime sleepiness and of the HAI[65].

Other surgical procedures used are the suspension of the initial hyoid bone in the lower mandible and then the upper limb of the thyroid cartilage, having the effect of decreasing daytime sleepiness but also reducing the severity of OSAS, its objective being the decrease of HAI[66].

Another surgical procedure used in ENT surgery is radiofrequency ablation, a minimally invasive procedure, applied in several therapeutic sessions, using radio waves with frequencies in the range of 300 KHz - 1MHz[67]. These, by heating, act on the submucosa, decreasing the size of tissues[68]. It can be applied in nasal corneal hypertrophy, tongue and tonsil hypertrophy, along with corneal rhinitis, thus causing reduction of HAI and daytime sleepiness[69,67].

An invasive treatment method, applied only to patients with severe OSAS, but also to those with multiple comorbidities such as morbid obesity, severe cardiac pathology, craniofacial malformations is tracheostomy, the purpose of which is to increase the dimensions of the upper airways. It plays a role in the removal of apnea episodes, the decrease in somnolence (Thatcher, Maisel, 2003), but it is marked by the occurrence of pulmonary and local infections with increased risk of post-operative bleeding[72,73].

In 2014 in the USA, the FDA approved a new OSAS treatment method, which by stimulating the hypoglossal nerve determines the increase of the activity of the genioglossus muscle, thereby causing the

opening of the upper airways. This surgical procedure is applied to patients affected by moderate and severe forms of OSAS, determining the decrease of the HAI by 68%, of the daytime sleepiness. The therapeutic procedure consists of mounting an electrode in the hypoglossal nerve, a pressure sensor between the internal and external intercostal muscles, a neuro-stimulator in the right infaclavicle region. The pressure sensor has a role in monitoring ventilatory efficiency. When it detects difficulties in ventilation, the neuro-stimulator will transmit impulses to the hypoglossal nerve, causing it to increase the muscular activity of the genioglossus[74], thus opening the airways. As side effects, there may be difficulties in installing the neuro-stimulator, pain in the incision, but also the decrease in the muscularity of the tongue in the first 2 to 3 weeks post-surgery[75].

The frequent association of OSAS with psychiatric pathology, such as depression, has led to monitoring the effect of the medication on these patients with OSAS. In this respect, the beneficial effect of tricyclic antidepressants and selective serotonin inhibitors on depression and OSAS was shown[77, 78]. Of the selective serotonin selective inhibitors, the most studied were Fluoxetine and Paroxetine, showing their role in increasing the tone of the upper airway dilatation muscles, resulting in improved HAI in the non-REM phase, but having reduced effects on diurnal symptoms[79, 80]. It is known that benzodiazepines and other sedative, hypnotic drugs used are not recommended for patients with OSAS because they decrease the tone of the airway muscles, along with the increase in the duration of the apneic episode and of the HAI[77]. Non-benzodiazepine drugs such as zopiclone, zolpidem and eszopiclone have similar therapeutic effects to those of benzodiazepines for hypnotic and sedative effects, but because the muscle relaxant effect is weaker, it allows them to be used for short-term OSAS and insomnia patients and are considered adjunctive in growing patient compliance with CPAP treatment[81, 77]. Also, psychostimulants are contraindicated in OSAS due to the fact that they cause sleep alteration[77], the only licensed psychostimulant medication being Modafinil, used in sleeplessness due to narcolepsy, idiopathic hypersomnia, obstructive sleep apnea, and chronic sleep disorder caused by working in shifts[82,83].

The frequent association of memory disorders with OSAS has led to clinical trials demonstrating the beneficial role of drugs used in patients with Alzheimer's disease on OSAS. Thus, Donepezil reduced HAI and daytime sleepiness and, in combination with Ondansetron and Fluoxetine, reduced the HAI by 40.5%[80].

As adjunctive agents of OSAS therapy, anti-inflammatory drugs such as Fluticasone, used in allergic rhinitis, may be used to lower HAI[80]. Last but not least, measures such as smoking avoidance and alcohol consumption avoidance are needed in the evening, increasing both the frequency and duration of obstructive airway episodes, especially in the first hour of sleep[84,85].

Because more than 50% of patients with OSAS are obese, weight loss causes a reduction in OSAS severity. Clinical trials have shown that any weight gain of 10% will increase the severity of OSAS by 26%. Decreased weight is achieved according to its degree, but also by the existence of the associated pathology, and it can be achieved by various therapeutic methods such as increasing physical activity, following a food diet, preferably done under the strict

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guidance of the nutritionist, to prevent the rebound effect. So, if the BMI is of 25 kg/m^2 the loss of weight is done by food diet, and if the BMI is higher than 27 kg/m^2 drugs can also be indicated. The existence of a BMI higher than 35 kg/m^2 associated with other comorbidities or the existence of a BMI higher than 40 kg/m^2 indicates the performance of bariatric surgery[86]. Medication treatment of obesity can be applied to patients with BMI higher than 30 or BMI higher than 27, but other existing pathologies are associated such as type 2 diabetes, hypertension, dyslipidaemia. As drugs, Lorcaserin hydrochloride, Osymia can be used. *Other drugs have been used over the years, but have been withdrawn from the US such as Fenfluramine, Dexfenfluramine[87], Sibutramine and Rimonabant due to the existing adverse effects*[88].

Decreasing body weight with bariatric surgery is indicated for patients with morbid obesity (BMI > 40kg/m^2) or with BMI > 35 kg/m^2 but who also have other serious comorbidities[16]. There are several reversible surgical methods, being classified on account of being reversible, such as implantation of the adjustable gastric ring and irreversible methods such as gastric bypass, gastric sleeve, biliopancreatic deviation. All of these surgical procedures, in addition to weight loss, also reduce the incidence of cardiovascular disease, diabetes[89, 90], but are marked by the occurrence of adverse reactions more pronounced in irreversible interventions such as vitamin B 12, calcium, iron, folic acid absorption disorders, causing the need for supplementation[91].

In 2014, the FDA approved a new weight reduction treatment for patients who did not respond to previous obesity treatment and who had a BMI greater than 35 kg/m^2 and at least one comorbidity such as hypertension, dyslipidaemia[92, 93, 94]. It is the intermittent blocking of the vagus nerve (vBLOCK), which by intermittent stimulation of the vagus nerve reduces the feeling of hunger, leading to a 5-10% decrease in body weight[95,96].

Conclusions

- The aetiology of OSAS is multifactorial, which consists of a complex interaction between the anatomical and neuromuscular factors, which determines the collapse of the upper respiratory tract.
- There are now different treatment options for effective OSAS management. CPAP is very effective in controlling symptoms, improving the quality of life, and reducing the clinical consequences of sleep apnea, and is indicated as a first line of treatment. Bi-PAP and Auto-CPAP may be useful for patients who do not tolerate

CPAP, but the high cost of these devices often limits patients' access to this treatment. Mandibular repositioning devices can be offered as a viable alternative to patients with mild and moderate OSAS and those who do not tolerate PAP. Surgical methods in the ENT area, such as tonsillectomy, uvulopalatopharynoplasty, radiofrequency ablation, tonsillectomy, correction of nasal septum deviation are the most commonly used procedures in the treatment of OSAS.

- Weight gain is one of the most important determinant factors of OSAS recidivism. Although achieving and maintaining weight reduction is difficult, the results are extremely beneficial. A multidisciplinary approach and the implementation of educational programs significantly improve disease management.
- General and behavioural measures such as weight loss, avoidance of alcohol consumption before bedtime, body position during sleep are the main lines to follow in treating the disease.
- In conclusion, OSAS should be promptly diagnosed and treated by multidisciplinary medical teams, while continuing to improve the treatment of this condition, such as neuro-stimulation, along with intermittent blocking of the vagus nerve (vBLOCK).

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