Chapter

Elements of Diagnosis and Non-surgical Treatment of Obstructive Sleep Apnea in Adults from the Dental Medicine Perspective

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Abstract

Dentists hold a key role in the context of ever-growing concerns regarding the management of Obstructive Sleep Apnea (OSA) in adults. Dentists' contribution in this domain starts with the screening of patients with possible OSA. An earlier intervention for correcting a dento-maxillary anomaly or a parafunction will often serve as a preventive treatment with regard to possible OSA. Furthermore, dental medicine offers nowadays, apart from orthodontic and surgical treatment, a set of therapeutical methods, the most commonly used being the oral appliance and myofunctional therapies. Another important sphere of professional responsibility of the dentist involved in the treatment of OSA consists of periodical examinations focused on assessing clinical evolution, corrective interventions on oral appliances and interventions for preventing local complications. On the other hand, recent studies indicate the potential of different pharmacotherapy agents on OSA patho-physiology, severity and treatment. These agents have shown promising results in improving the efficacy of other therapies dedicated to OSA, therefore, current topics in modern scientific research include the evaluation of standard, even higher doses of single agents or the combination of different agents on the evolution of OSA, as well as the assessment of the association of diverse pharmacotherapy agents with other OSA therapies.

Keywords: Obstructive Sleep Apnea, Dental Sleep Medicine, Oral Appliances, Myofunctional Therapy, Pharmacotherapy Agents

1. Introduction

Sleep disorders represent an increasingly common pathology, whose undesirable effects could profoundly affect patients' every-day life. The sleep-related breathing disorders (SRBD) are placed by the American Academy of Sleep Medicine (AASM) among the six categories of sleep disorders in the International Classification of Sleep Disorders, Third Edition (ICSD-3) [1–3]: insomnia; sleep-related breathing

disorders; central disorders of hypersomnolence; circadian rhythm sleep–wake disorders; parasomnias; sleep-related movement disorders. Moreover, seep-related breathing disorders - that are characterized by abnormalities of respiration during sleep - are classifies into four major categories: OSA (obstructive sleep apnea); CSA (central sleep apnea); sleep-related hypoventilation disorders; sleep-related hypoxemia disorder [4].

Obstructive Sleep Apnea (OSA) in adults represent a pathology included in the SRBD, which is associated with repetitive episodes of partial or complete collapse of the upper airway during sleep. As a result of these episodes, reduced (hypopnea) or absent (apnea) airflow lasting for at least 10 seconds is registered [3, 4]. In this specific context, the blood oxygen saturation is reduced and the brain is therefore alarmed, so "micro arousals" ("cortical arousal") appear during sleeping. Apnea episodes can repeat hundreds of times a night, without the patient being aware of them. However, the sleep-quality becomes poor, physiological sleep-pattern is disturbed and the individuals are constantly tired during the day, their work performance is affected and their quality of life decreases; moreover, individuals can even cause various work, road or domestic accidents due to excessive day-time sleepiness. OSA is a potentially life-threatening disease, its consequences including high blood pressure, diabetes, heart attack or stroke [3–5].

Obstructive sleep apnea (OSA) is traditionally quantified initially with testing during sleep by the apnea-hypopnea index (AHI), respiratory disturbance index (RDI) or respiratory event index (REI) [1, 4]. AHI results after analyzing a polysomnography (PSG) that is usually done in a sleep laboratory, and includes total episodes of apneas and total hypopneas per hour of sleep. RDI represents the sum of total apneas, total hypopneas and respiratory efforts related to arousals per hour of sleep. REI is a measure of respiratory events in a certain sleep unit of time, when using a home sleep apnea testing (HSAT); it is estimated that REI can underestimate the real index of respiratory events and OSA severity. However, the diagnosis of OSA is frequently based on the combination of clinical assessment and a diagnostic sleep study (an in-laboratory polysomnography/PSG or a home sleep study) [6].

OSA evidence-based therapeutic options includes: medical, surgical, behavioral strategies and adjuvant therapy/pharmacotherapy agents. Medical therapy is represented by PAP - positive airway pressure - therapy (CPAP/continuous positive airway pressure - the device deliver a steady pressure rate for both inhalation and exhalation); BPAP/bilevel positive airway pressure - the device deliver different pressure rates for inhalation and exhalation); APAP/automatic positive airway pressure - automatically adjusts to meet each specific person's night breathing needs) and oral appliances therapy (OAT), which aim is to reposition intraoral or craniofacial structures in order to increase the pharyngeal airway space, thus preventing pharyngeal collapse [4, 6].

Surgical options dedicated to OSA patients include: the reduction of soft tissues (i.e. adeno-tonsillectomy, uvulo-palatopharyngoplasty, tongue reduction), maxillomandibular surgery, hyoid repositioning, the increment of nasal patency [7], hypoglossal nerve stimulation (HGNS).

On the other hand, behavioral strategies are represented by the following: weight loss - ideally up to a body mass index BMI <25 kg/m^2; exercising; avoiding the consumption of tobacco and recreational substances; avoiding caffeine and alcohol before bed [1, 8]; positional therapy (non-supine position during sleep) [6, 9–12]. Different studies highlighted that weight loss is an important tool in OSA treatment, being effective in lowering OSA severity and reducing cardiovascular risks [6, 13–15].

PAP treatment is considered first-line treatment for OSA, however, its adherence is often poor [5]. The necessity for novel treatment options to help those who cannot

adhere to positive airway pressure treatment is highly emerging. Regarding OAT therapy, which is enthusiastic received and applied by specialized trained dentists, several barriers were also identified, including the difficulty to accurately predict which patients will receive therapeutic benefit from this therapy and the possible side-effects related to oral appliances (OA). On the other hand, different classes of medication have been tested with regards to their effect on OSA severity. This paper will present dentists' key role in the context of ever-growing concerns regarding the management of OSA in adults, in conjunction with relevant arguments that indicate the rising potential of different pharmacotherapy agents on OSA.

2. Dentist's role in screening and treating OSAS

2.1 Identification of possible sleep disorders

In order to provide high-quality healthcare services to patients with OSAS, medical practitioners - including dentists - should adhere to the latest standards of care and should be able to participate effectively and efficiently in the management of these pathologies, according to evidence-based practices [1, 16]. Medical interdisciplinary collaboration represents a major element for diagnosis and treatment of patients with OSA. The expanding medical knowledge and the new advancements in scientific research on diverse OSA therapies place the dentist in a key-role position in the context of managing OSA in adults. Along with other medical specialists (sleep medicine specialists, pneumologists, ENT - ear, nose, and throat specialists, neurologists, cardiologists, endocrinologists, bariatric surgeons, maxillofacial surgeons, psychiatrists, psychologists), the specialists in the domain of dental sleep medicine (DSM) can participate both in the identification of possible sleep disorders and in the treatment of certain types of sleep pathologies (snoring, bruxism, mild or even moderate OSA), as well [17].

The specificity of the theoretical and practical content of dental medicine offers the practitioner of dental medicine the chance to contribute to solving medical-dental problems for a large number of patients, whose age can range from youngest to oldest. The professional and social responsibility requires that the dentist pays special attention to specific morpho-functional aspects at the level of the dento-maxillary apparatus (stomatognathic system) which, for certain patients, can suggest the presence of earlier or more advanced OSA manifestations.

Therefore, dentist's role in the management of OSA starts with the screening of the patients visiting the dental office. The screening guidelines for detection of possible sleep disorders recommend that data can be collected even from anamnesis and clinical - general and local - direct observations. The "suspect patient" with possible OSA often has a specific profile, reporting: daytime sleepiness; difficulties in daily activities; chronic fatigue; attention, concentration and memory problems; behavioral disorders: irritability, anxiety, aggressiveness; episodes of wheezing, gasping, choking, snoring or bruxism during sleep (bruxism occurs in up to 95% of patients with OSA) [3, 4]; tooth tapping; night-sweating; leg or arm movements during sleep; frequent urination during night; dry mouth sensation in the morning; morning headaches and dizziness. These elements are frequently observed: obesity; large neck-size (>43 cm for men; >40 cm for women); hypertension; gastro-esophageal reflux; age over 50; dysmenorrhea, amenorrhea, menopause; smoking; alcohol consumption [3, 4].

Along with these general aspects, dentist should notice and register local aspects that can be related to possible sleep disorders: large tonsils, voluminous posterior palatal soft tissues, hypotonic palatal or lingual musculature, tongue

size (macro-glosia), tongue indentation, maxillary compression, maxillary micro-gnatism, micro-gnathism, mandibular retrognatism, deep palate, dental malposition, partial edentulous areas, tooth wear, narrow superior air-ways, oral breathing, deviated nasal septum, nose shape (narrowing) and obstructions [3, 4].

Nevertheless, patients with possible OSA will receive a thorough, complete oral examination of soft and hard tissues, and a direct examination of the temporomandibular joint (TMJ) [18]. Intraoral and extraoral photographs, full dental arch impressions for obtaining dental study casts, intraoral scanning for obtaining digital models, conventional radiological exams and additional CBCT (Cone-beam computed tomography) exams are recommended.

Application of specific questionnaires represents another important "tool" in the screening of patients with possible OSA in the dental practice; the most used questionnaires are EPWORTH and STOPBANG questionnaires [17]. Ideally, dentists should apply the questionnaires for all patients that are susceptible of OSAS. Based on data collected from anamnesis, clinical and para-clinical investigations, and on questionnaires' results, the dentists should refer the patients with possible OSA to the sleep medicine specialist.

2.2 Diagnosis and treatments of OSA: an interdisciplinary collaboration

In order to evaluate the sleep disorders, the sleep medicine specialists will perform specific clinical examinations and para-clinical tests on patients with possible sleep apnea, that were referred by the dentists (i.e. polysomnography – an overnight test that includes the monitoring of the patient's airflow through the nose and mouth; blood oxygen level/pulse-oximetry; blood pressure; electrocardiographic activity/ECG; brain wave pattern/electroencephalogram/EEG; eye movement/Electrooculography/EOG; movement of respiratory muscle and limbs). Additionally, interdisciplinary collaboration between sleep medicine specialists and pneumologists, cardiologists, E.N.T. - ear, nose, and throat - specialists, neurologists, endocrinologists or psychiatrists is very useful for obtaining relevant data regarding the patient's general health status. The sleep medicine specialists will establish the diagnosis and severity of OSA based on previously collected data [3, 4, 16], mostly determined by the combination of clinical assessment and a diagnostic sleep study (an in-laboratory polysomnography/PSG or a home sleep study) [6].

OSA are classified as central, obstructive and combined, depending on their specific ethio-pathogenic mechanism. As previously stated, apnea-hypopnea index (AHI) is a very important element in establishing the severity of OSAS; it represents the number of times in an hour when a sleeping person either stops breathing completely or inhales limited air-flow. Each episode must last at least 10 sec. AHI is a major indicator for obstructive sleep apnea, as follows: AHI of 30 or more events in an hour indicates severe sleep apnea; AHI = 15–30 events suggests moderate apnea; AHI = 5–15 events indicates mild apnea [3, 4].

The sleep medicine specialists are responsible for establishing the proper therapy for OSA patients. The therapeutic conventional options for OSA in adults are: medical, behavioral, surgical and adjuvant - pharmacotherapy agents.

CPAP (Continuous Positive Airway Pressure) Therapy - introduced by Sullivan in 1981 - is considered the main treatment for OSA (severe, moderate and mild forms). The evaluation of the evolution of OSA under this specific therapy is assessed according to: reduction of daytime sleepiness, specific evaluation of OSA, patient and family satisfaction, adherence to therapy, achieving an optimal amount of sleep per day, practicing proper sleep hygiene, weight reduction, evaluation of factors that may aggravate the condition, titration (polysomnography/PSG) [3, 4]. CPAP therapy (Continuous Positive Airway Pressure Therapy) is frequently recommended

for severe sleep apnea. On the other hand, specific recommendations are usually accepted with regard to the oral appliance therapy [1, 16, 19, 20]. Oral appliance therapy should be used only when the patient cannot endure or refuses the CPAP therapy, as some specific problems related to the use of CPAP therapy can appear: dry mouth, eye watering, chest pressure, cold sensation, frequent awakenings, noise, mask-leak, skin irritations, claustrophobia [3, 4]. Adherence to CPAP therapy (defined as > 4 h average nightly use) is considered poor with only 46–83% being adherent, even for severe and moderate OSA [3, 4, 6, 21]. Additionally, the effectiveness of oral appliances in these severe cases of OSA is estimated to be also poor. On the other hand, oral appliance therapy can be recommended as an additional treatment in the case of moderate apnea and can be the first-choice treatment in mild apnea cases. Moreover, the sleep medicine specialist who diagnoses the OSA refers the patients who could eventually benefit from OAT (oral appliance therapy) to the special trained dentist; following the complete specialized examination of the recommended patients, the dentist will decide the possibility of applying the oral appliance therapy (OAT).

2.3 Oral appliance therapy (OAT)

Oral appliance therapy (OAT), is considered - for more than 20 years - a minimally invasive and effective treatment of OSAS. Oral appliances are represented by tongue retaining devices/TRD (which hold the tongue in a more anterior position) and mandibular advancement devices/MAD (mandibular advancement appliances or mandibular repositioning appliances/MRAs) [3, 4, 6, 22]. The reviewed scientific studies highlighted that the largest evidence base and guidelines exist for mandibular advancement devices [6]. These devices include a custom-made adjustable monobloc or double occlusal splint (corresponding to the upper and lower dental arches) that has the role to anteriorly reposition the mandible and the adjacent soft tissues (including the tongue) during sleep. This stabilized position of the mandible will enable a larger opening of the pharynx lumen, which mechanically keeps the upper airway open during sleep, by preventing the soft tissue of the throat and the tongue from collapsing into the airway [17, 20, 23]. It is strongly advisable that OSA treatment should never be initiated by a dentist without the patient's assessment by a sleep medicine specialist. At this specific stage, interdisciplinary collaboration with orthodontists, specialists in prosthodontics, radiologists, specialists in geriatric dentistry, gerontologists, air-way prosthodontic specialists, TMD (temporomandibular disorders)/Oro-facial pain specialists or maxillo-facial surgeons is recommended in order to carefully prepare the sequences of the treatment plan. The results obtain via general and local examination performed by the dentists are essential not only in identifying patients with possible OSAS, but in the confirmation of the proper candidates for oral appliance therapy [18]. Moreover, the selection of the appropriate oral appliance for a specific clinical case is the responsibility of the dentists who are specialized in the treatment of sleep apnea [3, 4], and is influenced by diverse elements, as follows: characteristics of cranio-facial structures; oral condition (number, location and health-status of remaining teeth; periodontal tissues status; soft tissue health); oral functionality; anticipated dental restorative needs; reported allergies and/or sensitivities; patients' manual dexterity, visual acuity and cognitive ability; patients' comfort; financial considerations [1, 3, 4]. At the moment, more than 100 types of oral appliances are available on the medical market (i.e.: IST – Intraoral Snoring Appliance; Monoblock, Klearway; TAP-T Thornton Adjustable Positioner; Erkodent – Silensor; Somnodent; boil and bite – ready-made splints etc). A custom, titratable appliance is recommended versus a non-custom oral device [16, 19], as a successful oral appliance therapy (OAT) is considered to be

an integrated, customized treatment. The oral appliances are small-sized, portable, easy to tolerate and easy to clean.

The two occlusal splints of the oral appliance are connected by a special system that allows the stabilization of the mandible in a protrusive position. 75% of the maximum protrusion of the mandible, i.e. approximately 8-9 mm on average, is usually recommended to be determined and registered for the most oral appliances; this amount of protrusion is considered to be the maximum allowed for an oral appliance therapy dedicated to OSAS. The adjustment of mandibular advancement level (titration) is recommended to be included in the specific monitoring of OSA patient (part of the immediate check-ups and long-term follow-ups, as well).

Obtaining an oral appliance involves several successive steps: conventional impressions of the dental arches or intraoral scanning; obtaining the models of the dental arches (cast models, 3D printed models or digital ones); registration of the protrusive position of the mandible; project and fabrication of the oral appliance; oral appliance delivery: intra-oral placement, control and adjustments; use and homecare instructions delivery.

Regarding the registration of the protrusive position of the mandible for OAT, findings in medical literature suggest that a 25–75% protrusion is ranged as comfortable and yet therapeutic [24, 25]. On the other hand, maximizing the mandibular protrusion with oral appliances may be more important in severe cases of apnea. Different studies highlighted that the treatment results with oral appliances are better when the mandibular advancement is greater - however, possible associated local side effects should be observed and fixed [24, 26]. The protruded mandibular position can be determined and registered with special devices (i.e. "The George Gauge™ Kit").

As stated before, patients undergoing oral appliance therapy should be informed and educated about the correct night-wear of the appliance, about its insertion, disinsertion and proper cleaning; morning exercises (using, for example, the Occlusion Trainer [18]), gymnastics and facial, head and neck massages are recommended as well [1, 19].

Nevertheless, patients should be aware of the importance of weight control and sleep hygiene; a proper lifestyle, which involves a healthy diet, gymnastics, sports, avoiding caffeine, alcohol, tobacco or recreational substances [1, 3, 4, 8] can have a positive effect on the results of oral appliances therapy. Additionally, positional therapy is considered to be a beneficial adjunct to oral appliance therapy, in order to reduce AHI across total sleep time [6, 25, 27].

Oral myofunctional therapy (OMT) is also recommended to be associated with OA therapy [4]. Suzuki et al. showed that application of OMT was accompanied with a decrease of AHI by approximately 50% in a group of students with high Epworth Sleepiness Scale (ESS) [28]. Upper airway muscle training (oropharyngeal exercises, breathing, speech, swallowing, chewing exercises, movement of the tongue, nose, cheeks, and jaw) completed for 3 months (one hour per day) could decreased the AHI by 39% in patients with moderate OSA [29].

Immediate check-ups and also long-term follow-ups are needed after the insertion of a mandibular advancement device (MAD). Appointments are made within the first days or, at least, within the first two weeks after the delivery of the oral appliance; patient comfort and the efficacy of the applied treatment should first be assessed by the dentists, along with small adjustments of the appliance that are also recommended, such as reduction of the pressure against the teeth or marginal fit adjustments. Titration/calibration of the oral appliance is a very delicate and important aspect in oral appliance therapy. Continued gradual advancement of the mandible may bring further improvement of the symptoms related to OSA [1, 3, 4, 16]. On the other hand, sometimes reduction of the mandibular protrusion is necessary,

if adverse local effects are registered. The oral appliance therapy outcomes are evaluated by the sleep medicine specialists three months after the initiation of the OA treatment; a control polysomnography is recommended and the progress and benefits of the treatment should be registered.

Periodical examinations focused on assessing clinical evolution, corrective interventions on oral appliances, as well as the interventions for preventing the oro-dental complications - that oral appliances can generate - represent another sphere of professional responsibility of the dental practitioner involved in the OSA treatment. Periodical dental and medical check-ups (every six months or at least once a year) are strongly recommended for long-term monitoring of patients with OSA. The management of this patients in long term imply permanent communication between the dentists, the patient's physician and other healthcare professionals that were involved in the treatment. The dentist should check and register: patient comfort; oral appliance efficacy; persistence of previously resolved symptoms related to OSA; the structural integrity and the occlusal stability of the oral appliance; wear, fractures; bacterial or fungal growth on the appliance [1, 4]. During this periodical dental examinations the appearance of possible side effects correlated to oral appliance therapy can be observed: muscle and joint soreness; soft tissue or gingival inflammation; excessive salivation or, on the contrary, dry mouth sensation; tooth mobility or fractures; teeth migrations and occlusion disturbances [3, 4, 30]. All side effects produced by the oral appliance therapy should be registered, documented and managed; it is important to determine the possible causes of these unpleasant side-effects and to try to reduce the damage. Balance between the actual need of oral appliance therapy and the severity of generated side effects should be evaluated in order to determine if oral appliance therapy should be discontinued and if the patient agree with another form of therapy recommended by the physician. Yet, Lavigne [4] consider that the adverse effects of oral appliances are generally considered to be negligible, mild or transient among most patients.

3. Pharmacotherapy agents and OSA pathophysiology

The use of medical-dental therapies, as stand-alone or in combination with other therapeutical alternatives for controlling OSA, represent a viable option in certain clinical cases, depending on the OSA clinical severity and/or the patient's acceptance of the suggested solution. As pharmacotherapy agents have shown good results in improving the efficacy of other therapies dedicated to OSA, modern scientific research in the field of OSA focuses on the evaluation of diverse doses of single agents or the combination of different agents on the evolution of OSA. Another important aspect regards the association of diverse pharmacotherapy agents with other conventional OSA therapies.

Hypnotics represent a group of pharmacological agents that promote sleep and moderate sedation by depressing the central nervous system. Hypnotic use is relatively frequent for people diagnosed with OSA, as they usually experience current insomnia [31]. Interest has grown steadily in the current scientific research to determine the specific effects of hypnotics on OSA severity, pathophysiology, their possible side-effects.

Benzodiazepines have sedative-hypnotic, myorelaxant, and anticonvulsive actions, in higher doses being commonly prescribed for insomnia [31]; early studies suggested that their use in patients with OSA has been controversial and can possibly worsen overnight hypoxemia in OSA [32, 33].

Hoijer et al. [32] reported in 1994 that nitrazepam did not adversely influence apnea intensity or severity in patients with mild to moderate sleep apnea; the

authors suggested that contraindicating benzodiazepine use in sleep apnea may be restricted to the patients with severe sleep apnea.

Late in 2011, a study conducted by Wang et al. [33], showed that mild–moderate OSA patients with higher awake central chemosensitivity have higher breathing impairment during sleep following the use of a hypnosedative - temazepam; in this context, the authors highlighted the clinical importance of phenotyping the individual OSA response to temazepam using ventilatory chemoreflexes during wakefulness.

A relatively recent study, conducted by Lin BM et al. [34] confirm that the use of benzodiazepine receptor agonists is not associated with increased odds of snoring in middle-aged and elderly women. On the other hand, the administration of certain benzodiazepine sedatives in chronic pain patients on opioids induces mild respiratory depression, which is associated with reduced severity of OSA, probably increasing the arousal threshold [35]. However, some studies reported that benzodiazepines can produce poor motor coordination, dizziness or next-day drowsiness, and can alter the cognitive process and driving ability [31].

Certain pharmacological agents used to treat depression also have sedative effects, and thus are administered to improve night-sleep. As there is an increase need to augment OSA early detection, treatment options and strategies, emerging therapies such as non-benzodiazepine sedative hypnotics (NBSH) could be considered good alternative treatments, along with weight loss, positional therapy, oral appliances, or surgery [6]. Subjects with OSA usually demonstrate a low arousal threshold or propensity to wake easily in response to a disturbance. Sedatives were tried as a therapy for OSA, and different studies highlighted that sedative agents can increase arousal threshold [6, 36–39], for example, trazodone (100 mg, taken orally, 90 min. before bedtime) - a non-myorelaxant sleep-promoting agent - increases the respiratory effort-related to arousal threshold [36] and eszopiclone (3 mg, immediately prior to sleep) also increases the arousal threshold and lowers the AHI in obstructive sleep apnea patients [38].

Recently, Chen et al. [40] studied the effect of sedative antidepressants on the severity of OSA in stroke patients, as these medication is frequently prescribed for stroke patients due to their high prevalence of depression and insomnia. Patients were administered 100 mg of trazodone (*Trazodone Tab, Taoyuan, Taiwan*) just before polysomnography. The authors reported that trazodone may decrease OSA severity without increasing nocturnal hypoxia in OSA patients with comorbid ischemic stroke. On the other hand, it is acknowledged that trazodone - a tricyclic antidepressant - can cause severe toxicity at excessive doses [31].

Z-drugs represent a class of non-benzodiazepine agents (zolpidem, zopiclone, eszopiclone, zaleplon), with certain properties that make them more attractive: they have less adverse side effects, do not reduce deep sleep, and cause less residual daytime effects [31, 41].

The effects of zopiclone – a nonbenzodiazepine sedative – on the arousal threshold and on genioglossus muscle activity were analyzed in a group of patients with predominantly severe OSA [42]; thus, the potential effects of zopiclone on obstructive sleep apnea (OSA) severity was studied. The results of this study showed that zopiclone (7.5 mg, taken orally, immediately prior to sleep) increased the arousal threshold without reducing genioglossus muscle activity; the authors noted that these aspects may be favorable for some patients with OSA.

However, despite of these promising results of different scientific studies, Eckert et al., early in 2014, [37], pointed out that no trial or evidence has demonstrated a clear and significant improvement in severity of sleep disordered breathing when sedative therapy is applied, even in patients with a low arousal threshold.

Moreover, Carter et al. [42] stated that zopiclone may worsen hypoxemia in some patients with OSA.

Yet, the effect of non-benzodiazepine sedative hypnotics (NBSH) on continuous positive airway pressure (CPAP) adherence in patients with obstructive sleep apnea (OSA) was highlighted in a recent study [43]: the authors concluded that non-benzodiazepine sedative hypnotics administered in OSA patients may increase CPAP adherence (defined as CPAP use for >4 h/night, on >70% of nights); additionally, they noted that especially eszopiclone showed the most significant effect on CPAP adherence, however, the effect of zolpidem and zaleplon on CPAP adherence requires further investigation.

Recently, orexin antagonists have been recommended primarily for people with insomnia [31, 44]. Certain roles of orexin neuropeptides (that are produced by neurons in the lateral hypothalamus) are represented by the regulation of sleep and arousal, as well of circadian rhythms; orexin neurons are activated during wakefulness, but during sleep they are inhibited [45]. Consequently, dual orexin receptor antagonists (DORAs: almorexant, lemborexant, filorexant, suvorexant) may be considered an additional pharmaceutical option to treat insomnia in some patients [44]. For example, suvorexant showed a more balanced sleep architecture profile and greater potency than almorexant, yet, no clinically meaningful respiratory effects during sleep were observed in patients with mild or moderate OSA, receiving a single dose (40 mg) or multiple doses of suvoxerant [46]. As the influence of suvorexant in patients with severe OSA have not been profoundly studied, this medication must be used with caution and administered at lower doses in patients with OSA [44].

Along with the pharmacological agents listed and presented above, antihistamines (histamine antagonists) - that are often recommended in case of respiratory allergies - have also been used to treat mild insomnia. However, they are not associated with dependence, but tolerance can occur with their long-term use.

Additionally, Carter et al., in 2021 [31], concluded that common hypnotics can increase the respiratory arousal threshold by approximately 15–30% and have inconsistent effects on next-day alertness; however, in case of obese patients, severe OSA, higher respiratory arousal threshold, or at high doses, hypnotics can worsen overnight hypoxemia.

A stated before, different mechanisms can contribute to multifactorial OSA pathophysiology [5], including: increased collapsibility of the passive upper airway; impaired neuromuscular tone (relative hypotonia of upper airway dilator muscle/genioglossus muscle) and sympathetic neural activity; greater the loop gain; anatomic craniofacial features (increased anterior facial height, decreased pharyngeal airspace, inferiorly placed hyoid bone); high body mass index (obesity); rostral fluid shifts. This heterogenous pathogenesis can generate opportunities for therapies with diverse mechanisms of action: antihypertensive medication (acetazolamide; spironolactone), anti-inflammatory agents, antidiabetic medications, antidepressant medications or synthetic cannabinoids [5]. Moreover, Lavigne, in 2009 [3], stated that "of all the metabolic syndrome components, OSA has been most strongly linked with hypertension". Different scientific studies confirm this statement. Eskandari et al. [47], conducted a study in a group of men participants with moderate to severe OSA, which was divided in three sub-groups depending on the received treatment: acetazolamide therapy only; continuous positive airway pressure (CPAP) therapy only; acetazolamide plus CPAP therapy; the authors pointed out that a reduction in AHI was found in all three experimental groups, with the greatest reduction noted in the acetazolamide plus CPAP group. It was also demonstrated that spironolactone administered to patients with moderate–severe OSA and resistant hypertension produces a change in AHI from 36.6/hour at

baseline to 14.8/hour [48]. In the same line, Fiori et al. [49], showed that spironolactone plus furosemide daily reduced AHI by 14.4%, after one week of treatment, versus sodium-restricted diet that reduced AHI by 22.3% and versus 0.8% reduction of AHI correspondent to the placebo monotherapy.

As regard of Sodium-glucose Cotransporter-2 inhibitors (SGLT-2 inhibitors), there are previous studies indicating that SGLT-2 inhibitors may reduce OSA severity. Furukawa et al. [50] found that dapagliflozin might improve moderate to severe sleep-disorders breathing in Japanese patients with obesity and type 2 diabetes mellitus (mean AHI decreased from 25/hour to 19/hour). Tang et al. [51] considered that dapagliflozin could demonstrate therapeutic value for patients with T2DM (type-2 diabetes mellitus) combined with OSA; this study highlights that dapagliflozin can significantly reduce glucose, BMI, blood pressure and AHI and improve hypoxemia during sleep, therefore, indicates that dapagliflozin has potential as an effective treatment approach for OSA.

On the other hand, limited studies have been conducted in patients with OSA in order to demonstrate reduction in AHI with synthetic cannabinoids use. Yet, recently, Taranto-Montemurro L et al. [52] showed for the first time that the combination of a norepinephrine reuptake inhibitor (atomoxetine/80 mg at bedtime) and an antimuscarinic (oxybutynin/5 mg at bedtime) clearly reduces OSA Severity (>50%); the authors suggested these results may reorient future treatment of OSA.

4. Conclusions

It is well acknowledged the complexity of OSA, its heterogeneity in terms of risk factors and consequences, pathophysiological phenotypes, clinical presentation, and comorbidity [6, 53]. We understand more and more the importance of phenotyping patients with OSA (clinical, anatomical, genetic and polysomnographic phenotyping, biomarkers assessment, life style factors evaluation) and identifying the patients that can benefit from a pharmacotherapy that targets their major predisposing factors [4, 6]. This aim implies advanced validation of the phenotyping tools and algorithms that should be used to identify the principal factors precipitating OSA in individual patients [53]. The interconnected risk factors for OSA needs to be considered in order to achieve precision medicine in OSA [4]. Pharmacotherapy agents may have an important role as monotherapy in the treatment of mild OSA, or could be used in association with other therapies in moderate-to-severe OSA, including oral appliances therapy (OAT), provided by dentists trained in dental sleep medicine (DSM). Additionally, as patient-centered care is the future, recognizing and understanding patient profound medical needs, preferences, their psychological status, expectations and beliefs [4] contribute in the successful implementation of OSA complex therapies.

Moreover, considering the interest shown in the field of TMD (temporo-mandibular disorders) and oro-facial pain for under and post-graduate students training, and given the important role of the dentist in the early detection, treatment and monitoring of patients with OSA and sleep bruxism, it is necessary that the aspects related to dental sleep medicine (DSM) should also be found in a multi- and inter-disciplinary organized form in university curricula (stand-alone disciplines, courses, practical training), this approach corresponding to the growing need for treatment of this pathology in the general population.

An important issue is the one related to the actual "dental/clinical complex symbiosis" in OSA therapy, that should lead to improved personal medical care.

The combined modern therapies for OSA (medical, surgical, behavioral strategies, pharmacotherapy agents) have to be adjusted continuously, in respect to recent scientific research, in order to deliver the best results for patients, emphasizing their quality of life in addition to medical care.

Current - Western allopathic medicine benefits from the accumulation of large fundamental biomedical knowledge, special equipment, modern materials and techniques.

Medical specializations and supra-specializations offer increased chances for therapeutic success, provided that the early diagnosis and therapeutic indication are as accurate as possible and the patient has proper, legitimate access to the health services provided by the medical staff.

The complexity of clinical cases varies between patients, and the clinical complexity of a single clinical case can evolve towards simplification or, on the contrary, towards increased complexity. The greater the complexity of a clinical case is, the greater is the need for multidisciplinary collaboration, in order to increase the accuracy of medical decisions.

In our opinion, the previous considerations are also valid in the case of OSA, whose etiopathogenic and clinical complexity requires such an approach. To meet such a requirement - that focuses on the quality of life of the patient, with his unique bio-psycho-social-cultural profile, unlikely repeatable - health care systems, along with socio-economic, cultural or political systems must act in multiple directions.

First of all, the health systems should be provided with the necessary medical personnel, having various clinical specializations; nevertheless, medical personnel should have a balanced territorial distribution and it should be open to continuous training and inter-disciplinary collaboration.

Secondly, regarding the rapidly evolving topic represented by OSA, which obviously represents an interdisciplinary chapter of human pathology, it would be interesting to organize university courses with interdisciplinary content, that are opened to all students in both medicine and dentistry. This approach can create a strong basis for future interdisciplinary clinical collaborations between post-graduates. Importantly, the medical management between the dental and clinical disciplines should be optimally and formally integrated. This aspect involves the promotion of clinical guidelines suitable for dental practitioners' use, and proper training for the next generation of dentists.

Additionally, medical dental practitioners contribution in OSA management could be found in the clinically justified concern of phenotyping OSA patients, so that each patient is recommended the best (simple or combined) therapeutic variant, adjusted to the individual etiopathogenic context and to the severity of the disease.

On the other hand, properly designed both clinical and dental research studies could contribute to better specification of the various "subsets" of patients, which could thus benefit more from the application of a proper therapeutic variant. In this context, dentistry could become more useful and more effective in the management of OSA patients and cases of "over-treatment" or cases of malpractice could thus be avoided.

The role of dentistry and the involvement of dental sleep medicine specialists in prevention, detection, treatment of mild or moderate forms of OSA, and in long term management of OSA is acknowledged. Moreover, multidisciplinary and interdisciplinary medical path allow a holistic approach of the patient, thus providing best therapeutic results.

Promising results were achieved in the field of pharmacotherapy of OSA - as stand alone or in combination with other therapies. Nevertheless, more scientific

research and consistent clinical trials are needed in order to offer great perspectives for this fascinating medical domain.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

AAMS	American Academy of Sleep Medicine
AHI	Apnea-Hypopnea Index
APAP	automatic positive airway pressure
BMI	body mass index
BPAP	bilevel positive airway pressure
CBCT	cone-beam computed tomography
CPAP	continuous positive airway pressure
CSA	central sleep apnea
DORAs	dual orexin receptor antagonists
DSM	dental sleep medicine
ECG	electrocardiographic activity
EEG	electroencephalogram
ENT	ear, nose, and throat specialist/surgeon
EOG	electrooculography
ESS	Epworth Sleepiness Scale
HGNS	hypoglossal nerve stimulation
HSAT	Home Sleep Apnea Testing
IST	Intraoral Snoring Appliance
MAD	mandibular advancement devices
MRAs	mandibular repositioning appliances
NBSH	non-benzodiazepine sedative hypnotics
OA	oral appliance
OAT	oral appliance therapy
OMT	oral myofunctional therapy
OSA	obstructive sleep apnea
PAP	positive airway pressure
PSG	polysomnography/polysomnogram
RDI	Respiratory Disturbance Index
REI	Respiratory Event Index
SGLT-2 inhibitors	Sodium-glucose Cotransporter-2 inhibitors
SRBD	sleep-related breathing disorders
TAP	T Thornton Adjustable Positioner
TMD	temporo-mandibular disorders
TMJ	temporomandibular joint
TRD	tongue retaining device
T2DM	type-2 diabetes mellitus

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