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Featured Review Article

Oral appliances for obstructive sleep apnea

Serena Incerti Parenti [a], Francesco Bortolotti [b], Giulio Alessandri-Bonetti [c,*]

[a] Research Fellow, Unit of Orthodontics, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[b] Visiting Professor, Unit of Orthodontics, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[c] Associate Professor, Unit of Orthodontics, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

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ABSTRACT

Importance: Obstructive sleep apnea (OSA) is a major public health issue that can have serious medical consequences. Although continuous positive airways pressure (CPAP) is currently the first-line treatment for OSA, there is increasing evidence on the effectiveness of oral appliances (OAs) which show higher treatment adherence compared with CPAP. This review focuses on indications, effectiveness and side effects of treatment with OAs in adult OSA patients. The role of dentists in the multidisciplinary diagnosis and management of OSA is also discussed and the most up-to-date scientific evidence for an evidence-based clinical decision-making process is summarized.

Observations: Qualified dentists in dental sleep medicine can screen patients for OSA using questionnaires and evaluating the presence of anatomic risk factors during routine examinations. Sleep physicians confirm the diagnosis of OSA, determine whether treatment is indicated and may recommend OAs. Qualified dentists evaluate patients for suitability of OAs and begin therapy with the proper device. A collaborative follow-up should be performed during treatment, with patients being periodically monitored by sleep physicians for objective sleep testing and, also, by qualified dentists for OA adjustment and management of any side effect.

Conclusion and Relevance: Custom-made and titratable OAs are indicated for adult OSA patients who do not tolerate or who are not good candidates for CPAP. A multidisciplinary approach allows to establish the least possible amount of mandibular advancement while achieving the highest reduction of OSA severity, thus optimizing the treatment effectiveness, reducing the occurrence of side effects and decreasing the risk of treatment discontinuation.

1. Introduction

Obstructive sleep apnea (OSA) is a common chronic sleep-related breathing disorder characterized by the recurring upper-airway collapse during sleep, which causes snoring, cessation of breathing, intermittent hypoxia, and sleep fragmentation. Repetitive episodes of intermittent hypoxia disrupt the physiologic interactions between sleep and the cardiovascular system, determining a chain of events (e.g., sympathetic activation, endothelial dysfunction, oxidative stress, inflammation, increased platelet aggregability, metabolic dysregulation) that can be implicated in the initiation and in the progression of cardiovascular diseases, such as drug-resistant systemic hypertension, myocardial infarction, atrial fibrillation, congestive heart failure, and stroke [1–6]. Moreover, metabolic alterations that are commonly observed in patients with OSA, such as insulin resistance, type 2 diabetes, and altered serum lipid profile, may further contribute to increase the risk of cardiovascular morbidity and mortality [7,8].

Symptoms of OSA include excessive daytime sleepiness, irritability, and deficits in the cognitive domains of attention/vigilance, with negative effects on quality of life and work performance [9,10] and, also, on the risk of motor vehicle crashes [11]. In fact drowsiness is a well-recognized cause of motor vehicle crashes, and drivers with OSA have roughly twice the risk of crash as compared with healthy drivers [11].

The presence and the severity of OSA are defined by the apnea-hypopnea index (AHI), which is the number of episodes of complete (apnea) or partial (hypopnea) upper-airway obstruction per hour.

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* Corresponding author: Department of Orthodontics, School of Dentistry, University of Bologna, Via San Vitale 59, 40125 Bologna, Italy.
E-mail address: giulio.alessandri@unibo.it (G. Alessandri-Bonetti).

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OSA is classified in the adult patient as mild ($5 \leq$ AHI < 15), moderate ($15 \leq$ AHI < 30), or severe (AHI ≥ 30). In children, the AHI cutoffs are quite different, being mild with $1 \leq$ AHI < 5, moderate with $5 \leq$ AHI < 15 and severe with AHI ≥ 15.

A recent large population-based study suggests that sleep-disordered breathing is highly prevalent, reporting that 49.7% of men and 23.4% of women older than 40 years have an AHI ≥ 15 [12]. Considering excessive daytime sleepiness associated with AHI ≥ 5, the reported prevalence of OSA is 5.9% in women and 12.5% in men older than 40 [12].

2. Diagnosis of OSA

With regard to the pathogenesis, OSA is very often a multifactorial disorder that is not only caused by local obstructions of the upper airways. In fact, the anatomic aspect has to be considered only one piece of a puzzle in which, especially when OSA goes untreated or undiagnosed for a long time, the effect of upper-airway obstruction can be enhanced by additional functional factors, including an inability of the pharyngeal muscles to hold open or stiffen the airway, an oversensitive ventilatory response to a respiratory disorder (the so-called high-loop gain), and a low arousal threshold [13–15].

Because of this complex interplay between anatomic and nonanatomic factors in the pathogenesis of OSA, a multidisciplinary approach is necessary for an adequate diagnosis of this potentially life-threatening disease. Many experts from different specialty areas of medicine should be involved, and the diagnosis should be adapted to the individual characteristics and to the cause of the obstruction.

The diagnosis can be suspected in presence of characteristic symptoms, such as daytime sleepiness or other cardiovascular and metabolic comorbidities. However, we must remember that OSA begins long before any of these symptoms become apparent and that our goal should be to make an early diagnosis to prevent the onset of complications.

A full medical and sleep history should be obtained, and a physical examination should be performed. History of snoring, witnessed apneas, gasping/choking episodes, excessive sleepiness not explained by other factors, nocturia, morning headaches, sleep fragmentation, or decreased concentration/memory should be collected. During the examination, attention should be paid to the presence of physical characteristics that may be suggestive of the presence of OSA, such as large neck circumference (>17 inches in men, >16 inches in women), an increased body mass index (≥ 30 kg/m^2), macroglossia, tonsillar hypertrophy, and enlarged/elongated uvula [16]. Finally, a standard otolaryngological clinical evaluation including an oral examination, with evaluation of the uvula, soft palate, tonsillar pillars, tongue, and tonsil size grading, is essential to identify signs of an obstruction of the upper airways. Using awake endoscopy, an otolaryngologist also can try to locate the level of the obstruction using a static and dynamic assessment of the upper airways, simulating the apnea with the Muller's maneuver, a forced inhalation having both the nose and mouth closed. This clinical evaluation helps to identify the site and the degree of the obstruction.

Recently, otolaryngologists also have introduced in the OSA diagnostic path the drug-induced sleep endoscopy, a diagnostic tool for the endoscopic evaluation of the upper airways in patients during a pharmacologically induced sleep, which provides a precise assessment of obstruction sites and, consequently, is essential for a more accurate therapeutic indication.

After these evaluations, an objective testing is required to make a definitive diagnosis of OSA and, also, to establish the severity of the disease. This is accomplished by the polysomnography that records multiple physiological characteristics simultaneously during sleep, including brain activity, chest and abdominal movements, eye movements, oronasal airflow, and oxygen saturation. All these parameters allow establishment of the quality of the patient's sleep.

According to the last version of the International Classification of Sleep Disorders (ICSD-3), the diagnosis of OSA requires either signs/symptoms (e.g., associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance, or observed apnea) or associated medical disorder (e.g., hypertension, coronary disease, atrial fibrillation, congestive heart failure, stroke, diabetes, cognitive dysfunction, or mood disorder) coupled with five or more obstructive respiratory events (apneas, hypopneas, or respiratory-efforts arousals) per hour of sleep [17]. Alternatively a frequency of obstructive respiratory events ≥ 15 satisfies the diagnostic criteria, even in the absence of associated symptoms or disorders [17]. Even if the ICSD-3 states that the respiratory event index may be derived from out-of-center sleep testing, the gold standard test for the diagnosis of OSA remains polysomnography [17].

3. Treatment of OSA

The therapy must be individualized, aiming to remove the obstruction and to prevent or correct the comorbidities. The types of specialists who may be involved in the comprehensive medical care of OSA include the nutritionist, the pulmonologist, the otolaryngologist, the maxillofacial surgeon, and the dentist. Dentists must be experts in sleep disorders and should have attended a specific training course.

The first treatment recommendation includes behavioral measures, such as weight loss, alcohol avoidance, or changing sleep position. There are also several surgical options that may be indicated to remove the upper-airway obstruction: otolaryngological surgery (i.e., uvulopalatopharyngoplasty, laser-assisted uvuloplasty, and genioglossus advancement with hyoid bone suspension) aims to change the soft tissues surrounding the upper airways, whereas maxillofacial surgery, including maxillo-mandibular advancement, aims to change the hard tissues and, as a consequence, the soft tissues.

Among nonsurgical options, the first-line treatment for most patients affected by OSA is the continuous positive airway pressure (CPAP), which acts as a pneumatic splint and opens the upper airway during sleep to prevent the collapse responsible for apneas. Although CPAP is highly effective in reducing AHI, patient tolerance and adherence are often low [18–20] and side effects are common [21].

A valuable alternative therapy for OSA is represented by the forward repositioning of the mandible by means of an oral appliance (OA) that widens the size of the pharynx, mainly in the lateral dimension, stretches tongue muscles counteracting the tongue's retrolapse during sleep, stabilizes the hyoid bone and the soft palate, and prevents the posterior rotation of the jaw [22–24].

Myofunctional therapy also could be used as an adjunct to other treatment options for OSA.

4. The use of CPAP versus OAs in the treatment of OSA: efficacy versus effectiveness

A systematic review and meta-analysis published in 2018 included only randomized controlled trials on the effects of CPAP versus OAs in adult patients with OSA to provide the most up-to-date evidence for this clinical decision-making process [25]. CPAP decreased posttreatment AHI significantly as compared with OAs (difference in means = −8.243; 95% confidence interval [CI] −13.132 to −3.354). This finding indicates a higher ability of CPAP to prevent the occurrence of obstructive events as assessed by AHI and, therefore, a higher treatment efficacy for CPAP versus OAs. Accordingly, a network meta-analysis published in 2017 found that CPAP decreased AHI more (mean treatment effect = −25.27 events/hour; 95% CI −28.52 to −22.03) than OAs (−15.20 events/hour; 95%

CI −19.50 to −10.91) [26]. Also, oxygen desaturation index (ODI) decreased more in patients treated with CPAP (−20.40; 95% CI −25.19 to −15.62) as compared with patients treated with OAs (−12.58; 95% CI −18.84 to −6.32). Moreover, the differences were significant between CPAP and OAs for both AHI (−10.06; 95% CI −14.21 to −5.91) and ODI (−7.82; 95% CI −13.04 to −2.59).

Although treatment efficacy (i.e., how well an intervention works under ideal circumstances in terms of eliminating or reducing parameters of sleep apnea severity, such as AHI and ODI) is achieved more by CPAP as compared with OAs, it should be acknowledged that treatment effectiveness (i.e., how well an intervention really performs under conditions that are not controlled) is a combination of both efficacy and patient adherence. From a clinical perspective, it is essential to consider this concept in the management of a chronic disease, such as OSA [27]. In fact, CPAP is generally not well-tolerated and has a lower compliance compared with OAs [25]. Therefore, despite higher treatment efficacy of CPAP versus OAs, its effectiveness in terms of long-term health effects can be compromised by a worse usage profile (Fig. 1).

Accordingly, no statistically significant differences were observed in quality of life, functional outcomes, or cognitive function outcomes in patients treated with CPAP versus those treated with OAs [25]. No significant differences were found in average posttreatment subjective daytime sleepiness as measured by Epworth Sleepiness Scale (ESS) [25], with the differences between CPAP and OAs for improvement in ESS being not significant [26].

Patients' adherence should be monitored throughout treatment and OAs should be recommended as an alternative in adult patients with OSA who do not tolerate or are not good candidates for CPAP, as recommended by the American Academy of Sleep Medicine (AASM) and the American Academy of Dental Sleep Medicine. These guidelines suggest that OAs are indicated for adult patients requesting treatment for primary snoring who do not respond to behavioral therapy like weight loss, positional therapy, and alcohol deprivation and for adult patients with OSA who are intolerant to CPAP or who request an alternative therapy [28]. A recent article suggests that if patients have a clear preference for OA, it is important to prescribe it as a first-line therapy because such a patient may be more likely to adhere the treatment [29]. The orthodontist should therefore treat patients with a diagnosis and a prescription made by a sleep physician also considering the patient's requests.

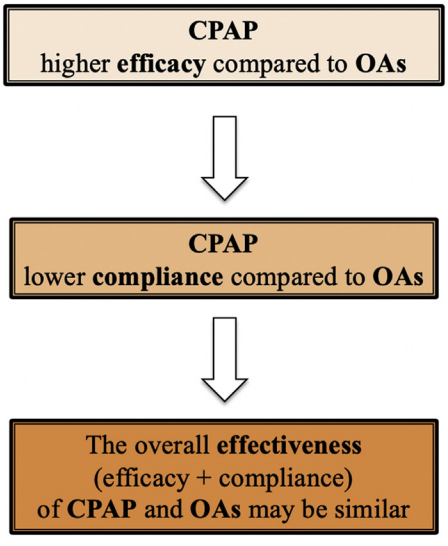

Fig. 1. CPAP versus OAs in the treatment of adult patients affected by OSA.

4.1. Contraindications

An adequate number of healthy teeth (at least 6 to 10 teeth) [30] should be present to anchor the OAs, and patients should be able to protrude the mandible forward and open the jaw without significant limitations to be suitable for treatment with OAs. The repair or replacement of inadequate restorations or prothesis should be performed before the beginning of treatment.

4.2. Design

OAs include both the maxillary and mandibular dental arches. They can be custom-made (i.e., fabricated with patient-specific design features obtained from impressions) or not custom-made (i.e., prefabricated and, subsequently, needs modifications to fit the individual patient) and, also, titratable (i.e., a mechanism allows the mandible to be moved forward in increments over time) or nontitratable (i.e., the mandible is held in a single forward position).

A randomized controlled cross-over trial conducted in 2008 has shown first that custom-made devices are more effective than thermoplastic boil-and-bite devices in reducing AHI and increasing oxygen saturation, mainly due to better appliance retention and to a more consistent and reproducible degree of advancement [31]. This finding should be taken into proper account due to the increasing number of dental appliances bought directly by consumers at drugstores and on the Internet [32].

Accordingly, AASM and American Academy of Dental Sleep Medicine guidelines suggest the use of custom-made and titratable OAs [28]. A systematic review conducted by Ahrens et al. [33] concludes that OAs are generally effective irrespective of their design features, and the most effective is the one that is the most acceptable for the patients and that meets success criteria at the same time.

There is a certain variability with respect to the degree of mandibular advancement during treatment with OAs. Currently, there is no well-defined protocol that indicates the extent of protrusion from which to start and the mandible is moved forward without specific guidelines, with patients being generally advanced to either 50% or 75% of maximum mandibular protrusion. Therefore, we performed a systematic review with meta-regression analysis to explore the effectiveness of different amounts of mandibular advancement in reducing AHI in patients with OSA treated with OAs [34]. Although a linear and proportionally increasing effect between the amount of mandibular advancement and treatment success was expected, it was found that the AHI improvement was not proportional to the mandibular advancement increase. This finding indicates that there is no dose-dependent effect of mandibular advancement on treatment success with OAs and further emphasizes the relevance of a proper understanding of the complex interplay between nonanatomic and anatomic factors in the pathophysiology of OSA as well as the need for an accurate and multidisciplinary diagnosis.

It is advisable to provide an individualized therapy for each patient based on relevant patient pathophysiologic characteristics, with gradual increments over time in the amount of mandibular protrusion through the use of titratable OAs. The subjective response to titration should be progressively evaluated and the device should be adapted to the minimum effective mandibular advancement. It is better to start with a slight mandibular advancement and gradually increase it until the highest reduction in AHI is achieved. It is necessary to identify the minimum amount of mandibular advancement required for an individual patient while getting the highest reduction in AHI to optimize treatment efficiency while reducing the risk of side effects and, also, improving treatment adherence [35,36]. The key factor for an

individualized therapy is a multidisciplinary diagnosis that takes into account all the anatomic and nonanatomic factors that are essential to phenotype pathophysiological traits. Under these conditions, the social and economic health burden of OSA and the associated life-threatening morbidities should be reduced [37].

4.3. Predictors of treatment success

A high interindividual variability exists in response to the treatment with OAs, and current research is focusing on the identification of variables that reliably discriminate between poor and good responders before manufacturing the device, thus avoiding treatment delays and waste of resources. Lateral cephalometry represents a simple and widely available method to identify craniofacial characteristics that can have an impact on treatment response, but most of the dento-skeletal and soft tissue cephalometric measurements analyzed in a systematic review have been recognized as not prognostic for OA treatment outcome [38]. Even if controversial and limited data are available on the predictive role of some cephalometric parameters (e.g., cranial base angle, mandibular plane angle, hyoid to mandibular plane distance, posterior nasal spine to soft-palate tip distance, anterior nasal spine to epiglottis base distance, and tongue/oral cross-sectional area ratio) [38], a recent study aimed at comparing the three-dimensional craniofacial anatomy between responders and nonresponders to treatment with OAs using cone beam computed tomography imaging, found no significant between-group differences in upper-airway morphology and in anatomic structures surrounding the upper airway [39]. These findings corroborate the concept that the craniofacial anatomic structures alone cannot explain the response to treatment with OAs and that, in this context, it is essential to phenotype the pathophysiologic traits of patients with OSA. In fact, although the predisposition to anatomical collapsibility of the upper airways is important in the concept of apneic events, it may not be the leading factor for the development of OSA, as nonanatomic pathophysiologic traits (e.g., loop gain and arousal threshold) could play a role in the development of apneas and hypopneas, and their recognition could facilitate the choice of tailored therapeutic options [14,40].

4.4. Side effects

Most side effects of treatment with OAs are temporary and gradually disappear during the first few months of treatment. These minor side effects include mucosal dryness, tooth discomfort, and hypersalivation [41]. A prospective controlled cohort study comparing 27 patients with OSA with 27 age- and sex-matched healthy volunteers showed a significant modification over time in the pressure pain thresholds of masticatory muscles followed by a return to baseline levels after 6 months of treatment with OAs. An immediate stretch of muscle fibers (which physiologically tend to recover their original length by increasing their activity) followed by a physiologic adaptation could explain these results [42].

In the long-term, the main side effects are represented by dento-skeletal changes. The protrusion of the mandible induced by OAs generates reciprocal forces on the soft tissues and the muscles that attempt to move the mandible backward to restore its normal position. These forces are transmitted to the teeth and to the bone to which the OA is anchored and, thus, can produce dento-skeletal changes. A study conducted with cephalometric analysis after a mean period of 3.5 years of treatment with OAs showed a statistically significant decrease in the anteroposterior position of the maxilla with a retroclination of the upper incisors, accompanied by a statistically significant downward rotation of

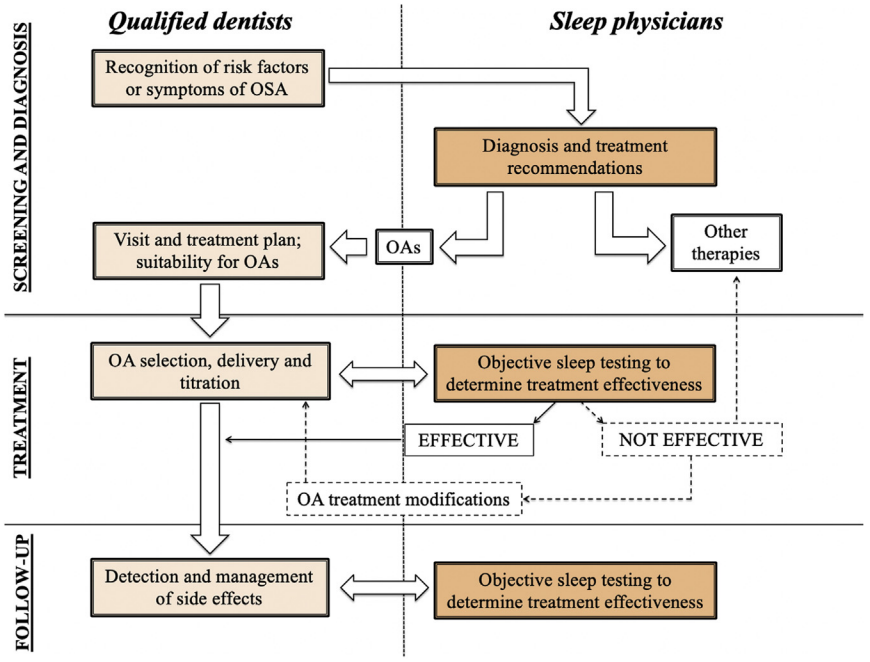

Fig. 2. The role of qualified dentists and sleep physicians in the multidisciplinary decision-making process in the treatment of adult patients with OSA with OAs. At the beginning of this process, qualified dentists can recognize patients with suspected OSA and refer them to sleep physicians for diagnosis. Otherwise, sleep physicians can directly screen and diagnose patients for OSA and refer them to a dentist, if deemed appropriate. At this stage of the decision-making process, qualified dentists are the only health care providers with sufficient knowledge and skill to evaluate patient suitability for OAs and to initiate therapy with the proper device. A collaborative and multidisciplinary relationship is required during appliance titration, because the sleep physician and the qualified dentist should discuss the possibility of further titration or alternative treatment if objective sleep testing indicates treatment is not effective. During periodic follow-up, a regular relationship should be maintained between the dentist and the patient's referring sleep physician to ensure the most effective patient care. In fact, patients need to be periodically monitored over time by a sleep physician for objective sleep testing to improve or confirm treatment effectiveness and, also, by a qualified dentist for periodic visits to identify and address any adverse effect.

the mandible with a proclination of the lower incisors. A decrease in upper space discrepancy, overjet, and overbite was also observed with three-dimensional dental cast analysis [43]. The distally directed forces on the upper arch and the forwardly directed ones on the lower arch produced by OAs can explain these dento-skeletal changes. A recent systematic review with meta-regression analysis of 21 studies with a follow-up period varying between 2 and 11 years of treatment with OAs, confirms as reported side effects a reduction in overjet, overbite, and in the upper incisor inclination, and, also, an increase in lower incisor inclination, in the relation of maxilla and mandible to each other and in anterior facial height [44]. A significant correlation between the duration of the therapy and the change of these parameters also emerges from this study [44]. The finding that dento-skeletal side effects during treatment with OAs are progressive is of the utmost importance, because a forward shift of the lower arch accompanied by a distal shift of the upper arch will reduce the possibility to further advance the mandible, thus putting at risk the long-term efficacy of treatment with OAs [45].

5. The role of qualified dentists in the diagnosis and treatment of OSA

Qualified dentists in dental sleep medicine can play an essential role in the reduction of the underdiagnosis of OSA, a problem that is of great importance because, if left undiagnosed and untreated, OSA can lead to serious medical consequences. During routine examinations, dentists can recognize patients with suspected OSA through the identification of anatomic risk factors (e.g., obesity, neck circumference) or symptoms (e.g., daytime sleepiness, choking, snoring, witnessed apneas). They should administer appropriate screening questionnaires and refer patients at risk of OSA to sleep medicine physicians, thus being involved in the multidisciplinary recognition of OSA.

Sleep medicine physicians make a definitive diagnosis of OSA and may recommend treatment with OAs. At this stage of the decision-making process, qualified dentists are the only health care providers able to confirm the suitability of OAs and, if deemed appropriate, to initiate therapy with the proper custom-made and titratable device [46].

During treatment with OAs, a regular relationship should be maintained between the dentist and the patient's referring physician to ensure the most effective patient care. In fact, patients need to be periodically monitored over time by a sleep physician for follow-up sleep testing to improve or confirm treatment effectiveness and, also, by a qualified dentist for periodic follow-up visits to identify and address any adverse effect (Fig. 2). These collaborative follow-up visits should allow for obtaining the least possible amount of mandibular advancement while achieving the highest reduction of AHI, thus optimizing the effectiveness of treatment, reducing the occurrence of side effects, and decreasing the risk of treatment discontinuation (Fig. 2).

The use and interpretation by dentists of the home sleep apnea test (HSAT), an alternative to polysomnography through the use of cardiorespiratory portable monitors, as a tool to diagnose OSA or to evaluate the effectiveness of OAs should be strongly discouraged. In fact, according to the position statement of the AASM, HSAT must be ordered by a physician. Moreover, data from polysomnograms or other sleep studies, such as HSAT, must be interpreted by a physician who is either board-certified in sleep medicine or overseen by a board-certified sleep medicine physician [47] and the results of diagnostic testing such as HSAT, polysomnogram, or pulse oximetry must not be used "to make treatment decisions in isolation from medical expertise" [46].

Among qualified dentists in dental sleep medicine, orthodontists can be considered specifically suited for the screening and management of OSA. The same examination used for orthodontic check-up could be adopted to screen patients for craniofacial characteristics potentially indicative of OSA. Moreover, orthodontists are more suited to manage OAs and, also, to detect and address potential side effects during treatment because the practice management of OAs is similar to that of removable orthodontic appliances, such as activators.

It also should be acknowledged that the role of orthodontists is not limited to the management of OAs in the context of OSA. In fact, during routine examinations of growing children, orthodontists have the chance to identify risk factors for potential airway-related problems, establishing the appropriate medical or orthodontic intervention to develop an optimal physiologic airway and breathing pattern [48].

Orthodontists also can play an important role in adult patients with OSA with concomitant dentofacial deformities who are not good candidates for CPAP, for which orthognathic surgery may be considered as an appropriate treatment. In these cases, orthodontists are involved in the orthodontic preparation or in dental arch fixation before surgery [49].

6. Conclusions and clinical relevance

In conclusion, we still have a long way to go when it comes to fully understanding OSA, and high-quality scientific research is needed. It is important to spread the idea that a multidisciplinary approach to OSA is essential for the diagnosis, the decision-making process, and the monitoring of treatment response.

As dentists we also must be aware that not all the problems related to OSA can be solved only by means of mandibular protrusion. Clinicians should keep well-informed on the most up-to-date scientific evidence to provide an evidence-based clinical decision-making process for the treatment of OSA, from which more patients would reliably benefit.

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References

[1] Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension 2011;58:811–7.
[2] Kasai T, Floras JS, Bradley TD. Sleep apnea and cardiovascular disease: a bidirectional relationship. Circulation 2012;126:1495–510.
[3] Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA 2012;307:2169–76.
[4] Floras JS. Hypertension and sleep apnea. Can J Cardiol 2015;31:889–97.
[5] Kim YS, Kim SY, Park DY, Wu HW, Hwang G-S, Kim HJ. Clinical implication of heart rate variability in obstructive sleep apnea syndrome patients. J Craniofac Surg 2015;26:1592–5.
[6] Al-Falahi Z, Williamson J, Dimitri H. Atrial fibrillation and sleep apnoea: guilt by association? Heart Lung Circ 2017;26:902–10.
[7] Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet 2014;383:736–47.
[8] Jullian-Desayes I, Joyeux-Faure M, Tamisier R, et al. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. Sleep Med Rev 2015;21:23–38.
[9] Simões EN, Padilla CS, Bezerra MS, Schmidt SL. Analysis of attention subdomains in obstructive sleep apnea patients. Front Psychiatry 2018;9:435.
[10] Mulgrew AT, Ryan CF, Fleetham JA, et al. The impact of obstructive sleep apnea and daytime sleepiness on work limitation. Sleep Med 2007;9:42–53.
[11] Tregear S, Reston J, Schoelles K, Phillips B. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. J Clin Sleep Med 2009;5:573–81.
[12] Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3:310–8.

[13] Wellman A, Eckert DJ, Jordan AS, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. J Appl Physiol (1985) 2011;110:1627–37.
[14] Bosi M, De Vito A, Kotecha B, et al. Phenotyping the pathophysiology of obstructive sleep apnea using polygraphy/polysomnography: a review of the literature. Sleep Breath 2018;22:579–92.
[15] Edwards BA, Andara C, Landry S, et al. Upper-airway collapsibility and loop gain predict the response to oral appliance therapy in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2016;194:1413–22.
[16] Epstein LJ, Kristo D, Strollo PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 2009;5:263–76.
[17] Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest 2014;146:1387–94.
[18] Wolkove N, Baltzan M, Kamel H, Dabrusin R, Palayew M. Long-term compliance with continuous positive airway pressure in patients with obstructive sleep apnea. Can Respir J 2008;15:365–9.
[19] Lee CHK, Leow LC, Song PR, Li H, Ong TH. Acceptance and adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea (OSA) in a Southeast Asian privately funded healthcare system. Sleep Sci 2017;10:57–63.
[20] Tan B, Tan A, Chan YH, Mok Y, Wong HS, Hsu PP. Adherence to continuous positive airway pressure therapy in Singaporean patients with obstructive sleep apnea. Am J Otolaryngol 2018;39:501–6.
[21] Ulander M, Johansson MS, Ewaldh AE, Svanborg E, Broström A. Side effects to continuous positive airway pressure treatment for obstructive sleep apnoea: changes over time and association to adherence. Sleep Breath 2014;18:799–807.
[22] Dieltjens M, Vanderveken OM, Heyning PH, Braem MJ. Current opinions and clinical practice in the titration of oral appliances in the treatment of sleep-disordered breathing. Sleep Med Rev 2012;16:177–85.
[23] Hoekema A, Stegenga B, De Bont LG. Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. Crit Rev Oral Biol Med 2004;15:137–55.
[24] Chan ASL, Sutherland K, Schwab RJ, et al. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax 2010;65:726–32.
[25] Schwartz M, Acosta L, Hung Y-L, Padilla M, Enciso R. Effects of CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: a systematic review and meta-analysis. Sleep Breath 2018;22:555–68.
[26] Iftikhar IH, Bittencourt L, Youngstedt SD, et al. Comparative efficacy of CPAP, MADs, exercise training, and dietary weight loss for sleep apnea: a network meta-analysis. Sleep Med 2017;30:7–14.
[27] Sutherland K, Philips CL, Cistulli PA. Efficacy versus effectiveness in the treatment of obstructive sleep apnea: CPAP and oral appliances. J Dent Sleep Med 2015;2:175–81.
[28] Ramar K, Dort LC, Katz SG, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. J Clin Sleep Med 2015;11:773–827.
[29] Le JQ, Rodgers JL, Postol K. Oral appliance therapy should be reimbursed as a first-lline therapy for OSA. J Dent Sleep Med 2019;6.
[30] Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. Sleep 2006;29:244–62.
[31] Vanderveken OM, Devolder A, Marklund M, et al. Comparison of a custom-made and a thermoplastic oral appliance for the treatment of mild sleep apnea. Am J Respir Crit Care Med 2008;178:197–202.
[32] Masse JF. Over the counter oral appliances: cause for concern? J Dent Sleep Med 2019;6.
[33] Ahrens A, McGrath C, Hägg U. A systematic review of the efficacy of oral appliance design in the management of obstructive sleep apnoea. Eur J Orthod 2011;33:318–24.
[34] Bartolucci ML, Bortolotti F, Raffaelli E, D'Antò V, Michelotti A, Alessandri Bonetti G. The effectiveness of different mandibular advancement amounts in OSA patients: a systematic review and meta-regression analysis. Sleep Breath 2016;20:911–9.
[35] Anitua E, Durán-Cantolla J, Almeida GZ, Alkhraisat MH. Minimizing the mandibular advancement in an oral appliance for the treatment of obstructive sleep apnea. Sleep Med 2017;34:226–31.
[36] Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Effects of an oral appliance with different mandibular protrusion positions at a constant vertical dimension on obstructive sleep apnea. Clin Oral Investig 2010;14:339–45.
[37] Deacon NL, Jen R, Li Y, Malhotra A. Treatment for obstructive sleep apnea. Prospects for personalized combined modality therapy. Ann Am Thorac Soc 2016;13:101–8.
[38] Alessandri-Bonetti G, Ippolito DR, Bartolucci ML, D'Antò V, Incerti-Parenti S. Cephalometric predictors of treatment outcome with mandibular advancement devices in adult patients with obstructive sleep apnea: a systematic review. Korean J Orthod 2015;45:308–21.
[39] Chen H, Aarab G, Lobbezoo F, et al. Differences in three-dimensional craniofacial anatomy between responders and non-responders to mandibular advancement splint treatment in obstructive sleep apnea patients. Eur J Orthod 2019. https://doi.org/10.1093/ejo/cjy085. [Epub ahead of print].
[40] Owens RL, Edwards BA, Eckert DJ, et al. An integrative model of physiological traits can be used to predict obstructive sleep apnea and response to non positive airway pressure therapy. Sleep 2015;38:961–70.
[41] Fritsch KM, Iseli A, Russi EW, Bloch KE. Side effects of mandibular advancement devices for sleep apnea treatment. Am J Respir Crit Care Med 2001;164:813–8.
[42] Alessandri-Bonetti G, Bortolotti F, Bartolucci ML, Marini I, D'Antò V, Michelotti A. The effects of mandibular advancement device on pressure pain threshold of masticatory muscles: a prospective controlled cohort study. J Oral Facial Pain Headache 2016;30:234–40.
[43] Alessandri-Bonetti G, D'Antò V, Stipa C, Rongo R, Incerti-Parenti S, Michelotti A. Dentoskeletal effects of oral appliance wear in obstructive sleep apnoea and snoring patients. Eur J Orthod 2017;39:482–8.
[44] Bartolucci ML, Bortolotti F, Martina S, Corazza G, Michelotti A, Alessandri-Bonetti G. Dental and skeletal long-term side effects of mandibular advancement devices in obstructive sleep apnea patients: a systematic review with meta-regression analysis. Eur J Orthod 2019;41:89–100.
[45] Marklund M. Update on oral appliance therapy for OSA. Curr Sleep Med Rep 2017;3:143–51.
[46] Quan SF, Schmidt-Nowara W. The role of dentists in the diagnosis and treatment of obstructive sleep apnea: consensus and controversy. J Clin Sleep Med 2017;13:1117–9.
[47] Rosen IM, Kirsch DB, Chervin RD, et al. Clinical use of a home sleep apnea test: an American Academy of Sleep Medicine position statement. J Clin Sleep Med 2017;13:1205–7.
[48] Berley K. ADA Policy statement on sleep disordered breathing from a lawyer's perspective. Available at: https://dentalsleeppractice.com/legal-ledger/ada-policy-statement-on-sleep-disordered-breathing-from-a-lawyers-perspective-by-ken-berley-dds-jd-dabdsm/. [Accessed 14 January 2019].
[49] Alessandri Bonetti G, Incerti Parenti S, Gracco A. Passive archwires for intermaxillary fixation in surgical cases. J Can Dent Assoc 2011;77:b159.