CHEST

Oral Appliances for the Management of OSA
An Updated Review of the Literature

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Oral appliances (OAs) are becoming increasingly recognized not only as an alternative to but also possibly as an adjunct treatment modality for OSA. Compared with CPAP, the gold standard therapy, OAs are less efficacious but are more accepted and tolerated by patients, which, in turn, may lead to a comparable level of therapeutic effectiveness. Different OA designs currently exist, and more are constantly emerging. Additionally, state-of-the-art technologies are being used in the fabrication of many; however, all the currently available OAs employ the same mechanism of action by targeting the anatomical component involved in the pathogenesis of the disease. Furthermore, the scope of use of OAs is expanding to include patients who are edentulous. For patients with OAs, the dentist is a member of an interdisciplinary team managing OSA, and constant communication and follow-up with the sleep physician and other team members is necessary for disease management. CHEST 2018; 153(2):544-553

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OSA is an increasingly prevalent sleep disorder characterized by recurrent episodes of partial and/or complete obstruction of the upper airway (hypopneas and apneas, respectively). Untreated OSA is associated with multiple adverse health outcomes, including stroke, hypertension, coronary artery disease, atrial fibrillation, decreased quality of life, and increased mortality.[1] Disease severity is classified according to the apnea-hypopnea index (AHI). An AHI $>$ 5 and $<$ 15 is considered mild OSA, 15 to 30 is moderate, and $>$ 30 is severe OSA.[2]

Management of OSA can be classified into four categories: (1) lifestyle modification, (2) upper airway surgery, (3) CPAP, and (4) oral appliance (OA) therapy.[3] Hypoglossal nerve stimulation is also a promising treatment modality in some patient populations.[4] The aim of this review is to provide a summary of the current aspects and concerns in the field of OAs as a treatment for OSA.

Classification of OAs

OAs are classified into those that protrude the tongue and those that protrude the mandible. The former are termed "tongue-retaining devices" or "tongue-stabilizing devices" (TSDs) and occasionally are prescribed for patients with mild to

ABBREVIATIONS: AHI = apnea-hypopnea index; OA = oral appliance; OA_m = OA that repositions the mandible forward; TSD = tongue-stabilizing device

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moderate OSA or those who fail to use CPAP.[5] OAs that reposition the mandible forward (OA_m) are the most commonly used type of OAs and different terms refer to this category of appliances, including "mandibular advancement devices," "mandibular advancement splints," and "mandibular repositioning appliances." Following the publication of the initial position statement by the American Academy of Sleep Medicine in 1995,[6] the clinical use of and research on OA_ms increased in quality and quantity. With the compilation of evidence supporting the use of OA_ms, the 1995 guidelines were revised and published in 2005[5] and again in 2015.[7] Similar to previous guidelines, the latest guidelines recommend the use of OA_ms for primary snoring and as an alternative to CPAP for patients who prefer OAs or those who refuse to use or are unable to tolerate CPAP. The 2015 guidelines do not specify a particular disease severity for OA_m use, which opens up the use of this therapy for severe OSA cases beyond what has been suggested in the previous guidelines. This change could be attributed to the growing body of high-quality evidence demonstrating the efficacy of OAs, their improvement in outcomes so that they are comparable with those of CPAP at various disease severities, and their suggested higher adherence rates.[8]

Pathophysiologic Traits of OSA and Mechanism of Action of OAs

Various structural and functional factors can contribute to the narrowing and collapse of the airway and there is increasing evidence demonstrating the multifactorial nature of OSA. Besides the well-known anatomical factors, neuromuscular control, an oversensitive ventilatory control system (high loop gain), and low respiratory arousal threshold are some of the other key factors identified.[9,10] This emerging evidence has led to the belief that more than one phenotype of OSA exists.[10]

Anatomically, there are both soft tissues and bony structures surrounding the upper airway. If the anatomical balance is disrupted because of obesity (increase in surrounding soft tissue), a smaller maxilla or mandible, or an imbalance between soft and hard tissues, then upper airway collapsibility increases.[11] Available treatment options that target the anatomical imbalance can be classified into causal and symptomatic treatments. Causal treatment includes lifestyle modification, such as weight loss for patients who are obese, and surgeries, such as maxillomandibular advancement, that advance the maxilla and mandible in an attempt to ameliorate anatomical discrepancies.

Symptomatic treatment includes CPAP and OA_ms, the latter being the focus of this review. To date, studies have shown that OA_ms mainly target the anatomical component in the pathogenesis of the disease by increasing the upper airway size, particularly the velopharyngeal cross-sectional area. This reduces pharyngeal collapsibility and disease severity.[12,13]

Eckert et al[10] demonstrated that there are different phenotypic traits for patients with OSA and that 69% of the patients have one or more nonanatomical pathophysiologic traits; therefore, because OA_ms mainly target the anatomical imbalance,[12,14] it is reasonable to expect that OA_ms might not be effective in all patients with OSA. Accordingly, OA_m therapy is completely effective in only 36% to 70% of OSA cases.[15]

Even though both OA_ms and TSDs increase upper airway dimension, a greater increase in velopharyngeal and oropharyngeal cross-sectional area has been demonstrated with tongue protrusion than with mandibular protrusion. This finding could be attributed to the greater anterior displacement of the tongue produced by TSDs in comparison with that produced by OA_ms.[13] Both treatments are effective in reducing apneas, though OA_ms are slightly superior to TSDs, which supports the notion that a decrease in AHI may not be proportional to the increase in upper airway size. To date, there are only a few studies assessing TSDs, and their use in clinical practice is limited.

Types of OA and Indications for Use

An OA_m can be custom made (made by qualified dentist) or prefabricated (ie, boil and bite), one piece (monobloc, one piece with no mouth opening) or two piece (duobloc, separate maxillary and mandibular plates), fixed or titratable (with various types of adjustable mechanisms), and can be fabricated from a hard or soft material.[7,16,17] There are more than 100 different appliance designs currently on the market.

Similarly, TSDs can be custom made or prefabricated, and, despite both OA_ms and TSDs having similar efficacy in terms of AHI reduction, TSDs are less comfortable than OA_ms are. Nonetheless, TSDs are a viable option for patients who are completely or partially edentulous.[18] Custom-made, titratable, duobloc oral appliances are superior to monobloc and nontitratable appliances (Fig 1).[2,17,19] Within the custom-made duobloc category of appliances, different designs seem to have comparable efficacy.[20,21]

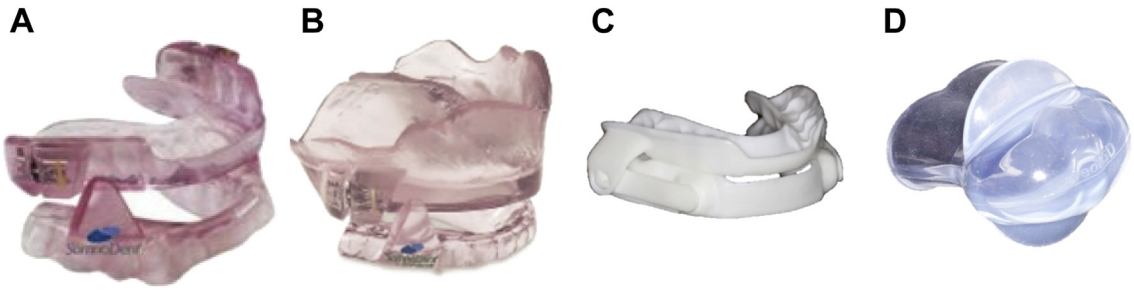

Figure 1 – *Examples of commercially available oral appliances. A, SomnoDent Flex, a custom-made oral appliance that moves the mandible forward (OA_m) for the dentate patient. B, SomnoDent Edentulous, a custom-made OA_m for patients with an edentulous maxilla. C, Narval, a custom-made OA_ms for the dentate patient. D, AveoTSD, a prefabricated Tongue Stabilizing Device (TSD).*

For OSA patients with bruxism, metal reinforcement of the occlusal surface of the OA_m will help increase the longevity of the appliance. For the edentulous OSA patient, treatment options are limited. Tooth loss seems to increase upper airway obstruction during sleep.[22] Although some studies found that the use of dentures during sleep reduces OSA, Almeida et al[23] reported that the use of dentures instead of OAs during sleep for patients with mild OSA increased the AHI, especially in the supine position. Alternative options for edentulous patients include implant-retained OA_ms and surgical treatment.[24] Hoekema et al[25] reported the use of implant-retained OA_ms in six edentulous patients, and the findings of de Carlos et al[26] indicate that the use of orthoimplants, a type of dental implant used for orthodontic anchorage, improved AHI in patients with mild OSA who were edentulous. Studies on edentulous patients are mostly case reports, so future focus on this population is necessary.

For OA_ms, a healthy dentition and periodontal tissues are necessary without active dental caries or periodontal disease. Additionally, a minimum of eight to 10 healthy teeth need to be present in the mandibular arch (the maxillary arch can be edentulous) to retain most types of OA_ms, and a protrusion range of $\geq$ 5 mm is a prerequisite.[5] The presence of temporomandibular disorders is not a contraindication for OA_m use.

Titration

Managing OSA by using OA_m therapy requires an interdisciplinary team approach that starts with an assessment by a physician, followed by a consultation and oral examination by a qualified dentist. Impressions of the patient's teeth and bite registration are obtained by the dentist to create a custom OA_m. Appliance titration is attained by means of progressive mandibular advancement that incrementally moves the mandible forward.[27]

Different advancement mechanisms exist depending on the appliance design. Kato et al[28] examined dose-dependent effects of mandibular advancement and showed that each 2-mm advancement was associated with a 20% improvement in the oxygen desaturation index. Most studies have reported that patients require advancement > 50% of maximum protrusion to achieve the desired effects.[29-31] Nevertheless, a recent systematic review and meta-analysis showed that advancements > 50% may not necessarily improve the success rate; a limitation, however, was that confounding variables that may affect success were not controlled for in the included studies.[32]

After approximately 1 month of OA_m use, the dentist checks for side effects such as tooth, tissue, and joint pain and assesses the perceived efficacy as reported by the patient or sleep partner. The dentist adjusts the OA_m to eliminate any pain or discomfort. The titration phase normally involves several visits over a 3- to 5-month period. Following titration, the dentist confirms efficacy by referring the patient back to the sleep physician for an objective assessment via a sleep test. Additionally, the use of portable sleep monitoring during titration or conducting a titration polysomnography could also facilitate ideal titration.[33-35] The American Academy of Dental Sleep Medicine recommends that patients be seen by the dentist a minimum of once every 6 months for the first year and at least once annually thereafter (Fig 2). The dentist must evaluate carefully the occlusion, appliance wear, and possible adverse effects. The average life of an OA_m is approximately 3 years; cracks, discoloration, and lack of retention indicate a need for replacement.[2,5,36,37]

Predictors of Treatment Response

OA_m treatment response may be influenced by a number of factors that include: device features, patient characteristics and pathophysiologic traits, in addition to the clinical expertise of the provider.[15] Predictors of

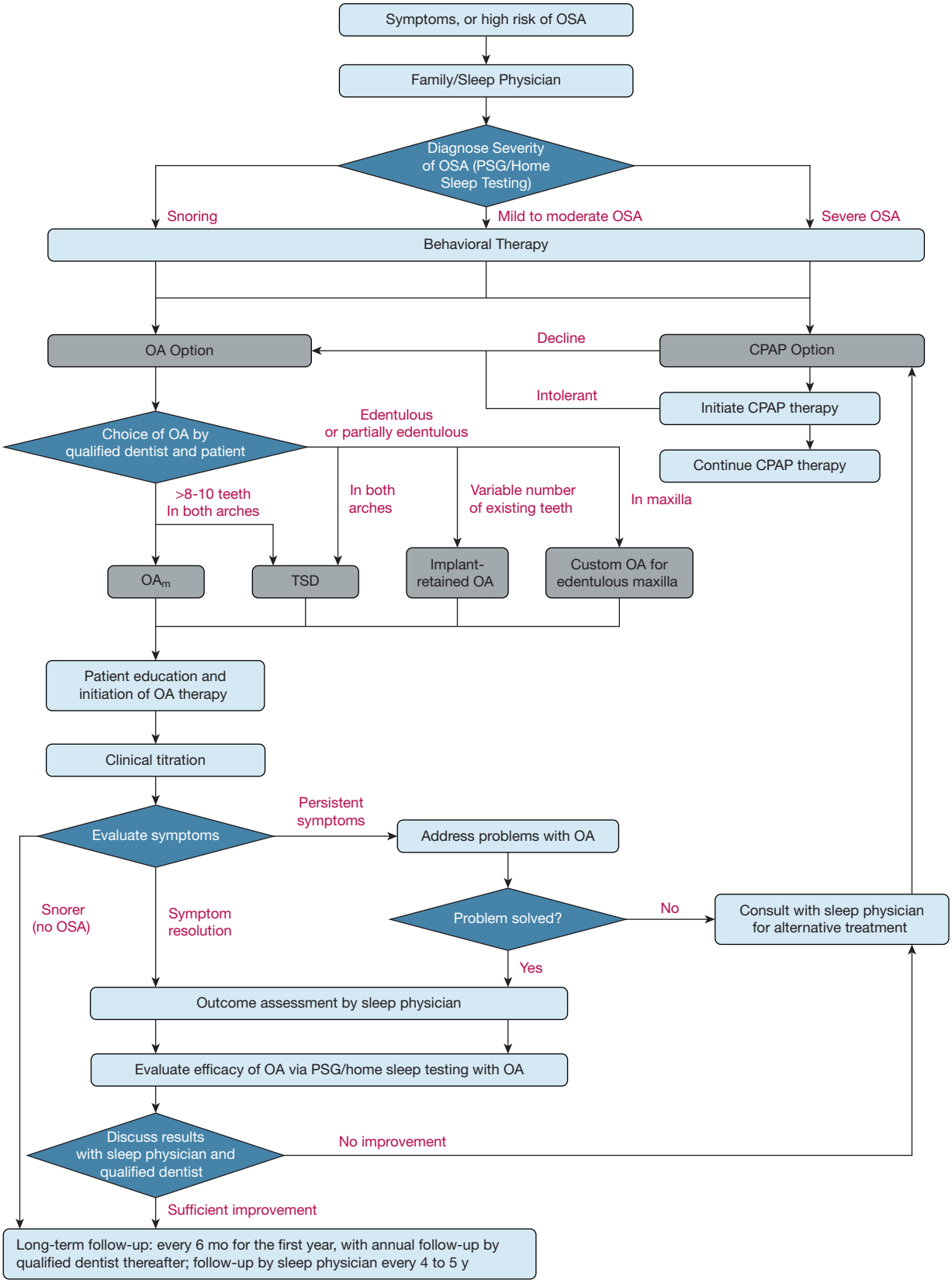

Figure 2 – *Flow chart showing oral appliance decision-making and management process for OSA patients. OA = oral appliance; OA_m = OA that repositions the mandible forward; PSG = polysomnography; TSD = tongue-stabilizing device.*

treatment response to TSDs have not been studied yet. The most effective OA_ms are described as the custom-made, two-piece (duobloc) OA_ms that have minimal vertical opening and that are titratable appliances (incorporate an adjustable mechanism that permits mandibular advancement over a range of at least 5 mm and allows for the reversal of the advancements).[2,17,19]

Patient characteristics include anthropomorphic factors, with positive predictors including younger age, female sex, lower BMI, smaller neck circumference, smaller oropharynx, and smaller overjet. Cephalometric positive predictors are a shorter soft palate, longer maxilla, shorter distance between the mandibular plane and hyoid bone, bigger ANB angle (A point-nasion-B point) and smaller SNB angle (sella-nasion-B point). Polysomnographic positive predictors are less severe OSA and supine-dependent OSA.[38]

The American Academy of Dental Sleep Medicine guidelines recommend that treatment of OSA with an OA should be provided by a qualified dentist who has the technical skills and acquired knowledge and judgment regarding the outcomes and risks of this treatment modality.[7] This skill set is important to be able to choose a good appliance, to understand and address transient side effects, to adjust and titrate mandibular protrusion optimally, and to follow up patients properly. Nasal endoscopy, CT scanning, MRI, drug-induced sleep endoscopy, and overnight titration studies help predict treatment response. Nonetheless, their routine use in the clinical setting is limited because they are still costly or are inconvenient to use. Despite major efforts, prediction of OA_m efficacy has a sensitivity of no greater than 70% or has inconclusive results in 20% to 30% of cases.[38,39] On the basis of these numbers, OA_m success is hard to predict, and contraindications to OA_m use today are limited to an edentulous mandibular arch and a BMI > 35 kg/m^2. Although there are limited studies in the obese population, an increase in weight may be correlated with a decrease in OA efficacy.[40]

Definition of Treatment Success

Even though there seems to be a consensus on the definition of treatment success with OA_ms as being a treated AHI of < 5/h, a consensus is lacking on the definition of partial treatment success. Partial treatment success frequently is defined as $> 50\%$ reduction in baseline AHI with or without a treated AHI below a prespecified level such as 10/h or 20/h. The definition of partial treatment success also may include symptomatic improvement.[19] Reported success rates greatly depend on the definition of treatment success used,[41] making it more challenging to compare the results of different studies.

Treatment Efficacy vs Effectiveness

In OSA management, efficacy reflects the ability of treatment, when used, to minimize or prevent the occurrence of obstructive breathing events.[42] Both CPAP and OA_ms reduce upper airway collapse during sleep, with CPAP having superior efficacy in moderate to severe OSA.[43] Although treatment efficacy refers to how well an intervention works under ideal, well-controlled circumstances, effectiveness indicates how well an intervention performs under circumstances that more closely approximate the real world, employing less standardized and less controlled conditions.[42] Therefore, treatment effectiveness is particularly important in the management of chronic disease. Adherence is an important determinant of effectiveness and has been defined by the World Health Organization as "the extent to which a person's behaviour—taking medications, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider."[44] Furthermore, the World Health Organization report on adherence to long-term therapies indicates that health outcomes cannot be assessed accurately if they are measured predominantly by the efficacy of interventions because outcomes predicted by treatment efficacy data cannot be achieved unless adherence rates are considered. Hence, it is imperative to assess adherence objectively to evaluate treatment outcomes.

Comparative Effectiveness of CPAP and OA_ms

CPAP is superior to OA_ms in terms of reducing OSA parameters on polysomnography, such as eliminating obstructive breathing events and improving nocturnal oxygen saturation and arousals.[8,45,46] Although CPAP consistently demonstrates normalization of AHI, this is not necessarily the case with OA_ms.[45] However, this greater efficacy of CPAP does not necessarily translate into better health outcomes. Randomized controlled trials comparing CPAP with OA_ms and varying in baseline OSA severity from mild to severe have shown similar results in improving symptoms such as sleepiness,[45,47] quality of life,[46] and simulated driving performance.[48] In terms of cardiovascular outcomes, there were no differences between the two treatments with respect to short-term effects on blood pressure[49]

and reducing the risk of mortality in patients with severe OSA.[50] This comparable effectiveness has been attributed, in theory, to differences in adherence rates. However, to our knowledge, no trial has objectively compared adherence to both treatments and the effect of this adherence on long-term effectiveness.

OA_m Adherence

Although a patient is considered adherent to CPAP if the patient uses it for > 4 h per night during 70% of nights, these cutoff values were chosen based on average usage values observed in earlier CPAP adherence studies[51] and are not necessarily values that result in optimal outcomes. More recent studies have shown a positive correlation between improvement in outcomes and usage duration.[52,53] In 2016, the Sleep Apnea Cardiovascular Endpoints trial[54] failed to show cardiovascular improvements with CPAP, likely because of low adherence (average of 3.5 h per night). Furthermore, 20% to 50% of patients with OSA are unable or unwilling to comply with CPAP, limiting its long-term effectiveness.[53]

Objective monitoring of CPAP usage has been possible for many years,[55] but OA_m monitoring, until more recently, predominantly relied on self-reporting.[5] Studies comparing subjective reporting of CPAP adherence with objective data revealed that patients generally overestimate their CPAP usage by approximately 1 h.[56,57] Subjective reporting, therefore, is not the most reliable method of evaluating patient adherence, and the studies that have objectively evaluated OA_m adherence are still limited. Dieltjens et al[58] reported an objective adherence of 6.7 ± 1.3 h per night over a 3-month period,[59] which was maintained at > 6 h per night at 1 year. Adherence has been claimed to be higher with OA_ms than with CPAP.[8] A thermosensitive microsensor embedded in the OA_m can be used to record OA_m wear time and, hence, provides the means to assess adherence objectively. The three microsensors that are currently commercially available have shown high accuracy and reliability.[60]

Mean Disease Alleviation and Sleep Adjusted Residual AHI

OSA is a chronic disease, and the treatments available are not curative; therefore, they are considered lifelong treatments, so adherence to OSA treatment is imperative. Disease alleviation of a treatment that is fully effective results in an AHI < 5 and could be 100% if always used, 0% if never used, and partially effective when sometimes used.[61] The absolute number of hours a treatment is being used does not seem to be as important as the number of hours of treatment use relative to the total sleeping time. If the patient is using treatment for one-half of the total sleep time, the true AHI is poorly represented by AHI on treatment. Therefore, it has been proposed that treatment comparisons should be made after adjusting for hours of usage over total sleep time.[42,56]

Investigators in previous studies, who found similar health outcomes for CPAP and OA_ms despite the presence of residual apnea in patients using OA_ms, hypothesized that the suboptimal efficacy of OA_m therapy is counterbalanced by the superior adherence relative to that for CPAP.[48,62,63] To explain this hypothesis, long-term effectiveness (efficacy and adherence) has been described as the mean disease alleviation.[64] The mean disease alleviation, expressed as a percentage, is calculated as follows: (adjusted objective adherence × therapeutic efficacy)/100.[42,58,59] Mean OSA alleviation by means of CPAP has been described as being 52%,[64] whereas the mean OSA alleviation by means of OA_m use was 51%.[59] Additionally, a Sleep Adjusted Residual AHI (SARAH Index) has been proposed as a more accurate assessment of treatment effectiveness and possibly a better indicator of long-term health benefits. It takes into account the time on and time off treatment relative to the total sleeping time.[42]

Merely using the AHI on treatment to demonstrate therapeutic effectiveness is an oversimplistic approach because it fails to take into consideration the hours per night that the treatment is physically used. It also fails to take into consideration whether the treatment is being used during the time of night with concentrated rapid eye movement sleep and sometimes more severe OSA (rapid eye movement sleep tends to take place more toward the early morning hours, which is the time that most patients typically discontinue using their treatment). It also fails to take into consideration the long-term adherence rate, which is known to decline progressively with all therapies.

Determinants of OA_m Adherence

Although adherence to therapy is crucial to achieving long-term effectiveness, predictors of OA_m adherence have not been a subject of extensive research, and previous studies were limited to self-reported use and lacked an objective adherence measurement. In a study

using mailed questionnaires, the most frequent reasons for discontinuation of OA_m use were that it was uncomfortable or had little or no effect.[65] Only more recently has an objective adherence monitor become available, and the only assessment of the treatment parameters that correlate with objectively measured adherence showed that absence of adverse effects, a decrease in visual analogue scale score for snoring, and a lower baseline AHI were predictors of higher objective mean wearing time at 3-month follow-up.[66] Being able to predict which patients will adhere to treatment and the treatment that they are most likely to adhere to is a step toward achieving "precision medicine," a term that refers to "the tailoring of medical treatment to the individual characteristics of each patient."[67]

Research has shown that medical treatment plans involving and valuing patient participation usually produce the most positive patient outcomes. Studies have shown that patient participation in chronic disease management leads to improved treatment adherence and a higher quality of life.[68] Efficacy alone is not sufficient for decision making in OSA management. Furthermore, it is neither respectful of patient autonomy nor beneficial for patients to impose a particular option on them, regardless of the clinical evidence for its efficacy. Based on a review that compared patient preference for CPAP with that for OA_ms,[16] four of six cross-over trials asking for patient treatment preference at the end of the trial found a higher preference for OA_m treatment. One study showed slightly more preference for CPAP, and another study showed an equal preference for both.[16] Using a discrete choice experiment, Krucien et al[69] and Trenaman et al[70] highlighted the importance of communicating with the patient prior to the implementation of OSA treatment. Almeida et al[71] conducted a qualitative study to understand participants' perspectives and preferences regarding CPAP and OA_ms. Results suggested that matching treatment with participant preference could achieve greater therapy adherence and, thus, better health outcomes.

Combination Therapy

It is reasonable to expect that using more than one therapy would lead to additive or synergistic effects, yet studies using a combination of OA_ms with other therapies are relatively scarce. To our knowledge, only one study investigated the applicability of alternating treatment between CPAP and OA_ms on a regular basis.[72] It demonstrated that an enhancement in the reduction of symptoms could be achieved with the availability of both treatments for the patient to use interchangeably. It could be hypothesized that, because patients were less likely to occasionally drop treatment, the long-term effects on alleviating daytime sleepiness were further consolidated. Therefore, a combination of treatments would likely permit greater flexibility and improve treatment outcomes.

Dieltjens et al[73] evaluated the effect of combining positional therapy in patients with supine-dependent OSA with OA_ms and found that the combination led to a higher therapeutic efficacy compared with that of each treatment alone. Dort and Remmers[74] assessed the combination of an OA_m with a tongue-retention bulb and found that the combination could reduce respiratory events compared with results with an OA_m without a tongue-retention bulb. A study examining the combination of an OA_m with surgery demonstrated that the use of an OA_m following uvulopalatopharyngoplasty could keep the cross-sectional area of the stenosis site bigger than could treatment with uvulopalatopharyngoplasty alone.[75] Attempts to use both OA_ms and CPAP concomitantly have shown that the combination helps reduce the required CPAP pressure, which increases patient comfort.[76,77] With only a few trials conducted on OA_m combination therapies, there is a paucity of research in this area in which specific patient needs may be addressed.

Side Effects of OA_ms

Although OA_ms are well tolerated, there are short-term and long-term side effects associated with therapy. The most common short-term side effects are increased salivation or dryness, pain or discomfort in the teeth or gums, perception of an abnormal occlusion in the morning, muscle tenderness, and jaw stiffness. These side effects being mostly mild and transient.[15] Long-term side effects are predominantly dental and occlusal changes in the form of retroclination of the maxillary incisors and proclination of the mandibular incisors with subsequent decrease in overjet and overbite, mesial tipping of the mandibular molars, and distal tipping of the maxillary molars.[78-83] Additionally, increased mandibular arch length and downward rotation of the mandible have been reported by some researchers.[79,80,82] These long-term changes are usually irreversible.

To our knowledge, in the longest follow-up study published to date that assessed side effects (11.1 $\pm$ 2.8 years of follow-up), the investigators showed that the mean reductions in overbite and overjet were 1.9 and 2.3 mm, respectively.[83] Studies have shown that the magnitude of the changes is not related to appliance

design or to baseline characteristics (such as baseline AHI, BMI) but rather to the duration of therapy and the amount of forward protrusion of the mandible.[78,83] To our knowledge, all studies published to date assessing OA side effects have relied on self-reporting of appliance usage duration.

Although these side effects may seem substantial, they are outweighed by the benefits gained from using an OA_m, especially considering the potentially life-threatening nature of OSA. Therefore, patients should not discontinue OA_m therapy unless they are willing to adhere to another treatment modality. It is also imperative that the patients are informed of the possible long-term side effects prior to therapy initiation.

Future Direction: Patient-Centered Medicine

Currently, there is an emerging trend towards a shift to P4 medicine, which is medicine that is predictive, preventive, personalized, and participatory where the ultimate objective is to maximize wellness for each individual rather than simply to treat disease.[84] Although research has been well under way for many decades on OSA management and OA_m therapy, still more needs to be known to be able to select a treatment that is targeted to the individual on the basis of the individual's phenotypic traits instead of using a one-for-all approach. Having the ability to readily identify the pathophysiologic traits of OSA at the level of the individual (phenotyping[85]) will bring us a step closer to being able to prescribe personalized treatment. Furthermore, there is a need to develop validated methods to predict OA_m treatment response prior to the initiation of treatment. Being able to choose the ideal treatment on an individual basis prior to treatment initiation will lead to more efficient use of time and resources, as well as avoiding patient frustration and loss of cooperation.

To serve the same purpose, predictors of adherence and methods to enhance adherence warrant further investigation. Additionally, developing methods to minimize side effects and mitigate the deleterious effects of treatment, if they occur, are important factors that require greater in-depth study. More rigorous studies are needed to assess whether combination therapies have any added benefits.

Conclusions

Even though many different treatment modalities are available for managing OSA, CPAP and OA_ms are the most commonly used disease-specific therapies. CPAP has the advantage of greater efficacy, yet OA_ms remain a viable and promising treatment option that seems to have better patient adherence and acceptance. There is currently no single variable that can reliably predict treatment outcome with OA_ms, and there is no sole determinant of treatment success, but a constellation of features exist that if present or absent can possibly give an indication of treatment response. Similarly, there is no single ideal OA_m design; an ideal appliance is custom made, protrudes the mandible, keeps the vertical opening to a minimum, and can be adjusted to achieve the optimum efficacy while being comfortable and well tolerated by the patient.

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