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Critical Issues in Dental and Medical Management of Obstructive Sleep Apnea

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Abstract

This critical review focuses on obstructive sleep apnea (OSA) and its management from a dental medicine perspective. OSA is characterized by ≥10-s cessation of breathing (apnea) or reduction in airflow (hypopnea) ≥5 times per hour with a drop in oxygen and/or rise in carbon dioxide. It can be associated with sleepiness and fatigue, impaired mood and cognition, cardiometabolic complications, and risk for transportation and work accidents. Although sleep apnea is diagnosed by a sleep physician, its management is interdisciplinary. The dentist's role includes 1) screening patients for OSA risk factors (e.g., retrognathia, high arched palate, enlarged tonsils or tongue, enlarged tori, high Mallampati score, poor sleep, supine sleep position, obesity, hypertension, morning headache or orofacial pain, bruxism); 2) referring to an appropriate health professional as indicated; and 3) providing oral appliance therapy followed by regular dental and sleep medical follow-up. In addition to the device features and provider expertise, anatomic, behavioral, demographic, and neurophysiologic characteristics can influence oral appliance effectiveness in managing OSA. Therefore, OSA treatment should be tailored to each patient individually. This review highlights some of the putative action mechanisms related to oral appliance effectiveness and proposes future research directions.

Keywords: machine learning, sleep bruxism, arousal, headache, mandibular advancement, precision medicine

Introduction

Sleep apnea is defined by breathing cessation (apnea) or airflow reduction (hypopnea) lasting ≥10 s and occurring >5 times per hour of sleep, and it is associated with cortical sleep arousals (to restore breathing) and/or oxygen desaturation (3% or 4% threshold; Berry et al. 2012; Mansukhani et al. 2019). When associated with upper airway obstruction, nasal/craniofacial anomalies, or obesity, it is classified as obstructive sleep apnea (OSA), whereas when caused by aberrant respiratory drive from the brain (too high or too little), it is classified as central sleep apnea (Mohammadieh et al. 2017). Central sleep apnea is frequently associated with heart failure, morbid obesity, or central nervous system depressant medications (e.g., opioids and benzodiazepines; Marshansky et al. 2018) and is not covered here.

OSA is a potentially life-threatening condition. When untreated, it is associated with major health problems (e.g., mood, cardiac) and mortality (Javaheri et al. 2017; Lisan et al. 2019) in adults and altered learning performance and physical growth in children (Marcus et al. 2012). In the era of precision medicine, it is important to target more at-risk individuals. Older men (≥50 y) presenting high body mass index, hypertension, or history of snoring or witnessed apnea have a higher likelihood of moderate to severe OSA (odds ratio = 3.8; Jung et al. 2017). For younger males and women of all ages, reports of sleepiness, fatigue, or cognitive complaints or comorbidities such as persistent morning headache, hypertension, and diabetes are screening indicators (Vgontzas et al. 2019).

The objective of this review is to offer to dental practitioners an overview of OSA and its management, to highlight putative action mechanisms related to oral appliance (OA) effectiveness (Fig. 1), and finally to propose future research directions (Table 1) for the field of dental sleep medicine.

Updated Prevalence of OSA and Influence of Sex, Age, Obesity, and Ethnicity

The earliest study of the prevalence of OSA in the general US population reported that 4% of males and 2% of females present sleep-disordered breathing (Young et al. 1993). A more recent polysomnography (PSG) study in the United States identified moderate to severe OSA (apnea-hypopnea index [AHI] ≥15/h) in 10% of men aged 30 to 49 y and 17% aged 50 to 70 y (Peppard et al. 2013). Yet only 3% of women aged 30 to 49 y and 9% of women aged 50 to 70 y presented this

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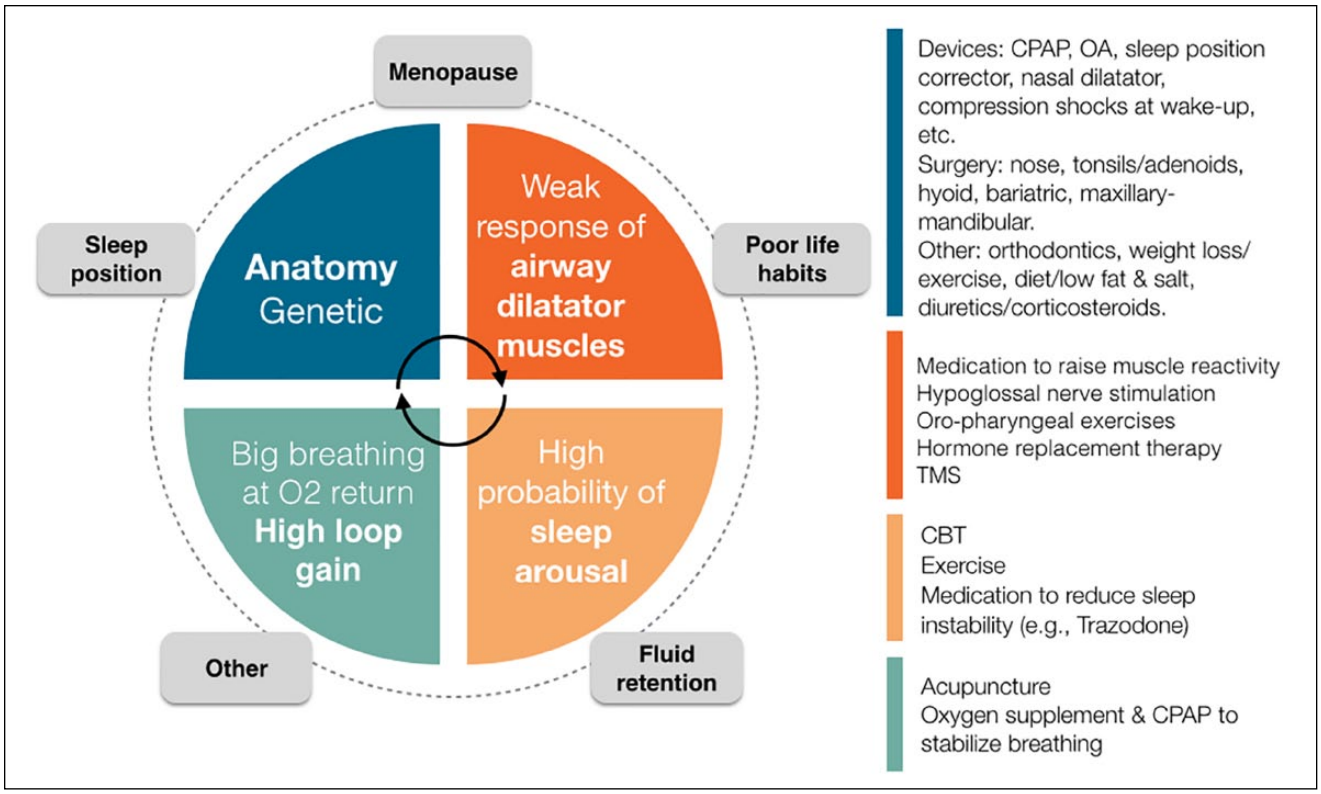

Figure 1. Vulnerability factors associated with obstructive sleep apnea, with variable dominance according to subject traits and examples of therapeutic targets (not exclusive to each factor). CBT, cognitive behavioral therapy; CPAP, continuous positive airway pressure; OA, oral appliance; TMS, transcranial magnetic stimulation.

severity level. Females tend to be protected from sleep apnea until menopause, at which time the prevalence rises with complaints of poor sleep quality (Eichling and Sahni 2005; Peppard et al. 2013; Valiensi et al. 2019). Thus, postmenopausal women present 3- to 6-times higher OSA prevalence (Heinzer et al. 2015; Matsumoto and Chin 2019).

Obesity is another critical influential factor for OSA onset and prevalence. A recent cluster analysis by the Sleep Apnea Global Interdisciplinary Consortium of self-reported OSA-related complaints from 6 countries (including Asian, Caucasian, and South America subjects) confirmed that midage (44.6 to 54.5 y) and obesity are dominant risks, although differences in demographics and AHI were observed (Keenan et al. 2018). However, prevalence across countries should be compared with caution due to ethnic and environmental variations. The Sleep Apnea Global Interdisciplinary Consortium study indicates that although weight gain does not significantly worsen OSA in African Americans, a slight weight gain in Asians and South Americans strongly influences OSA severity, with Caucasians somewhere in the middle (Sutherland, Keenan, et al. 2019). Obesity, albeit a risk factor, does not explain everything, as thin individuals may also present OSA, which could be related to other at-risk phenotypes (see Putative Action Mechanisms of OAs and Other Therapeutic Devices; Fig. 1).

Notably, OSA prevalence has risen over the last 2 decades, by 14% and 55%, depending on age and sex (Young and Peppard 2000; Peppard et al. 2013). Thus, patients with OSA are generally older and predominantly male. However, these results must be interpreted with caution because the rise could be explained by greater public awareness of OSA-related health risks, more accessible diagnosis, more women presenting OSA, and rising obesity (Benjafield et al. 2019). Additionally, the variability in prevalence rates may depend on the tools used (questionnaire or PSG data) and the cutoffs for case definition (≥5 or ≥15 AHI or 3% or 4% hypoxia). For example, the American Academy of Sleep Medicine modified its criteria in 2012: oxygen desaturation was reduced from 4% to 3%, resulting in a 12.5% rise in "captured" cases (Heinzer et al. 2015; Won et al. 2018; Mansukhani et al. 2019).

Other Risk Factors: Craniofacial and Oropharyngeal Characteristics, Lifestyle Habits, and Sleep Variables

Recently, anatomic and physiologic phenotypes have been identified as critical variables for treatment choice and success (Eckert et al. 2013; Eckert 2018; Sutherland, Lee, et al. 2018). Clinical craniofacial and oropharyngeal characteristics associated with OSA risk include large neck, retrognathia/retracted mandible and maxilla, narrow and deep palate, long soft palate, and large adenoids.

However, some common clinical beliefs should be clarified with stronger methods. An example is the widespread dogma

Table 1. Critical Research Issues to Improve OSA Management (Diagnosis and Treatment) in the Era of Precision Medicine.

Prevalence studies to better assess the influence of tools (questionnaires, polysomnography) and cutoffs for case definition based on calculated prevalence and consensual evidence-based standards.
Revisit the strength of commonly accepted clinical affirmations of risk factors, such as retrognathia, ethnicity, and other variables as causes or aggravating factors.
AHI and RDI are not unequivocal OSA markers, and there is a need to derive better markers of disease burden.
Development of causality markers, outcome predictors, and treatment success predictors.
Deeper exploration of OA and CPAP mechanisms, which are not fully understood.
OSA trait stability across time is unclear.
Develop data collections based on large sample sizes to improve the understanding of OSA phenotypes, causes, and mechanisms as well as diagnosis accuracy and treatment efficacy.

AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; OA, oral appliance; OSA, obstructive sleep apnea; RDI, respiratory disturbance index.

that Asians more frequently present mandibular retrognathia and that more obesity is present in African Americans and South Americans in relation to OSA risks. With research-based evidences, such notions have to be revisited (Okubo et al. 2006; Sutherland et al. 2012; Sutherland, Keenan, et al. 2019). Another craniofacial developmental study challenged the frequent finding that dominant retrognathia is a risk factor for OSA in Caucasians. A similar range of retrognathia (around 20%) was observed among Caucasians, Chinese, and Latinos, with rates lower in African Americans and higher in White individuals and Brazilians (Joshi et al. 2014). Thus, retrognathia may contribute, but whether it is a concomitant characteristic or a cause of OSA onset or aggravation remains to be demonstrated.

Some behavioral habits or lifestyle factors may also contribute to OSA risk, including smoking, alcohol, sedentary lifestyle, sleep position, fatty meals, and late-evening eating habits (Trakada et al. 2014; Heinzer et al. 2018; Lopes et al. 2019). Some central nervous system depressant substances or medications (e.g., alcohol, opioids, benzodiazepines) may increase the OSA risk (Kolla et al. 2018; Marshansky et al. 2018). Moreover, fatigue should be considered a possible contributory factor (Kim et al. 2017; Rizzo et al. 2018). Regarding sleep position, more patients with OSA tend to spend a majority of their sleeping time in a supine position, which aggravates AHI: up to 75% of patients with OSA versus 50% of the general population sleep predominantly in a supine position (Heinzer et al. 2018).

There is no current consensus on the dominant role of numerous anatomic and physiologic phenotype variables or traits (see Putative Action Mechanisms of OAs and Other Therapeutic Devices) that could help explain OSA mechanisms or treatment efficacy. In the era of precision medicine and artificial intelligence, we need to 1) develop clinical data collection consortiums to characterize specific OSA phenotypes and 2) develop algorithms (adjusted for ethnic, sex, and other variables) to improve OSA management, diagnosis, and treatment (Cistulli and Sutherland 2019).

OSA Management: Diagnosis, Treatment, and Follow-up

OSA is typically categorized as mild, moderate, or severe based on the AHI (i.e., the number of breathing disturbances per hour of sleep). Diagnosis is made by a sleep physician with the help of PSG when indicated. Today, the respiratory disturbance index is frequently used, as it incorporates other events called *respiratory effort-related arousals*. The search for a global predictive index to provide a more informative assessment of treatment effectiveness and morbidity/mortality risk as compared with the AHI remains an open research issue, which requires caution in data interpretation. Therefore, because neither the AHI nor the respiratory disturbance index is an unequivocal marker of OSA risk, clinicians should perform a global health assessment when managing sleep apnea.

Although OSA and other sleep-disordered breathing conditions are generally diagnosed by a sleep physician, OSA is managed by an interdisciplinary team through respectful interprofessional collaboration (see Fig. 2; Ramar et al. 2015). Specifically, the sleep physician assesses medication and alcohol use, exercise level, and the presence of relevant conditions, such as obesity, depression or anxiety, diabetes, hypertension, and metabolic syndrome. The sleep physician then refers the patients for medically supervised sleep testing and recommends treatments based on medical condition and test results. Currently, the continuous positive airway pressure (CPAP) device, which acts to improve oropharyngeal patency during sleep, remains the standard of care to manage sleep apnea.

Armed with higher education or OSA awareness (also called collective social bias) and guided by the sleep physician, today's patients are more apt to choose their treatment according to their individual degree of acceptance and willingness to collaborate and according to the severity of the condition and the presence of comorbidity. This approach is widely known as *patient partnership/patient centered*. Although most sleep clinics tend to offer the most efficacious treatment first, with CPAP being the choice for more severe cases (Nakai et al. 2018), outcomes may differ when patients can make their own choice. In a comparative crossover trial, when patients were allowed to select between CPAP and OA over 1-mo use, 51% preferred OA, 23% liked CPAP, 21% liked both, and about 5% liked neither (Phillips et al. 2013). This study is under replication by Almeida and Huynh in Canada (ClinicalTrials.gov NCT02242617) over a longer period and with a monitoring chip to confirm OA use (Vanderveken et al. 2013; Gjerde et al. 2018). Generally, clinicians should consider variables that are known to contribute to treatment adherence and compliance, including patient preference, expectations, and lifestyle (Almeida et al. 2013).

"Solo practitioner" OSA management is no longer realistic due to the high burden of disease in the general population. Thus, OSA prevalence is rising with increasing obesity and other lifestyle factors (Peppard et al. 2013; Heinzer et al. 2015; Phillips et al. 2015). New interdisciplinary care models are required to efficiently and cost-effectively address the OSA burden. Interprofessional collaboration is essentially a teamwork approach that pools the expertise of diverse specialists: family physicians and dentists to screen and monitor health changes, sleep specialists to perform medically supervised sleep treatments, respiratory therapists to provide CPAP treatment, dental sleep medicine–qualified dentists to manage OA, speech and physical therapists to recommend oropharyngeal exercises, dieticians to implement nutrition programs, and psychologists to conduct cognitive behavioral therapy (Table 2). In addition, nose and upper airway/maxillary-mandibular deficiencies are corrected by otorhinolaryngology and maxillofacial surgeons and obesity by bariatric surgeons. Hence, there are no stand-alone treatments for OSA (Almoznino et al. 2017; Lorenzi-Filho et al. 2017; Schwartz et al. 2018; Sarkissian et al. 2019).

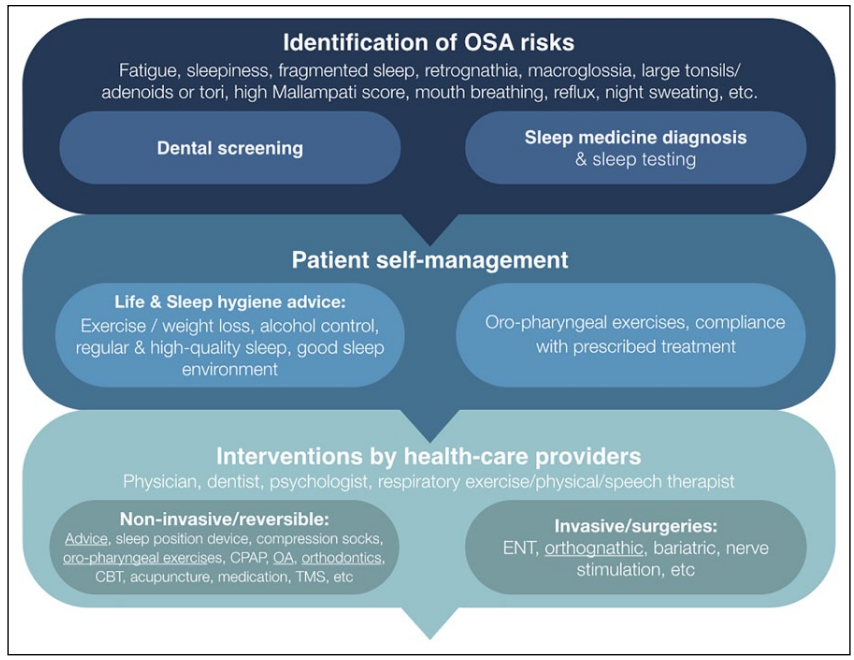

Figure 2. Proposed clinical algorithm for dental management (according to obstructive sleep apnea [OSA] severity). CBT, cognitive behavioral therapy; CPAP, continuous positive airway pressure; ENT, ear, nose, and throat; OA, oral appliance; TMS, transcranial magnetic stimulation.

In this review, OSA treatments are classified into 2 main groups (see Fig. 2). The first line comprises a range of so-called active treatments that are self-applied by patients. The second line is divided into 2 categories: 1) noninvasive (general and specific oropharyngeal exercises, CPAP, OA, diet control, and cognitive and behavioral therapy) and 2) invasive (nose surgery, upper airway surgery, maxillary/mandibular surgery, bariatric surgery for obesity, and hypoglossal nerve stimulation in more severe cases).

The main role of the dental sleep medicine dentist is to screen for OSA risk factors, provide sleep hygiene and health advice for preventive management, deliver OA treatment when recommended, and refer patients to the sleep physician for objective assessment of successful titration. It would be imprudent to provide treatment in the absence of sleep medicine expertise. When managing sleep bruxism and temporomandibular disorder/pain, dentists should rule out other conditions, such as insomnia, headache, or gastroesophageal reflux disorders that are concomitant with OSA (see Fig. 2; Ramar et al. 2015; Almoznino et al. 2017). In children, attention should be paid to parental reports of bedwetting, inattention or hyperactive behavior, regular sleep sweating, and recurrent ear infection, with anatomic observations of narrow jaw, deep palate, retrognathia, or enlarged tonsils. Full OSA management in children includes otorhinolaryngologic examination for nasal and pharyngeal obstruction, speech therapy, and orthodontic/palatal expansion. CPAP or OA is rarely used due to the side effects on craniofacial growth (Marcus et al. 2012).

OA versus CPAP

The OA, also called a *mandibular advancement appliance/device*, is an appliance that passively and mechanically prevents closure of the upper airway by protruding the lower jaw and probably acting as a mandibular and tongue retainer. It is usually made of acrylic or nylon and is adjusted to fit on the patient's upper and lower teeth. It can be either monoblock (no mandible freedom) or biblock (allowing some freedom of movement). The OA is usually the second treatment choice after CPAP, being recommended for mild to moderate OSA and as an alternative for severe OSA when the CPAP cannot be tolerated (Ramar et al. 2015; Gjerde et al. 2016). Prior to its use, the dentist should assess the feasibility of OA treatment by evaluating possible contraindications, such as periodontal damage, presence of decay, or poor oral hygiene, and performing necessary dental treatments before OA insertion. Occlusal changes and exacerbations of temporomandibular joint disorders should be considered and discussed with the patient as well (Marklund 2019).

The benefits for cognition and health, such as improved blood pressure and reduced mortality, are relatively equipotent over time for CPAP and OA (Anandam et al. 2013; White and Shafazand 2013; Dal-Fabbro et al. 2014; de Vries et al. 2018; Schwartz et al. 2018). One possible explanation for the similar effectiveness is that OA tends to be used for longer sleep periods as compared with CPAP, according to the mean disease

Table 2. Route of OSA Treatment via an Interprofessional Management Approach.

1	Behavioral approaches, such as advice on diet and sleep hygiene. Correction/modification of poor sleep habits, beliefs, and misinformation. Improved sleep environment. Low to moderate evidence but clinically intuitive. Note: Cognitive behavioral therapy, performed by a trained professional to improve sleep quality, is a recognized approach. It is also available online for first-line treatment, with no direct professional supervision.
2	With medical recommendation, alternative approaches, such as sleep-positioning devices to correct frequently reported supine sleep habits and/or compression socks to reduce lower limb fluid retention, frequently reported as swollen or painful legs. Moderate evidence; needs medical collaboration.
3	Oral appliances and orthodontic treatment. Moderate evidence, acceptable compliance, used for most of the sleep duration. Some patients with mild OSA may be nonresponders.
4	If the clinician has the training, acupuncture to improve breathing and sleep quality. Moderate evidence, probably a responder- and beliefs-related option.
5	Collaborative dental and medical follow-up is mandatory.

OSA, obstructive sleep apnea.

alleviation concept (Vanderveken et al. 2013). OA is used for about 6 h per night versus about 4 to 5 h for CPAP (Phillips et al. 2013; Vanderveken et al. 2013; Nadal et al. 2018; Schwartz et al. 2018). It can be hypothesized that when patients wake in the middle of the night (to urinate or other reason), they may not reuse their CPAP, leaving more than half of the sleep period without treatment (Varga and Mokhlesi 2019). Moreover, late-night sleep is characterized by a dominance of REM sleep, a critical period thought to increase the OSA health risk (Mokhlesi et al. 2014; Varga and Mokhlesi 2019).

It should be acknowledged that neither CPAP nor OA is 100% effective: most patients show 50% to 70% reduction in AHI, while others derive less benefit. Patients with mild to moderate cases are more responsive to OA, and those with moderate to severe cases are more responsive to CPAP. About 5% to 15% of individuals cannot tolerate CPAP or OA due to many factors, including discomfort, mask claustrophobia, perception of no great benefit, face/tooth/joint pain, nose or oral dryness, and inelegance in front of sleep partner. A major OA issue is the lack of solid data on biological or demographic factors to assess and predict treatment outcomes. However, more sophisticated and promising methods are in development, such as drug-induced sleep endoscopy and remotely controlled mandibular protrusion, used for OA titration during sleep to determine the optimal mandible position and airway patency (Cunha et al. 2017; Remmers et al. 2017; Sutherland et al. 2017; Huntley et al. 2018; Op de Beeck et al. 2019).

Complementary Management

If the medical sleep study confirms OSA in a dominant supine position, positional therapy, such as a lower back cushion (e.g., Zzoma) or electronic device (e.g., Night Shift or Nightbalance), may be used alone in mild cases or in addition to CPAP or OA (Benoist et al. 2017; de Ruiter et al. 2018; Levendowski et al. 2018). Such cases require the input of a sleep physician.

In specific cases with lower limb fluid retention, some sleep physicians also recommend that compression socks be worn below the knee during the day (Perger et al. 2018). This is based on another putative mechanism associated with OSA exacerbation, whereby supine fluid accumulation in the neck compresses the upper airway and increases OSA likelihood (White et al. 2015; Perger et al. 2018). For some patients, referral to acupuncture may be a valid adjunct option (Lv et al. 2016).

These complementary therapies for OSA can be used as bi- or cotherapy with CPAP and OA, with the caveat that they are supported by low to modest evidence. Pharmacologic innovations—for example, medications to improve muscle tone (e.g., noradrenergic and antimuscarinic agents) and to reduce arousal (e.g., trazodone) or inflammation (e.g., corticosteroids; Eckert et al. 2014; Taranto-Montemurro et al. 2019)—and new techniques, such transcranial magnetic stimulation, are not part of the dentist's toolkit but may be in the future (Herrero Babiloni et al. 2018; Cistulli and Hedner 2019).

Follow-up

Dental follow-ups for OA are initially at 2 to 4 wk, then at 6 and 12 mo, and then annually. The objective is to assess comfort, efficacy, side effects (e.g., tooth displacement, temporomandibular complaints, tooth clenching or grinding with headache or pain exacerbation), and subjective response/benefit to treatment. When clinical impression of successful titration is obtained (improvement of patient symptomatology), referral to the sleep physician to evaluate improvement of objective indexes through PSG or home sleep test should be done. Improvement of subjective symptoms, such as fatigue or sleepiness, may reflect a more stable sleep architecture but do not necessarily indicate an improvement of apnea and oxygen desaturation, which are considered the cause of OSA's resultant comorbidities. Thus, repeating PSG studies while undergoing treatment is essential. Additionally, medical sleep follow-up is recommended after 1 y and sooner if nonresponse, perceived nonbenefit, or medical events are reported. Symptoms of nonresponse to OA include persistent fatigue or night sweating, morning headache, sleepiness, and snoring or bruxism sounds. Dentists should also inquire about OA discomfort in the gingival and dental tissues, lack of motivation, salivation issues, supine sleep position, lingual tonsils, excessive or too little mandibular titration (some cases may require remotely controlled mandibular protrusion testing during sleep to find the optimal OA forward position; Remmers et al. 2017;

Sutherland et al. 2017), and changes in health status. Patients should further be informed of the risk of concomitant changes in occlusion with OA (Hamoda et al. 2019; Marklund 2019).

Putative Action Mechanisms of OAs and Other Therapeutic Devices

It is commonly agreed that airway collapse is the dominant OSA mechanism (Neelapu et al. 2017). This is further supported by the finding that 81% of the OSA population presents a collapsible airway, as measured by the critical pressure to close airway patency (Pcrit). These are subjects with anatomic OSA versus 19% of individuals with OSA without clear anatomic factors (Sutherland et al. 2012; Eckert 2018). Four traits have been proposed to contribute to OSA (Fig. 1): 1 anatomic (upper airway patency; i.e., narrow, crowded, or collapsible upper airway) and 3 nonanatomic (impaired muscle responsiveness, low arousal threshold, and impaired ventilator control; Deacon et al. 2016; Eckert 2018; Osman et al. 2018).

Currently, OA appears to work mainly on the anatomic traits, by mechanically opening the airway, preventing closure, and probably acting as a mandibular and tongue retainer. OA may also reduce sleep arousals in a subgroup of patients with OSA, and it appears to be more effective in individuals presenting a low loop gain of the ventilatory control reflex (see Nonanatomic Traits). CPAP may have additive actions to OA on anatomic and nonanatomic traits. OA effectiveness assessment is part of the ongoing efforts of international collaborative researchers (Almeida et al. 2014). Possible and probable mechanisms and characteristics contributing to the effectiveness of OA in patients with OSA are summarized in Figure 3.

Anatomic Traits

Anatomic factors include retrognathia, high arched/deep palate, narrowed maxillary arch, high Mallampati score, large tonsils on pillars behind the tongue (Freidman criteria), large tongue size/volume, obesity (high body mass index), and large neck, as well as restricted oropharyngeal lateral wall space, compressed airway, hyoid bone position, and tongue fat accumulation (as observed in imaging studies). According to recent reports, 80% of subjects at risk for OSA may present some of these characteristics (Sutherland et al. 2012; Kim et al. 2014; Friedman et al. 2017; Neelapu et al. 2017; Eckert 2018; Turnbull et al. 2018).

In general, OA responders (i.e., reduction of AHI by 50% or <5, although controversial) are more likely to be younger and female and to have a low body mass index, a smaller neck, a narrower airway space/volume, and supine-dominant positional OSA (Eckert et al. 2013; Edwards et al. 2016; Eckert 2018; Sutherland, Lee, et al. 2018; Petri et al. 2019). Sleep position is also a critical factor for accurate OA assessment. A recent original study of which variables better predict OA-monobloc success concluded that positional OSA is the strongest OA-predictive variable (specificity and sensitivity = 70% and 80%), above sex, age, neck circumference, body mass index, and AHI (Petri et al. 2019). It remains to be confirmed whether positional OSA success is habit related or due to behavioral, physiologic, or medical (e.g., gastric reflux, back pain) causes. Additionally, the presence of oral tori is an additive anatomic risk factor that could be related to the impact of sleep position on exacerbation of OSA severity (to be confirmed; Ahn et al. 2019).

Nonanatomic Traits

The first nonanatomic trait is the impaired response of airway dilatator muscles to reopen the airway. This is linked to the Pcrit. In patients with OSA and obesity, oropharyngeal muscle activity did not change with increased mandibular advancement, and Pcrit measures were performed with a CPAP and an OA in the mouth (Bamagoos et al. 2019). This complex experimental protocol suggests that OA induces little change in muscle responsiveness, supporting the passive action of OA. This topic merits further exploration.

The second nonanatomic trait is the low threshold to trigger a sleep arousal that contributes to airway opening. Sleep arousals are part of a natural repetitive physiologic activity during sleep that ensures survival in case of life-threatening events, such as low oxygenation or an external predator event. These are repeated 8 to 15 times per hour of sleep in an age-dependent manner. Arousal consists of a brief activation (3 to 10 s) of the autonomic cardiac and respiratory systems with a rise in brain activity at the cortical and subcortical levels, combined with a rise in upper airway and jaw muscle tone (Mayer et al. 2016). Sleep arousals are also closely linked to sleep bruxism onset in young healthy subjects. In relation to OSA, the cortical arousal increases genioglossus and tensor palatini muscle tone. Respiratory-related arousals occur mainly during the inspiratory phase (two-thirds) and less in the expiratory phase (one-third; Amatoury et al. 2018). In the expiration phase, much higher activity occurs in the tensor palatine muscle, which, importantly, is associated with snoring in the inspiratory phase. A systematic review/meta-analysis supports that OA may contribute significantly to reduce AHI and sleep arousal, although a thorough cause-and-effect analysis remains to be performed (Okuno et al. 2014).

The third nonanatomic trait is instability of the ventilator chemoreflex feedback control, called *loop gain*. When the oxygen level drops, the carbon dioxide rises in parallel. Over a certain delay, the system reacts under the control of the carotid sinus and respiratory brainstem center to force a higher breathing amplitude. A series of large breathing events that cause sleep instability is then seen on PSG traces. High loop gain is more effectively controlled by CPAP treatment. A study with a small sample size suggested that OA works better in individuals who present low loop gain (less breathing amplitude overshoot). These patients, called *responders*, represent a subset of subjects with a determined phenotype: mild anatomic compromise and lower loop gain (Edwards et al. 2016). Hence, OA may act by subtle passive and active mechanisms that trigger OSA events in a subgroup of patients with OSA.

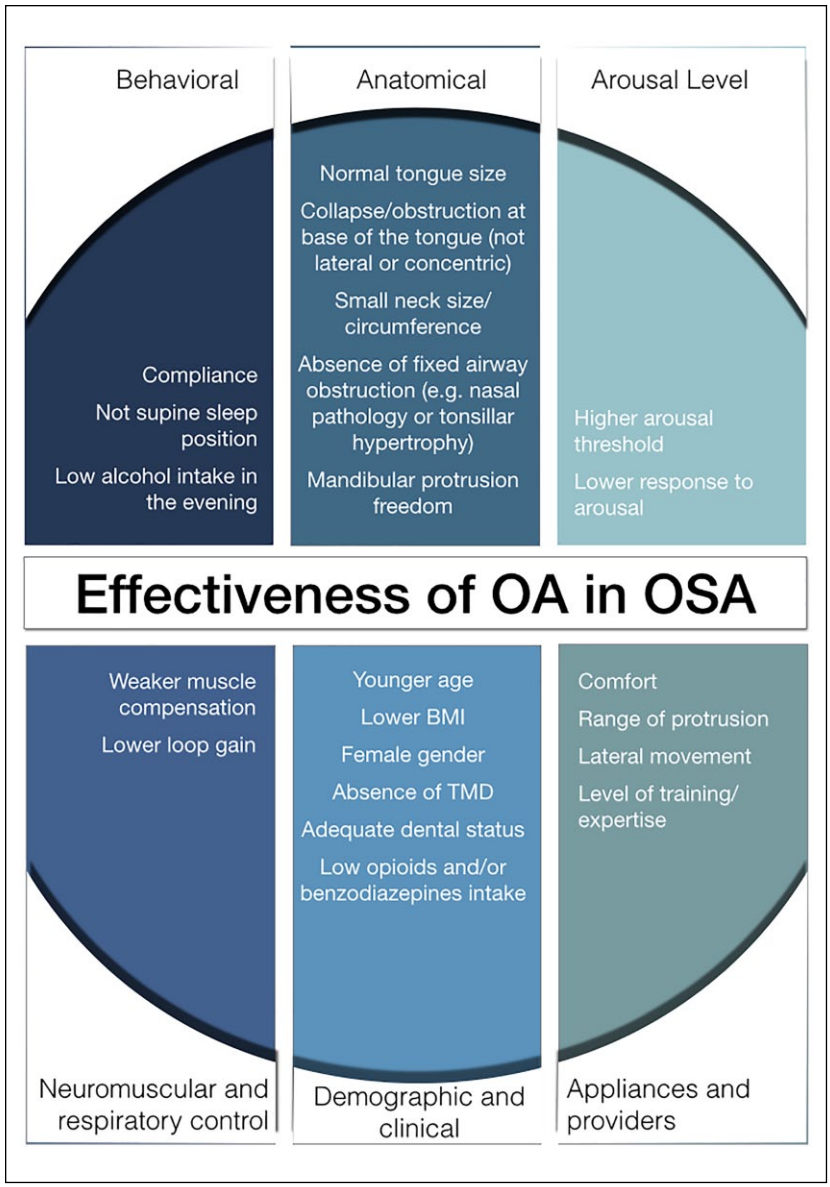

Figure 3. Possible and probable mechanisms and characteristics contributing to oral appliance success in treating obstructive sleep apnea. BMI, body mass index; TMD, temporomandibular disorder.

Identification of treatment action mechanisms may help clinicians improve OSA treatment selection according to individual characteristics and traits, thereby improving the success likelihood. Although identification methods have progressed, many unresolved issues linger. In particular, trait stability over a night and over time is poorly understood. Furthermore, the causal role of traits in OSA is not well established: they could be consequences of OSA rather than causes. Moreover, although algorithms applied to clinical PSG and ideal mandible titration are promising, the measurement of these traits is not routinely available in clinical practice (Okuno et al. 2016; Shin et al. 2016; Sutherland et al. 2017; Cunha et al. 2018; Sutherland, Kairaitis, et al. 2018; Sutherland, Chapman, et al. 2019).

Dental Sleep Medicine: Future Directions

Dental sleep medicine can be defined as a discipline performed by qualified dentists that "focuses on the management of OSA and sleep-related breathing disorders with OA therapy and upper airway surgery. It is also the discipline concerned with the study of the oral and maxillofacial causes and consequences of sleep-related problems" (Aarab and Lobbezoo 2018; Essick 2019). Given the challenges of treatment adherence (compliance) and efficacy/effectiveness, a multimodal approach to OSA management is now considered the standard of care (Figs. 1, 2; Table 2; Almeida et al. 2013; Phillips et al. 2013; Malhotra et al. 2015; Deacon et al. 2016; Shin et al. 2016; Eckert 2018). Consequently, treatments must be managed according to individual characteristics. Many issues remain to be more deeply explored and clarified (Table 1) to 1) improve diagnosis and 2) better assess the action mechanisms and modes of various treatments, including OAs. The aim is to determine the optimal OA design with the strongest effectiveness for each patient phenotype. One promising avenue is to develop algorithms to assist clinical decision making. Another is to apply machine learning approaches to advance the field of precision dental sleep medicine. The predictability of treatment choices (CPAP or OA with or without adjunct alternatives to surgery) according to individual characteristics needs to be improved (Sutherland, Almeida, et al. 2018; Cistulli and Sutherland 2019). Finally, further data should be obtained on some important oral health–related issues associated with the feasibility of OA implementation and its success, such as risk of caries, periodontal disease, and oral health–related quality of life.

Author Contributions

G.J. Lavigne, A. Herrero Babiloni, C. Dal Fabbro, P.A. Cistulli, contributed to conception, design, and data acquisition, drafted and critically revised the manuscript; G. Beetz, contributed to design and data acquisition, drafted and critically revised the manuscript; K. Sutherland, N. Huynh, contributed to conception and data acquisition, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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