VILNIUS UNIVERSITY
FACULTY OF MEDICINE

Dentistry Programme

Institute of Dentistry

Jasper Carl Fernando Schmolck, Year 5, Group 2

INTEGRATED STUDY MASTER'S THESIS

Prosthetic Interventions for Obstructive Sleep Apnea

Supervisor Assist. Prof. Dr. Rita Trumpaitė-Vanagienė

Head of Institute of Dentistry Prof. Dr. Vilma Brukienė

Vilnius, 2024.

Student's email: fernando.schmolck@mf.stud.vu.lt

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ABBREVIATIONS

OSA	Obstructive sleep apnea
CPAP	Continuous positive airway pressure
OA	Oral appliance
MAD	Mandibular advancement device
TRD	Tongue-retaining device
AHI	Apnea hypopnea index
RDI	Respiratory disturbance index
BMI	Body mass index
PSG	Polysomnography
UPPP	Uvulupalatopharyngoplasty
TMJ	Temporomandibular joint
OJ	Overjet
OB	Overbite
RCT	Randomized control trial
MB	Mono-bloc
DB	Duo-bloc
ODI	Oxygen desaturation index
LSAT	Lowest oxyhemoglobin desaturation
QoL	Quality of life
VO	Vertical opening

SEARCH STRATEGY

For the purpose of this master's thesis on prosthetic interventions for obstructive sleep apnea, the data was gathered from scientific articles, reviews, and studies. The literature search was conducted in PubMed, Science Direct, Research Gate, and Google Scholar databases, with the addition of targeted research in dental journals and libraries. Keywords such as "OSA", "MAD", "TRD", and "CPAP" served as the basis for the search approach.

Among the publications included in this literature review are retrospective analyses, meta-analyses, and systematic reviews that were chosen for inclusion based on their methodological quality and applicability to the topic of interest. Particular attention was drawn to studies on prosthetic interventions for the treatment of obstructive sleep apnea: their design, mechanism of action, as well as its effects on clinical parameters such as sleep, quality of life and adherence. The literature search was conducted up to April 2024, with 48 sources being included in this literature review. These sources were published by international authors, to ensure a broad scientific basis and research results.

ABSTRACT

The purpose of this literature review is to analyse the methods of prosthetic interventions used for the treatment of obstructive sleep apnea (OSA). The literature search was conducted in PubMed, Science Direct, Research Gate, and Google Scholar databases, enhanced by specific research in dental journals and libraries. The search strategy was based on keywords such as "OSA", "MAD", "TRD", and "CPAP". Scientific literature sources were selected based on their methodological quality and relevance to the topic, including retrospective analyses and meta-analytical and systematic reviews.

Firstly, obstructive sleep apnea and its risk factors were defined. In the second part, the two most common prosthetic appliances used for the management of obstructive sleep apnea – mandibular advancement device (MAD) and tongue-retaining device (TRD), their advantages and drawbacks were reviewed. Also, patient-centred outcomes, comparing oral appliances to continuous positive airway pressure (CPAP) therapy were described. It was concluded that MAD therapy should be considered as a first-line treatment option for OSA due to its comparable efficacy and superior adherence rates compared with CPAP.

Keywords: OSA, MAD, TRD, CPAP

I) INTRODUCTION

Patients suffering from Obstructive sleep apnea (OSA) often experience symptoms such as excessive daytime sleepiness (EDS) derived from unrefreshing sleep, fatigue and snoring (1). To prevent negative effects on the patient's health, which may include cardiovascular comorbidities and depression, several different treatment strategies have been suggested (1,2). Currently, continuous positive airway pressure (CPAP) is regarded to be the "gold-standard" treatment option for OSA (3). However, despite its high efficacy, adherence rates are low. Thus, alternative treatment options must be considered for patients who are not adhering to CPAP treatment. Promising alternatives are oral appliances (OAs) consisting of the most used mandibular advancement devices (MADs) and tongue-retaining devices (TRDs) (4).

II) OVERVIEW AND IMPACT – OBSTRUCTIVE SLEEP APNEA

2.1 OSA DEFINITION AND CLASSIFICATION

Alterations in breathing during sleep can lead to sleep-disordered breathing (SDB). One of these sleep-disordered breathing diseases is the collapse of the upper airway during sleep, also known as obstructive sleep apnea (OSA). Patients with OSA experience recurrent periods of reduced airflow (hypopnea) or discontinuation of respiration (apnea), which are accompanied by disturbed sleep, awakenings, and reductions in saturation of oxygen (5).

The American Academy of Sleep Medicine (AASM) developed a screening manual for the scoring of respiratory events during sleep using polysomnography. If the respiratory effort signal drops by 90% or more of the pre-event baseline for 10 seconds or more and there is maintained or increased inspiratory effort from the chest and/or abdomen, the condition is classified as obstructive apnea.

When the respiratory effort drops by 30% or more of the pre-event baseline for 10 seconds or more and is accompanied by a 3% (AASM criteria) decrease in oxygen saturation, the condition is referred to as hypopnea.

If the inspiratory nasal pressure flattens for 10 seconds or more, triggering an awakening from sleep but not matching the criteria for apnea or hypopnea, a Respiratory Effort-Related Arousal (RERA) is recorded.

Both the Apnea Hypopnea Index (AHI) and the Respiratory Disturbance Index (RDI) determine the severity of OSA. The AHI is calculated based on the number of apneas and hypopneas in the total duration of sleep. The calculation of the RDI includes the number of apneas and hypopneas plus RERAs in the total duration of sleep. For adults, an AHI of less than 5 per hour is considered normal, 5-14.9 per hour indicates mild OSA, 15-29.9 indicates moderate OSA and 30 or more indicates severe OSA (6).

2.2 RISK FACTORS AND PREVALENCE

Unmodifiable and modifiable factors are influencing the risk of OSA. Race, male sex, age, genetic predisposition, and narrow airways due to cranial facial anatomy are among the unmodifiable risk factors. Among the modifiable risk factors are alcohol consumption, nasal congestion or obstruction, and obesity (1,7).

When analysing the prevalence of OSA in different ethnicities, significant differences may be found. Studies indicate that white individuals are affected the least commonly by OSA with a prevalence between 17% and 32%, followed by blacks with 20% to 32%. Chinese people have the greatest OSA prevalence, at 39% [4]. It appears that cranial-facial structural characteristics are linked to the well-known risk factor of the Asian race (7).

When comparing men and women with similar body mass indices (BMI), men have a higher risk of OSA than women do. For instance, men may be more susceptible to upper airway collapse due to increased testosterone levels. However, once women reach menopause, their risk reaches the level of men's risk. This indicates that the change of hormones, such as a decline in progesterone contributes to a higher risk of OSA. The stronger propensity for android fat distribution, which results in a larger neck circumference, as well as a typically longer upper airway, which has a negative impact on airway collapsibility, is more common in men than in women (1,7,8).

With age comes an increased risk of OSA. According to the results of the study, mild OSA was found in 23% of men between the ages of 65 and 72, and 30% of men over 80 years of age. However, the prevalence in certain elderly populations may reach up to 90% in men and 78% in women. In contrast, 10% of men aged between 30 and 40 had moderate OSA. Slow wave sleep, which guards against airway collapse and SDB, decreases with ageing and may be the cause of the increased risk of OSA with age (1,7).

Genetics play a major role in upper airway anatomy, neuromuscular activity, and ventilation control stability. This is particularly true for specific ethnic groups, that tend to have narrow airways due to cranial facial anatomy. African Americans for example, are more likely to have enlarged soft palates, which may lead to restricted upper airways. As mentioned previously, Asians with OSA are more likely to have craniofacial anomalies. This includes a shorter cranial base, jaw length, and positioning differences (7). Certain genes have been linked to an increased risk of obesity and OSA, according to previous research (9). Nevertheless, studies analysing candidate genes have mostly been insignificant and have not been repeated (10). However, additional factors have been proven to constrict the airway. Airways may narrow due to an increase in soft tissues, inflammation of upper airway soft tissues, which contributes to

pharyngeal airway narrowing, and loss of muscular tone, which disrupts the balance between forces that tend to dilate and collapse airways, particularly in the elderly (7).

Although the effects of alcohol on OSA remain under investigation, and the existing research is contradictory, it is believed that alcohol intake can cause or worsen OSA and thus, is regarded as a modifiable risk factor. The peripheral muscle relaxant property of alcohol may worsen oxygen saturation, snoring, and OSA by collapsing the upper airways (11,7).

About 50–60% of upper airway resistance is caused by the nose. There are two categories of nasal congestion and obstruction: on the one hand, being caused by rhinitis, either allergic or nonallergic, and on the other hand, being caused by anatomical abnormalities such as deviated septum, enlarged turbinates, and nasal polyps (12). The oropharynx, which experiences negative downstream pressure due to nasal airway obstruction upstream, results in pharyngeal collapse. The body compensates by using mouth breathing to bypass the nasal airway if the obstruction persists beyond a certain level. Mouth breathing causes the tongue to retract, the pharyngeal lumen to narrow, and the pharyngeal airway to narrow even further (13,7).

Obesity has been linked to pharyngeal airway narrowing by enlarging soft tissues around and within the airway. Another contributing factor is fat accumulation in the tongue, soft palate, uvula, and beneath the lower jaw, which possibly results in a neck circumference, increasing the risk of OSA (38 cm in women and 43 cm in men) (14,15).

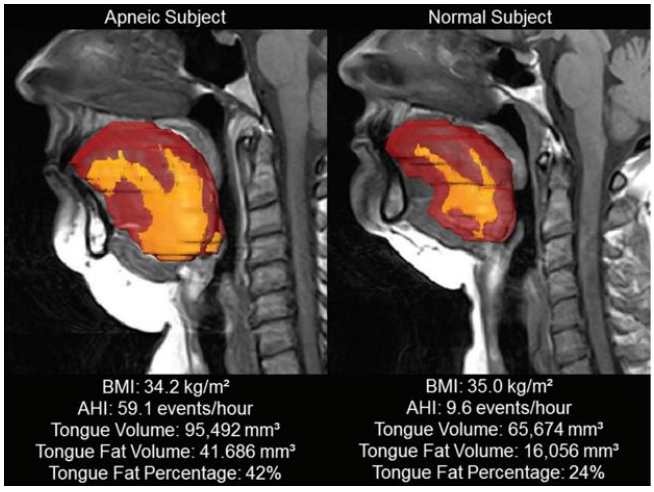

Figure 1. MRI tongue size/ fat deposition, OSA vs. non-OSA patient (16)

Recumbent position, along with increased abdominal fat mass, decreases lung capacity considerably. Lastly, reduced lung volume may cause airway narrowing by lowering pharyngeal wall tension and longitudinal tracheal traction forces (14,15).

An increase in the prevalence of OSA is expected, as obesity increases worldwide, affecting children and adults, and the global population ages. OSA is predicted to affect one billion people worldwide between the ages of 30 and 69, with 70% to 80% remaining undiagnosed.

According to studies, the global prevalence of moderate OSA ranges from 9% to 38%, with men being more commonly affected, whereas severe OSA affects 6% to 17% of people (7).

2.3 HEALTH CONSEQUENCES AND IMPACT ON QUALITY OF LIFE

Untreated OSA can have a wide range of serious consequences on the health of patients. The most often reported symptom of EDS results from disrupted sleep cycles leading to unrefreshing sleep. EDS, fatigue, and inattention, all of which are associated with OSA, increase the risk of accidents. Especially drowsy driving, caused by unrefreshing sleep, can lead to motor vehicle accidents. Drivers with untreated OSA are 6 times more likely compared to the general population to be involved in traffic accidents (1,2).

Furthermore, the oral cavity is affected by the health consequences of OSA.

Snoring may be provoked by the narrowing of the upper airway, leading to turbulent airflow which causes the oscillations of the pharyngeal tissues during respiratory cycles (7). Partially collapsed airways or blocked nasal passages may be compensated by mouth breathing, negatively affecting the salivary flow rate. The reduced salivary flow results in a subjective sensation of oral dryness, commonly experienced by patients with OSA. Studies have indicated that the prevalence of hyposalivation and therefore the subjective sensation of dry mouth/ xerostomia increases with the severity of OSA (13,17).

The cardiovascular system, which is affected by OSA, contributes to several comorbidities such as hypertension, heart arrhythmia, myocardial infarction, and congestive heart failure. All these health consequences of OSA have a negative impact on the quality of life (QoL), which is the most significant patient-reported outcome of OSA.

Another factor influencing the QoL negatively is depression, which might be associated with OSA. Symptoms such as EDS, poor concentration, fatigue, irritability, and loss of energy are attributed to both OSA and depression. Emotional modulation changes in the frontal lobe may result from unrefreshing sleep, frequent arousal, and sleep fragmentation, frequently found in OSA. Studies have revealed that symptoms of depression can be improved by the treatment of OSA. Thus, not only physical health but also mental health is improved by OSA treatment, which results in an improvement in the QoL of patients suffering from OSA (1,2). It is crucial to remember that the degree of OSA-related deterioration of the QoL differs between individuals, and the severity of health consequences influences the degree of its impact.

2.4 INTERDISCIPLINARY APPROACH TO OSA MANAGEMENT

OSA is a multifaceted disorder that can affect various aspects of an individual's physical and mental health as well as overall well-being. Evidence suggests that a multidisciplinary team consisting of various healthcare specialists, such as sleep medicine specialists, Ear, Nose, and

Throat specialists, dentists, and maxillofacial surgeons must work together to provide a comprehensive assessment and subsequent adequate care for OSA patients. Making decisions as a team, together with the patient provides superior individual care and outcomes compared to decisions made by individuals. Especially for patients who have failed initial airway treatment, so-called “difficult-to-treat” patients, a team approach that is more structured and systematic is particularly important (18,19). A single healthcare specialist alone may not have enough expertise to deal with all aspects of OSA and its consequences.

To determine the presence and severity of OSA and to make an accurate diagnosis, sleep medicine specialists may carry out a sleep study, such as Polysomnography (PSG) or Home Sleep Apnea Testing (HSAT), and use screening tools such as the Berlin or STOP-BANG questionnaire (6)

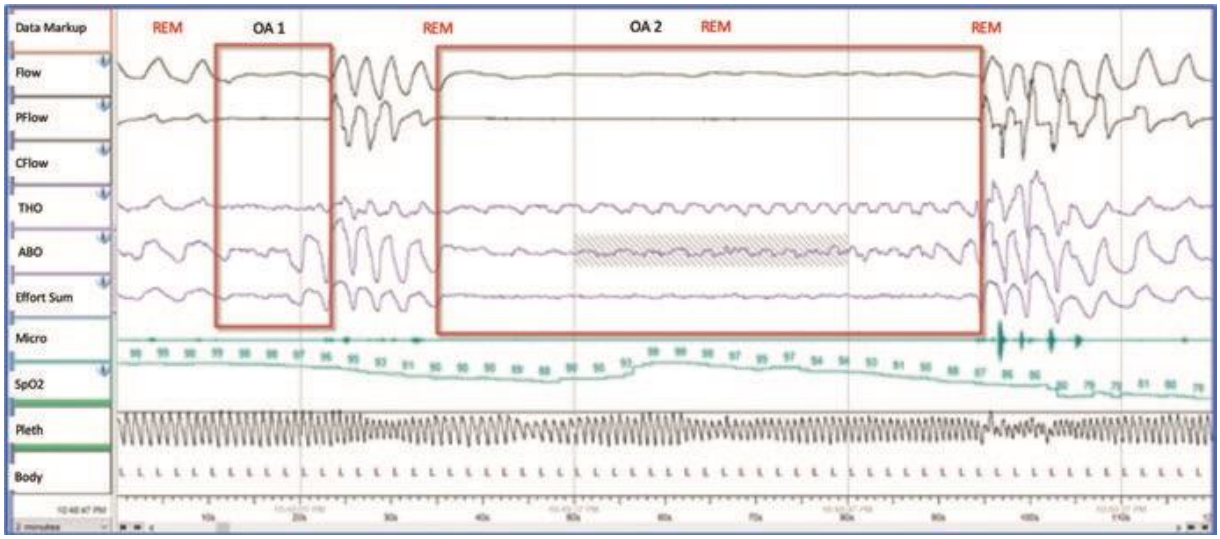

Figure 2. Polysomnography - Obstructive Sleep Apnea (7)

BERLIN QUESTIONAIRRE		
CATEGORY 1		
Do you snore?	☐ Yes ☐ No ☐ Don't know	
Your snoring is?	☐ Slightly louder than breathing ☐ As loud as talking ☐ Louder than talking ☐ Can be heard in adjacent room	
Describe your snoring frequency?	☐ Nearly everyday ☐ 3-4 times a week ☐ 1-2 times a week ☐ 1-2 times a month ☐ Never or nearly never	
Has your snoring ever bothered other people?	☐ Yes ☐ No	
Has anyone noticed that you quit breathing during your sleep?	☐ Nearly everyday ☐ 3-4 times a week ☐ 1-2 times a week ☐ 1-2 times a month ☐ Never or nearly never	
CATEGORY 2		
How often do you feel tired or fatigued after you sleep?	☐ Nearly everyday ☐ 3-4 times a week ☐ 1-2 times a week ☐ 1-2 times a month ☐ Never or nearly never	
During your wake time, do you feel tired, fatigued or not upto mark?	☐ Nearly everyday ☐ 3-4 times a week ☐ 1-2 times a week ☐ 1-2 times a month ☐ Never or nearly never	
Have you ever nodded off or fallen asleep while driving a vehicle?	☐ Yes ☐ No	
If yes, how often does it occur?	☐ Nearly everyday ☐ 3-4 times a week ☐ 1-2 times a week ☐ 1-2 times a month ☐ Never or nearly never	
CATEGORY 3		
Do you have high blood pressure	☐ Yes ☐ No	
Body Mass Index (kg/m²)		
INTERPRETATION		
☐ Category 1 Positive (≥2) ☐ Category 2 Positive (≥2) ☐ Category 3 Positive (1 or BMI > 30 kg/m²)		

Figure 3. BERLIN questionnaire (20)

Yes	No	
○	○	**Snoring?** Do you snore loudly (loud enough to be heard through closed doors or your bed partner elbows you for snoring at night)?
○	○	**Tired?** Do you often feel tired, fatigued, or sleepy during the daytime (such as falling asleep during driving)?
○	○	**Observed?** Has anyone observed you stop breathing or choking/gasping during your sleep?
○	○	**Pressure?** Do you have or are being treated for high blood pressure?
○	○	**Body mass index more than 35 kg/m²?**
○	○	**Age older than 50 years?**
○	○	**Neck size large? (measured around Adam's apple)**
○	○	For male, is your shirt collar 17 inches or larger?
○	○	For female, is your shirt collar 16 inches or larger?
○	○	**Sex = male?**

Notes: Scoring criteria (for general population): low risk of OSA, yes to 0–2 questions; intermediate risk of OSA, yes to 3–4 questions; high risk of OSA: yes to 5–8 questions, yes to 2 of 4 STOP questions + individual's sex is male, yes to 2 of 4 STOP questions + BMI >35 kg/m², yes to 2 of 4 STOP questions + neck circumference (male) 17″/(female) 16″. Property of University Health Network.
Abbreviations: OSA, obstructive sleep apnea; BMI, body mass index.

Figure 4. STOP-BANG questionnaire (21)

To treat OSA adequately, multidisciplinary teams develop treatment plans, frequently including a variety of treatment approaches, monitor patients, and schedule follow-up appointments. Dentists provide prosthetic care for OSA patients with the help of various OAs, which preserve a patent airway, e.g., by protruding and stabilizing the mandible. Prior to this event taking place, a dental evaluation must be carried out to determine the patient's suitability for OA therapy, select a suitable appliance, and ensure the correct fit (3,18,20).

III) PROSTHETIC INTERVENTIONS IN OSA

3.1 PROSTHETIC APPROACH

Treatment modalities for OSA can be divided into two main groups, either surgical or non-surgical. Behavioural management, CPAP therapy, and oral appliances (OAs) are part of the non-surgical treatment approaches. The surgical treatment approaches for OSA include different kinds of surgeries in the orofacial/ head and neck region. Uvulopalatopharyngoplasty (UPPP), tracheostomy, and maxillomandibular advancement surgery are some of the most frequent surgical approaches.

Retroglossal obstructions, which are located behind the base of the tongue, and retropalatal obstructions, which are located behind the soft palate, are the most common sites of airway obstruction in OSA. Despite the fact, that UPPP is the most common surgical treatment approach in treating OSA, it only addresses retropalatal obstruction but does not correct retroglossal obstruction (3,4,6).

OAs address both the retroglossal and retropalatal obstructions and exist in various forms. OAs improve the oropharyngeal airway patency, by expanding the lateral portion of the upper airway. There are more than 150 accepted appliances for the treatment of patients with OSA and snoring; however, their efficacy varies widely. Despite this, they can be divided into two broad categories, mandibular advancement devices (MADs) that move the lower jaw anteriorly, and tongue-retaining devices (TRDs) which protrude the tongue. Each provides a non-invasive, simple, and economical therapy for OSA, snoring, or both (6,20,4,22).

There are not only many different appliances but also different terminologies to describe OAs. For example, appliances that advance the mandible can be termed mandibular advancement devices (MAD), mandibular advancement splints (MAS), mandibular advancement appliances (MAA), etc. To avoid confusion in the terminology, the term MAD is used below for mandibular advancement devices and TRD for tongue-retaining devices (18).

MADs can be either custom-made or non-custom-made and exist in a mono-bloc (MB) or duo-bloc (DB) configuration, determining whether they are titratable or non-titratable. The amount of mandibular protrusion can be varied with titratable OAs using a special mechanism, whereas

the mandibular protrusion of non-titratable OAs cannot be changed during treatment and remains in its initial position. The custom-made OAs are made of biocompatible materials and engage both arches of the maxilla and mandible. They are made in the dental laboratory from models after the dentist has taken an impression of the patient's oral structures. Non-custom-made OAs, which are also known as "self-moulded devices", are prefabricated splints made of thermoplastic materials, that are customised to the patient's oral structures to a certain extent (18,23).

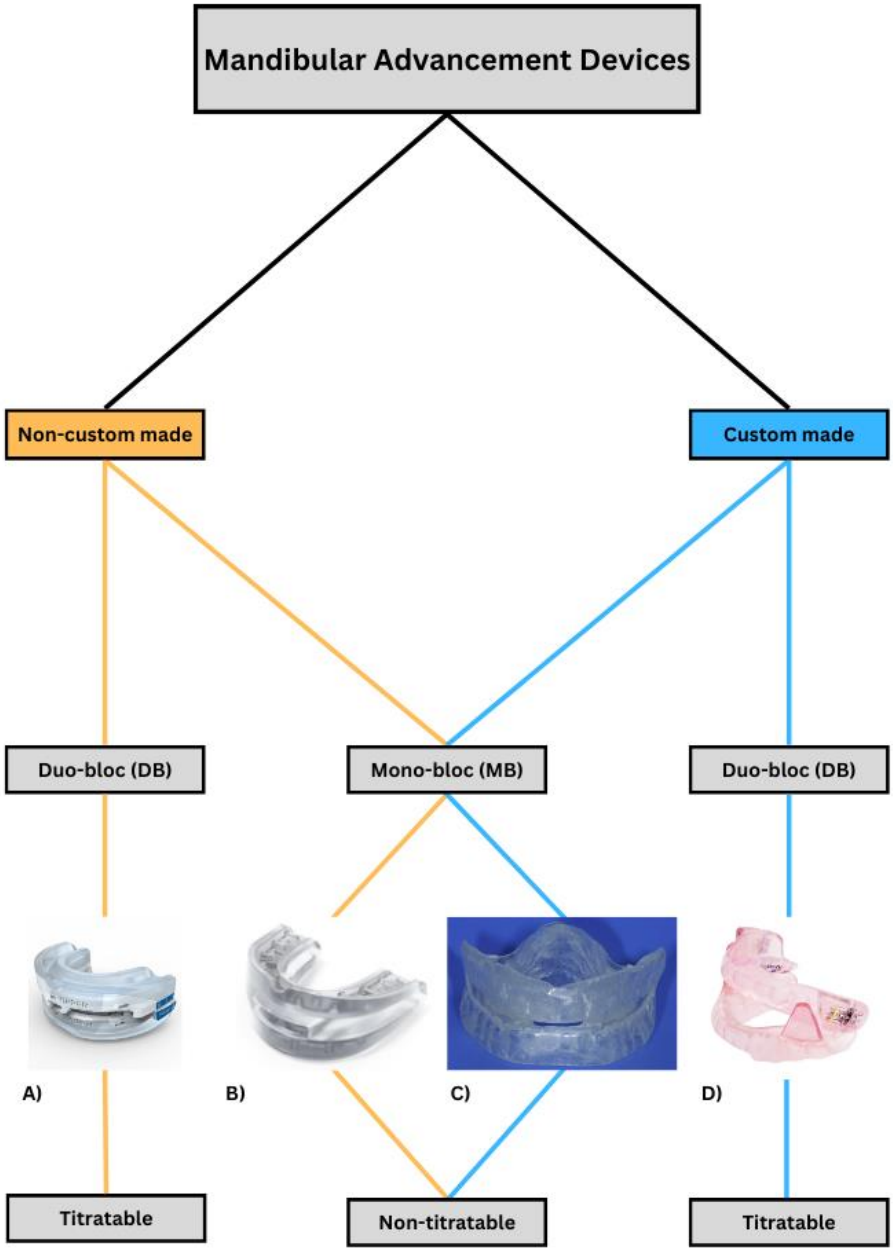

Figure 5. Flowchart Mandibular Advancement Devices: A) Non-custom made duo-bloc device (24), B) Non-custom made mono-bloc device (25), C) Custom made mono-bloc device (22), D) Custom made duo-bloc device (7)

TRDs can be either custom-made or non-custom-made and are made of soft silicone suitable for medical use. The appliance has a small plastic bulge in the front area determined for the tongue and may cover the maxillary and mandibular dental arch additionally.

The tongue is pulled forward and is held in place by the negative pressure generated by the appliance. This is caused by the displacement of air in the lingual space. This prevents the tongue from falling back into the throat, thus, blocking the airway. Instead, the retroglossal space is enlarged and the lower jaw and hyoid bone are stabilised (20,22,26).

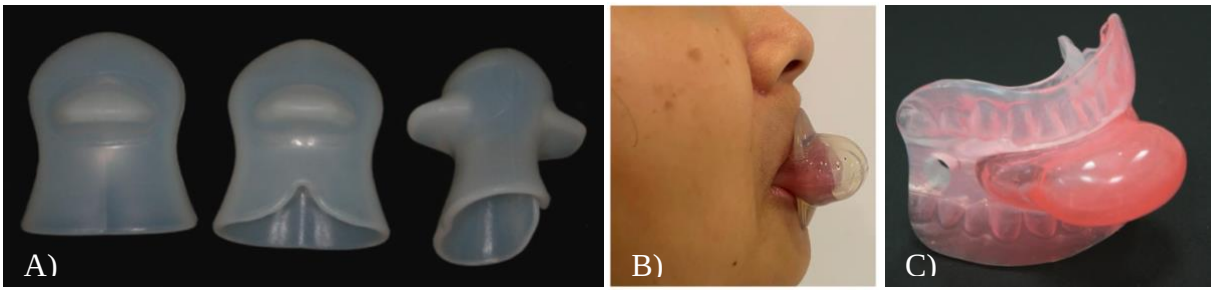

Figure 6. TRDs: A) (27) and B) (26) without dental coverage, C) (28) with dental coverage

By reducing the AHI, snoring, and arterial blood pressure, and improving the oxygen saturation during sleep, OAs have demonstrated their effectiveness in treating patients with OSA (29).

Most patients favour treatment with OAs rather than CPAP therapy or surgical treatment, and tolerate it well, with a compliance rate between 40% and 80% (3).

Currently, CPAP therapy is the gold standard among the non-surgical treatment approaches and should always be considered before surgical intervention. However, the rate of non-adherence, the use of CPAP for less than 4 hours per night, is between 46% and 83%. This is due to various factors, such as claustrophobia, inability to fall asleep with it, unintentional removal of the mask during sleep without waking up, mask leakage or no effect (3,20). But even a gold-standard treatment method such as CPAP is ineffective in case the patient refuses or does not accept it. Hence, those patients must be offered an alternative non-surgical treatment method.

The use of OAs, particularly MADs, which are the most effective and widely prescribed, is particularly effective in the treatment of mild-to-moderate OSA. They can also be used to treat selected cases of severe OSA in case the patient is unable to tolerate other forms of treatment, such as CPAP.

Before starting the treatment with OAs, a qualified dentist must determine the patient's suitability for this treatment method, which should be part of a routine examination for patients with OSA. The dentist examines the patient's face and oral cavity, with a special focus on the anatomy and health of the teeth.

The finding of incompetent lips, a long face due to increased anterior face height, a steep mandibular plane angle, and/ or a retrognathic mandible during the facial examination are

common findings in patients with snoring/ OSA. Patients may also manifest with bruxism, which is expressed by grinded/ worn-out posterior teeth. This causes mandibular retrusion as the flat cusps lose their key occlusion. Malocclusion, a narrow dental arch or V-shaped maxillary arch, a high-arched palate, and a low position of the tongue on the mandibular teeth are further oral findings the dentist must be aware of (20,22,23,30). The tongue position is assessed by the Mallampati score, examining the oropharynx as well as the position of the tongue relative to the soft palate. During the examination, tongue positions are compared between rest and protruded positions while the mouth is held open. An increased risk for OSA can be seen with rising degrees of obstruction of the soft palate and oropharyngeal airway (7).

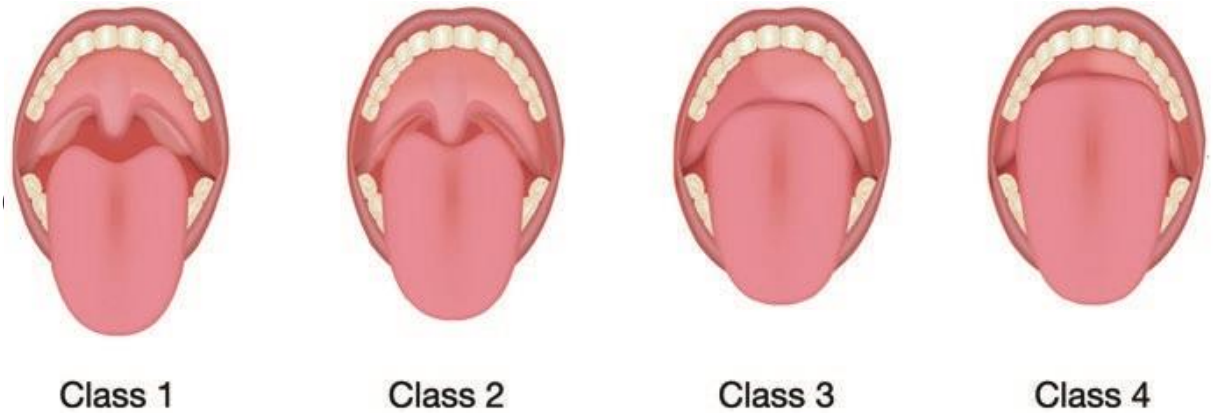

Figure 7. Mallampati scoring (7)

To ensure sufficient retention of the MAD, the patient should not have less than 6 to 10 functional teeth per dental arch. However, the location of teeth is more important than their quantity, as posterior teeth offer better retention. Nevertheless, MAD can also be prescribed successfully in certain edentulous patients, provided that the dentoalveolar ridges are well preserved.

Furthermore, periodontal health is examined to rule out periodontitis, as teeth may be moved unintentionally due to untreated disease. The last part focuses on the health of the temporomandibular joint (TMJ), assessing the ability of mandibular protrusion and mouth opening, as well as determining any signs/ history of TMJ disease.

As soon as the dentist has identified a safe and suitable situation from a dental health point of view, the selection of the right appliance can begin.

Although there are a variety of different appliances and designs available, two of them are most used. MADs, that are customised and titratable are the desired type of OAs according to recent data, if applicable to the patient's oral conditions. If oral conditions do not allow for MAD treatment or the patient does not respond to MAD treatment, TRDs should be used if the patient wishes to be treated with OAs (20,22,23,30).

3.2 MANDIBULAR ADVANCEMENT DEVICE

3.2.1 TITRATION AND CUSTOMISATION

As previously mentioned, mandibular advancement devices exist in a variety of forms. They can be either non-custom-made or custom-made but can also have other differences in the respective category. Although MADs come in different varieties, they have some common mechanical requirements. The necessity of good support to the maxillary and mandibular teeth/ alveolar ridges to protrude and fixate the lower jaw to the upper jaw is a feature which is present in all types of MADs (30).

MAD mono-bloc appliances are appliances, where the maxillary and mandibular splints are fused to a one-piece appliance. The thermoplastic MB, which is usually manufactured in a non-custom-made manner, is the simplest type of MAD. The device is placed in boiling water to soften its thermoplastic polymer material. After the removal from the water, the patient inserts the splint into their mouth under the supervision of the dentist, to mould it to its teeth. During insertion, the patient must bite into the material and protrude the mandible to approximately 50% of maximum advancement as long as the material is still soft. This position must be maintained until the splint is cooled and the material is fully set.

Custom-made monoblock appliances that are non-triable are manufactured in a way, that the maxillary and mandibular splints are fused by steel wire. The mandibular protrusion is set in the permanent advanced position, which is usually between approximately 50% and 80% of maximum mandibular protrusion (22,30,31). This reduces the costs and speeds up the time to treatment compared to more complex devices such as the duo-bloc that allows for mandibular titration (31).

MAD duo-bloc appliances are appliances, where the maxillary and mandibular splints can be separated but must be connected to each other to achieve the desired effect. The fixation mechanism exists in a variety of forms and can be made out of elastic or plastic connectors, hook connectors, metal pin and tube connectors, magnets or acrylic extensions, to name a few. The relation between the two splints is determined by their connectors or blocks, which protrude the mandible to the desired level during sleep, allowing the jaw to move in vertical and lateral directions. The most efficient and tolerable mandibular protrusion is achieved by an invariably adjustable attachment design, that allows titration (22,30–32). In contrast to MB appliances, DB devices allow for mandibular titration and jaw movement which is reported to be more comfortable for patients. Furthermore, a more efficient mandibular protrusion can be achieved, increasing the therapeutic effect, and decreasing adverse effects (32).

To date, research could not identify a gold-standard protocol for the titration of mandibular protrusion. Thus, the optimal position of advancement is achieved in a "trial and error" manner. MADs that allow for gradual titration are the preferred kind of devices, since the amount of mandibular advancement can be tailored according to the patient's tolerability and the positive effects on breathing efficacy, promising the best therapeutic effect.

It is important to note, that the amount of mandibular advancement to achieve the desired therapeutic effect cannot be generalised and is patient-dependent. That is why it is so difficult, almost impossible to create a gold-standard titration protocol that is effective for each individual patient. Although some authors see an advancement of 75% of maximum mandibular protrusion as standard, it was found that the actual needed protrusion for a therapeutical effect ranges between 50% and 90% of maximum mandibular protrusion. Currently, the conventional method to find the optimal effective titration is based on subjective symptom resolution. Instead, a more accurate method should be chosen in which the mandible is protruded to its greatest comfortable limit. Although this method could increase the risk of adverse effects, it is believed to be advantageous over the subjective feeling of symptom improvement.

Nevertheless, it is important to find the optimal amount of mandibular advancement and not to advance the mandible too far, even within the comfortable limit, since over-titration can change the airway dimensions from a wide lateral to a narrow lateral diameter. Thus, reducing its efficacy (23,32). Conclusively, the therapeutic effect to be achieved is not equally related to the amount of mandibular protrusion, but to a dose-related decrease in airway collapsibility.

Usually, the first month of treatment with MADs is used to allow the patient to get used to the new device. After that, two to three further months are needed to increase the mandibular protrusion progressively. A different approach is to use a MAD device with a motorised or hydraulic titration mechanism during a single-night titration study. The amount of mandibular advancement can be adjusted remotely, without waking the patient during sleep, identifying the amount for protrusion with the greatest therapeutical effect. The advantages are, that it can be determined whether the patient is suitable for MAD therapy or not, and that the optimal advancement amount has already been determined. The boundaries of this method are, that skipping the initial phase without a slow increase in tolerance might lead to considerable discomfort to the patient, preventing the needed protrusion from being identified (33).

3.2.2 AIRWAY MECHANICS

Mandibular protrusion to the correct therapeutical degree has several beneficial effects on the airway and its connected structures. It is assumed that changes in the complex connections, between diverse muscle groups controlling the upper airway caliber, are caused by anatomical

modifications in the oropharynx (32,29). Especially in the retropalatal area, the airway caliber is increased by shifting forward of tongue and tongue-base muscles, leading to lateral expansion and displacement of parapharyngeal fat pads. This was found during airway imaging with cone-beam computed tomography (CBCT), magnetic resonance imaging (MRI) and nasal endoscopy (22). Thus, a reduction in the collapsibility of the upper airway is achieved by the dose-dependent protrusion of the mandible, leading to structural changes. Reduced measurement of upper airway closing pressure during sleep and upper airway critical closing pressure indicates the achievement of reduced collapsibility. The passive mechanical properties of the upper airway are reflected by these measurements (32). Airway collapse is thought to be caused by neuromuscular decontrol. Studies have found, that after the treatment with MADs, the electrophysiological activity of the genioglossus muscle has been elevated. Thus, MADs may stabilise the upper airways during sleep by stimulating neuromuscular reflex pathways. However, the effect of MADs on the neuromuscular function of the upper airway has not been confirmed by all research studies (29,32). Furthermore, MADs may counteract increased airway length when lying in a supine position, decreasing its length slightly but considerably (22). Nevertheless, the exact mechanism may differ between patients and remains to be investigated further (30).

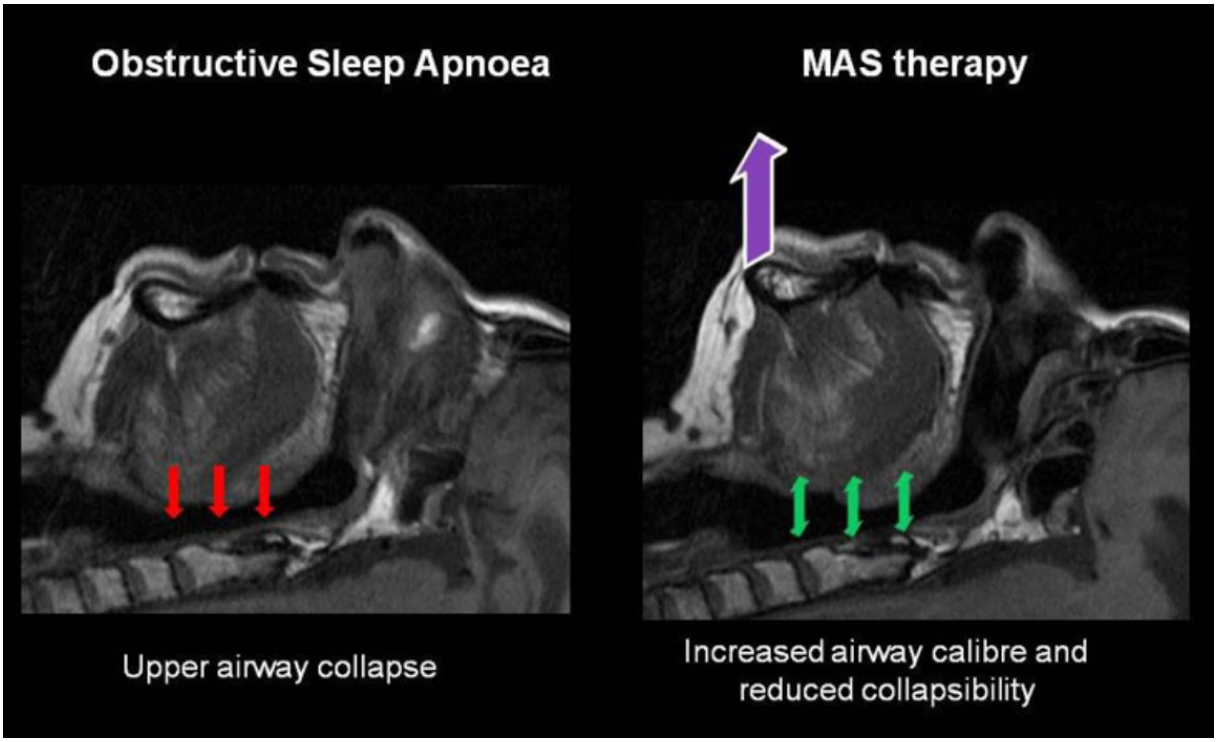

Figure 8. Airway mechanics in OSA with and without MAD (MAS therapy) (33)

3.2.3 CHALLENGES

Although MADs have numerous advantages over other treatment modalities such as CPAP or surgery, patients may encounter challenges during its therapy.

The patient's economic status may predetermine what type of appliance will be used during the course of treatment. MADs that are simpler in their production and usage, such as non-customised appliances, are generally cheaper and therefore more accessible, however, their tolerance is generally inferior. The TOMADO study found discomfort, poor retention and adherence for simple thermoplastic devices. More advanced MADs, such as customised titratable devices, frequently require dental experience and take more time to manufacture. They come at a higher cost, limiting their accessibility (23,30). Another challenge is the appearance of side effects. The majority of them are transient and mild but they may be demotivating, especially as they often occur during the initial treatment phase, although they tend to resolve with time (22). Especially patients who use over-the-counter MADs should seek a dentist's advice, although it is not necessarily proposed by the manufacturer. As described earlier, the suitability for OA therapy must be evaluated before treatment. This can prevent these patients from having a bad first impression of MADs in case the application does not proceed as they expected (30). Consequently, patients are encountered with extra dental visits, potentially leading to additional stress.

3.2.4 ADVERSE EFFECTS

As with any other treatment method, the use of MADs has certain shortcomings. It is important to inform the patient that mild side effects can appear at any phase of treatment. Advancing and keeping the mandible in a protruded position is the key mechanism of MADs. Conversely, its mechanical pressure may result in reciprocal forces on the jaw, teeth, and gums, possibly resulting in acute symptoms, such as pain and others (33). However, their duration is usually short and will often resolve without considerable intervention (4).

Patients may encounter hypersalivation, pain in the TMJ and teeth, as well as headaches most commonly, but symptoms such as tongue discomfort, dry mouth and a sense of suffocation were described by patients as well (31,22).

A major side-effect, appearing with long-time use of MADs, is the shifting of teeth resulting in occlusal changes. Especially incisors are affected, as the maxillary dentition experiences posteriorly directed forces leading to retroclination of maxillary incisors, and the mandibular dentition experiences anteriorly directed forces, resulting in the proclination of mandibular incisors (31). The inclination of mandibular incisors increased by 2.07° according to a meta-analysis, resulting in a decrease in overjet (OJ) of 0.99 mm and a decrease in overbite (OB) of

1.0 mm. However, they did not find significant changes regarding the inclination of maxillary incisors or the interincisal angle. The prevalence of anterior crossbites, and decrowding of mandibular teeth due to enlarged mandibular arch width, as well as reduced crowding in the maxillary arch due to enlarged maxillary arch width, increased. Temporary difficulties with chewing may result from the development of a posterior open bite due to reduced posterior occlusal contacts (22). However, dental changes resulting in altered occlusal contacts are not automatically disadvantageous. No changes in occlusion were reported by 14% of patients whereas 41% of patients experienced an improvement in occlusion (33). Research on craniofacial changes yields different results. Long-term use of MADs (for more than two years) resulted in a significant increase in anterior facial height (lower and total) according to researchers. Contrary, no significant skeletal changes were found by a meta-analysis investigating MAD-related skeletal changes (22).

During the initial titration period, patients may experience temporary TMJ discomfort and muscle soreness (22). However, temporomandibular disorder (TMD) signs and symptoms, which were pre-existing in some patients, did not aggravate during MAD therapy. Thus, the presence of TMD should not necessarily be considered as a contraindication to treatment with MADs (30). A study, investigating the prevalence of TMD, did not find an increase in TMD prevalence with MAD treatment after a 5-year follow-up (34). Although research remains divided regarding the classification of TMD as a contraindication, the AASM and AADSM (American Academy of Dental Sleep Medicine) mention in their clinical practice guidelines that TMDs may be deteriorated by oral appliances, however, avoid specifying the use of OAs concerning TMD (35).

Differences in the prescribed appliance, its mandibular protrusion degree, and the experience of the dentist are likely to be related to the differences in the frequency of side effects. Side effects will be present in 6% to 86% of patients, according to a side-effect profile concluded from several studies. However, with frequent application and correct adjustments to the MAD during dental visits, the resolution of symptoms can be seen within days to weeks (33). It is important to weigh the potential risks against the benefits of MAD therapy for the treatment of OSA (30).

3.3 TONGUE-RETAINING DEVICE

3.3.1 DESIGN AND CUSTOMISATION

The tongue-retaining device is an alternative OA treatment option to MAD therapy for treating OSA (36). As previously mentioned, TRDs are manufactured from soft silicone, suited for medical use, and exist in custom-made and non-custom-made forms (26,22). Non-custom-made

devices exist in different stock sizes or a “boil and bite” form, therefore being minimally customised to the patient’s dental arches (22,32).

The initial device design was inspired by mouthguards, where retention was achieved by coverage of the maxillary and mandibular dental arches with an anterior flexible bulb to retain the tongue in a protruded position. Nowadays, the design of TRDs has been optimised and adapted. Dental coverage is renounced, and the bulb to retain the tongue has decreased in size, using suction forces to retain it in place rather than dental coverage (27). Additionally, recent designs assist in tongue-retaining by external vertical flanges, being placed on the extraoral side of the lips (32).

Therefore, TRDs may be prescribed in case patients present with hypodontia or edentulism, not being suited to guarantee sufficient retention needed for MAD treatment, or compromised periodontal health (23,30). However, the research remains scarce, with only a few studies employing small cohort numbers and a variety of appliance designs (27). Its clinical usage is limited based on discomfort and side effects despite its efficacy in decreasing sleep apnea, snoring and daytime sleepiness. Therefore, TRDs are mainly prescribed for patients not responding to MAD therapy but still wishing to be treated by OAs (26,22).

3.3.2 MECHANISM OF ACTION

Airway obstruction by falling back of the tongue into the throat is prevented by gentle suction and adhesion of saliva, that protrudes the tongue and keeps it at the desired position. Air displacement from the lingual compartment is achieved by the formation of negative pressure by the TRD, being the reason behind the tongue protruding mechanism (26,22). Once the device is rinsed with water and inserted into the mouth, suction is generated by protruding the tongue as far as comfortable into the bulb, followed by repeated squeezing and releasing of the bulb until satisfactory retention is achieved. In case of insufficient retention or loosening of the device, further tongue protrusion and squeezing can be performed. Vice versa applies when reduction of suction is needed such as for removal or due to discomfort (27).

3.3.3 AIRWAY MECHANICS

The protruded tongue position achieved by the TRD counteracts diminished muscular tone that may lead to the collapse of the tongue base into the airway against the pharyngeal wall (31). Thus, the obstruction of the oropharyngeal space, especially of the tongue base, is aimed by TRDs. It prevents the collapse of the tongue causing airway obstruction in the anterior-posterior palatal region by retrolingual space obstruction and posterior displacement of the soft palate (26). The lateral aspect of the airway is increased by traction on interpharyngeal connections through the tongue base resulting in a greater degree of airway AP diameter increase as well as

retropalatal and retroglossal cross-sectional area (CSA) compared to MADs (22). A meta-analysis investigating 15 articles verified the effectiveness of TRDs by a decrease in AHI by 53% on average. It was found that TRDs are especially effective in patients with moderate to severe OSA, decreasing the AHI by more than 50% (36).

3.3.4 ADVERSE EFFECTS

The use of TRD is accompanied by certain shortcomings. Unfavourable effects that the patient may encounter are usually mild to severe and were found to last at least 3 weeks. Due to negative pressure that protrudes the tongue, numbness may appear which manifests as a tingling sensation, and could last 30 to 60 minutes. It may also cause soft tissue irritation, such as minor ulceration of the lingual frenum. Especially this finding is problematic, as it may prevent sufficient tongue protrusion to fit into the TRD. Thereby, not only the efficacy but also compliance may be reduced (27,26). A randomised control trial, investigating 27 patients treated with TRDs found that soft tissue irritations were present in 50% of the cohort (27).

Furthermore, patients complained about adverse effects regarding salivation. Due to the increased vertical mouth opening with TRDs, swallowing appeared to be more difficult. Excessive salivation and the sensation of dry mouth were reported by the same study, with 86.4% and 59.1% respectively (27).

Interestingly, a retrospective study analysed the efficacy and side effects of TRDs in 84 patients with OSA. Although the rate of hypersalivation is high (86.4% as reported by the randomised control trial) it led to discontinuation of TRD therapy in only 8% of patients. Also, dryness of mouth only caused 3% of patients to discontinue the treatment. The main reasons for discontinuation were foreign body sensations in 49% and pain in 31% of patients. Pain arising from TRD therapy can be divided into two groups: acute pain and chronic pain. Chronic tongue pain, similar to tongue numbness, may be explained by the design of TRDs (28). Further device development concerning customisation to the patient's tongue anatomy and physiology may improve the comfort and effectiveness of fit (36). Thus, it could possibly reduce adverse effects and improve compliance.

3.4 PROSTHETIC INTERVENTIONS COMPARED TO OTHER FORMS OF TREATMENT

Because CPAP therapy is currently being considered the "gold standard" treatment method, especially for moderate to severe OSA, any alternative treatment must be compared to it (29,37). CPAP devices maintain upper airway patency utilizing pneumatic pressure. The pressure at which the upper airway collapses is exceeded, which prevents the collapse immediately from the start of treatment. This mechanism is highly effective, decreasing AHI,

blood pressure, sleepiness and disease severity significantly (4,37). However, its compliance rates are low due to various reasons such as mask leakage, problems falling asleep with it, removal of the mask as well as the necessity for continuous use and negative effects on intimate life (20,38).

Figure 9. CPAP masks (20)

OAs, such as MADs and TRDs, are accompanied by certain downsides as well, as previously mentioned. The greatest inconveniences lie in the possible dental changes and variations in effectiveness that may differ between patients (39). Nevertheless, the treatment of OSA with OAs has its advantages compared to CPAP, which gives it its justification for existence. In particular, the comfort and ease of use, not least due to the smaller size of the applications allowing for easier transport, are reasons that increase compliance, especially accounting for MADs. The powerless application of OAs not only saves usage costs but also enables more unrestricted use while sleeping, for example when travelling (4). It was also reported that the sleep quality amid bed partners improves to a greater degree with MADs than with CPAP (35). A more invasive form of treatment, a surgical approach to OSA is the UPPP. Nowadays, UPPP is accompanied by other surgical procedures, as it was discovered that UPPP alone was not efficient enough. During its surgery, the soft palate and uvula are excised conservatively and tissues from the lateral pharyngeal wall are resected. Thus, UPPP surgery is designed to address the anatomical factors causing OSA (40).

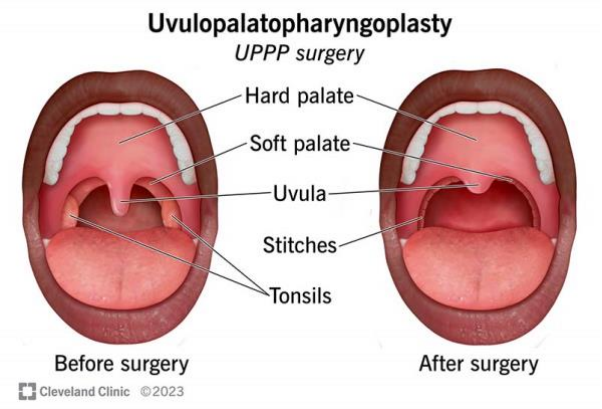

Figure 10. UPPP scheme (41)

However, the outcome is not always successful, and its efficacy decreases with time, according to long-term follow-ups. Further disadvantages include difficult patient selection, complications such as tissue edema potentially leading to a loss of airway, prolonged post-operative bleeding, a mild but permanent alteration of speech and voice, as well as elaborate post-operative care (40).

In conclusion, when selecting the most suitable treatment option for the patient, it is important to consider the patient's individual factors, the severity of OSA and their preferences. CPAP on the one side is believed to be the "gold standard" treatment approach, however, its compliance rates are low, which excludes certain patients from this treatment option. UPPP on the other side treats the cause of OSA rather than the symptoms, at the price of being invasive in nature and not promising high efficacy rates. OAs, especially MADs, appear to be a good mediocrity, promising comparable efficacy and higher compliance than CPAP and being less invasive than UPPP.

IV) PATIENT-CENTERED OUTCOMES AND CLINICAL EFFECTIVENESS

4.1 CLINICAL EFFICACY OF PROSTHETIC INTERVENTIONS

The efficacy of OAs depends on the patient since the correct amount of mandibular protrusion determines the maximal therapeutic effect, which may be adjusted to varying advancement levels for specific patients (32,23).

4.1.1 MB MAD vs. DB MAD

A systematic review of 50 randomised control trials (RCT) with meta-analysis, that investigated the effectiveness of different MAD designs in OSA therapy, compared MB with DB devices. They concluded, however with a significantly low-quality body of evidence, that MB devices are more effective than DB in lowering AHI and improving the minimum oxygen saturation. Literature regarding the effectiveness of MB compared to DB remained indefinite. A greater AHI reduction by MBs and equal effectiveness without significant differences of MB and DB devices in improving objective PSG parameters was found by 3 studies each. The treatment efficacy in decreasing AHI was not influenced by changes in the vertical opening of MADs as evaluated by one study (42).

Two out of three further studies came to the result, that the most effective form of MADs are custom-made devices (42). Other literature identified a significant advantage of custom-made appliances compared to non-custom-made appliances as well. They concluded that custom-made devices gain superior retention and that the non-restriction of vertical and lateral mandible movements results in TMJ comfort. However, no significant difference was found in different types of custom-made MADs (4).

The question, of whether MB or DB MADs are more successful remains debatable.

The meta-analysis of 50 RCTs came to the result, that MB MADs have a greater success rate than DB MADs with 82.1% and 54.7% respectively. These findings are thought to be attributed to the minimal post-rotation and an increased mandibular protrusion range of the mandible present in MB MADs (42). However, a retrospective analysis of 805 patients found DB MADs to be more successful with 56.8% compared to MB MADs with 47%. The benefit of custom-made titratable MADs was shown to be especially important in patients with severe OSA. No difference in terms of AHI treatment and proportion of successfully treated patients could be found at 50% and 75% of maximum protrusion in mild-to-moderate OSA, with 79% and 73% respectively. Conversely, titration to 75% of maximum protrusion achieved treatment success in 52% of patients, whereas only 31% of patients achieved treatment success at 50% of maximum protrusion in severe OSA (43).

As mentioned earlier, DB appliances are reported to have a greater therapeutic effect than MB appliances. These findings are attributed to a more efficient mandibular protrusion and the ability to move the mandible to a certain extent (32).

Furthermore, the European and American guidelines recommend the use of custom-made titratable MADs (43).

4.1.2 CPAP vs. MAD

Comparing the effectiveness in normalising respiratory events during sleep, MADs seem to be slightly behind CPAP, not suggesting that MADs are ineffective (44). The AHI is effectively reduced by MADs, although as previously mentioned there is some individual variability. However, the AHI is significantly better reduced by CPAP devices than by MADs according to the AADSM as well (22). From the first moment of use, AHI values are reduced by CPAP, unlike MAD. Nonetheless, when comparing baseline to 6 and 12 months, both CPAP and MAD are effective in reducing AHI values (44). The treatment effects of CPAP and titratable MADs in patients with severe OSA were compared by a meta-analysis, that investigated 4 RCTs. They found that CPAP devices reduced AHI and oxygen desaturation index (ODI) significantly better than MADs in severe OSA (43).

The minimum arterial oxygen saturation (SaO_2) is effectively reduced by MADs, in a nonlinear dose-dependent relationship with the amount of mandibular protrusion. The oxygenation was improved marginally better with CPAP than MAD by 3.11% (22). An analysis of 13 studies, that included 429 patients with OSA, investigated the effect of OAs on the improvement of low oxyhemoglobin desaturation (LSAT) in mild-moderate and severe OSA. In mild-moderate OSA, OAs were found to elevate LSAT by 5.03, however, in severe OSA OAs improved LSAT

by 10.44 oxygen saturation percentage points. The OA-related changes in ODI in mild-moderate and severe OSA were compared by 13 studies with 492 patients. The ODI was improved in both groups comparably, with 52% and 57% respectively (45). Comparing the changes in medium saturation of peripheral oxygen (SpO_2) between CPAP and MAD, its values increased in the CPAP group from baseline to 12 months and were lower in the MAD group. Comparing baseline to 6 and 12 months, both interventions, CPAP and MAD are effective in reducing the RDI (44).

No significant difference in blood pressure comparing CPAP to MAD was found in a network meta-analysis: the systolic blood pressure decreased by 2.5 mm Hg and 2.1 mm Hg (CPAP vs. MAD) and the diastolic blood pressure decreased by 2.0 mm Hg and 1.9 mm Hg (CPAP vs. MAD) (22).

Patients are exposed to an increased risk of cardiovascular disease, such as systemic hypertension and congestive heart failure, as a consequence of having OSA (4). Thus, efficacious treatment to decrease the patient's risks should be the main aim.

4.1.3 TRD

Beforehand, as mentioned earlier, the paucity of research, with a limited quantity of studies including small cohort numbers, leaves the role of TRDs to be further investigated (27).

A meta-analysis that researched 15 studies came to the result, that TRDs are especially effective in patients with moderate to severe OSA, lowering the AHI by more than 50%. They also concluded that TRDs decrease the AHI statistically significantly, as found in each of the 15 studies, with 53% on average (36). A prospective case-control study of 30 patients with moderate to severe OSA has found that TRDs reduced AHI by 44%, being less than stated by the previous study. They even referred to previous studies which described that TRDs reduce the AHI by up to 38% to 59% (26).

Investigating the results of polysomnography after a 5-year median follow-up time, retrospective analysis has found that 71% of cases have been effectively treated by TRDs (28).

A systematic review and meta-analysis have investigated the outcomes of TRDs in the treatment of OSA. Seven studies have documented an LSAT increase by 4.1 oxygen saturation percentage points on average and the ODI was found to be decreased by 56% according to 4 studies (36).

4.1.4 MAD vs. TRD

The effects of MAD and TRD on AHI were found to be akin, as revealed by a short-term randomised controlled study. However, superior symptomatic improvement, compliance, and patient preference were found with MAD (27). In mild, moderate and severe OSA, MADs were

found to be more efficient than TRDs, although not significantly accounting for the last two groups. The therapeutical effectiveness of OAs (MAD and TRD), with a 61% improvement in overall AHI was corroborated by a meta-analysis of 42 studies including 2265 patients. The highest rate of improvement at 67% was found in moderate OSA by the same study, contrary to preceding findings (45). When comparing the treatment outcomes for mild, moderate and severe OSA, no significant variance could be found between MAD and TRD treatment (27).

4.2 IMPACT ON SLEEP PARAMETERS

As mentioned above, objective sleep measurements such as AHI and minimum arterial oxygen saturation, were found to be effectively reduced by CPAP and MADs. Furthermore, the arousal index is decreased by both therapy options, remarkably improving the subjective and objective sleep measurements of sleepiness with MAD treatment (4).

The arousal index was found to be decreased with OAs, regardless of whether with MAD or TRD. Studying the effectiveness of CPAP devices concerning arousal index, a drop in its values was found when comparing the baseline to 6 months. When comparing its values from 6 to 12 months, however, an increase in arousal index was witnessed (44).

Sleep quality was found to be improved in 100% of patients treated with MAD and 45% of patients treated with TRD, according to Ferguson et al who investigated the effects of sleepiness in an evidence-based review of 87 articles (27).

An RCT investigated sleep architecture differences between CPAP and MAD. An increase in the duration of the N3 and Rapid eye movement stages and an N1 stage reduction were found in both CPAP and MAD, without a significant difference between the two therapy options. This leaves them to have a similar impact on sleep (43). The subjective daytime sleepiness is considerably improved by MADs as assessed by the Epworth Sleepiness Scale (ESS) (22). A meta-analysis included 10 studies that stated ESS values for 965 OSA patients being treated with OAs. The ESS scores were reduced by MAD treatment in mild, moderate, and severe OSA by 5.18, 5.15, and 5.47, respectively. They concluded that OAs are effective in improving sleepiness, according to their results in improving subjective sleepiness (45). However, differences in daytime sleepiness between CPAP and MAD are more unclear. Both CPAP and MADs are effective in reducing ESS scores, however, a marginally greater decrease by 0.8 points on average can be seen with CPAP (22). It remains the question, of whether a 0.8-point difference is of any significance, resulting in a preferential treatment option regarding subjective sleepiness. MADs and CPAP devices have a similar impact on daytime sleepiness according to Barnes et al and no differences could be found after 6 or 12 months in EDS in patients with mild OSA (4,44).

According to a retrospective analysis of 84 OSA patients, TRDs were found to have a significant effect on daytime sleepiness, being similar to MADs (28). In contrast, recent international literature states that TRDs reduce the ESS by just about 2.8 points (36).

Presumed, that TRDs are comparably effective to MADs in reducing daytime sleepiness, this would also mean that TRDs are comparably effective to CPAP. However, MADs have a mean improvement in ESS scores by 5.26 points, TRDs conversely of only 2.8 points (45,36). This difference in ESS values should be put into relation when comparing the effectiveness of different means of treatment concerning daytime sleepiness.

Subjective estimations of snoring are treated more effectively by TRDs than MADs, with a significant reduction of 68% compared to 45-50%, respectively (28). However, subjective evaluation of snoring frequency and severity were regarded by patients and their partners in a different study (RCT). They found that MADs were superior to TRDs in improving sleep parameters. MADs reduced snoring frequency and intensity by 18% and 15.8% respectively, as found by O'Sullivan and colleagues. The frequency of snoring was significantly reduced in the 61-70 decibel range, however, it did not result in changes in other decibel ranges with TRDs, as described by Kingshott and colleagues. The study concluded that nocturnal symptoms, daytime sleepiness, and other OSA parameters can be improved within 4 weeks of treatment with MADs and TRDs (27).

4.3 IMPACT ON QUALITY OF LIFE

Without treatment of OSA, alterations in health-related quality of life (QoL) may appear, such as hypersomnolence (22). Hypersomnolence impairs the ability to function, by preventing to stay awake throughout major waking hours, resulting in EDS and the need for an uncontrollable urge for sleep (46). Thus, reducing the QoL. Sleep-specific Functional Outcomes of Sleep Questionnaire (FOSQ) and generic Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) are usually used to measure the function and QoL (22).

As described above, objective sleep measures fundamentally improved with MAD treatment. Their effectiveness includes improvements in sleep measurements of sleepiness, daily monitored blood pressure, and QoL. Improvements in subscale and total FOSQ scores and SF-36 scores are present in the MAD group (4,22). An increased QoL could be seen in patients who were treated with custom-made titratable MADs compared to non-titratable MADs (47). Improvements in daytime functional outcomes, measured by the same two parameters, showed marginal differences comparing CPAP to MAD treatment. The influence on QoL was similar, regardless of whether the treatment was with MADs or CPAP (4,22). Thus, both treatment options are similarly affecting the QoL and no clear differences were discovered (43).

Research remains scarce, investigating the effects of TRDs on the QoL. QoL changes regarding MAD and CPAP treatment or OA therapy in general, are predominately investigated.

4.4 PATIENT ADHERENCE AND SATISFACTION

Many different factors contribute to the satisfaction of patients and the resulting treatment adherence. These factors can be positive or negative in nature, their balance determines the result.

The side effects of MADs that were previously mentioned could be regarded as being negative, however, they are often mild, provoke only negligible discomfort, and can even be advantageous. Patients tend to tolerate MADs well, generally better than CPAP, especially concerning symptomatic control. Particularly the self-reported short-term compliance, with 76% to 95% is high in patients treated with MAD (23,44). Furthermore, MADs are favoured by patients when comparing their subjective self-reported compliance with the objective recorded compliance of CPAP (22).

Reasons for a preferred treatment with OAs rather than CPAP include the size and simplicity of the devices, their comfortable fit and the comfort of transfer, as mentioned by patients. Patients also preferred a smaller vertical opening (VO) with their OAs, as studied by Pitsis et al, by exposing patients to different VOs (4 mm and 14 mm) while undergoing the same amount of mandibular protrusion. The amount of VO does not interfere with AHI values, however with satisfaction and compliance. Resultingly, OAs are superior to CPAP regarding nocturnal use, ranging between 6.6 to 6.8 hours and 4 hours of use per night respectively (4,42). Another study states a mean nocturnal OA usage of 6.4 to 6.6 hours per night based on objective measurements after 3 months of application (22).

When investigating and comparing the adherence between CPAP and MADs, MADs are generally superior. The duration of nocturnal use and percentage of nights that the device was used, based on short-term controlled trials, and objective adherence, based on long-term observational studies, were found to be superior for MAD than CPAP treatment. Similar findings were discovered in crossover trials, in which patients preferred MAD treatment over CPAP, after being treated with both devices in a random sequence (31). Most patients favoured MAD treatment over CPAP, even though CPAP is more efficient in reducing AHI and ODI values (43). This reinforces the comment I made at the beginning, that a gold-standard treatment as CPAP is ineffective if not being used correctly and that alternative treatment methods need to be provided for those who cannot tolerate it.

Annapurna et al stated that both OA MB and DB (Herbst) appliances are effective for treating OSA and that MB devices are preferred by patients due to their simpler application and the

relief of symptoms to a greater extent (29). Nevertheless, a systematic review with meta-analysis concluded, that DB MADs are more effective in treating OSA than MB MADs, as they improve minimum oxygenation saturation and the success rate to a greater extent (42).

The preferred form of OA therapy is suggested by contemporary research, suggesting the use of custom-made, DB MADs (22).

Coming back to the subjective compliance of MADs but this time, comparing it to TRDs instead of CPAP. An RCT stated, that 81.8% of patients that were analysed preferred treatment with MADs whereas 27.3% of patients preferred TRD treatment based on subjective compliance following regular application. 86.4% of TRD patients removed their appliances unintentionally throughout the night, whereas only 9% of MAD patients experienced the same issue. Furthermore, after being treated with TRDs for 3 weeks, 63.3% of patients have already stopped their use. As a result, only 59.1% of TRD patients were satisfied with its treatment, with three patients expressing profound dissatisfaction (27).

4.5 PREDICTORS OF SUCCESS

To improve the therapy of OSA with OAs clinically and cost-effectively, it is important to identify those patients, who are likely to respond to OA treatment (30). Thus, the anatomical reason for airway obstruction, risk factors, and economic status need to be determined. Various studies define treatment success differently, resulting in MAD response rates ranging from 29% to 80% with considerable individual variability (31).

Anatomical reasons for OSA that determine response or nonresponse to MAD therapy were found during drug-induced sleep endoscopy (DISE). Patients are more likely to respond to MAD treatment if they have a tongue base collapse, or if their ventilatory control is stable and the collapsibility is low. In contrast, nonresponse to MAD therapy is predicted with complete lateral oropharyngeal collapse and complete concentric collapse at the palatal level (23).

A controversial approach to predicting treatment success is the measurement of craniofacial landmarks using lateral cephalometry. A shorter soft palate, retrognathic mandible and a more inferior position of the hyoid bone, as well as a narrow airway, were proposed to be positive predictors of successful MAD treatment by some studies (31,37).

Furthermore, implementing an upper airway model for the prediction of MAD responsiveness could be included in the routine examination. The model evaluates the influence of MADs on the upper airway volume and resistance by combining imaging of the upper airway and computational fluid dynamics (23). Other strategies comprise pharyngeal volume visualisation in relation to mandibular protrusion, either during overnight PSG or nasal DISE using remote-controlled MAD titration (31).

Interestingly, successful treatment with MADs may be predicted if risk factors for OSA are absent or the contrary is present. According to the author Ng, increased effectiveness is seen in patients who are: female, younger, have OSA that is supine-dependent, have a lesser neck circumference (neck circumference as risk factor: male > 43cm, female >38cm), have a reduced BMI, and have a lower AHI (22). However, the literature provides dissimilar findings concerning predicting success based on gender, age and AHI. Burlon et al, as well as other studies, state that gender and age do not considerably predict MAD success, conflicting with the previous statement. That the initial OSA severity degree is not influencing the treatment success was concluded by Mints et al, who studied 510 patients with mild, moderate, and severe OSA. Contrary, according to the retrospective study by Burlon et al a nonresponse to MAD treatment was predicted, with baseline ODI values greater than 3% (48).

Another positive predictor of successful MAD treatment concerns patients who are already treated with CPAP. If their titrated pressure is low, chances are high that MAD therapy will be successful (31).

The presence of supine-dependent OSA in combination with an airway obstruction present in one site is thought to be the most reliable predictor for successful TRD treatment (22). A retrospective study performed by Lazard et al listed clinical factors that predict TRD compliance and efficacy, which may ultimately influence the prediction of TRD treatment success. Poor compliance was found in patients with Class II and III malocclusion, whereas patients with Class I occlusion were more compliant. In patients who discontinued TRD treatment due to discomfort, nasal obstruction was present in 69% of them, being either anatomic or secondary to allergic rhinitis. Another negative predictor of treatment success was a protrusion distance $\leq$ 7 mm for patients older than 60 years of age. A greater protrusion threshold of more than 7 mm should be used exceeding 60 years of age since oropharyngeal tissues may become more vulnerable to negative pressure during apneas with ageing (28).

Similarly to QoL, research regarding the prediction of treatment success with TRD appliances is limited. As previously assumed, compliance and efficacy also influence the success of treatment, as poor compliance often leads to discontinuation of treatment and thus prevents treatment success. However, no accurate prediction factors of success can be derived from predictors of compliance and efficacy, as despite their similarities and interdependent relationship, there are distinctions between the two.

V) CONCLUSION

When treating patients with OSA, MADs seem to be a promising alternative to CPAP therapy. OSA is a widespread disease, that remains undiagnosed for most of the population. This increases their risk of health consequences considerably.

To date, treatment with CPAP devices is regarded to be the gold-standard approach for OSA treatment. However, it was shown that CPAP devices are predominantly effective in reducing AHI values in severe OSA cases. Yet, patients prefer treatment with OAs, especially MADs due to their superior adherence rates. MADs reduce AHI values well in mild to moderate OSA cases and can even be used in severe OSA when patients fail to adhere to CPAP.

The most advantageous characteristic of MADs is its superior adherence and satisfaction rates, which ultimately lead to improved effectiveness. To increase the effectiveness of MADs, custom-made titratable DB devices should be chosen, allowing them to protrude the mandible to the maximum therapeutical level while guaranteeing a perfect fit. Minimising the VO has been shown to improve acceptance among patients.

TRDs show similar rates of effectiveness as MADs, however, are at a disadvantage to MADs due to their inferior compliance rates. TRDs' greatest advantage is its design, which does not require teeth for retention. Thus, TRDs can be used for patients with compromised periodontal health, hypodontia or edentulism.

Based on the superior patient preference, adherence and comparable efficiency to CPAP – I would suggest regarding MAD as the gold-standard treatment option for OSA. MADs could be used as a first-line/ preferred treatment for mild and moderate OSA cases in patients with an increased likelihood of successful treatment, whereas CPAP could still be chosen for severe OSA at first. Patients with mild to moderate OSA could increase their nocturnal therapy duration while still having the option to switch to MADs if they do not adhere to CPAP.

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