VILNIUS UNIVERSITY
FACULTY OF MEDICINE
INSTITUTE OF DENTISTRY

Charlotte Brune
Fifth Course, Second Group

Master's Thesis

Mandibular Advancement Device for Obstructive Sleep Apnea Management

Scientific Supervisor: Lekt. Rolandas Pletkus

Vilnius

2023

Table of Contents

Abbreviations

AHI	Apnea hypopnea Index
CBCT	Cone Beam Computed Tomography
CPAP	Continuous Positive Airway Pressure
CSA	Central sleep apnea
ENT	Ear, Nose and Throat
FDA	Food and Drug Administration
ICSD	International Classification of Sleep Disorders
MAD	Mandibular advancement device
MMA	Maxillo- Mandibular advancement
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
PSG	Polysomnogram
TOMADO	Trial of Mandibular Advancement Devices for Obstructive Sleep Apnea
UPPP	Uvulopalatopharyngoplasty

Summary:

The primary aim of this systematic review is to provide a comprehensive overview of diagnostic measurements for obstructive sleep apnea (OSA) and its management options with a particular focus on dentistry and the use of mandibular advancement devices (MAD). This review also covers other Management options, such as continuous positive airway pressure (CPAP) therapy and surgical interventions. In total, 1567 articles were initially screened based on their titles and abstracts, with 24 articles ultimately selected for inclusion in this thesis. Obstructive Sleep apnea is a condition caused by the collapse and narrowing of the throat during sleep, leading to breathing cessation. It is characterized by its severity, which is mild, moderate, or severe. Clinical symptoms of OSA can vary in severity and may include snoring, daytime sleepiness, choking or gasping at night, heartburn, morning headaches, obesity, hypertension and more. A proper diagnosis is important, as untreated OSA can lead to complications such as heart disease, stroke, and cognitive impairment. Diagnosis is done using tests including respiratory polygraphy, polysomnography, mallampati score, cephalometric evaluation, and CBCT volumetric airway measurements. Treatment modalities include lifestyle changes, mandibular advancement devices, continuous positive airway pressure or surgical interventions. It has been shown that MAD and CPAP have similar clinical effects due to greater MAD compliance achieving net similar AHI reduction. The American academy of sleep medicine suggested that the treatment with custom made MAD is preferred over non titrable MAD. It has been demonstrated that, wearing custom made appliances show a success rate of 80%, as well as a greater reduction in AHI and polysomnographic readings.

Introduction

Many people unknowingly suffer from obstructive sleep apnea (OSA).[1] OSA has been negative impact on human's health. [2]

Actuality of this study: this review discusses a relevant topic in contemporary dentistry. As it is of great importance for dentists to understand how to diagnose or detect OSA during daily practice and its management options.

Objectives:
The aim of this comprehensive literature review is to write a paper on the most up to date knowledge concerning:

- the diagnosis & clinical examination of obstructive sleep apnea focused on the dentist's perspective.
- its management focused on Mandibular advancement device (MAD) including the mechanism of action, types of MAD, effectiveness, and side effects.

Hypothesis: Is that obstructive sleep apnea can be detected by a dentist using simple scores and x-rays and MAD's can be used to manage OSA in mild to moderate cases. This prediction was made from previous knowledge.

1. Materials and methods

Search strategy

Study Selection:

The literature search generates a total of 2247 references of PubMed. PubMed was used because it is a free, publicly, huge, reliable, and highly authoritative resource for MEDLINE and other National Library of Medicine resources and it is one of the most widely accessible biomedical recourses globally. A total of 1600 results remained after removing the duplicates. The articles were screened based on title and abstract. A total of 62 articles remained. The remaining articles were screened, and 38 articles were excluded due to either articles that applied to other diseases (30) or articles with conflict of interest (8). 24 articles are included in this thesis (Fig n.1.)

A search of articles was carried out in PubMed using the Keywords: Obstructive sleep apnea, Mandibular advancement device, Appliances, CPAP, Side effects.

Those specific key words were used since they cover the topic of the master thesis and include a synthesis of the most relevant meanings related to the topic of my research. They provide the newest and most adequate knowledge for my research.

Inclusion criteria:

- Full text articles available
- Language: English or German
- Date of publication: no older than 2012 (with the exceptions of a few articles)
- Only healthy individuals

Inclusion exceptions:

- Articles older 2012 that feature classifications, definitions, or guidelines

Exclusion criteria:

- No full text available
- Literature written in other languages than English or German
- Articles/ reviews with conflict of interest
- Articles reviews based on other diseases

In general, my criteria were based on quality features regarding the articles. I chose to only review articles that are available in full text, to ensure there are not any missing information,

since it could sophisticate the results and outcome of this thesis. I also choose to not include articles older than the year 2012, because the thesis is based upon the newest knowledge available. Conflict of interest articles were excluded because of its subjective opinion of the author. The included studies were only based on healthy individuals without comorbidities to prevent these from distortion of the outcome.

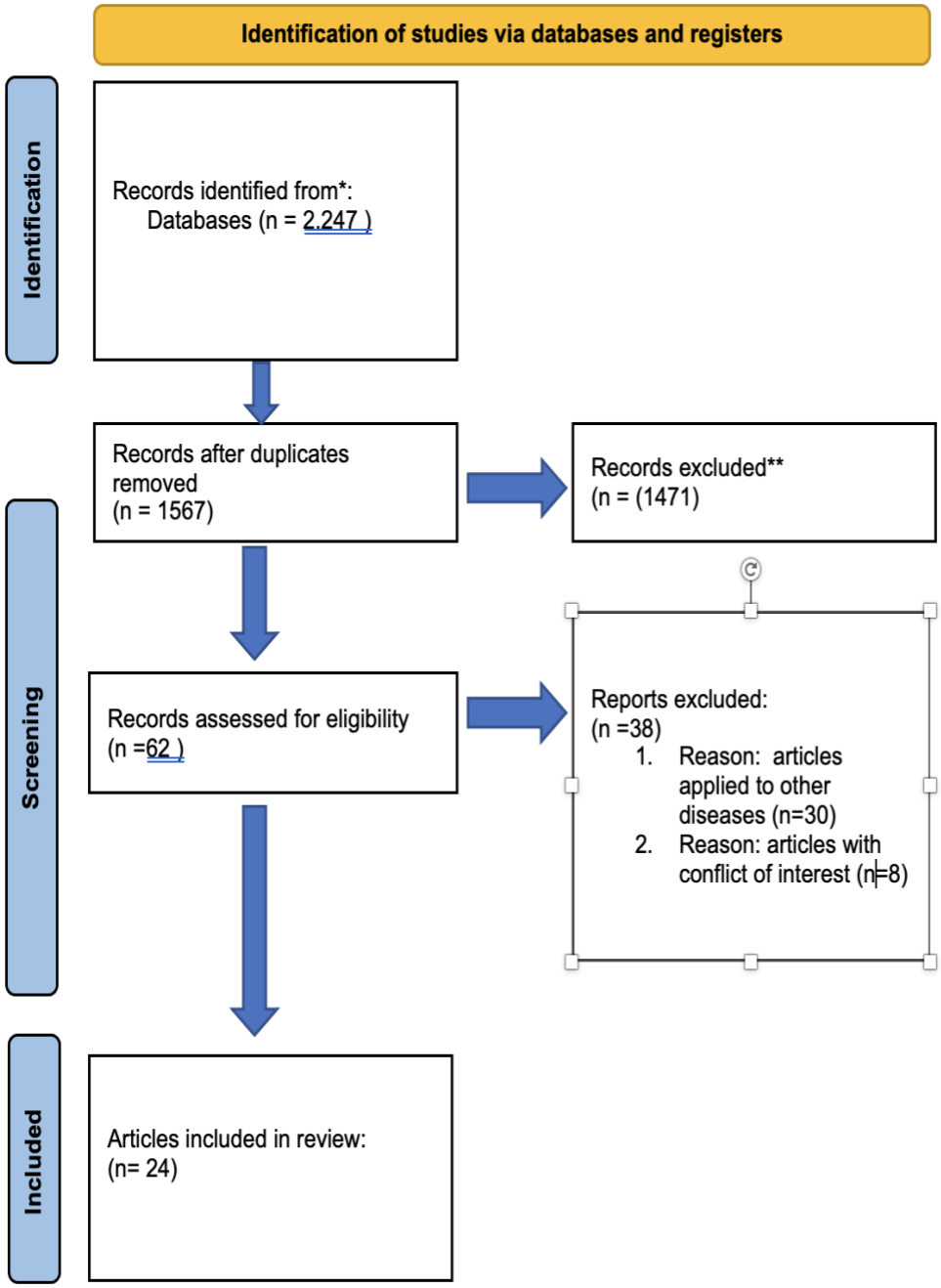

Figure 1. PRISMA Flow Diagram.

Results

2. Types of Apneas

The term sleep apnea, also known as sleep apnoea, is derived from the Greek etymology meaning "want of breath/without breath", meaning that a person stops breathing for a short period of time. Both synonyms (apnea and apnoea) are used in this thesis. Patients with heart failure commonly present with sleep disturbances, which may include apnea and episodes of paroxysmal dyspnea, typically presenting as sudden (paroxysmal) shortness of breath when lying down, which can lead to abrupt awakening. Many patients then must interrupt their sleep, sit up or must get up. Abnormal breathing patterns at night are observed (and termed sleep-disordered breathing). The most common forms of sleep-related breathing disorder are central sleep apnea, obstructive sleep apnea, or a mixed pattern of the two called mixed or combined sleep apnea. [3]

2.1 Central Sleep apnea

Idiopathic central sleep apnea-hypopnea (hypopnea – event during respiration in which there is a reduction in respiratory flow) is characterized by recurrent apnea episodes, without obstruction of the upper airways during sleep, resulting in oxygen desaturations, daytime symptoms, and recurrent arousals. Central sleep apnea (CSA) can occur in individuals with alveolar hypoventilation. CSA is a sleep disorder characterized by periods of interrupted or decreased breathing during sleep, typically lasting between 10 to 30 seconds and occurring intermittently or in cycles. In some cases, CSA can manifest as a rhythmic pattern, advancing, and waning pattern of respiratory phases, including episodes of apnea (breathing failure). This is called Cheyne-Stokes breathing. This pattern of sleep-disordered breathing is to be distinguished from what is known as obstructive sleep apnea.[4]

When breathing becomes shallow or stops for prolonged periods during sleep, it can result in decreased blood oxygen levels, which can have harmful repercussions. Patients may experience frequent awakening during the night, leading to difficulty falling back asleep, daytime fatigue and insomnia. This lack of oxygen can also stimulate the sympathetic nervous system, that regulates the blood pressure as well as heart rate and directly affect the cardiovascular system.[5]

2.2 Obstructive sleep apnea

Obstructive sleep apnea is a breathing restriction caused by partial obstruction of the upper airways. This is often associated with snoring and is characterized by an interruption in breathing due to the obstruction of normal airflow in the upper airways. Depending on the age

of the patient, different causes predominate.[6] The obstructive sleep apnea is explained and covered in section 5.

2.3 Mixed/ Combined Sleep apnea

Mixed sleep apnea or complex sleep apnea is a combination of central and obstructive sleep apnea symptoms. Mixed sleep apnea cases most often begin with obstructive sleep apnea and the patient stops breathing 20 to 30 times per hour every night. The treatment of complex sleep apnea starts with treatment for obstructive sleep apnea: The Continuous positive airway pressure (CPAP) therapy. It has been shown that the breathing problem is not completely alleviated by the CPAP. Once the CPAP is applied to the patient with complex sleep apnea, the obstruction seems to disband, but without properly breathing. Then symptoms of central sleep apnea appear. [7]

3. Definition of OSA /Clinical presentation of disease/condition

Obstructive sleep apnea (OSA) is a common clinical condition characterized by the recurrent partial or complete collapse and narrowing of the throat during sleep, leading to obstructive sleep apnea events. The basis of OSA is disturbed breathing with apneas and hypopneas caused by pharyngeal obstruction and hypoventilation. The condition is diagnosed according to the Classification of sleep disorders (ICSD-3)[8] when the breathing disorder is unexplained by another sleep disorder, medical condition, or medication. In addition, there must be an apnea-hypopnea index (AHI) > 15/h sleep time or an AHI ≥ 5/h sleep time in combination with typical clinical symptoms or relevant comorbidities[9]. The AHI Index is used to determine the severity of OSA. It is calculated as the number of obstructive events per hour of sleep and obtained by nocturnal cardiorespiratory monitoring[10]. 5-14 events per hour are considered mild, between 15 and 29 events as moderate and more than 30 events as severe. [11]

This respiratory failure causes the oxygen level in the blood to drop (hypoxemia), hypercapnia, rushes of sympathetic activity, cortical arousals, and an increase in respiratory efforts, resulting to secondary sympathetic activation, oxidative stress, and systemic inflammation. [12]

3.1 Epidemiology, prevalence

The frequency of OSA occurs predominantly in middle-aged and older adults. [13]

Patients who suffer from OSA are usually overweight and mostly present a persistent history of snoring and immoderate daytime sleepiness. [14]

The occurrence of OSA is associated to serious long- term adverse health consequences, such as cardiovascular co-morbidity including hypertension, arrhythmias, stroke, coronary heart disease, atherosclerosis and in general increased cardiovascular mortality. Moreover, metabolic dysfunction and neurocognitive deficits are also associated to that. [2]

While in older literature initial studies in the USA indicated the prevalence of OSA as 4% of the male and 2% of the female population,[15] more recent studies found in Switzerland, reflect a much higher prevalence of obstructive sleep apnea in the population aged from 40-80 years ranged from 49,7% of all men and 23,4 % of all women for moderate and severe OSA (AHI >15/h) in 2015. The prevalence including all types of severity (mild, moderate, and severe) increased up to 83,8 % in men and 60,8 % in women. [16]

The new International Classification of Sleep Disorders (ICSD-3) also determined a prevalence of OSA among people of age groups over 40 years for 79,2% in men and 54,3 % in women.[17]

Due to the often-missing clear dissociation of snoring from OSA, the data for prevalence for snoring varies from 2% - 86,5%[18]

Another more recent study from 2010 estimated that more than 18 million adults in the United States are affected with OSA.[19]

3.2 Diagnosis of obstructive sleep apnea from a medical perspective

3.2.1 Clinical manifestation of OSA

Clinical manifestations of OSA include a variety of symptoms. The classic symptoms of OSA include snoring, excessive daytime sleepiness, pauses in breathing during sleep followed by choking or gasping at night, night sweats, neurocognitive impairment, heartburn, morning headaches, maintenance insomnia and decreased libido. When examining an individual, findings of OSA include obesity, enlarged neck circumference, crowded upper airway, hypertension, accentuated P2 heart sounds (pulmonary hypertension), retrognathia/overjet, nasal obstruction, decreased oxygen saturation, S3 heart sound (congestive heart failure) and lower extremity edema (heart failure). [20]

OSAS are characterized by the combination of clinical symptoms and typical findings in a sleep study (pulse oximetry, respiratory polygraphy, polysomnography).[21]

3.2.2 Anamnesis

Primary symptoms are an increased tendency to fall asleep during the day, unrefreshing sleep, and habitual, loud, irregular snoring. These symptoms may lead to difficulties in concentrating

or staying alert while driving, putting the individual and others at risk. Bedpartner observations of apneas during sleep are also common, although not specific to OSA. Short-lasting choking sensations during the night and morning headaches are characteristic symptoms of OSA, yet they are often underreported by patients and not spontaneously disclosed during clinical evaluation. Marital problems, job loss, and accidents are serious social complications of OSA. Epidemiological studies have shown an impressive association of OSA with arterial hypertension, myocardial infarction, and cerebrovascular accidents.[22]

3.2.3 Pulsoxymetry

Nocturnal pulse oximetry is a non-invasive method used to measure the pulse and the oxygen saturation in the capillary blood using a light source to measure the amount of oxygen that is carried in the blood. The device is used of at least 6 hours duration on either a person's fingertip, earlobe, or toe (Fig. n2.). Depending on the interpretation criteria used, it has a high specificity or a high sensitivity. [23] The high specificity stems from studies with a high clinical pre-test probability for OSA. Nocturnal pulse oximetry alone is therefore not the method of choice for the definitive diagnosis of OSA.[24]

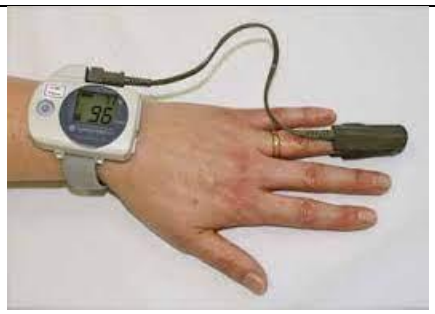

Figure 2. Finger pulsoxymetry with data memory for nocturnal saturation measurement or for stress tests.

3.2.4 Respiratory polygraphy

Respiratory polygraphy is a type of sleep study that measures various physiological parameters during sleep, including airflow, breathing effort, oxygen saturation, and heart rate. It is a less complex and less expensive alternative to polysomnography. Respiratory polygraphy is commonly used for diagnosing OSA and other sleep-related breathing disorders. There are different devices, some of which evaluate different parameters, but are of comparable quality. Electrophysiological variables are not recorded.[25]

3.2.5 Polysomnography

The first line instrument of sleep medicine diagnostics in the sleep laboratory is the polysomnography (PSG). PSG is the gold standard for the diagnosis and differential diagnosis of OSA and sleep-disordered breathing. In addition to respiratory excursions, respiratory flow, oxygen saturation and cardiac activity, muscle tone, eye movements and an electroencephalogram are also recorded by laboratory equipment (Fig. n3.).[26]

In the process, the physiological signals are recorded that are required for a quantitative assessment of sleep, sleep disorders and diseases associated with sleep in accordance with International Classification of Sleep Disorders 3 (ICSD-3). [27]

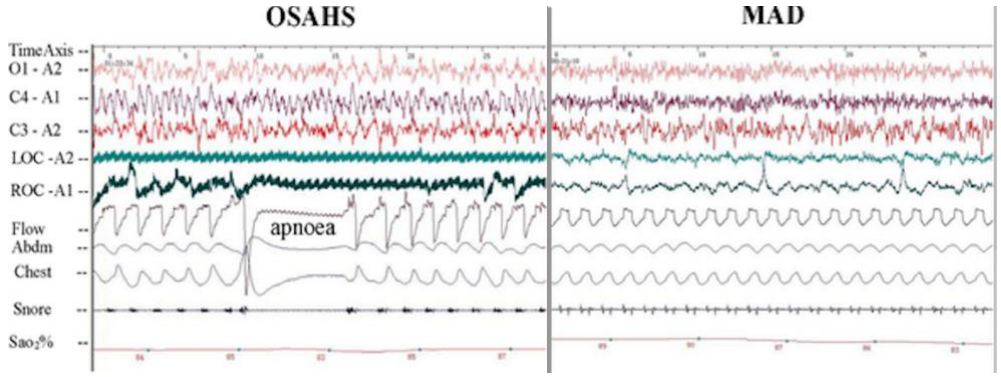

Figure 3. Polysomnography records for OSA patients without using MAD vs. with MAD.

3.3 Diagnosis of obstructive sleep apnea from a dental perspective

3.3.1 Mallampati Score

The diagnostic begins with a clinical examination, to identify anatomical changes at the upper airways, nose, oral cavity, and pharynx or in the area of the facial skull that may be the cause of OSA. When examining the oral cavity, it is necessary to pay attention to the size of the tongue, the condition of the mucous membranes and the dental findings (Fig. n.4). The position of the tongue in relation to the oral cavity and soft palate, defined as the (modified) Mallampati score, can be used for diagnostic assessment as these correlates clinically with the severity of OSA. [28]

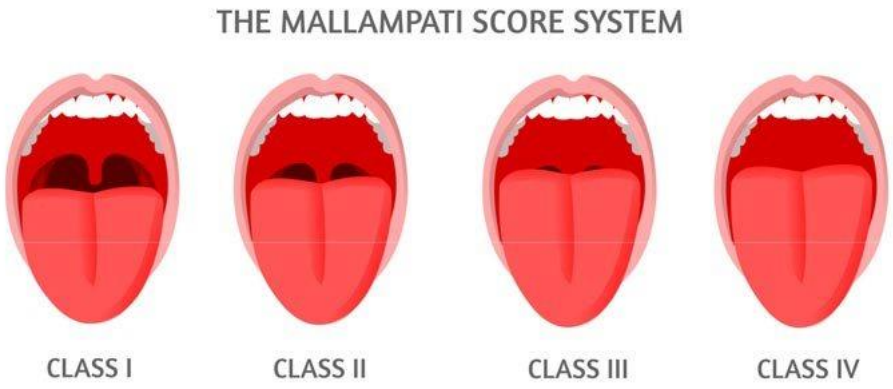

Figure 4. Mallampati score system

3.3.2 Epworth Sleepiness Scale

Medical sleep complaints are primarily determined via the anamnesis, but also via self-assessment questionnaires or interviews in the case of sleep-related breathing disorders.

The most commonly used sleepiness instrument is the Epworth Sleepiness Scale (ESS) [29]. It is always used when information is required to limit attention and concentration during the day over a longer period of time.

The Epworth Sleepiness Scale is a method of measuring daytime sleepiness using a very short questionnaire.[30]

The Pittsburgh Sleep Quality Index (PSQI) [31], the Berlin Questionnaire [32] and, in recent years, the STOP-BANG Questionnaire [33] are used in large international studies. The diagnostic value of these questionnaires is examined in the sense of a prediction in comparison to each other and in comparison, to polysomnography [3435]

3.3.3 STOP BANG questionnaire

The STOP BANG (snoring, tiredness, observed, pressure) questionnaire was developed to provide a reliable, concise, and easy-to-use screening tool. It consists of eight easily administered questions. The 8 questions relate to the clinical features of obstructive sleep apnea and is scored based on Yes/No answers. Each question that is answered in the affirmative counts as one point. (Total 0 to 8). The scoring criteria indicates whether low risk, intermediate risk, or high risk of OSA. Low risk of OSA is indicated if "Yes" was given to 0 to 2 questions. Intermediate risk of OSA is indicated if "Yes" was given to 3 to 4 questions and high risk of OSA is indicated if "Yes" to 5 to 8 questions were given. [36]. The sensitivity of a STOP BANG score > 3 to detect moderate to severe OSA (AHI > 15) is 93% and 100% for severe sleep apnea (AHI > 30).

The STOP BANG questionnaire has been considered helpful to rule out patients having moderate to severe OSA. A recent study has shown that with an increase in the STOP BANG score, there was an associated increase in the predicted probability or/and specifically for having OSA, moderate/severe OSA. [37]

Table1: STOP-BANG Questionnaire[38]

Snoring? Do you snore loudly (loud enough to be heard through closed doors, or your bed partners elbows you for snoring at night?	Yes	No
Tired? Do you often feel tired, fatigue, or sleepy during the daytime (such as falling asleep during driving?	Yes	No
Observed? Has anyone observed you stop breathing or choking/gasping during your sleep?	Yes	No
Pressure? Do you have or are you being treated for high blood pressure?	Yes	No
Body mass Index more than 35 kg/m2?	Yes	No
Age older than 50 years old?	Yes	No
Neck size large (measured around adams apple)? Is your shirt collar 16 inches or larger?	Yes	No
Gender (biologic sex) = male?	Yes	No

3.3.4 Cephalometric measuring points

Considering the pathophysiological meaning of craniofacial changes, cephalometry is a focal indicative instrument for dental specialists. This estimation on the lateral cephalometric image of the skull has been utilized to measure anatomical or constructed measuring points, angles, and distances and to define metrically conceivable, reproductible assertion about craniofacial conditions in sagittal and vertical relation as well as related impacts on the upper airways (Fig. n.5,6). Measurements describing the skeletal proportions of the facial skull, indicating: Retro position of the maxilla; Elongation of Hard and soft palate, tongue, and pharyngeal airway space; Normal size and position of mandible; Increased anterior facial height by an inferior displacement of mandibular body and normal nasopharynx but the oropharynx and hypopharyngeal airway is decreased by an average of 25 %, which could increase OSA symptoms. [39]

Overall, conclusions can be drawn about the etiology and severity of sleep disorder breathing. Craniofacial abnormalities can be clearly diagnosed. A detailed evaluation of these parameters is an essential part of the basic examination for therapy.[40]

A study from Grossmann et al. concluded that the severity of OSA cannot be deduced from the cephalometric analysis. The parameters collected in the analysis of the lateral cephalometric images of the facial skeleton do not provide any direct diagnostic information about the severity of OSA.[41]

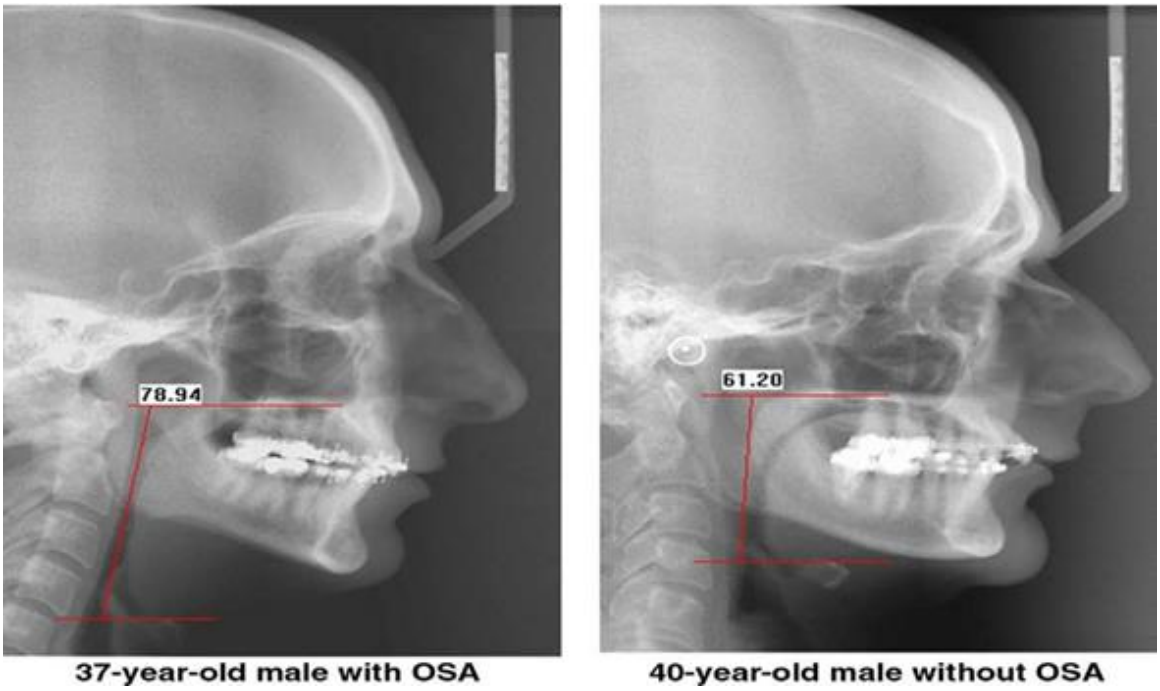

Figure 5. Example of cephalometric measurement of airway length in an OSA patient and non OSA patient [42]

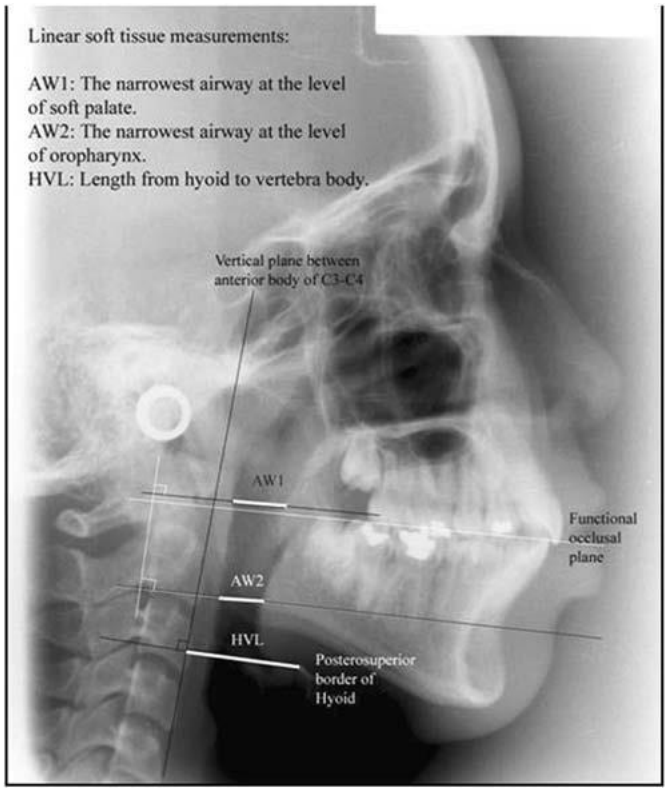

Figure 6. Lateral cephalometric X-ray sowing linear soft tissue measurements.

3.3.5 Cone Beam Computed Tomography volumetric airways measurements. :

As technological advancements in imaging and computer analysis have advanced and converged over the past few years, three-dimensional evaluation and measurement of the airway have increased in popularity. The ability to comprehend and diagnose OSA and its connection to the airway and craniofacial anatomy has benefited particularly from these developments. The increased accessibility of Cone beam computed tomography (CBCT), 3-D imaging, and computer simulation in dentofacial analysis and treatment planning has made it easier to use these techniques for assessing the airway for OSA. The addition of cross-sectional and 3-D imaging to the usual cephalometric would result in more comprehensive and accurate diagnostic and treatment planning information. The cross-sectional area and the volumetric 3-D representation of the entire airway can both be evaluated using lower radiation with a rapid scan up to half a minute. [43]The minimum surface area of the oropharyngeal region, as well as its anterior-posterior and lateral dimensions, are the most frequently used CBCT measurements to compare the static morphology of the upper airway between OSA patients and non-OSA patients (Fig. n.7,8). A patient with OSA has a smaller and laterally narrowed airway.[44]A normal person's upper airway volume during the expiration and inspiration phases of sleep was observed using 3-D volumetric software to vary slightly between 9 and 11 cm3. In a habitual snorer, it varied slightly between 3.74 cm3 and 9.91 cm3, but significantly between 2.73 cm3 and 16.01 cm3 in an OSA patient.[45]

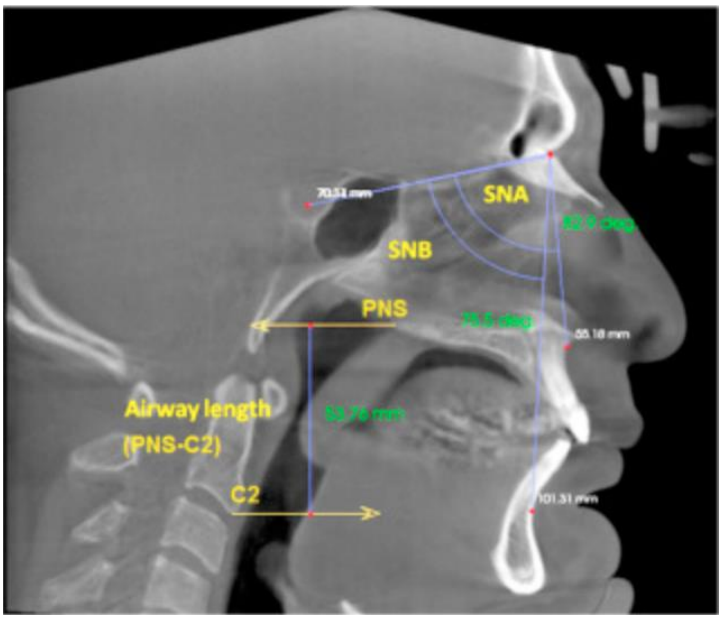

Figure 7. CBCT Analysis of Upper Airway Measurement from PNS to C2 in Patients with OSA.

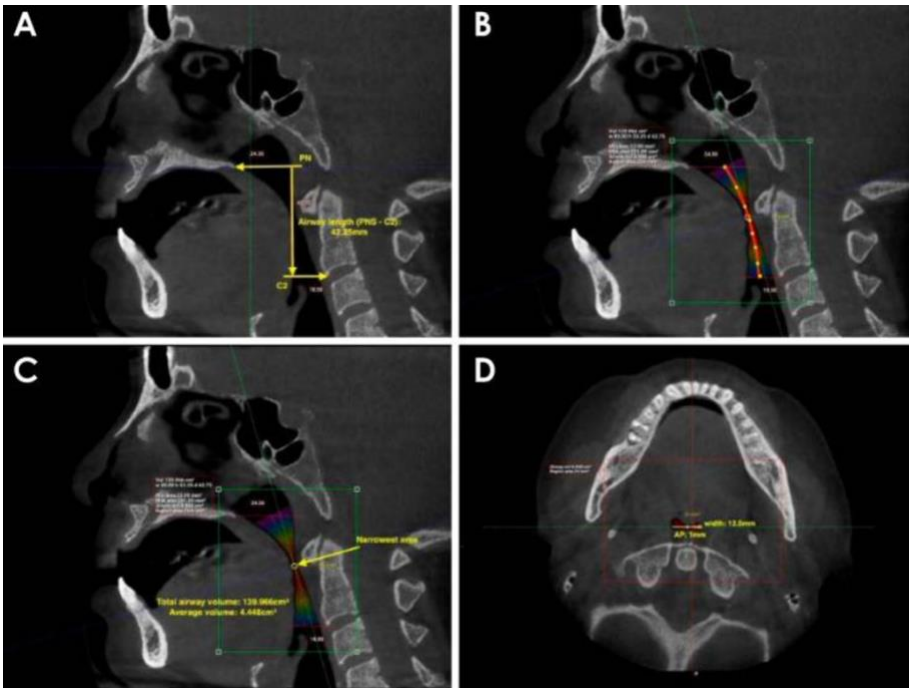

Figure 8. CBCT analysis of upper airway dimensions with width measurements.

4. OSA Modalities

4.1 General / Systemic

The least invasive way to manage OSA is through lifestyle change including weight loss, which has been shown to have highly effective outcomes of reducing AHI. It has been predicted that a weight loss of 10 % not only decreases the AHI of 26% the entire body health benefits from weight loss. [46]

Another non-surgical method can be positional therapy for individuals that sleep on their backs. Myofunctional therapy can be prescribed in some patients suffering from OSA. The therapy includes soft palate exercise, tongue exercise and facial muscle exercise. A meta-analysis has shown that myofunctional therapy resulted in a 50% decrease of the AHI. [47]

Currently, there is a lack of evidence that supports the use of drugs as a beneficial treatment option for patients diagnosed with OSA. While some small studies have shown that promising effects of certain agents on short term outcomes, it is essential to run longer studies that include measures of the following: 1) symptomatic responses of cholinergic agents, which are drugs that stimulate the parasympathetic nervous system by simulating the effects of acetylcholine, which is a neurotransmitter and 2) upper airway lubricants, which are substances that help reducing the friction and resistance to airflow in the upper airways. That is why a better

understanding for predominant mechanisms of OSA for patients is required for better treatment outcomes. To conclude one can say, that at the moment drug therapy is non-recommended as a treatment option for OSA. [48]

4.2 Surgical interventions

6.2.1 Soft Tissue Surgery

The surgical procedures are divided into resective and non-resective surgical methods and procedures that shift the facial skeleton (osteotomies). There are several ENT (Ear, Nose and Throat) and maxillofacial surgical intervention options available for the surgical treatment of OSA.

If the pharyngeal tonsils are enlarged, adenotonsillectomy (AD/TE) may be considered. This opens the space that was partly displaced and narrowed by the enlarged anatomy of the tonsils. This surgical therapy method is a well-founded measure to eliminate the constrictions in the pharynx, especially in the case of hyperplastic or inflammatory enlargements.[49]

Uvulopalatopharyngoplasty (UPPP) aims to reduce and tighten the soft palate and uvula. Excess soft tissue is partially removed and repositioned. The uvula is reattached to the palate. Various multilevel surgical techniques and plastics have become established in ENT medicine, which start in the area of the tongue base, hyoid and genioglossus muscle The use of radiofrequency ablation enables a minimally invasive procedure. Postoperatively, 24-hour intensive care monitoring should be carried out [50]. The UPPP achieves an up to 60 percent reduction in AHI events compared to preoperative findings.[51]

Both tonsillectomy and UPPP are treatment options for mild to moderate obstruction if the anatomical starting point is right. The OSA pathophysiology lies in the retropharyngeal area, meaning limitations of those interventions, logically going down by the airway pathway. [52]

There is also the option of using a hypoglossal pacemaker to stimulate the tongue muscles. The pacemaker prevents the tongue from descending and thus counteracts airway obstruction.[53]This represents a therapy for patients in whom previous attempts have shown no effect and there are no anatomical triggering or causal constrictions. [54]

An improvement in nasal breathing (conchotomy/septoplasty) is not to be equated with therapy for the respiratory disorder, but it has been proven that snoring, daytime sleepiness and the acceptance and effectiveness of CPAP are improved.[55]

6.2.2 Maxillomandiblar advancement surgery

The patency of the pharyngeal airways is largely determined by the facial skeleton and the shape and position of the jaws. [56]As a result, osteotomies for the advancement of the upper and lower jaw (maxillo-mandibular advancement (MMA)) can enlarge the pharyngeal airway and consequently increase the pharyngeal muscle tone. In addition, the genioglossal and geniohyoid muscles can be tightened by shifting the edge of the chin (genioplasty) in an anterior direction (Fig. n.9). [57] Both effects synergistically reduce the collapsibility of the pharynx. This can represent a highly effective and curative therapy for OSA patients, as described by Kuo et al. in 1979. [58]

In a meta-analysis with 627 patients, 86 percent reported a substantial improvement, and 43.2 percent achieved an AHI < 5. [59] In further studies, a success rate of 90 to 100 percent was achieved [60]. The results also show long-term stability. As a positive side effect, in addition to the therapy for OSA, over 90 percent of patients state an aesthetic improvement in their facial profile caused by MMA. [61] Operationally, connection to an intensive care unit is recommended since patients with OSA have a special risk constellation during surgical interventions and an increased risk of perioperative complications. [62]

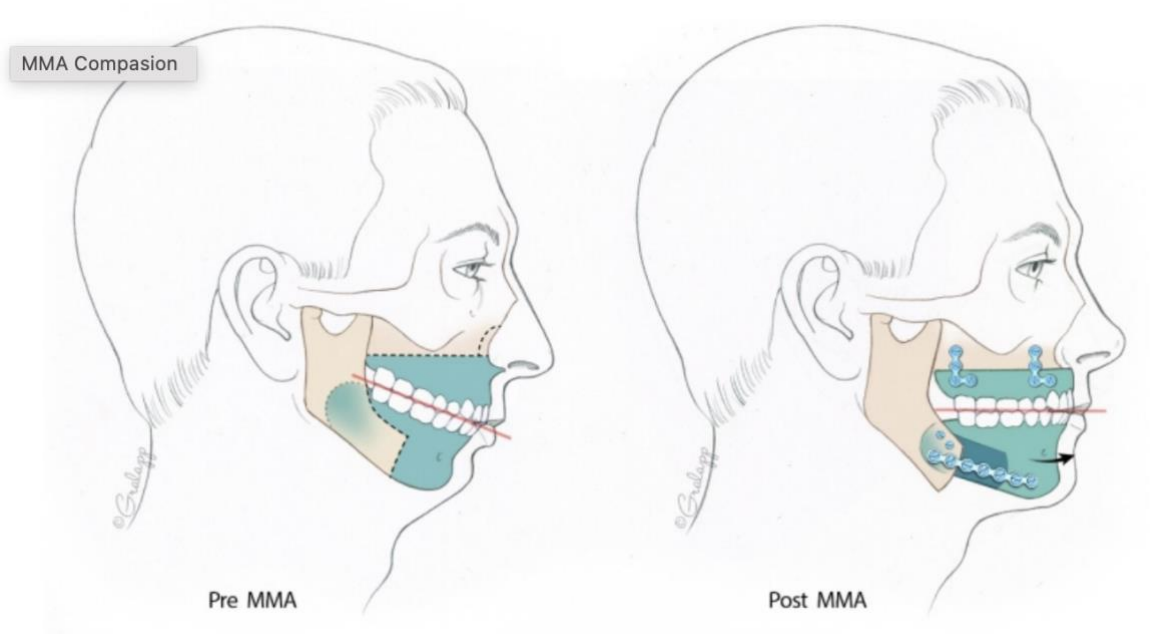

Figure 9. demonstration of Pre Maxillomandibular surgery versus after Maxillomandibular surgery.

5. Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) is esteemed as the golden standard in treatment for OSA. The indication for initiating positive pressure therapy is an AHI of 15/h.[63] With CPAP therapy, a constant overpressure is generated that keeps the upper airways open (Fig. n.10). The pressure forces the soft tissues out of the airway, allowing for uninterrupted breathing during sleep with no pauses in breathing[64]. To establish the diagnosis of OSA diagnostic sleep studies, polysomnogram and or a home sleep study are carried out in order to the achieve the best possible therapeutic success.[65]

Figure 10. Continuous Positive Airway Pressure device.

5.1 Inconvenience Of CPAP usage

CPAP masks have a standardized shape and cannot be individually adjusted. In view of many different face shapes, it often happens that the mask does not fit properly or slips unnoticed during sleep and the air escapes, meaning necessary overpressure of breathing air is then no longer ensured and restful sleep is affected.[66] The escaping airflow can cause eye irritation and even conjunctivitis. [67] The CPAP mask can leave painful marks on the patient's skin and can result in sores, rashes, or ulcers. [68] Pressure-related side effects include nasal dryness, dry mouth and throat, rhinorrhea, and congestion which 65% of CPAP wearers suffer from. Reduced face growth due to CPAP use has been reported in a few cases. The CPAP interfered with the mid-facial development, resulting in mid-facial hypoplasia. [69]

Other side effects include vocal changes, the development of complex sleep apnea, device noise and claustrophobia.[70]

6. Mandibular Advancement devices

6.1 Concepts and mechanism of action

Orthotic dental devices, also known as bite or occlusal splints are either removable or fixed dental appliances, designed to adjust a patients bite and/or position of the jaw to a comfortable resting position. The devices are prescribed to individuals for a variety of conditions such as temporomandibular joint disorders, bruxism, or sleep apnea. Mandibular advancement devices (MAD) are specifically designed for individuals that have been diagnosed with OSA. Also referred to as “mandibular advancement splints” or “mandibular repositioning appliances”.

They have been used as a CPAP substitute for many years. With so many different appliances on the market today, it is impossible for a clinician to recommend just one appliance that will produce the expected results with the least amount of damage to the perioral structures. [71]
By moving the lower jaw forward, the device's goal is to widen the upper airway. In addition, MAD increases the activity of the muscles of the tongue and its related muscles to strengthen and refine the airway. According to reports, the appliance therapy for OSA effectively results in a lower AHI by gradually protruding the lower jaw (Fig. n.11).[72]

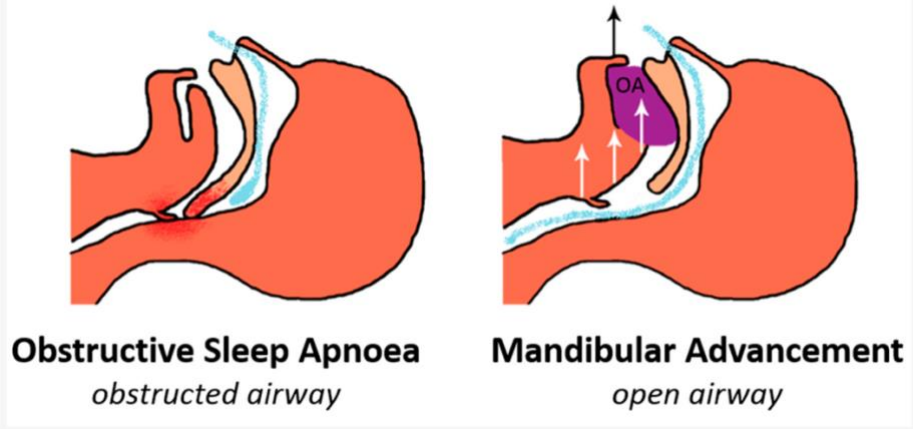

Figure 11. OSA without MAD vs. OSA with MAD.

A comprehensive study conducted by Kim et al. utilized CBCT to assess skeletal and dental changes in three dimensions during MAD treatment. The study revealed that mandibular protrusion results in linear increase in vertical height between the mandible and maxilla, as well as anterosuperior displacement and rotation of the hyoid bone. Notably, this therapy also leads to an improvement of nighttime oxygenation in adult patients with varying degrees of disease severity, leading to plenty of positive outcomes for patients' health and well-being.[73]
The goal of MAD therapy is to keep the upper airway open while sleeping by reducing resistance, the frequency and duration of apneas and hypoapneas, respiratory effort- related arousals and snoring. [747576]

6.2 Types of MAD

The first MAD, which was a rigid mandibular repositioning appliance was introduced in the 1980s by Meier- Ewert. [77] Back then there was a spread in the development of various mockups of MAD but the deficiency of standardization for design of the device often interrupts the interpretation concerning adjustments in clinical use and research results.[78] The Major MAD types approved by the Food and Drug Administration (FDA) can be made from different materials and can have different designs. The FDA approved more than 150 devices for the treatment of snoring and OSA. Some of the MADs have the capability of progressive

advancement and lateral movements. These appliances are classified as either prefabricated or custom-made in a single block, which is called monoblock or two block, called bi-block or duo-block. The custom-made appliances can be adaptable with latitude in lateral movements. [79]Adaption of the choice of material must be made to oral structure and patients physical needs for modulation of MAD. [80]

6.2.1 Prefabricated appliances

Prefabricated appliances, also known as "Boil and bite" or "thermoplastic" appliances have been available on the market for many years (Fig. n.12). These appliances are cheaper, sold over the counter, made from thermoplastic material, and do not need a dental laboratory for production. In terms of ability to maintain a stable mandibular protrusion while sleeping, these appliances tend to be large. As a result, this type of MAD is more likely to lose effectiveness and cause discomfort for the patient. However, a recent study demonstrates the effectiveness of a titratable thermoplastic MAD in reducing OSA and its associated symptoms in patients with mild to severe OSA. Thermoplastic appliances are now produced with very high quality and clinically perceptive design features and materials. The benefit of these devices is that they can be delivered in only a single visit, and they are custom fitted. By heating the prefabricated appliance sections in a hot water bath, these appliances are easily shaped to the individual teeth and jaw formation. After the cooling the appliances retain the accurate impression and individual bite registration. The treatment with these devices can start the same night. The fitting or try on can be done by a dentist, otolaryngologist, or ENT physician.[81]

Figure 12. Prefabricated intraoral mandibular advancement device titratable thermoplastic MAD Bluepro.

6.2.2 Custom made appliances

The custom-made appliances are more expensive compared to the prefabricated ones since they are specifically tailored to the dentition of the patient by either taking impressions or scans of the lower and upper jaw in order to produce the appliance in a dental laboratory-controlled advancement. The devices can be either non titratable which are one piece (monoblock) or titratable devices, which consist of a separate upper and lower part (biblock or duoblock) (Fig. n.13).[82] Non titratable appliances are made in a fixed protrusive position that does not change throughout the treatment. Titratable (biblock/duoblock) appliances can be used in advanced

procedures (e.g. titration process) with the goal of improving the treatment's effectiveness, the patient's comfort, and their quality of life. These custom-made devices have been allied with increased patient-reported comfort, increased therapeutic effectiveness and a larger range of protrusive movement. [8384]

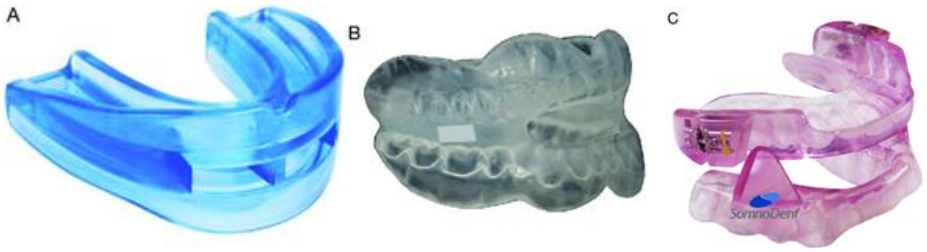

Figure 13. (A) "Boil and Bite" device; (B) monoblock appliance; (C) adjustable appliance.

6.3 Coupling mechanism

Various coupling mechanisms, such as elastic straps, bars, lateral fins, springs, telescopic rods, and tube connectors, can be used in the design of a non-adjustable MAD.[85] Because MADs maximize the space for the tongue and allow the mandible to move laterally and protrusively. MADs with lateral coupling mechanisms typically provide more comfort than other systems. N. Norrhem et al. showed that coupling mechanisms are more efficient when they permit a specific degree of opening and prevent the jaw from ever moving backwards while opening the mouth. [86] With the integration of elastic bands, mouth opening can be restricted. [87]

Despite the variety of protrusive movement vary between individuals, a study of Marklund et al. in 2012 indicated that the capacity to enhance the jaw is a characteristic feature in success of MAD therapy. He also analyzed that it depends on the amount of advancement needed to decrease snoring and AHI. [88]

The mandibular protrusion mechanism must show progressive growth of 1 mm or less, with a minimum range of 5 mm. [89] By allowing for small growth that enables the evaluation of crucial parameters, temporomandibular disorders can be decreases and comfort increased. Recent research indicated that at least 50 % of a patient's protrusive range is at the initial position, but it is unclear whether the measurement should start from the maximum intercuspation or maximum retrusive mandibular position. In order to effectively treat side effects and adapt to the patients' health-related dynamics, the coupling mechanism must be reversible. [90]

Furthermore, vertical adjustment is an additional subject in designing the oral appliances. It has been shown, that due to increased vertical dimension the patient acceptance decreased. [91]Nevertheless, an increase in vertical dimension during mandibular protrusion during treatment

with MAD resulted in a minor retrusion due to posterior rotation of the lower jaw. As a result, vertical increase should be avoided. [92]

6.4 MAD indications

MAD are produced for patients diagnosed with OSA. Recommended are these devices for patients with mild to moderate OSA. However, MAD's can also be used in patients with severe who do not react to or who fail the treatment with CPAP. [93]

Prior MAD treatment oral hygiene, periodontal damage as well as caries lesions or other pathologies should be evaluated und treated before MAD insertion. Moreover, discussion with the patient for exacerbation of the temporomandibular joint disorders or risk of occlusal changes is necessary.[94]

Normally MAD are used in a single therapy, but it can be combined with CPAP or other therapeutic modalities for better control of OSA. It has been reported that patient's preference and compliance rates for treatment of MAD is higher than with CPAP devices. [95]

According to the American Academy of Sleep Medicine, one of the main causes of MAD is persistent snoring.[96] As claimed by other studies, there may be a connection between endothelial dysfunction and atherosclerosis, two factors linked to a greater risk of developing cardiovascular disease. However, there is a normalized classification of primary snoring frequency or severity present when such treatment indication occurs. [97]

6.5 MAD effectiveness

With increased improvements in quality of life and daily functions achieved by MAD, MAD treatment has demonstrated success as measured by reduction of AHI, arousals, and oxygen desaturation rate. Also, Improvements of polysomnographic based outcomes comparing baseline PSG with posttreatment Polysomnogram have been seen. [98]

It was stated that MAD is less effective in AHI improvement compared to CPAP in moderate to severe OSA. More recent study from Scherr et al. has shown, that oral appliances and CPAP were equally effective to help reduce daytime sleepiness, high blood pressure, neurocognitive function, cardiovascular mortality, and quality of life. [99]Another study compared MAD and CPAP polysomnographs after 8 weeks of treatment, when an AHI <5 was reached or until it caused discomfort. Results have shown that, MAD therapy was effective in 21 out of 25 patients with mild OSA (84.00%) and CPAP therapy was effective in 20 out of 25 patients with severe OSA (80.00%). [100]

The effect of the treatment depends on design features such as materials, method of the manufacture and adjustability of the device together with the severity of OSA. It has been

proven, that an advancement higher than 50 % of patient's maximum protrusion is required for higher efficiency. [101102] The American academy of sleep medicine in 2015 suggested for OSA treatment custom made titratable appliances over nonadjustable prefabricated appliances. The success rate for OSA with treatment of these devices has been shown to be approximately 80%. AHI reduction and a comparison of baseline and posttreatment polysomnograms are two ways that treatment success is measured. [103] It has been demonstrated that patients with mild to moderate sleep apnea who use titratable oral appliances show a greater reduction in AHI and polysomnographic readings. [104]

The study of Prescinotto et al. reported that, the success of MAD treatment was considerably decreased for patients with anatomical features resulting in nasal resistance. The treatment was less effective for patients who had increased nasal resistance, but treatment adherence was not influenced by the presence of facial skeletal- or upper airway abnormalities. [105]

The drug-induced sedation endoscopy was used on patients receiving MAD therapy as an objective method for visualizing upper airway obstruction. The endoscopy revealed that MAD has improved airway permeability.[106]

Different computed tomography (CT-scan) and magnetic resonance imaging (MRI) studies have been carried out on awake patients to clarify tissue changes after MAD therapy that could predict breathing improvement during sleep. These performances revealed that after MAD incorporation, significant changes in the airways were seen in the transversal dimension, which restricts the ability to render two-dimensional cephalometric images of the sagittal plane and obviates the ability to predict treatment outcomes in an accurate manner. Through a tree-dimensional analysis, the effects of MAD on wakefulness and sleep were studied. Examine the retro-lingual and palatal spaces revealed that MAD increases them, which is a crucial sign of successful treatment. Furthermore, it showed that the soft palate was getting shorter.[107108]

6.6 Patients' phenotypes

Evidence has shown that OSA is a recognized medical condition with a variety of etiologies in terms of clinical presentation, risk factors, risk of comorbidity, pathophysiology or response to treatment. As a result, the customized therapy approaches, which guarantee a higher effectiveness of the chosen treatment, are a crucial step for OSA.[109]

Sutherland K et al.'s recent study 2015 research on patient's phenotypes responding to MAD therapy revealed that one-third of the study participants had no to minimal improvement in OSA severity.[110]

These findings indicate that urgent requirement for identifying the patients who are most likely to experience a favorable treatment outcome, which would then optimize the selection of the treatment modality and the look for adjuvant therapies. [111] Drug induced sleep Endoscopy titration can be used as a predictor of MAD therapy outcome based on a direct assessment of the obstruction of upper airway sites and a way to later determine which treatment will achieve the highest treatment response for each patient and which mandibular protrusion should be targeted.[112]

Muscle response capacity, arousal threshold, and anatomical and physiological phenotypes like the critical pressure to close the upper airway play all important roles in the pathophysiology of OSA. [113] These phenotypes have been found to affect treatment selection and success prediction for OSA. Additionally, it has been demonstrated that the response to MAD treatment can be negatively impacted by hypertension and/or other sleep disorders, such as insomnia.[114]

6.7 Reasons for failure of MAD

Reasons for failure of MAD treatment could be a shortened dental arch or missing teeth. A shortened dental arch effects masticatory functions as well as distal extension removable partial dentures which are commonly used to for edentulous people. It has been reported that patients wearing removable partial dentures due to a distally reduced mandibular dental arch do not relate on greater observed satisfaction, function, or quality of life. [115116]

The retrospective controlled study of a single center university hospital of Helsinki, Finland between the years 2006 and 2013 investigated reasons for failure using MAD for management of OSA. The study has shown that patients with missing molars failed significantly more in the MAD therapy compared to patients with no missing molars. Furthermore, the use of CPAP before MAD tend to fail with MAD treatment. On the other hand, patients who are already familiar with the use of occlusal sprints prior to MAD treatment, have a higher success for MAD treatment.

The study has presented, that MAD treatment success is not affected by gender, age, Body mass Index (BMI), systemic or psychiatric diseases, sex, TMD, dental overset, or sleep apnea severity. According to the results, there is no appearance to be a definite reason for treatment failure.

The results of the retrospective controlled study of Helsinki university and previous results of Mintz et al. Are very similar. Mintz et al. Also did not find an explicit reason for MAD treatment failure. Instead, they found various reasons for MAD treatment failure for example masticatory

muscle pain, TMJ, bite changes, tooth loss and pain, lack of retention, gagging and difficulties in tolerating MAD. [117]

6.8 MAD compared to CPAP

As already mentioned above, CPAP is considered the standard treatment in OSA. It is very efficient in reducing OSA events by measuring the AHI. On the other hand, the low adherence of CPAP can influence the efficacy of treatment. 29% to 83% of the population reported failure of treatment after applying the minimum acceptable CPAP compliance threshold of 4 hours. [118] There are several studies that comparing CPAP to MAD in mild to severe OSA. Sharples LD et al. who did a meta-analysis comparing MAD to CPAP for OSA rules out that all studies used AHI as the primary outcome of efficiency. Secondary outcomes were also used including oxygen desaturation index and arousal index. The results of this meta-analysis have shown that MAD is less effective at reducing sleep disordered breathing and OSA (AHI <5). [119]

Polysomnogprahic results have shown, that CPAP does not achieve better health outcomes compared to MAD. It has been said that the higher efficiency of CPAP is compensating by greater MAD compliance. MAD and CPAP achieve the same improvements in excessive daytime sleepiness and quality of life. [120] The compliance of CPAP was 5.2 hours per night, whereas the compliance for MAD was at 6.5 hours per night. [121] Due to these results, it can be said that MAD and CPAP have similar clinical effects due to greater MAD compliance achieving net similar AHI reduction. [122]

The randomized controlled trial of oral mandibular advancement devices for OSA (TOMADO) study concluded, that adherence influences health economics. It was proven by Almeida FR et al. that, MAD is more reasonable than CPAP when CPAP compliance drops below 90 % of MAD use. Thus, factors that influence compliance should be determined, to decide which therapy is initiated. [123] A study that analyzed surveys filled out by CPAP and MAD users, concluded that the four important factors that determine whether the choice of treatment is CPAP or MAD are transportability, device effectiveness, embarrassment, and cost-effectiveness. [124] Various trials have analyzed that MAD is preferred more often compared to CPAP.[125]

6.9 MAD in combination with CPAP

Another treatment option is therapy with a combination of MAD and CPAP. It is then suggested for patients with OSA, who are intolerant to CPAP and do not respond to MAD. When the MAD alone is not enough to induce a safe sleep profile, the improved pharyngeal patency made

possible by mandibular advancement and stretching of the pharyngeal muscles enables the CPAP to be used at lower pressures. [126]

6.10 Side effects

The use of MAD is considered as a non-invasive procedure. However, depending on the design of the MAD and patient-related factors, side effects can occur during and after wearing the device while sleeping [127][128]

Careful information about the side effects of MAD should be carried out and is an essential condition for good patient adherence. It must precede the patient's decision for this intervention and be recapitulated during MAD therapy. The evidence on recommended measures to avoid side effects is low and of low quality[129]. The education should also include measures that only reduce the severity of possible side effects and limit their effects in time. Side effects can be reversible and transient in the short term after incorporation of the MAD. The American Academy of Dental Sleep Medicine (AADSM) established an order of consensus recommendations for the management of side effect from oral appliance therapies in 2016.

Initially, excessive salivation and, in rare cases, increased dryness in the mouth can be expected. The edge of the splint can lead to irritation and inflammation of the gingiva. The teeth themselves can also be sensitive during the first few nights. These complaints quickly subside after an adjustment phase, or disappear after corrections to the MAD. [130]

In the short to medium term, it can also lead to feelings of tension and even pain in the masticatory muscles and in the area of the jaw joints. These complaints are due to the protrusion of the lower jaw for several hours at night. The nature of these complaints is similar to the symptoms of classic temporomandibular dysfunction (TMD). In general, the pain decreases after a longer period of wearing. Patients who already had TMD symptoms or signs prior to MAD therapy do not experience any significant exacerbation of their symptoms. In order to reduce or even avoid these TMD symptoms, accompanying measures such as jaw gymnastics, physiotherapy, the temporary use of frontal bites or medication can be useful. Noises in the temporomandibular joints can also occur during MAD therapy, but these are usually transient and disappear on their own and do not require further treatment after the patient has been informed.[131]

Irreversible changes in the area of the teeth can affect occlusion and tooth position. Occlusion disorders can manifest themselves in a posterior open bite. According to a study by Perez et al. within two years of wearing the MAD, the incidence of posterior open bite increased by almost 18%.[132]

However, almost a third of the affected patients did not even notice this change themselves. In the anterior region, proclination of the lower teeth and retroclination of the upper teeth can lead to an overall reduction in the vertical and sagittal overbite[133]. Patients with an Angle class III should be particularly informed about these unfavorable side effects. In some cases, the proximal contacts of the teeth can widen, leading to impaction of food debris, especially with prolonged wear[134]. Changing the MAD design, wearing a retainer during the day or restoring the gaps can be appropriate countermeasures. Fractures of teeth or restorations can be the direct result of strong retention or occlusal changes in MAD therapy. Dental corrections to the MAD or restorations to the teeth may then be necessary[135]. The MAD may chip or fracture during treatment, most of which can be repaired. Restrictions on the use of MAD therapy can be allergies, gagging or anxiety states[136].

In a few cases, side effects such as persistent TMD symptoms, change in tooth position or occlusion, persistent dry mouth and periodontal problems lead to discontinuation of the MAD therapy. However, MAD therapy was terminated significantly more frequently because of persistent OSA symptoms[137]

Tissue related side effects, damage to teeth and appliance issues belong to the categories of side effects, that are not constricted to oral appliance therapy. Nevertheless, the categories of side effects including temporomandibular joint (TMJ) and occlusal changes can be dynamically handled to the point where the symptoms go relatively unrecognized.[138]

6.11 Positive side effects

These undesirable side effects are offset by the desired positive effects on breathing, sleep, daytime sleepiness, the cardiovascular system and quality of life. That means in the sense of a risk assessment, the patient accepts these side effects - as with any medical treatment and in dialogue with the therapist - because the benefit of the therapy is significantly greater than the damage that may result. These risks can be reduced by regular checks ups.[139]

In addition to the positive medical effect of the MAD therapy on OSA and snoring, favorable dental effects could also be proven. A reduction in episodes of bruxism during sleep could be demonstrated[140], which in turn has a positive effect on the associated loss of tooth structure, morning headaches and other orofacial pain.[141]

7. Conclusion:

Obstructive sleep apnea is a common condition characterized by the recurrent or partial collapse and narrowing of the throat during sleep, leading to obstructive sleep apnea events. Obstructive

sleep apnea is characterized by its severity: mild, moderate and severe. The prevalence of obstructive sleep apnea cannot be certainly distinguished due to the often-missing clear dissociation of snoring from obstructive sleep apnea, but it has been shown that approximately 79,2% of men over 40 years old and 54,3% of women over 40 years old are affected by obstructive sleep apnea. Clinical manifestations of OSA include snoring, excessive daytime sleepiness, choking or gasping at night, night sweats, neurocognitive impairment, heartburn, morning headaches, maintenance insomnia, erectile dysfunction, obesity, enlarged neck circumference, crowded upper airway, hypertension, pulmonary hypertension, retrognathia/overjet, nasal obstruction, decreased oxygen saturation, congestive heart failure and lower extremity edema.

Obstructive sleep apnea diagnosis is made by various medical tests including pulsoxymetry, respiratory polygraphy and polysomnography. From the dental perspective, there are self-assessment questionnaires (STOP BANG and Epiworth sleepiness scale) to measure daytime sleepiness and to indicate the risk of obstructive sleep apnea. The radiology evaluation is carried out by either cephalometric evaluation to measure skeletal proportions of the facial skull and in the case of obstructive sleep apnea especially the upper airways, Cone beam computer tomography to measure the airway volume and its connection to the upper airway and the craniofacial anatomy. Intraoral examination is perfomed called Mallampati score to identify anatomical changes at the upper airways, nose, oral cavity, and pharynx or in the area of the facial skull, especially the position of the tongue in relation to the oral cavity and soft palate.

Obstructive sleep apnea modalities include lifestyle change (e.g. weight loss), positional therapy for patients who sleep on their backs, myofunctional therapy, and drug therapy. All these modalities reduce the apnea- hypoapnea index.

Surgical interventions can be conducted either when the pharyngeal tonsils are enlarged by an adenotonsillectomy or Uvulopalatopharyngeoplasty to reduce the soft palate and uvula. Another intervention could be the use of a hypoglossal pacemaker to stimulate the tongue muscles. The pacemaker prevents the tongue from descending and thus counteracts airway obstruction. Lastly, Maxillo- mandibular advancements include osteotomies and genioplasty, which enlarge the pharyngeal airway and consequently increase the pharyngeal muscle tone. Both effects synergistically reduce the collapsibility of the pharynx.

The golden standard for obstructive sleep apnea in moderate to severe cases is Continuous positive airway pressure therapy. The device produces a constant overpressure that keeps the upper airway open. Since the mask are standardized in shape, they do not fit properly on every individual face and slips during sleep, the air escapes and the overpressure of breathing air is

then not generated anymore. This effects restful sleep and has other negative side effects such as sores, rashes, ulcer, nasal dryness, dry mouth & throat, rhinorrhoea, congestion, vocal changes, claustrophobia and reduced face growth.

Mandibular advancement devices are oral appliances that are used for managing mild to moderate obstructive sleep apnea or patients with severe obstructive sleep apnea who does not tolerate or even fail continuous positive airway pressure therapy. Its mechanism is to increase the muscle activity of the tongue and its related muscles to strengthen and open the upper airway. Its goal is to keep the upper airway open while sleeping by reducing the resistance, frequency, and duration of apneas and hypo apneas.

They are either prefabricated or custom-made appliances. Prefabricated appliances also known as “boil and bite” appliances do not need a laboratory for production and are considered less effective and can cause discomfort for the patient, while custom-made appliances are fabricated in the lab requiring dental impressions and can either be monoblock or biblock appliances, which can be titratable or non titrable. They are used to protrude the mandible forward to prevent a narrowing of the upper airways.

Prefabricated Mandibular advancement devices have a variety of different coupling mechanisms in design. Devices with a lateral coupling mechanism provide more comfort than other systems and are more efficient when it permits a specific degree of opening and preventing the jaw from moving backwards while opening the mouth.

The mandibular protrusion must show an increasing growth of 1 millimeter or less with a maximum range of 5 millimeters.

Mandibular advancement devices shown a success in improving quality of life and daily functions, as well as reduction of Apnea- hypo-apnea index in mild to moderate obstructive sleep apnea, arousals, and oxygen desaturation rate. It has been shown that mandibular advancement devices are equally effective to continuous positive airway pressure in reducing daytime sleepiness, elevated blood pressure, cardiovascular mortality, quality of life and neurocognitive functions.

The effect of treatment depends on the design and material choice, method of manufacturing and adjustability of the device combined with the severity of obstructive sleep apnea. It has been shown that an advancement higher than 50 % of the patient’s maximum protrusion is required to achieve a better outcome of efficiency. Patients who use a titrable device show a greater reduction of apnea hypo-apnea index in mild to moderate cases.

However Mandibular advancement device treatment can be negatively affected by hypertension, sleep disorders like insomnia.

Reasons for failure include shortened dental arch or missing teeth. Another reason could be the use of continuous positive airway pressure prior to mandibular advancement device treatment. Otherwise, one can say that the treatment success is not affected by gender, body mass index, systemic/psychiatric diseases, age, TMD, dental overjet or sleep apnea severity.

Side effects can be expected like excessive salivation or increased dryness of the mouth. Temporomandibular disorder pain and in the masticatory muscles is also a very common side effect experienced by mandibular advancement device use. During wearing it is possible to have irritation or gum inflammation due to the edges of the appliances. Occlusion changes can lead to a posterior open bite. However, all these symptoms can be treated until they go unrecognized.

To conclude one can say, that mandibular advancement devices are equally effective in management of obstructive sleep apnea compared to continuous positive airway pressure therapy in mild to moderate cases in reducing AHI and achieving better quality of life.

8. References

[1] Patel SR. Obstructive Sleep Apnea. Ann Intern Med. 2019 Dec 3;171(11):ITC81-ITC96. doi: 10.7326/AITC201912030. PMID: 31791057.

[2] Kirsch DB. Obstructive Sleep Apnea. Continuum (Minneap Minn). 2020 Aug;26(4):908-928. doi: 10.1212/CON.0000000000000885. PMID: 32756228.

[3] Bounhoure JP, Galinier M, Didier A, Leophonte P. [Sleep apnea syndromes and cardiovascular disease]. Bulletin de L'academie Nationale de Medecine. 2005 Mar;189(3):445-459; discussion 460-4. DOI: 10.1016/s0001-4079(19)33558-7. PMID: 16149210.

[4] Bradley, T.D., Phillipson, E.A. Central sleep apnea. Clin Chest Med 1992;13:493-505

[5] Guilleminault, C. and Robinson, A. Central sleep apnea. Neurol Clin 1996;14:611-628.

[6] Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet. 2014 Feb 22;383(9918):736-747. doi: 10.1016/S0140-6736(13)60734-5. Epub 2013 Aug 2. PMID: 23910433; PMCID: PMC3909558.

[7] Khan, M. T., & Franco, R. A. (2014). Complex sleep apnea syndrome. *Sleep disorders*, *2014*, 798487. https://doi.org/10.1155/2014/798487

[8] American Academy of Sleep Medicine (2014) International classification of sleep disorders, (ICSD-3), 3. Aufl. American Academy of Sleep Medicine, Darien

[9] Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (DGSM), S3 Leitlinie „Schlafbezogene Atmungsstörungen bei Erwachsenen“ AWMF-Register Nr.063/001, 2017

[10] Berry R., Budhiraja R., Gottlieb D., Gozal D., Iber C., Kapur V., et al. (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. *J Clin Sleep Med* 8: 597–619.

[11] Penzel T, Glos M: Diagnostik der Schlafapnoe. In Schulz et al.: Kompendium der Schlafmedizin, Ecomed, Landsberg 2015

[12] Chan AS, Phillips CL, Cistulli PA. Obstructive sleep apnoea--an update. Intern Med J. 2010 Feb;40(2):102-106. doi: 10.1111/j.1445-5994.2009.02069.x. Epub 2009 Oct 7. PMID: 19811552.

[13] Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, Lavie L, Pépin JL. Obstructive sleep apnoea syndrome. Nat Rev Dis Primers. 2015 Jun 25;1:15015. doi: 10.1038/nrdp.2015.15. PMID: 27188535.

[14] Gupta RK, Chandra A, Verm AK, Kumar S. Obstructive sleep apnoea: a clinical review. J Assoc Physicians India. 2010 Jul;58:438-441. PMID: 21121210.

[15] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-5.

[16] Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3:310-8.

[17] 4. Andrea Rodenbeck G, Berlin, Peter Geisler, Regensburg, Hartmut Schulz, Erfurt III - 4.2.1 Internationale Klassifikation von Schlafstörungen, 3. Version (ICSD-3) 2014.

[18] Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie e. V. S3- Leitlinie Diagnostik und Therapie des Schnarchens beim Erwachsenen AWMF-Register-Nr 017/068 2019.

[19] Katz S, Pancer J, Dort L. Treatment Complications: Notes from the Fall 2009 Advanced Course in Oral Appliance Therapy. *Dialogue.* 2010;(2):20–22.

[20] Stansbury RC, Strollo PJ. Clinical manifestations of sleep apnea. J Thorac Dis. 2015 Sep;7(9):E298-310. doi: 10.3978/j.issn.2072-1439.2015.09.13. PMID: 26543619; PMCID: PMC4598518.

[21] American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999; 22:667-689

[22] Peppard P, Young T, Palta M, Skatrud J. Prospective study of the association between sleep disordered breathing and hypertension. New Engl J Med; 2000;342:1378-1384.

[23] Gugger M. Nützlichkeit der ambulanten nächtlichen Pulsoxymetrie. Schweiz Med Wochenschr 1995; 125:233-233.

[24] American Sleep Disorders Association Standards of Practice Committee. Practice parameters for the indications for polysomnography and related procedures. Sleep 1997; 20:406-422.

[25] Masa JF, Corral J, Pereira R, et al. Effectiveness of home respiratory polygraphy for the diagnosis of sleep apnoea and hypopnea syndrome. Thorax 20011; 66:567-573

[26] Rundo JV, Downey R 3rd. Polysomnography. Handb Clin Neurol. 2019;160:381-392. doi: 10.1016/B978-0-444-64032-1.00025-4. PMID: 31277862.

[27] Gugger M, Bassetti C, Bloch K.E:, Blois R, Colomb E, Wirz-Justice A et al. Richtlinien zur Zertifizierung von "Zentren für Schlafmmedizin" zur Durchführung von Polysomnographien. Schweizerische Ärztezeitung 1998; 79:2605-2614.

[28] Yu JL, Rosen I. Utility of the modified Mallampati grade and Friedman tongue position in the assessment of obstructive sleep apnea. J Clin Sleep Med. 2020 Feb 15;16(2):303-308. doi: 10.5664/jcsm.8188. Epub 2020 Jan 13. PMID: 31992434; PMCID: PMC7053038.

[29] Johns MW (1991) A new method for measuring daytime sleepiness. The Epworth Sleepiness Scale. Sleep 14:103–109

[30] Walker, N.A., Sunderram, J., Zhang, P. *et al.* Clinical utility of the Epworth sleepiness scale.*Sleep Breath* **24**, 1759–1765 (2020). https://doi.org/10.1007/s11325-020-02015-2

[31] Buysse DJ, Reynolds CF, Monk TH (1989) Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213

[32]Netzer NC, Stoohs RA, Netzer CM (1999) Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 131:485–491

[33] Ong TH, Raudha S, Fook-Chong S et al (2010) Sim- plifying STOP-BANG: use of a simple questionnaire to screen for OSA in an Asian population. Sleep Breath 14:371–376

[34] Farney RJ, Walker BS, Farney RM, Snow GL, Walker JM (2011) The STOP-BANG equivalent model and prediction of severity of obstructive sleep apnea: relation to polysomnographic measurements of the apnea/hypopnea index. J Clin Sleep Med 7(5):459–465

[35] Silva GE, Vana KD, Goodwin JL et al (2011) Identification of patients with sleep disordered breathing: comparing the Four-Variable screening tool, STOP, STOPBang, and Epworth Sleepiness Scales. J Clin Sleep Med 7:467–472

[36] F. Chung, R. Subramanyam, P. Liao, E. Sasaki, C. Shapiro, Y. Sun. High STOP- Bang score indicated a high probability of obstructive sleep apnoea. British Journal of Anaesthesia. 2012

[37] F. Chung, R. Subramanyam, P. Liao, E. Sasaki, C. Shapiro, Y. Sun. High STOP- Bang score indicated a high probability of obstructive sleep apnoea. British Journal of Anaesthesia. 2012

[38] *The Official STOP-Bang Questionnaire Website*. (n.d.). The Official STOP-Bang Questionnaire Website. http://www.stopbang.ca/osa/screening.php

[39] deBerry-Borowiecki B, Kukwa A, Blanks RH. Cephalometric analysis for diagnosis and treatment of obstructive sleep apnea. Laryngoscope. 1988 Feb;98(2):226-234. doi: 10.1288/00005537-198802000-00021. PMID: 3339937.

[40] Hierl T. 1997. XiV Kephalometrie, 1-5. Kompendium Schlafmedizin für Ausbildung, Klinik und Praxis. Ecomed Verlagsgesellschaft

[41] Anne-Chrstiane Grossmann. Kephalometrsiche Untersuchung nach der Kasund/Segner Analyse bei patienten mit obstruktiver Schlafapnoe. 2002

[43] Aboudara C, Nielsen I, Huang JC, Maki K, Miller AJ, Hatcher D. Comparison of airway space with conventional lateral headfilms and 3-dimensional reconstruction from cone-beam computed tomography. Am J Orthod Dentofacial Orthop. 2009 Apr;135(4):468-479. doi: 10.1016/j.ajodo.2007.04.043. PMID: 19361733.

[44] Cosentini T, Le Donne R, Mancini D, Colavita N. Magnetic resonance imaging of the upper airway in obstructive sleep apnoea. *Radiol Med* 2004; **108**: 404– 416.

[45] R. Strauss, N. Wang. (2012). Cone beam computed tomography and obstructive sleep apnoea. Australian dental journal. Volume 57. 61-71

[46] Peppard PE, Young T, Palta M, Dempsey J and Skatrud J (2000). Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* **284**: 3015-3021.

[47] Camacho M, Certal V, Abdullatif J, Zaghi S, Ruoff CM, Capasso R and Kushida CA (2015). Myofunctional Therapy to Treat Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *Sleep* **38**: 669-675.

[48] Randerath WJ, Verbraecken J, Andreas S, Bettega G, Boudewyns A, Hamans E, Jalbert F, Paoli JR, Sanner B, Smith I, Stuck BA, Lacassagne L, Marklund M, Maurer JT, Pepin JL, Valipour A, Verse T, Fietze I and European Respiratory Society task force on non Ctisa (2011). Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J* **37**: 1000-1028.

[49] Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (DGSM), S3 Leitlinie „Schlafbezogene Atmungsstörungen bei Erwachsenen“ AWMF-Register Nr.063/001, 2017

[50] Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (DGSM), S3 Leitlinie „Schlafbezogene Atmungsstörungen bei Erwachsenen“ AWMF-Register Nr.063/001, 2017

[51] Browaldh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. Thorax. 2013 Sep;68(9):846-853. doi: 10.1136/thoraxjnl-2012-202610. Epub 2013 May 5. PMID: 23644225.

[52] Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (DGSM), S3 Leitlinie „Schlafbezogene Atmungsstörungen bei Erwachsenen“ AWMF-Register Nr.063/001, 2017

[53] Kezirian EJ, Goding GS Jr, Malhotra A, O'Donoghue FJ, Zammit G, Wheatley JR, Catcheside PG, Smith PL, Schwartz AR, Walsh JH, Maddison KJ, Claman DM, Huntley T, Park SY, Campbell MC, Palme CE, Iber C, Eastwood PR, Hillman DR, Barnes M. Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes. J Sleep Res. 2014 Feb;23(1):77-83. doi: 10.1111/jsr.12079. Epub 2013 Sep 4. PMID: 24033656; PMCID: PMC4323268.

[54] Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (DGSM), S3 Leitlinie „Schlafbezogene Atmungsstörungen bei Erwachsenen“ AWMF-Register Nr.063/001, 2017

[55] Li HY, Wang PC, Chen YP, Lee LA, Fang TJ, Lin HC. Critical appraisal and meta-analysis of nasal surgery for obstructive sleep apnea. Am J Rhinol Allergy. 2011 Jan-Feb;25(1):45-49.

[56] Hochban, W: Schlafmedizin/Somnologie, MKG-Update 2017, Handbuch MKG 2017 S. 1–25., Verse T, Dreher A, Heiser C, Herzog M, Maurer JT, Pirsig W, Rohde K, Rothmeier N, Sauter A, Steffen A, Wenzel S, Stuck AB: HNO-spezifische Therapie der obstruktiven Schlafapnoe bei Erwachsenen, S2e-Leitlinie AWMF 017/069 der DGHNO-KHC 2015.

[57] Lindorf H, v.Wilmowksy C, Müller-Herzog, R: Das maxillo-mandibuläre Advancement zur Therapie der obstruktiven Schlafapnoe-Die Rolle der MKG-Chirurgie in einem interdisziplinären Ansatz.ZMK(1-2) S.032-041.2021.

[58] Kuo P C, West R A, Bloomquist D S, McNeil R W. The effect of mandibular osteotomy in three patients with hypersomnia sleep apnea. Oral Surg Oral Med Oral Path. 1979; 48 385-392.

[59] Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. Sleep Med Rev. 2010 Oct;14(5):287-297.

[60] Deutsche Gesellschaft für Schlafforschund und Schlafmedizin (DGSM), Teil-Aktualisierung S3- Leitlinie „Schlafbezogene Atmungsstörungen bei Erwachsenen“- AMWF-Register Nr.063-001,2020

[61] Penzel T, Glos M: Diagnostik der Schlafapnoe. In Schulz et al.: Kompendium der Schlafmedizin, Ecomed, Landsberg 2015.

[62] Vasu TS, Grewal R, Doghramji K. Obstructive sleep apnea syndrome and perioperative complications: a systematic review of the literature. J Clin Sleep Med. 2012 Apr 15;8(2):199-207.

[64] Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D, Boehlecke B, Brown TM, Coleman J Jr, Friedman L, Kapen S, Kapur VK, Kramer M, Lee-Chiong T, Owens J, Pancer JP, Swick TJ, Wise MS; American Academy of Sleep Medicine. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. Sleep. 2006 Mar;29(3):375-380.

[65] Sutherland, K., Kairaitis, K., Yee, B.J. *et al.* From CPAP to tailored therapy for obstructive sleep Apnoea. *Multidiscip Respir Med* **13,** 44 (2018). https://doi.org/10.1186/s40248-018-0157-0

[66] Lebret M, Martinot JB, Arnol N, Zerillo D, Tamisier R, Pepin JL, Borel JC. Factors Contributing to Unintentional Leak During CPAP Treatment: A Systematic Review. Chest. 2017 Mar;151(3):707-719. doi: 10.1016/j.chest.2016.11.049. Epub 2016 Dec 14. PMID: 27986462.

[67] Hayirci E, Yagci A, Palamar M, Basoglu OK, Veral A. The effect of continuous positive airway pressure treatment for obstructive sleep apnea syndrome on the ocular surface. Cornea. 2012 Jun;31(6):604-608. doi: 10.1097/ICO.0b013e31824a2040. PMID: 22410644.

[68] Ghadiri M, Grunstein RR. Clinical side effects of continuous positive airway pressure in patients with obstructive sleep apnoea. Respirology. 2020 Jun;25(6):593-602. doi: 10.1111/resp.13808. Epub 2020 Mar 24. PMID: 32212210.

[69] Roberts SD, Kapadia H, Greenlee G, Chen ML. Midfacial and Dental Changes Associated with Nasal Positive Airway Pressure in Children with Obstructive Sleep Apnea and Craniofacial Conditions. J Clin Sleep Med. 2016 Apr 15;12(4):469-475. doi: 10.5664/jcsm.5668. PMID: 26715402; PMCID: PMC4795272.

[70] Ghadiri M, Grunstein RR. Clinical side effects of continuous positive airway pressure in patients with obstructive sleep apnoea. Respirology. 2020 Jun;25(6):593-602. doi: 10.1111/resp.13808. Epub 2020 Mar 24. PMID: 32212210.

[71] Kim DI, Vich ML, Mayoral P, Miguez M. Three-dimensional changes in skeletal/ dental landmarks with use of mandibular advancement devices. J Dent Sleep Med. 2020;7(2):

[72] Kim DI, Vich ML, Mayoral P, Miguez M. Three-dimensional changes in skeletal/ dental landmarks with use of mandibular advancement devices. J Dent Sleep Med. 2020;7(2):

[73] Kim, D. I., & Lagravère, M. O. (2018). Assessing the Correlation between Skeletal and Corresponding Soft-Tissue Equivalents to Determine the Relationship between CBCT Skeletal/Dental Dimensions and 3D Radiographic Soft-Tissue Equivalents. *International journal of dentistry*, *2018*, 8926314. https://doi.org/10.1155/2018/8926314

[74] Mogell K, Blumenstock N, Mason E, Rohatgi R, Shah S, Schwartz D. Definition of an effective oral appliance for the treatment of obstructive sleep apnea and snoring: an update for 2019. J Dent Sleep Med. 2019;6(3):

[75] Scherr SC, Dort LC, Almeida FR, Bennett KM, Bumenstock NT, Demko BG, et al.Definition of an effective oral appliance for the treatment of obstructive sleep apnea and snoring: a report of the American Academy of Dental Sleep Medicine. J Dent Sleep Med. 2014;1(1):

[76] Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, et al.Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. J Clin Sleep Med. 2015;11(7):

[77] Chan ASL, Sutherland K, Cistulli PA. Mandibular advancement splints for the treatment of obstructive sleep apnea. Expert Rev Respir Med. 2020;14(1):

[78] Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. Sleep. 2006;29(2):

[79] Dal Fabbro C, Chaves CM, Tufik S. . A odontologia na medicina do sono. 2012;():

[80] Ahrens A, McGrath C, Hägg U. A systematic review of the efficacy of oral appliance design in the management of obstructive sleep apnoea. Eur J Orthod. 2011;33(3):

[81] Gagnadoux F, Nguyen XL, LeVaillant M, Priou P, Meslier N, Eberlein A, et al.Comparison of titrable thermoplastic versus custom-made mandibular advancement device for the treatment of obstructive sleep apnoea. Respir Med. 2017;131():

[82] Dieltjens, Marijke, and Olivier M. Vanderveken. 2019. "Oral Appliances in Obstructive Sleep Apnea" *Healthcare* 7, no. 4: 141. https://doi.org/10.3390/healthcare7040141

[83] Scherr SC, Dort LC, Almeida FR, Bennett KM, Bumenstock NT, Demko BG, et al.Definition of an effective oral appliance for the treatment of obstructive sleep apnea and snoring: a report of the American Academy of Dental Sleep Medicine. J Dent Sleep Med. 2014;1(1):

[84] Lettieri CJ, Paolino N, Eliasson AH, Shah AA, Holley AB. Comparison of adjustable and fixed oral appliances for the treatment of obstructive sleep apnea. J Clin Sleep Med. 2011;7(5):

[85] Dieltjens M, Vanderveken OM, Van de Heyning PH, Braem MJ. Current opinions and clinical practice in the titration of oral appliances in the treatment of sleep-disordered breathing. Sleep Med Rev. 2012;16(2)

[86] Norrhem N, Marklund M. An oral appliance with or without elastic bands to control mouth opening during sleep-a randomized pilot study. Sleep Breath. 2016;20(3):

[87] Bataller A, Cabrera JA, Garcia M, Castillo JJ, Mayoral P. Cam synthesis applied to the design of a customized mandibular advancement device for the treatment of obstructive sleep apnea. Mech Mach Theory. 2018;123():

[88] Marklund M, Verbraecken J, Randerath W. Non-CPAP therapies in obstructive sleep apnoea: mandibular advancement device therapy. Eur Respir J. 2012;39(5):

[89] Ahrens A, McGrath C, Hägg U. A systematic review of the efficacy of oral appliance design in the management of obstructive sleep apnoea. Eur J Orthod. 2011;33(3):

[90] Marklund M, Verbraecken J, Randerath W. Non-CPAP therapies in obstructive sleep apnoea: mandibular advancement device therapy. Eur Respir J. 2012;39(5):

[91] Scherr SC, Dort LC, Almeida FR, Bennett KM, Bumenstock NT, Demko BG, et al.Definition of an effective oral appliance for the treatment of obstructive sleep apnea and snoring: a report of the American Academy of Dental Sleep Medicine. J Dent Sleep Med. 2014;1(1):

[92] Mayoral P, Lagravère MO, Míguez-Contreras M, Garcia M. Antero-posterior mandibular position at different vertical levels for mandibular advancing device design. BMC Oral Health. 2019;19(1):

[93] Marklund M, Braem MJA, Verbraecken J. Update on oral appliance therapy. Eur Respir Rev. 2019 Sep 25;28(153):190083. doi: 10.1183/16000617.0083-2019. PMID: 31554705.

[94] Marklund M. Subjective versus objective dental side effects from oral sleep apnea appliances. Sleep Breath. 2020;24():

[95] Mogell K, Blumenstock N, Mason E, Rohatgi R, Shah S, Schwartz D. Definition of an effective oral appliance for the treatment of obstructive sleep apnea and snoring: an update for 2019. J Dent Sleep Med. 2019;6(3):

[96] Scherr SC, Dort LC, Almeida FR, Bennett KM, Bumenstock NT, Demko BG, et al.Definition of an effective oral appliance for the treatment of obstructive sleep apnea and snoring: a report of the American Academy of Dental Sleep Medicine. J Dent Sleep Med. 2014;1(1):

[97] Meira e Cruz M, Soca R, Kryger M. How much is too much after all? Primary snoring as a remaining unsolved issue. J Clin Sleep Med. 2020;16(6):

[98] Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, et al.Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. J Clin Sleep Med. 2015;11(7):

[99] Scherr SC, Dort LC, Almeida FR, Bennett KM, Bumenstock NT, Demko BG, et al.Definition of an effective oral appliance for the treatment of obstructive sleep apnea and snoring: a report of the American Academy of Dental Sleep Medicine. J Dent Sleep Med. 2014;1(1):

[100] Hoekema A, Stegenga B, Wijkstra PJ, Van Der Hoeven JH, Meinesz AF, Bont LG. Obstructive sleep apnea therapy. J Dent Res. 2008;87(9):

[101] Hoekema A, Stegenga B, Wijkstra PJ, Van Der Hoeven JH, Meinesz AF, Bont LG. Obstructive sleep apnea therapy. J Dent Res. 2008;87(9):

[102] Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial. Respiration. 2011;81(5):

[103] [103] Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. J Clin Sleep Med. 2015 Jul 15;11(7):773-827. doi: 10.5664/jcsm.4858. PMID: 26094920; PMCID: PMC4481062.

[104] [104] Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. J Clin Sleep Med. 2015 Jul 15;11(7):773-827. doi: 10.5664/jcsm.4858. PMID: 26094920; PMCID: PMC4481062.

[105] Prescinotto R, Haddad FL, Fukuchi I, Gregório LC, Cunali PA, Tufik S, Bittencourt LR. Impact of upper airway abnormalities on the success and adherence to mandibular advancement device treatment in patients with Obstructive Sleep Apnea Syndrome. Braz J Otorhinolaryngol. 2015 Nov-Dec;81(6):663-670. doi: 10.1016/j.bjorl.2015.08.005. Epub 2015 Sep 7. PMID: 26387988; PMCID: PMC9442756.

[106] Vroegop AV, Vanderveken OM, Van de Heyning PH, Braem MJ. Effects of vertical opening on pharyngeal dimensions in patients with obstructive sleep apnoea. *Sleep Med* 2012;13:314-316.

[107] Lee CH, Kim JW, Lee HJ, Seo BS, Yun PY, Kim DY, et al.Determinants of treatment outcome after use of the mandibular advancement device in patients with obstructive sleep apnea. Arch Otolaryngol Head Neck Surg. 2010;136(7):

[108] Lee CH, Kim JW, Lee HJ, Yun PY, Kim DY, Seo BS, et al.An investigation of upper airway changes associated with mandibular advancement device using sleep videofluoroscopy in patients with obstructive sleep apnea. Arch Otolaryngol Head Neck Surg. 2009;135(9):

[109] Cistulli PA, Sutherland K. Phenotyping obstructive sleep apnoea - bringing precision to oral appliance therapy. J Oral Rehabil. 2019;46(12):

[110] Sutherland K, Takaya H, Qian J, Petocz P, Ng AT, Cistulli PA. Oral appliance treatment response and polysomnographic phenotypes of obstructive sleep apnea. J Clin Sleep Med. 2015;11(8):

[111] Chen H, Eckert DJ, Van Der Stelt PF, Guo S, Emami E, Almeida FR, et al.Phenotypes of responders to mandibular advancement device therapy in obstructive sleep apnea patients: a systematic review and meta-analysis. Sleep Med Rev. 2020;49()

[112] Dieltjens M, Braem MJ, Op de Beeck S, Vroegop AVMT, Kazemeini E, Van de Perck E, et al.Remotely controlled mandibular positioning of oral appliance therapy during polysomnography and drug-induced sleep endoscopy compared with conventional subjective titration in patients with obstructive sleep apnea: protocol for a randomized crossover trial. Trials. 2019;20(1):

[113] Lai V, Carberry JC, Eckert DJ. Sleep apnea phenotyping: implications for dental sleep medicine. J Dent Sleep Med. 2019;6(2):

[114] Lee GS, Kim HK, Kim ME. Risk factors for the efficacy of oral appliance for treating obstructive sleep apnea: a preliminary study. Cranio. 2018;36(6):

[115] Reissmann DR, Wolfart S, John MT, et al. Impact of shortened dental arch on oral health-related quality of life over a period of 10 years, a randomized controlled trial. J Dent. 2019 Jan;80:55–62. DOI:10.1016/j.jdent.2018.10.006.

[116] Moore C, McKenna G. In patients with shortened dental arches do removable dental prostheses improve masticatory performance? Evid Based Dent. 2016 Dec; 17(4):114. DOI:10.1038/sj.ebd.6401204

[117] Mintz SS, Kovacs R. The use of oral appliances in obstructive sleep apnea: a retrospective cohort study spanning 14 years of private practice experience. Sleep Breath. 2018;22(2):541–546.

[118] Sawyer AM, Gooneratne NS, Marcus CL, et al. A systematic review of CPAP adherence across age groups: Clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011;15:343-356. 10.1016/j.smrv.2011.01.003

[119] Sharples LD, Clutterbuck-James AL, Glover MJ, et al. Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. *Sleep Med Rev* 2016;27:108-124. 10.1016/j.smrv.2015.05.003

[120] Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med*2013;187:879-887. 10.1164/rccm.201212-2223OC

[121] Gagnadoux F, Fleury B, Vielle B, et al.Titrated mandibular advancement versus positive airway pressure for sleep apnoea. *Eur Respir J*2009;34:914-20. 10.1183/09031936.00148208

[122] Vanderveken OM, Dieltjens M, Wouters K, et al. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. *Thorax* 2013;68:91-6. 10.1136/thoraxjnl-2012-201900

[123] Almeida FR, Bansback N. Long-term effectiveness of oral appliance versus CPAP therapy and the emerging importance of understanding patient preferences. *Sleep*2013;36:1271-2. 10.5665/sleep.2938

[124] Almeida FR, Bansback N. Long-term effectiveness of oral appliance versus CPAP therapy and the emerging importance of understanding patient preferences. *Sleep*2013;36:1271-2. 10.5665/sleep.2938

[125] Sutherland K, Vanderveken OM, Tsuda H, et al. Oral Appliance Treatment for Obstructive Sleep Apnea: An Update. *J Clin Sleep Med*2014;10:215-227.

[126] Luzzi V, Brunori M, Terranova S, Di Paolo C, lerardo G, Vozza I, Polimeni A. Difficult-to- treat OSAS: combined continuous positive airway pressure (CPAP) and mandibular advancement devices (MADs) therapy. A case report. Cranio 38:196-200, 2020. Doi: 10.1080/08869635.2018.1496628

[127] Sheats RD. Management of side effects of oral appliance therapy for sleep-disordered breathing: summary of American Academy of Dental Sleep Medicine recommendations. J Clin Sleep Med 2020;16:835.

[128] Marklund M, Braem MJA, Verbraecken J. Update on oral appliance therapy. Eur Respir Rev 2019;28.

[129] Sheats RD. Management of side effects of oral appliance therapy for sleep-disordered breathing: summary of American Academy of Dental Sleep Medicine recommendations. J Clin Sleep

Med 2020;16:835.

[130] Sheats RD. Management of side effects of oral appliance therapy for sleep-disordered breathing: summary of American Academy of Dental Sleep Medicine recommendations. *J Clin Sleep Med*. 2020;16(5):835.

[131] Fransson AM, Tegelberg A, Johansson A, Wenneberg B. Influece on the masticatory system in treatment of obstructive sleep apnea and snoring with mandibular protruding device: a 2-year follow up. Am J Orthod Dento-facial Orthop. 2004;126:687-693

[132] Sheats RD. Management of side effects of oral appliance therapy for sleep-disordered breathing: summary of American Academy of Dental Sleep Medicine recommendations. J Clin Sleep Med 2020;16:835.

[133] Fransson AMC, Benavente-Lundahl C, Isacsson G. A prospective 10-year cephalometric follow-up study of patients with obstructive sleep apnea and snoring who used a mandibular protruding device. Am J Orthod Dentofacial Orthop 2020;157:91-7.

[134] Doff MH, Finnema KJ, Hoekema A, Wijkstra PJ, de Bont LG, Stegenga B. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on dental side effects.
Clin Oral Investig 2013;17:475-482.

[135] Almeida FR, Henrich N, Marra C, et al. Patient preferences and experiences of CPAP and oral
appliances for the treatment of obstructive sleep apnea: a qualitative analysis. Sleep Breath 2013;17:659-666.

[136] Chen H, Lowe AA. Updates in oral appliance therapy for snoring and obstructive sleep apnea.
Sleep Breath 2013;17:473-486.

[137] Chen A, Burger MS, Rietdijk-Smulders M, Smeenk F. Mandibular advancement device: Effectiveness and dental side effects. A real-life study. Cranio 2020:1-10.

[138] Sheats RD. Management of side effects of oral appliance therapy for sleep-disordered breathing: summary of American Academy of Dental Sleep Medicine recommendations. *J Clin Sleep Med*. 2020;16(5):835.

[139] Dr. (F) H. Kares. FAAOP- Patientenaufklärung über die Behandlung mit einer Unterkieferprotusionsschiene. 2022

[140] Solanki N, Singh BP, Chand P, et al. Effect of mandibular advancement device on sleep bruxism score and sleep quality. J Prosthet Dent 2017;117:67-72.

[141] Jokubauskas L, Baltrusaityte A, Pileicikiene G. Oral appliances for managing sleep bruxism in
adults: a systematic review from 2007 to 2017. J Oral Rehabil 2018;45:81-95.

Pictures:

Picture 1: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. 2021. Accessed and downloaded 13th of April 2023.
http://prisma-statement.org

Picture 2: PD Dr. med Ladina Joos Zellweger. Pulsoximetrie. Aus dem Labor. 2014. Accessed and Downloaded on November 3rd 2022.
https://www.medline.ch/include_php/previewdoc.php?file_id=12069

Picture 3: Dechao Zhu, Wenjing Kang, Shilong Zhang, Haiyan Lu. Effect of mandibular advancement device treatment on HIF-1alpha, EPO and VEGF in the myocardium of OSA in rabbits. Accessed and Downloaded 13th of April 2023.
https://www.researchgate.net/publication/343484560_Effect_of_mandibular_advancement_device_treatment_on_HIF-1a_EPO_and_VEGF_in_the_myocardium_of_obstructive_sleep_apnea-hypopnea_syndrome_rabbits

Picture 4: What is the Mallampati Score? (2018): Myofunctional Therapy Excercises for Mouth Breathing, Sleep Apneas, Braces and Speech. Accessed and Downloaded on September 17th 2022. https://myfaceology.com/2018/10/mallampati-score/

Picture 5: Susarla et al. Cephalometric Measurement of Upper Airway Length. J Oral Maxillofac Surg 2010 Measurement of airway length in an obstructive apnea patient (lelft) nd non OSA patient (right). Assessed and downloaded on December 18th 2022.
https://www.researchgate.net/figure/Measurement-of-airway-length-in-an-obstructive-sleep-apnea-OSA-patient-left-and_fig5_46425656/actions#reference

Picture 6: Sm Banabilh, Suzina Sheikh ab hamib, Zamzil Amin Asha'ari. Prevalence of snoring and craniofacial features in Malaysian children from hospital– based medical clinic population. Researchgate.2008. Accessed and Downloaded 13th of April 2023.
https://www.researchgate.net/publication/5867441_Prevalence_of_snoring_and_craniofacial_features_in_Malaysian_children_from_hospital-based_medical_clinic_population

Picture 7:Suleiman M. Momany MBBS. Ghaida' Alljamal BDS, MS. Bassam Shugaa-Addin BDS, MSc. Yousef S. Kadher BDS, MSc.Cone Beam Computed Tomography Analysis of Upper Airway Measurements in Patients with Obstructive Sleep Apnea 2016. Accessed and downloaded 18th of December 2022.
https://www.amjmedsci.org/article/S0002-9629(15)41033-X/fulltext

Picture 8: Eow PY, Lin KY, Kohli S, Math SY. Cone-beam computed tomography assessment of upper airway dimensions in patients at risk of obstructive sleep apnea identified using STOP-Bang scores. Assesed and downloaded 13th of April 2023.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8695467/

Picture 9: Stanford Medicine Otolaryngology – Head & Neck Surgery. Maxillomandibular Advancement & Orthognathic surgery. Accessed and Downloaded on 18th of December 2022. https://med.stanford.edu/ohns/OHNS-healthcare/sleepsurgery/treatments/skeletal_surgery.html

Picture 10: Coherent Market Insights. Continous Positive Airway Pressure (CPAP) Interface devices Market 2019-2027. Future Gerowth by Top Players Salter Labs, medin Medical Innovations GmbH, Teleflex Inc., Circadiance, Invacare Inc., ResMed Inc. Accessed and downloaded on 18th of December 2022. https://www.openpr.com/news/1792587/continuous-positive-airway-pressure-cpap-interface-devices

Picture 11: Kate Sutherland,Peter A. Cistulli. Oral Appliance Therapy for Obstructive Sleep Apnoea: State of the Art. J. Clin. Med. 2019. Accessed and downloaded on September 30th 2022. https://www.mdpi.com/2077-0383/8/12/2121/htm

Picture 12 : BluePro Temporary Appliance: ClinicalProfile. Dental Sleep Practise. Accessed and Downloaded on October 3rd 2022. https://dentalsleeppractice.com/bluepro-temporary-appliance-clinical-profile/

Picture 13: Shadi Basyuni, Michael Barabas. An update on mandibular advancement devices for the treatment of obstructive sleep apnoea hypopnea syndrome. Journal of Thoracis Diseases 10(S1):S48-S56.2018. Accessed and downloaded on October 28th 2022. https://www.researchgate.net/publication/322669440_An_update_on_mandibular_advancement_devices_for_the_treatment_of_obstructive_sleep_apnoea_hypopnoea_syndrome