UNIVERSIDADE FERNANDO PESSOA

LONG-TERM SIDE EFFECTS OF MANDIBULAR ADVANCEMENT DEVICES IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA – NARRATIVE REVIEW

[Efeitos colaterais a longo prazo dos dispositivos de avanço mandibular em pacientes com apneia obstrutiva do sono – revisão narrativa]

Master's Thesis

[Integrated Master's in Dental Medicine]

Léa Louise Antoinette Legros

Supervisor:

Master Joana Sardinha

June 2024

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For everyone who supported me throughout this year

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ABSTRACT

Obstructive sleep apnea syndrome (OSAS) is estimated to impact approximately one-seventh of the world's adult population, spanning from mild to severe apnea. Common symptoms are loud snoring, compromised sleep quality, oral dryness, daytime drowsiness, and headaches. OSAS can lead to more severe complications, such as anxiety, depression, cardiovascular issues, metabolic disorders like type 2 diabetes or cerebrovascular incidents.

The gold standard for addressing sleep apnea is the use of continuous positive airway pressure (CPAP). However, some patients may have difficulty tolerating or responding positively to this treatment. Among the available treatment modalities, mandibular advancement devices (MAD) offer a therapeutic alternative. These devices work by repositioning the mandible forward thereby optimizing airflow to the lungs.

The MAD can be recommended in situations such as snoring, mild and moderate obstructive sleep apnea syndrome without additional health conditions, patient intolerance or refusal of CPAP use, or individuals who frequently travel, especially to underdeveloped countries without electricity. Despite being considered effective for patients with mild to moderate obstructive sleep apnea, its use is not without adverse effects. Up to 80% of patients using MAD report experiencing undesirable outcomes. The effects can be categorized into short-term and long-term, with our focus directed towards the latter.

This study aims to investigate the side effects associated with the prolonged use of mandibular advancement devices in patients with obstructive sleep apnea.

Keywords: "long term"; "side effects"; "mandibular advancement device"; "adult"; "obstructive sleep apnea".

RESUMO

A síndrome da apneia obstrutiva do sono (SAOS) estima-se que afete aproximadamente um sétimo da população adulta mundial, variando de apneia leve a grave. Os sintomas comuns são ronco alto, comprometimento da qualidade do sono, boca seca, sonolência diurna e dores de cabeça. A SAOS pode levar a complicações mais graves, como ansiedade, depressão, problemas cardiovasculares, distúrbios metabólicos como diabetes tipo 2 ou incidentes cerebrovasculares.
A abordagem reconhecida como padrão ouro no tratamento da apneia do sono envolve o uso de pressão positiva contínua nas vias aéreas (CPAP). No entanto, um subconjunto de pacientes pode enfrentar dificuldades em tolerar ou responder positivamente a esse tratamento. Entre as modalidades de tratamento disponíveis, o dispositivo de avanço mandibular (DAM) é uma alternativa terapêutica. Esses dispositivos visam reposicionar a mandíbula para a frente, otimizando o fluxo de ar para os pulmões. O DAM pode ser recomendado em situações como ronco, apneia obstrutiva do sono leve a moderada sem condições adicionais de saúde, intolerância ou recusa do uso de CPAP pelo paciente, ou para indivíduos que viajam frequentemente, como para países subdesenvolvidos sem eletricidade. Apesar de ser considerado eficaz para pacientes com apneia obstrutiva do sono leve a moderada, seu uso não é isento de efeitos adversos. Até 80% dos pacientes que utilizam o DAM relatam experienciar resultados indesejáveis. Os efeitos podem ser categorizados em curto prazo e longo prazo, sendo nosso foco direcionado para este último.

O objetivo deste estudo é investigar os efeitos colaterais associados ao uso prolongado de dispositivos de avanço mandibular em pacientes com apneia obstrutiva do sono.

Palavras-chaves: “longo prazo”; “efeitos colaterais”; “dispositivo de avanço mandibular”; “adulto”; “apneia obstrutiva do sono”

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ABBREVIATIONS AND ACRONYMS

AADSM: American Academy of Dental Sleep Medicine

AASM: American Academy of Sleep Medicine

AHI: Apnea-Hypopnea Index

AI: Apnea Index

ANB: Angle of difference between SNA and SNB

CAD: Computer Aided-Design

CAM: Computer Aided-Manufacturing

CPAP: Continuous Positive Airway Pressure

DISE: Drug-Induced Sleep Endoscopy

ESS: Epworth Sleepiness Scale

L1-MP: Angulation of the lower incisors in relation to the mandibular plane

MAD: Mandibular Advancement Device

NSAID: Non-Steroidal Anti-Inflammatory Drugs

OA: Oral Appliances

OB: Overbite

ODI: Oxygen Desaturation Index

OJ: Overjet

OSA: Obstructive Sleep Apnea

OSAS: Obstructive Sleep Apnea Syndrome

PSG: Polysomnography

QOL: Quality of Life

QSQ: Quebec Sleep Questionnaire

SNA: Angle referring to maxilla position in relation to the cranial base

SNB: Angle referring to mandible position in relation to the cranial base

TMD: Temporomandibular Disorder

TMJ: Temporomandibular Joint

1. INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a prevalent disorder characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, resulting in repeated respiratory disturbances (Evan Cumpston, 2023). These interruptions in breathing, known as apneas and hypopneas, can occur numerous times throughout the night, leading to fragmented sleep patterns and a host of debilitating symptoms. OSAS affects approximately 936 million people worldwide, with a prevalence ranging from 9% to 38% in adults, depending on factors such as sex, age, and underlying health conditions (Benjafield, et al., 2019).

The severity of obstructive sleep apnea (OSA) is typically assessed using the apnea-hypopnea index (AHI), which quantifies the frequency of apneas and hypopneas per hour of sleep. The American Academy of Sleep Medicine (AASM) grades OSA severity as mild (AHI=5-14.9 events/hour), moderate (AHI=15-29.9 events/hour), or severe (AHI≥30 events/hour) (Kapur, et al., 2017). However, other physiological indicators such as oxygen desaturation index (ODI), heart rate variability, arousal, sleep stage, and body position should also be considered when assessing OSA diagnosis (Soori, et al., 2022).

Various treatment options are available for OSA, including lifestyle modifications, Continuous Positive Airway Pressure (CPAP) therapy, surgical interventions, and oral appliances. Among these, mandibular advancement devices (MAD) have emerged as a promising non-invasive alternative to CPAP for patients with OSA (Ramar, et al., 2015). However, the long-term use of MAD is not without risks, and a balance must be struck between efficacy and side effects to ensure optimal treatment outcomes and patient compliance (Ng & Yow, 2020).

This study aims to investigate the extended use of MAD in patients with OSA and assess whether the benefits outweigh the long-term risks, thus providing insight into the suitability of this treatment approach.

2. MATERIALS AND METHODS

For this narrative review, the following digital databases were utilized: PubMed and Google Scholar. The bibliographic search was conducted between October 2023 and March 2024. The keywords used were: “Obstructive sleep apnea”; “Mandibular advancement device”; “side effects”; “adult”; and “long term” which were combined using boolean operators "AND" and "OR" to combine the keywords. Inclusion criteria incorporate articles published in English or French, released post-2000 (with limited exceptions), and those accessible without supplementary expenses. Exclusion criteria relate to articles published in languages other than English or French, published before 2000, concentrating on pathologies unrelated to OSAS, and those that are inaccessible. After applying the inclusion and exclusion criteria, 345 articles were found, with 32 on the PubMed platform and 313 on the Google Scholar platform. Duplicate versions were excluded, resulting in 334 articles. After screening titles and abstracts, 255 articles were excluded, yielding a total of 79 articles. Among these, after full-text reading, 63 articles were used for the development of this narrative review. The inclusion of 35 other articles was necessary for the final drafting, totaling 98 articles.

3. DEVELOPMENT

3.1 Obstructive Sleep Apnea

Obstructive Sleep Apnea (OSA) is a complex disorder with significant implications for an individual's health and well-being. It is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, which results in repeated respiratory disturbances and causes both immediate symptoms and lasting physiological effects (Evan Cumpston, 2023). These interruptions in breathing can lead to a host of debilitating symptoms ranging from snoring to significant implications for cardiovascular health, mental illness, quality of life (QOL), and driving safety (Slowik, et al., 2022).

OSA is notably more common among men, older individuals, and those with certain predisposing factors including obesity, anatomical anomalies of the upper airway, and a family history of sleep apnea (Punjabi, 2008). Lifestyle factors such as smoking, excessive alcohol consumption, unhealthy dietary habits, and sedative medication use can further increase the risk of developing OSA. In the case of alcohol, its consumption reduces muscle tone in the upper airway, leading to more frequent apneas and shallow breathing episodes during sleep. It also extends the duration of these respiratory events by delaying awakening, while also serving as a significant calorie source (Verbraecken, et al., 2022).

Obesity and being overweight are prevalent factors tightly linked to OSA. One key mechanism is the deposition of excess adipose tissue, particularly in the upper body and neck region, leading to the narrowing and collapse of the upper airway during sleep. Additionally, obesity is associated with alterations in respiratory mechanics, including decreased lung volumes and impaired diaphragmatic function, which further exacerbate airway collapsibility (Schwartz, et al., 2008).

Diagnosis of OSA typically involves obtaining a comprehensive medical and sleep history, conducting a physical examination focusing on characteristics suggestive of OSA, and potentially utilizing tools like awake endoscopy or drug-induced sleep endoscopy.

Polysomnography (PSG) remains the gold standard for diagnosing OSA, assessing its severity, and guiding treatment decisions according to established diagnostic criteria (Parenti, et al., 2019). PSG involves monitoring multiple physiological variables simultaneously during sleep, including brain activity (electroencephalography), eye movements (electrooculography), muscle activity (electromyography), airflow (nasal and oral airflow sensors), thoracic and abdominal movements (respiratory effort belts), oxygen saturation (pulse oximetry), and sometimes electrocardiography. These recordings enable the identification and quantification of apneas and hypopneas, along with associated oxygen desaturation and arousals from sleep (Markun & A, 2020).

Treatment approaches for OSA are diverse and often tailored to the individual patient's needs, severity of symptoms, and underlying health factors. As a first response to OSA patients, behavioral therapy and lifestyle modifications should be considered before any other treatment methods. Weight loss should be the primary action against OSA in obese patients as it has been shown to reduce AHI (Hudgel, et al., 2018). Unfortunately, lifestyle modifications don't always suffice in treating OSA, and other measures need to be taken (Verbraecken, et al., 2022).

Continuous Positive Airway Pressure (CPAP) therapy stands out as a gold standard approach for most individuals with moderate to severe OSA. CPAP delivers a continuous stream of pressurized air through a mask worn over the nose or both nose and mouth, thereby preventing upper airway collapse and maintaining unobstructed breathing during sleep. Despite its proven efficacy in reducing the frequency of apneic events and improving daytime symptoms, CPAP adherence remains a challenge for some patients due to issues such as discomfort, mask intolerance, or perceived inconvenience (Randerath, et al., 2021). Its effectiveness is potentially high, but considering the rather low acceptance and compliance, its actual effect and use remain relatively low, encouraging the search for reliable alternatives to CPAP in selected groups (Verbraecken, et al., 2022).

Surgical interventions offer an alternative option for individuals with anatomical abnormalities contributing to airway obstruction or those who cannot tolerate CPAP therapy.

The interventions can involve nasal surgery, palatal surgery, or even skeletal surgery. A commonly performed surgery for OSA is uvulopalatopharyngoplasty, which involves the removal of redundant tissue of the soft palate and uvula in addition to tonsillectomy. Maxillomandibular advancement is another surgical option offered to patients with OSA who are unable to tolerate CPAP or who have failed other surgical interventions. The aim is to widen the upper airway or reposition the jaw to alleviate obstruction, often resulting in significant improvements in sleep quality and daytime functioning. However, surgery is typically reserved for patients with severe OSA or those who fail to respond to conservative treatments (Suurna & Krieger, 2021).

In recent years, oral appliances have emerged as a promising non-invasive treatment option that has been progressively recommended with each iteration of the American Academy of Sleep for treating OSA for patients who do not tolerate or choose not to accept CPAP therapy (Ramar, et al., 2015). The most frequently prescribed type of oral appliance is the mandibular advancement device (MAD), which represents the main non-invasive alternative to CPAP for patients with OSA. These devices are worn intraorally at night and work by advancing the lower jaw forward during sleep, thereby preventing airway collapse and improving airflow. These oral appliances, custom-fitted by dental professionals and available in different varieties, can offer greater comfort and practicality compared to CPAP machines, though they may not be suitable for all patients (Verbraecken, et al., 2022).

Oral appliances (OA) have been shown to be the first line of therapy in adult patients with primary snoring, mild and moderate OSA, and in patients with severe OSA who are intolerant of or refuse treatment with nasal continuous positive airway pressure. For some patients, combination therapy with other treatments such as weight loss, surgery, and CPAP may be indicated, and this must be coordinated by the attending sleep physician (Almeida & Lowe, 2009).

Though effective, the use of MAD is not without risks. A balance must be struck between efficacy and side effects because an increase in adverse effects can reduce long-term

compliance, potentially leading patients to terminate MAD therapy prematurely. Adverse effects caused by MAD typically include dental alterations, changes in occlusion, craniofacial changes, temporomandibular disorders (TMD), as well as milder effects such as increased salivation, tongue discomfort, and a sense of suffocation (Ng & Yow, 2020).

Despite the diverse treatment options available for OSA, individualized care plans tailored to patient preferences, severity of symptoms, and underlying health factors are essential to optimizing treatment outcomes and enhancing overall quality of life (QOL). With the increasing interest in MAD as a treatment option for obstructive sleep apnea, there arises a need to explore the potential long-term side effects associated with their use.

3.2. Mandibular advancement device (MAD) as a treatment method

3.2.1. Historical introduction

The first reference to oral appliance therapy was introduced by Pierre Robin (1867-1950), a French physicist and dentist. In January 1923, while practicing at the Children's Hospital in Paris, Pierre Robin presented a case to the Academy of Medicine regarding a new cause that prevented pure nasal breathing. This obstruction was attributed to the base of the tongue pressing against the epiglottis, thereby closing the opening of the larynx—an issue Robin termed "glossoptosis."

Robin's observations revealed that adenoidectomy didn't always resolve mouth breathing, suggesting an alternative underlying cause of this problem. He found that airway obstruction ceased when the jaw was extended forward and lips kept open, distinguishing it from nasopharyngeal obstruction. Robin proposed using a monobloc (one-piece) functional oral appliance, hinting at future orthodontic treatments for obstructive sleep apnea in the 1980s (Demko, 2018).

Unfortunately, his method proposed in 1934 was not widely accepted. It was not until 1985 with Meier-Ewert and colleagues, that another intraoral protraction device was considered

for treating sleep apnea. Subsequently, there was an increase in articles discussing the therapeutic efficacy of using oral appliances to treat obstructive sleep apnea (OSA), legitimatizing them as an alternative to surgical treatment.

The oral appliances studied predominantly consisted of one-piece, hard acrylic, nonadjustable advancement appliances, as they were the most common type at the time (Warunek, 2004). However, the one-piece appliances were often described as uncomfortable. To address this concern, Lyon and colleagues developed a silicone orthodontic one-piece positioner in 1992 which proved to increase patient comfort for those suffering from snoring and mild to moderate sleep apnea (Lyon, et al., 1992). Although more comfortable, the use of silicone made them more prone to tearing especially when they were used in combination with embedded wires or clasps.

Furthermore, one-piece appliances could be ineffective due to limited mandibular movement and difficulty adjusting the amount of mandibular advancement. This limitation often resulted in a higher rate of refabrication. To overcome this issue, a two-piece appliance was developed by Rider in 1988 utilizing the Herbst appliance, to increase flexibility and adjustability (Warunek, 2004).

In 1995, the American Sleep Disorders Association published the first set of practice guidelines for the use of oral appliances in the treatment of snoring and obstructive sleep apnea (Thorpy, et al., 1995). With the proliferation of research on mandibular advancement devices (MAD) over the years, dentists now have access to a wide variety of materials and designs, allowing them to tailor solutions to each patient's unique needs. From traditional acrylic appliances to more modern heat-softening acrylic appliances and adjustable features, the evolution of MAD has revolutionized the treatment landscape for obstructive sleep apnea. This versatility enables dentists to craft personalized MAD that optimize effectiveness, comfort, and compliance, representing a significant advancement in personalized care for sleep-disordered breathing. Customized adjustable MAD have been demonstrated to be more effective in treating OSA compared to universal over-the-counter models. They achieve

similar reductions in apnea-hypopnea index (AHI) while enhancing arterial oxygen saturation (SaO2) and show a modest improvement in Epworth Sleepiness Scale (ESS) scores, a measure of daytime sleepiness (Ng & Yow, 2020; Suurma & Krieger, 2021).

3.2.2. Types of MAD and their mechanism of action

MAD can generally be divided into two groups: adjustable and non-adjustable. The non-adjustable models often referred to as boil-and-bite appliances, are simpler in design. They consist of a hard prefabricated outer shell filled with a thermoplastic material. When heated and inserted into the mouth, this material takes the impression of the dental arch, providing a customized fit. SnoreGuard is an example of such a device. For these one-piece non-adjustable devices, the amount of advancement is predetermined, either by the bite registration record or the in-office molding process (Clark, 1998). While the degree of protrusion in both one-piece and two-piece appliances may be similar, the key distinction lies in the ability to open the jaw. In a one-piece device, the mandible is held in a fixed anterior position, limiting jaw movement (Heidsieck, et al., 2018).

On the other hand, the Herbst appliance is an example of an adjustable MAD that precisely adjusts jaw positioning to optimize airway patency while maintaining a degree of jaw mobility. It features bilateral connectors that link the upper and lower dental arches through a compression-style attachment. This mechanism employs telescopic rods and screws, enabling gradual protrusion of the mandible. As a result, it functions as an efficient customizable device. Since their invention in the 1980s, the Herbst devices have been among the most extensively studied systems for decades. They have demonstrated efficiency comparable to other more classic devices such as monoblocs or traction-styled two-piece devices. However, they have been associated with statistically greater pain, primarily due to increased vertical opening. Nonetheless, the intensity of this pain has not been significant clinically (Vezina, et al., 2011; Amoric, 2013). Furthermore, due to its capacity for a wider opening of the jaw compared to a one-piece appliance, the tongue tends to rotate posteriorly,

impacting the effectiveness of the device in addressing obstructive sleep apnea (OSA). In this context, findings from a randomized controlled crossover trial demonstrated that monoblocs were found to be preferred over two-piece Herbst appliances, despite the latter being considered more contemporary. Notably, both devices were made of hard acrylic. This study, conducted in 2000, may yield different results if the devices were reevaluated today, given the advancements in mandibular application manufacturing since then (Bloch, et al., 2000).

Nowadays, advancements in materials science have broadened the spectrum of compounds utilized in the fabrication of these appliances. This includes heat-softening acrylics, resin acrylics like control cured poly (methyl methacrylate) (PMMA), thermoplastics such as Laser-sintered polyamide 12 body, or plastic with soft liners (Warunek, 2004) (Dioguardi & Al-Halawani, 2016). The integration of Computer-Aided Design (CAD) and Computer-Aided Manufacturing (CAM) technology has revolutionized the production of MAD, allowing for more precise and customized designs. This digital workflow enables the creation of highly accurate 3D models of patients' dental arches, facilitating the design of MAD that fit more comfortably and functions more effectively (Vanderveken et al., 2012).

Regarding design features, two-piece appliances can incorporate various components such as metallic rods and tube fittings, inter-arch elastic, metal or plastic connectors, or even magnets, all depending on the desired degree of mandibular protrusion (Barewal & Hagen, 2014). CAD/CAM technology allows for the precise integration of these components, ensuring optimal functionality and patient comfort. Studies indicate that customized and adjustable MAD, particularly those produced using CAD/CAM technology, generally exhibit superior efficacy compared to non-adjustable MAD. Non-adjustable MAD often require more frequent refabrication if the initial mandibular advancement calibrations are not accurately calculated (Almeida & Lowe, 2009; Dioguardi & Al-Halawani, 2016). The use of CAD/CAM in MAD production not only improves the accuracy of fit but also allows for easier adjustments and modifications, potentially reducing the need for frequent replacements (Vanderveken et al., 2012).

The use of a MAD in sleep apnea treatment relies on its capacity to alleviate airway obstruction by advancing the lower jaw and repositioning the tongue. This forward movement of the mandible works to enlarge the upper airway dimensions, particularly in the velopharyngeal region (Barewal & Hagen, 2014). By extending the lower jaw, the MAD stretches the soft palate, thus stiffening the velopharyngeal segment and reducing its collapsibility during sleep (Liu, et al., 2001). Additionally, the MAD helps resist the downward rotation and retrusion of the mandible that occur during sleep, further promoting upper airway patency. Collectively, these mechanisms contribute to improved airflow and decreased obstruction during sleep, making MAD an effective treatment option for sleep apnea and snoring (Verbraecken, et al., 2022).

3.2.3. Indications and contraindications

Although CPAP (Continuous Positive Airway Pressure) therapy has long been regarded as the primary treatment for obstructive sleep apnea (OSA), it is not always suitable for every patient. In cases where CPAP treatment shows poor compliance, or when patients have difficulty adapting to or rejecting CPAP therapy, a mandibular advancement device (MAD) should be considered as an alternative treatment option. Moreover, the recent guidelines by the American Academy of Sleep Medicine (AASM) and the American Academy of Dental Sleep Medicine (AADSM), recommend the use of MAD as primary treatment in a few select cases. These include patients requesting treatment for primary snoring who do not respond well to behavioral treatment as well as those with mild OSA or moderate OSA with lower body mass index and who process no significant nasal airway compromise (Barewal & Hagen, 2014). In some cases, a combination of MAD and CPAP may be recommended before committing fully to either treatment or until a sustainable and adapted plan is elaborated for the patient. Additionally, in cases of mild to moderate OSA, patients may experience some common symptoms such as persistent snoring, isolated episodes, nocturnal asphyxia or poor

sleep quality that are not adequately addressed by CPAP therapy. These patients may be suitable candidates for MAD instead (Sampol Rubio, et al., 2018).

Before using MAD, it is crucial to consider several factors. Studies typically exclude edentulous patients or those with insufficient teeth, suggesting a minimum of 10 teeth per arch or at least one premolar or molar per quadrant to ensure adequate device retention. Additionally, limited mandibular protrusion capacity (less than 6 mm) and periodontal disease serve as contraindications in OSA treatment (Cistulli, et al., 2004). Whether active or inactive, the elevated probability of tooth mobility resulting from periodontal disease affects the anchoring of the device, rendering it unstable and consequently ineffective. The efficacy of MAD depends on significant mandibular repositioning, leading to exclusion criteria such as temporomandibular ankylosis, craniomandibular dysfunctions, active pain or even bruxism, which can cause accelerated wear of the appliance and heightened discomfort. However, a clinical evaluation is necessary as temporomandibular dysfunction (TMD) is not necessarily a contraindicating to the use of a MAD, although exceptions may exist based on individual cases (Cohen-Levy, et al., 2009). Previously stated criteria are based on the presence of diseases or conditions that hinder the proper physiology of the oral cavity, yet another factor to consider is the possible anatomical alterations. In patients with mandibular tori, macroglossia or pronounced retrognathia, the use of a MAD can be significantly impacted, or even impossible (Barewal & Hagen, 2014).

3.3. Short-term effects of MAD

3.3.1. Improvement in sleep parameters

When using mandibular advancement devices (MAD) to treat obstructive sleep apnea (OSA), some sleep parameters show rapid improvements and noticeable changes can be observed within the first few months of treatment. When the device is well-suited to the patient's needs, it can result in an immediate enhancement in oxygenation during sleep, leading to higher oxygen levels and a more relaxed physiological state. This improvement is not only

significant but also critical, as it affects overall health and well-being. Consequently, nearly 90% of MAD users, regardless of the severity of their OSA, report experiencing deeper, more restful sleep with fewer awakenings. This restful sleep translates into greater daytime energy and increased activity, enhancing overall quality of life (QOL). Additionally, MAD users feel more alert and engaged in their daily tasks, a significant contrast to their pre-treatment state (Pliska & Almeida, 2012).

Objectively, multiple clinical studies corroborate these positive short-term effects, providing a strong basis for encouraging long-term adherence to MAD therapy. This efficacy can be monitored using several key indicators, including the Apnea-Hypopnea Index (AHI), the Epworth Sleepiness Scale (ESS) score, and arterial oxygen saturation (SaO2). For example, in one study, 62% of patients suffering from excessive daytime sleepiness experienced a full recovery from this symptom after using a MAD. Such a high percentage underscores the effectiveness of the device. A notable reduction in the AHI, which measures the severity of sleep apnea, can also be expected a few months after the initiation of the treatment. This reduction is often accompanied by a decrease in snoring and an enhancement in arterial oxygen saturation (SaO2), both of which are critical indicators of improved sleep quality and overall health (Vecchierini, et al., 2016).

Furthermore, the psychological benefits of improved sleep cannot be overstated. Enhanced sleep quality leads to better mental health, reducing symptoms of anxiety and depression, which are commonly associated with chronic sleep disorders. Patients frequently report an improved mood and a more positive outlook on life, which can have far-reaching effects on personal and professional relationships. The increased daytime energy and activity levels contribute to a more active lifestyle, further promoting health, potentially reducing the risk of comorbidities associated with OSA, such as cardiovascular diseases and metabolic disorders (Pliska & Almeida, 2012).

3.3.2. Tolerance and compliance

It is also important to understand the factors or variables that can affect and influence the treatment modality of MAD. Tolerance and compliance are two critically important factors that impact patient outcomes. Compliance refers to how well a patient's behavior aligns with medical or health advice. Meanwhile, tolerance involves the body's ability to avoid negative reactions to treatments, often demonstrated by the capacity to endure higher levels of discomfort without experiencing adverse symptoms. Specifically, "compliance" evaluates how consistently a patient uses an oral appliance, while "tolerance" assesses the psychological differences observed between users and non-users of these external appliances. In summary, both compliance and tolerance play pivotal roles in determining the success of treatments involving oral appliances. While compliance is a measure of how diligently a patient follows prescribed usage, tolerance indicates how well a patient can adapt to and sustain the use of the appliance without significant discomfort. Understanding and optimizing these factors can lead to better patient outcomes and more effective treatment strategies. (Cameron, 1996) In most studies, patients using MAD report high tolerance and compliance levels to the device (Chen, et al., 2008; Esteller-Moré, et al., 2010; Brette, et al., 2012; Chen, et al., 2008).

One study indicates that intolerance is a significant predictor of long-term MAD use. Specifically, 15% of patients who continued using the MAD reported intolerance, whereas 38% of patients who discontinued its use experienced intolerance. The statistical analysis reveals a p-value of 0.0006, underscoring the significance of this finding. Therefore, addressing and alleviating intolerance is crucial for improving patient adherence to MAD therapy in the long term. Effective management of intolerance could lead to higher retention rates and better overall outcomes for patients undergoing MAD treatment for obstructive sleep apnea. (Attali, et al., 2016)

Compliance is usually assessed through a questionnaire completed by the patients. Multiple studies on self-assessed compliance have shown a range from 76 to 95% for MAD therapy

and usually attest to patient satisfaction (Hammond, et al., 2007) (Vezina et al., 2011). One study in particular reported a 95.8% subjective compliance rate (Vecchierini, et al., 2016). More recent data indicates that subjective and objective long-term compliance rates with MAD therapy are similar. In most patients, but specifically younger patients, compliance is higher for MAD therapy than CPAP treatment (Rose, et al., 2002). Consequently, while CPAP remains the preferred treatment method in severe OSA cases, improved long-term adherence to MAD therapy could potentially reduce disparities between its clinical effectiveness compared to CPAP (Vecchierini, et al., 2016). Therefore, selecting appropriate candidates for these treatments can be critical for improving overall compliance success rates; avoiding unnecessary exclusions based on favorable patient profiles may help mitigate nonadherence issues (Amoric, 2013).

3.3.3. Adverse events in short-term use

Short-term use of MAD can lead to several side effects, including increased salivation or dry mouth due to stimulation of the salivary glands or mouth breathing, respectively. Patients frequently report discomfort in the teeth or gums due to the appliance, which is typically temporary and diminishes as they adapt to the device. The perception of an abnormal bite is also common, as the appliance can alter how the upper and lower teeth meet, causing temporary misalignment and chewing difficulties. These side effects frequently contribute to patients discontinuing treatment within the first year. There are two potential reasons why patients are likely to discontinue treatment; if they fail to achieve the desired therapeutic effect or if they experience significant side effects. For those reasons, it is necessary to establish continuous monitoring by dentists to proactively manage the emerging side effects and bring potentially adjust the device as well as keeping the patient motivated to continue the treatment (Cistulli, et al., 2004). Other common short-term effects of MAD treatment include complaints of pain in the temporomandibular joint, the jaw muscles and the teeth. (Frasson, et al., 2020)

MAD can cause mild and transient temporomandibular disorder symptoms in the short term, possibly due to muscle strain in the temporomandibular complex or increased occlusal vertical dimension during sleep. Concerning the temporomandibular joint, some joint clicking referred to as reciprocal click or crepitus can also be observed (Knappe, et al., 2017)

In the short term (up to one year), MAD use can cause significant dental changes (Martins, et al., 2018). Robertson et al. found reductions in overbite and overjet, and a decrease in maxillary arch length after six months. These changes result from the appliance's direct action on the incisors, leading to retroclination of the maxillary incisors and proclination of the mandibular incisors. Additionally, Robertson et al. noted skeletal changes within six months of treatment, including small but significant increases in face height and a downward shift of the mandible. By the 12-month follow-up, the primary change observed was the downward displacement of the mandibular symphysis. These skeletal alterations are largely attributed to dental changes induced by the appliance (Roberston, et al., 2003)

Despite these adverse events, it is essential to understand that they are usually minor and transient, resolving with appropriate dental follow-up except for headaches, joint noises and some muscle pains that tend to worsen with age. (Hamoda, Almeida & Pliska, 2019) Continuous follow-up and adjustment of the appliances are crucial to maximize the therapeutic effects on snoring and other OSA symptoms. Patients who do not achieve adequate treatment results are more likely to discontinue use and suffer more significant side effects (Araie, et al., 2018).

3.4. Long-term effects of MAD

3.4.1. Impact on the temporomandibular joint

While MAD effectively treats obstructive sleep apnea (OSA) by repositioning the mandible forward, concerns about its effects on the temporomandibular joint have emerged in recent years and few studies have investigated the long-term effects. One study used a

biomechanical model of the human masticatory system to evaluate the biomechanical effects of a MAD on the temporomandibular joints. The biomechanical analysis revealed that MAD use does not significantly increase stress on the TMJ structures at rest, regardless of the extent of mandibular advancement. However, as the degree of advancement increases, jaw closure requires more muscle activity, suggesting that any temporomandibular pain might stem from altered muscle dynamics rather than increased joint stress (Heidsieck, et al., 2018)

Temporomandibular disorders (TMD) are characterized as a group of clinical problems involving the masticatory muscles, the temporomandibular joint, and associated structures. They should not be considered a contraindication for MAD use in treating OSA as no significant evidence has been found to suggest that TMD affects the long-term efficacy of the treatment (Näpänkangas, et al., 2012). When compared to a CPAP treatment, it has been found that the use of MAD often results in a higher incidence of pain-related TMD compared to CPAP therapy (24% versus 6%, respectively). This pain is more frequent during the first two years of therapy but typically does not limit TMJ function. No direct link has been found between the degree of mandibular protrusion or the frequency of MAD use and the occurrence of pain or functional impairment, indicating that pain is more related to initial adjustments rather than ongoing stress (Doff, et al., 2012). The MAD do not seem to have a negative impact on the temporomandibular joint's function and overall health even in long periods of time. If TMD-related pains are experienced in the early stages of MAD use, they usually diminish after the first 2 years of treatment (Martins, et al., 2018). This could be explained by a remodelling of the temporomandibular joint to better adapt itself to the new positioning of the mandible in its resting position (Cohen-Levy, et al., 2009).

Over time, MAD use leads to minor adaptive changes in the occlusion and TMJ, moving the mandible to a more inferior and anterior position. Joint sounds may fluctuate due to these adaptational changes, and habits such as lip and cheek biting, tooth clenching, and eating difficulties might develop. However, with regular monitoring, these changes appear to be less harmful than previously reported, as long-term follow-ups have shown a reduction in severe complications (Knappe, et al., 2017).

During these follow-up consultations, if the patient experiences undesired symptoms, common interventions include palliative care (such as applying topical or systemic pain relief products, massages, physiotherapy, and anti-inflammatory medication), a comprehensive TMD evaluation, adjusting the appliance, reducing the protrusion degree, decreasing titration rate, and performing isometric contraction and passive jaw stretching exercises (Sheats, 2020).

A 5-year follow-up study reported mild, temporary side effects like muscle or temporomandibular joint discomfort but no significant increase in TMD prevalence (Ng & Yow, 2020). Furthermore, comparative studies suggest that long-term MAD use does not lead to craniomandibular dysfunction or joint pain. Research, including a 2-year study by Bondemark (1999) and a 5-year study by Marklund (2015), indicates that MAD may improve pre-existing temporomandibular joint symptoms by acting as occlusal splints, preventing teeth grinding and improving jaw alignment (Bondemark, 1999; Vanderveken, et al., 2008). Additionally, a survey by Shadaba (2000) reported that patients who initially had TMJ problems experienced normalization in joint function after using MAD (Shadaba, et al., 2000).

In summary, while short-term use of MAD can initially cause TMD-related symptoms, these typically decrease within one to two years of continuous use. Long-term use of MAD does not cause significant craniomandibular dysfunction or persistent joint pain and may even improve symptoms in some patients.

3.4.2. Changes in dental occlusion and dentoalveolar impact

The long-term utilization of mandibular advancement devices (MAD) in the management of Obstructive Sleep Apnea (OSA) has been associated with various dental and occlusal changes. One of the most prominent alterations observed with prolonged MAD use is the inclination of the anterior teeth, notably the lower incisors. A meta-analysis conducted by Ng and Yow (2020) reported a significant increase in lower incisor inclination by 2.07 degrees,

which corresponded to a decrease in overjet (OJ) by 0.99 mm and overbite (OB) by 1.0 mm. These changes are more pronounced with longer treatment durations, leading to an increase in anterior crossbites, and mandibular arch width, as well as a reduction in lower arch crowding. Additionally, there can be an increase in maxillary arch width and upper arch decrowding, though these changes are less consistently reported (Ng & Yow, 2020).

Fransson and colleagues (2020) found similar results, noting that MAD use led to a significant decrease in both OJ and OB, with mean changes of -1.8 mm and -1.5 mm, respectively. These changes were more substantial in long-term users compared to those who ceased using the device, highlighting the progressive nature of these alterations. Moreover, a significant number of MAD users developed a misalignment of the posterior teeth, which was absent in those who discontinued the use of the appliance, indicating a clear shift in occlusion in users (Frasson, et al., 2020). Furthermore, there is a tendency towards the development of bilateral crossbites in the premolar region after long-term MAD use, attributed to the mesial shift in occlusion. This shift causes the broader part of the mandibular dental arch to occlude with the narrower part of the maxillary arch. These modifications usually go unnoticed by patients and tend to stabilize over time, creating a new occlusion (Doff, et al., 2010). While some of these changes may seem unfavorable, they can also lead to improvement in a patient's occlusion if the initial bite is abnormal. For instance, patients with a large initial overjet or a Class II occlusion may find their occlusion normalizing during treatment, resulting in a more favorable dental alignment. Conversely, patients with Class I or Class III occlusions with overbite may experience discomfort due to the forward traction of the lower incisors, which is a common reason for treatment cessation (Marklund, et al., 2019).

Cohen (2009) reported that between 10% and 69% of patients experienced discomfort or dental pain upon waking, with a significant proportion reporting temporary occlusal changes after removing the device. These changes often normalize throughout the day, likely due to muscle contractions. However, prolonged use of MAD can lead to more permanent tooth displacements and possible skeletal changes, like those seen with orthopedic devices. Interestingly, despite subjective impressions of stable occlusion, many patients exhibit

objective occlusal changes within six months of MAD placement (Cohen-Levy, et al., 2009). Fransson's review also supports the findings of decreased overjet and overbite showing continued MAD use, with a consistent reduction over time. These changes, driven by the anterior force exerted by the mandible's natural repositioning efforts, suggest that the dentoalveolar alterations are progressive and cumulative (Frasson, et al., 2020).

Furthermore, studies indicate that the use of MAD can lead to changes in dental arch characteristics, such as increased intercanine width and reduced mandibular arch crowding. These modifications are generally progressive, with initial rapid changes that gradually taper off over extended periods (Pliska & Almeida, 2012). The impact on occlusion is complex and varies among individuals, with some patients experiencing significant improvements in dental alignment, while others may develop or exacerbate malocclusions. As such, understanding these potential changes is crucial for clinicians in managing and counseling patients undergoing MAD therapy for OSA (Amoric, 2013).

3.4.3. Skeletal changes

Regarding skeletal changes due to MAD use in treating OSA, the literature presents mixed findings regarding the nature and extent of these skeletal alterations, reflecting a complex interplay between dental and skeletal modifications. Early reviews on the effects of MAD use in treating OSA observed occlusal changes and significant dental changes like decreased overjet, overbite, and increased lower incisor inclination as previously elaborated. No skeletal alterations were noted, and no study could conclusively determine long-term effects (Hoekema, et al., 2004; Araie, et al., 2018; Patel, et al., 2019). Conversely, Bartolucci and colleagues were the first to find significant skeletal changes in the ANB angle (relationship between the maxilla and mandible) and anterior facial height, along with the expected dental effects (Bartolucci, et al., 2019).

However, some of these reviews had small sample sizes, limited treatment durations, and did not consistently utilize comprehensive cephalometric analysis - the gold standard for

assessing dental and skeletal changes through lateral cephalograms and anatomic landmarks like SNA (maxilla position in relation to the cranial base), SNB (mandible position in relation to the cranial base), ANB, and L1-MP (angulation of the lower incisors to the mandibular plane) angles. A thorough cephalometric evaluation is crucial for accurately identifying MAD-induced alterations (Martins, et al., 2018). Numerous cephalometric studies have documented varying effects of long-term MAD therapy. These studies evaluate the relationship between the maxilla and mandible, as well as their respective positions relative to the cranial base, and record the changes in the ANB, SNA, and SNB angles. Some studies found the ANB angle slightly decreased, indicating improved maxillary-mandibular alignment. This was attributed to an increase in the SNB angle (prognathic mandibular positioning) without changes in SNA. These changes translate to a downward and forward positioning of the mandible (Bondemark, 1999).

Alternatively, Robertson et al. noted a reduction in the ANB angle attributed to a decreased SNA angle while SNB remained unchanged. This resulted in an increased mandibular plane angle, indicating a more downward positioning of the mandibula relative to the cranial base (Robertson, 2001). In other studies, mandibular positioning was found to be downward and backward (Ringqvist, et al., 2003), well others found no significant changes altogether in relation to mandibular positioning (Rose, et al., 2002; Hammond, et al., 2007; Wang, et al., 2015). Contrarily, other investigations have reported an increased ANB angle, suggesting a greater skeletal discrepancy between the jaws. This was attributed to either a decrease in SNB without SNA changes (Hamoda, et al., 2019), or a reduced SNB combined with unchanged SNA (Doff, et al., 2012). Therefore, the effects on maxillary-mandibular relationships and jaw positions varied across studies, likely influenced by different factors such as treatment duration, appliance design, and individual anatomic variability (Tsolakis, et al., 2022).

Increased lower and total anterior facial heights were consistently observed with MAD use, implying increased anterior facial dimensions. (Almeida, et al., 2006a). While most studies did not find significant changes in posterior facial heights (Doff, et al., 2010; Wang et al., 2015), some studies did report contrary findings (Roberston, et al., 2003).

Similarly, mandibular length remained largely unchanged across most studies (Ringqvist, et al., 2003; Hammond, et al., 2007), with the exception of Bondemark (1999), who noted an increase (Bondemark, 1999). Additionally, Fransson and colleagues (2020) initially found no change after 2 years, but observed increases in mandibular length with extended 10-year treatment duration, even in patients who had discontinued therapy (Frasson, et al., 2020). Regarding maxillary length, it was found to remain unchanged, with no significant increase in size (Doff, et al., 2010).

Furthermore, MAD therapy may affect the positioning of the hyoid bone, with some studies reporting more inferior hyoid positions relative to mandibular and occlusal planes-a change that persisted even after discontinuation (Frasson, et al., 2020)

It is important to note that skeletal changes are not specific to MAD treatment but can also be noticed in users of CPAP machines. Studies have shown that long-term use of nasal CPAP masks, especially in children and adolescents, can result in mid-facial hypoplasia or reduced facial growth due to the pressure exerted by the mask on the malleable nasal, zygomatic, and maxillary areas. Even in adults, prolonged CPAP use has been associated with changes in craniofacial form, including reduced maxillary and mandibular prominence (Ghadiri, et al., 2020).

Despite conflicting findings across studies, the potential for both dental and skeletal alterations with long-term MAD use necessitates thorough follow-up to manage and mitigate any adverse effects on the craniofacial complex. Additionally, more long-term studies utilizing comprehensive cephalometric evaluations are required to accurately assess these changes (Tsolakis, et al., 2022).

3.4.4. Effects on the oral soft tissues

The soft tissues play an essential role in the treatment of OSA when using mandibular advancement devices (MAD). The appliance anchors itself on the teeth and applies forces on

the hard and soft tissues by forcing the mandible forward. This action stretches the pharyngeal soft tissues facilitating better air passage and improving airflow during sleep (Cohen-Levy, et al., 2013). The MAD increases the pharyngeal airway diameter more laterally than sagittally, at both retropalatal and retrolingual levels. The clockwise mandibular rotation and increased vertical dimension activate the genioglossus muscle, pulling the tongue forward and superiorly to prevent backward collapse during sleep. This initially stiffens the pharyngeal walls and widens the gap between the anterior and posterior pharyngeal pillars. The tensed palatopharyngeal and palatoglossal muscles subsequently reduce soft tissue vibration, further enhancing airway patency (Hoekema, et al., 2004). This reduction in soft tissue vibrations not only diminishes snoring but also allows for decreased edema and a roughly 10% increase in pharyngeal volume after 2 years of MAD treatment in patients with snoring and obstructive sleep apnea patients, as revealed by lateral cephalograms. The soft palate region in particular exhibits about 50% less soft tissue edema as the frequency and intensity of vibrations decrease with effective treatment. By tensing the musculature to minimize vibrations, mandibular advancement therapy can reduce edema and increase the pharyngeal airway space for these patients (Warunek, 2004). As a result, the soft palate thins and shortens allowing for a greater flexibility of the head, while the pharynx widens (Fransson, et al., 2002).

Forces generated during mandibular protrusion primarily result from the viscoelasticity of soft tissues rather than reflex phasic contraction of the elevator muscles like the masseter and temporalis. The soft tissues surrounding the jaw joints and involved in jaw movement have inherent viscoelastic properties, allowing them to store and dissipate energy upon deformation. Although reflexive muscle contractions attempting to resist the protrusion may contribute forces, it is believed that viscoelastic deformation of the soft tissues plays a more significant role (Cohen-Levy, et al., 2013). Thus, when forces are applied to the soft tissues during protrusion, they are largely transferred to the teeth and skeletal structures, contributing significantly to resultant occlusal shifts (Pliska, 2014). To elaborate further, when the oral appliance contacts the teeth and vertically separates the jaws beyond their normal postural position, the surrounding soft tissues (gums, muscles, mucosa, tongue, soft palate, connective tissue) stretch, exerting intrusive forces on the teeth (Rose, 2002).

It is also important to note that oral hygiene is essential to users' comfort and can protect the mucosa and tooth enamel from any damage. Regular cleaning avoids microbial colonization on MAD and controls halitosis, inflammation, and oral candidiasis. The most common oral soft tissue change experienced by these patients is irritation due to inefficient or inadequate oral hygiene (Deane, et al., 2009; Guimarães, et al., 2015).

3.4.5. Persistent dry mouth and salivation issues

Long-term use of mandibular advancement devices (MAD) can lead to persistent alterations in salivary flow, potentially resulting in dry mouth (xerostomia) or, conversely, excessive salivation. These issues, while often overlooked, can significantly impact patient comfort and oral health over time. Xerostomia is a common complaint among long-term MAD users, with studies reporting prevalence rates ranging from 30% to 86% (Cohen-Levy, et al., 2013). The etiology of MAD-induced dry mouth is multifactorial. Firstly, the device's presence can lead to altered lip seal and increased mouth breathing, exacerbating oral dryness. Additionally, the forward positioning of the mandible may affect salivary gland function, potentially reducing salivary flow rates over time (Fritsch, et al., 2001)

Conversely, some patients experience excessive salivation, particularly during the initial phases of treatment, caused by an increased stimulation of the salivary glands due to the device's presence and jaw position. While this often subsides, some patients continue to report hypersalivation even after years of use. Martínez-Gomis et al. (2010) found that 15% of patients still experienced excessive salivation after 5 years of MAD therapy (Martínez-Gomis et al., 2010).

The implications of these salivary disturbances extend beyond mere discomfort. Chronic dry mouth can increase the risk of dental caries, periodontal disease, and oral infections (Müller, et al., 2023). Furthermore, alterations in salivary pH and composition may impact the protective functions of saliva, potentially compromising oral health in the long term (Chibly, et al., 2022).

3.4.6. Myofascial pain and muscle fatigue

Studies have shown that myofascial pain is a common side effect of MAD therapy, with prevalence rates ranging from 10% to 30% in long-term users (Doff et al., 2012; Martínez-Gomis et al., 2010). Issues of myofascial pain and muscle fatigue stem from the prolonged anterior positioning of the mandible, which places continuous stress on the masticatory muscles and associated structures. The pain typically manifests in the masseter, temporalis, and lateral pterygoid muscles, often described as a dull ache or tension that may worsen upon awakening (Näpänkangas et al., 2012).

Muscle fatigue, characterized by a reduced capacity to generate force, is another frequently reported issue. Commonly experienced at the beginning of MAD treatments, some patients have also reported muscle fatigue in the long-term. This fatigue tends to increase with age and can lead to decreased bite force and chewing efficiency, potentially affecting nutritional intake and quality of life (Hammond, et al., 2007).

The etiology of these muscular problems is multifaceted. The continuous protrusion of the mandible leads to isometric contraction of the lateral pterygoid muscles and stretching of the elevator muscles, which can result in muscle fatigue over time. Additionally, the altered position of the temporomandibular joint may contribute to changes in muscle function and pain perception (Rathee & Jain, 2022). Some studies suggest that these muscular issues may diminish over time due to adaptation. While muscle pain is common in the first year of MAD use, it significantly decreased in subsequent years, possibly due to neuromuscular adaptation and tissue remodeling (Cohen-Levy, et al., 2009).

3.4.7. Impact on periodontal health

Long-term use of mandibular advancement devices (MAD) can have implications for periodontal health. Periodontitis, which may manifest as visible gingival inflammation or hidden inflammation in periodontal pockets, can be exacerbated by MAD use (Dioguardi & Al-Halawani, 2016). The continuous forces applied by the device, coupled with potential

changes in oral hygiene habits, can lead to various periodontal issues over time. Studies have shown that MAD therapy can result in increased tooth mobility, particularly in anterior teeth bearing much of the device's load, due to repetitive stress on periodontal ligaments (Barewal & Hagen, 2014). This mobility, easily checked with gentle pressure, must be addressed before device fabrication. Additionally, patients with high caries rates, active periodontal disease, and infrequent dental care may be better suited to alternative sleep-disordered breathing treatments, as the use of oral appliances could further compromise their oral health (Dioguardi & Al-Halawani, 2016).

Gingival recession is another concern associated with long-term MAD use. In one study, Vezina et al. (2011) found gingival recession in all groups followed throughout the study. However, it did not provide information on the severity of gum recession, only its presence or absence. It may be due to mechanical stress from the device, the duration of use and greater difficulty in maintaining proper oral hygiene (Vezina, et al., 2011). The presence of a MAD in the oral cavity can create new retentive areas for plaque accumulation, potentially leading to increased risk of gingivitis and periodontitis (Batoni, et al., 2001).

On the other hand, more recent studies such as the one by Heda et al. (2021), indicate no significant increase in clinical crown height or signs of periodontal disease in the lower anterior teeth. Periodontal assessments showed healthy gum conditions with normal probing depths, minimal recession, and clinical attachment loss within normal limits. The study concludes that long-term OA use does not appear to negatively impact periodontal health or cause significant gingival recession, even with the observed dental changes (Heda, et al., 2021).

3.4.8. Impact on quality of life

Mandibular advancement devices (MAD) have demonstrated significant improvements in quality of life (QOL) measures among patients with OSA. Numerous studies have reported

enhancements in subjective sleepiness, daytime functioning, sleep quality, fatigue levels and overall QOL scores with long-term MAD therapy (Aarab, et al., 2011).

In terms of subjective sleepiness, MAD use leads to substantial reductions in Epworth Sleepiness Scale (ESS) scores over time. A study by Attali and colleagues found 81% of patients had an ESS <10 after 2 years of treatment, with scores decreasing from an average of 11 at baseline to 7 at follow-up (Attali, et al., 2016). Supporting these findings, Hammond and colleagues reported that 83% of MAD patients rated their sleep as moderately or very refreshing (Hammond, et al., 2007). Improvements were also seen in the sleep-specific Functional Outcomes of Sleep Questionnaire (FOSQ) and in the generic short-form health survey (SF-36) assessing overall QOL. These findings were comparable to those observed with CPAP therapy (Ramar, et al., 2015).

Beyond simply reducing sleepiness, MAD improve various aspects of QOL such as fatigue, energy levels, emotional well-being and social functioning. Vecchierini and colleagues (2016) documented a 24% improvement across all domains of the Quebec Sleep Questionnaire (QSQ), used to evaluate QOL, regardless of OSA severity. This reduction in daytime sleepiness correlates with enhanced sleep quality and daily functioning (Vecchierini, et al., 2016). Gagnadoux (2009) and colleagues further observed superior improvements with MAD compared to CPAP in areas including physical mobility, social isolation, pain and emotional function (Gagnadoux, et al., 2009). Interestingly, although CPAP may more effectively lower the apnea-hypopnea index (AHI) compared to MAD (Aarab, et al., 2011), this difference may not be necessarily clinically significant, as subjective sleepiness and overall QOL improve similarly with both therapies over the long-term (Pliska & Almeida, 2012).

Importantly, these improvements appear to be maintained and even increase over time with consistent adherence to MAD (Attali, et al., 2016). Long-term follow-up studies consistently demonstrate a positive impact on QOL measures, including reductions in excessive daytime sleepiness, fatigue, and improvements in cognitive function and overall well-being, among patients using MAD therapy. Moreover, these benefits are consistent across genders, with both men and women reporting comparable improvements in sleep-related QOL indicators,

regardless of the severity of their OSA at baseline (Vecchierini, et al., 2016). Given the clear advantages for quality associated with the extended use of MAD, regular assessment of patient-reported outcomes is recommended to optimize obstructive sleep apnea management (Yu, et al., 2023).

4. DISCUSSION

4.1. Efficacy of MAD in long-term use

Objective measures of efficacy demonstrate that MAD significantly reduces key indicators of OSA severity in the long term. Meta-analyses have shown consistent reductions in the Apnea-Hypopnea Index (AHI), Apnea Index (AI), which measures the number of complete breathing pauses per hour of sleep, and Oxygen Desaturation Index (ODI) defined by the number of times per hour of sleep that the blood's oxygen level drops by a certain percentage from baseline (Vigié du Cayla, et al., 2019). Yu et al. (2023) reported average reductions of 16.77 events/hour for AHI, 6.87 events/hour for AI, and 16.93 events/hour for ODI. Additionally, MAD were found to increase the lowest oxygen saturation by an average of 7.77%. These improvements in objective measures suggest that MAD maintain efficacy in managing respiratory events associated with OSA over time (Yu, et al., 2023).

Subjective measures and quality of life (QOL) indicators also show long-term improvements with MAD use. The Yu et al. study has shown that significant reductions in daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS), have been consistently reported (Yu, et al., 2023). Similarly, Sampol Rubio found that patients often report sustained improvements in snoring, nocturia, and overall quality of life, contributing to high satisfaction rates and treatment adherence (Sampol Rubio, et al., 2018). Although efficacy over time was maintained for snoring, sleepiness, and ESS scores, it is important to note a mild reduction in MAD efficacy concerning nocturia, mouth opening, headache, unrefreshing sleep, and tiredness. This slight decrease in efficacy over time may be due to natural progression in OSA severity or device wear after several years of use (Attali, et al., 2016).

When compared to Continuous Positive Airway Pressure (CPAP), MAD show lower efficacy in reducing AHI and improving oxygen saturation. However, long-term outcomes regarding symptom control and QOL improvements are often comparable. This apparent contradiction is frequently attributed to better adherence to MAD therapy, as increased comfort and ease

of use may lead to more consistent and prolonged nightly use (Pliska & Almeida, 2012; Incerti et al., 2019).

Several factors can influence the long-term efficacy of MAD. Age-related changes in upper airway structures may decrease mechanical effectiveness over time (Liu, 2001). Weight gain and physical degradation of the device can negatively impact efficacy (Hammond, 2007), necessitating device replacement every 2-3 years (Attali, et al., 2016).

Long-term success rates for MAD therapy vary widely across studies, with success rates ranging from 30% to 94% when considering an AHI of less than 10 (Barewal & Hagen, 2014). However, these figures may be biased towards treatment successes, often excluding patients who discontinued treatment or were lost to follow-up. More conservative estimates suggest long-term effectiveness among initially unselected patients may be below 50%, depending on the patient population studied (Cistulli, et al., 2004).

To improve long-term outcomes, careful patient selection is crucial. The Attali study suggests that factors associated with better long-term results include absence of previous CPAP treatment, lower baseline AHI, positional OSA, significant AHI reduction in short-term follow-up, and absence of nocturia (Attali, 2019). Cistulli et al. (2004) and Iftikhar et al. (2017) agree that regular follow-up, periodic device replacement, early management of adverse events, and weight management are recommended to maintain treatment efficacy over time (Cistulli, et al., 2004; Iftikhar, et al., 2017).

While MAD may show a slight attenuation of effect over extended periods, they remain an effective long-term treatment option for many OSA patients. Iftikhar et al. (2017) and Sampol Ribui et al. (2018) concluded that their efficacy in reducing respiratory events, improving oxygen saturation, and alleviating symptoms is generally maintained over time. Despite being less effective than CPAP in normalizing AHI, the superior adherence profile to MAD often results in similar long-term health outcomes. This makes them a valuable alternative in the long-term management of OSA, particularly for patients who are unable to tolerate CPAP therapy (Iftikhar, et al., 2017; Sampol Rubio, et al., 2018).

For future research, Barewel and Hagen (2014) emphasize the need to refining patient selection criteria, optimizing device design for long-term use, and exploring potential combination therapies to enhance the long-term efficacy of MAD treatment in OSA (Barewal & Hagen, 2014). Additionally, periodic reassessment of OSA patients using MAD is crucial. Studies by Marklund (2015) and Ramar (2015) underscore the importance of including updated sleep studies to ensure the device maintains its therapeutic efficacy. Regular monitoring helps prevent a gradual decline in treatment effectiveness or complete loss of control over apneic events (Marklund, 2015; Ramar, et al., 2015).

4.2. Strategies for monitoring long-term side effects

Monitoring the long-term side effects of mandibular advancement devices (MAD) used in the treatment of obstructive sleep apnea (OSA) is crucial for ensuring both patient safety and the sustained effectiveness of the treatment. According to Sato and Nakajima (2020), regular follow-up visits are a key element of this monitoring process. These visits facilitate timely adjustments of the device and thorough evaluation of the patient's condition through clinical assessments and patient-reported outcomes. Such proactive monitoring allows for the early detection and correction of any issues, including dental displacements and occlusal modifications (Sato & Nakajima, 2020). Cephalometric radiographs and polysomnographic studies are used periodically to assess the effectiveness of MAD therapy and identify potential adverse effects. According to Fransson et al. (2012), cephalometric analysis aids in detecting skeletal and dental changes, including shifts in occlusion, dental movements, jaw position alterations, and other structural changes that may occur with prolonged use of MAD. This ensures immediate identification and resolution of issues that could lead to discomfort or reduced MAD efficacy over time (Fransson et al., 2020). For Epsein et al. (2009) and Vanderyeken et al. (2012), polysomnography is the primary monitoring method during follow-up visits, serving as a reliable and objective measure to evaluate treatment outcomes and adjust therapy as needed (Epstein et al., 2009; Vanderveken et al., 2012).

Simultaneously, polysomnography provides detailed information about the patient's sleep architecture, respiratory events, and overall sleep quality. By comparing baseline and follow-up polysomnography results, clinicians can effectively assess MAD efficacy and implement necessary adjustments (Epstein et al., 2009).

Another fundamental aspect of effectively monitoring patients during treatment is to properly educate patients about the potential side effects and the importance of regular follow-ups. Diran-Cantolla et al. (2015) concluded that clear communication ensures that patients report any discomfort or issues promptly, allowing for timely interventions. Providing patients with strategies to manage minor side effects at home can also enhance adherence to MAD therapy (Duran-Cantolla et al., 2015).

Regarding healthcare professionals, an interdisciplinary approach that includes dentists, orthodontists, sleep specialists, and other healthcare professionals ensures comprehensive care. This collaborative effort is essential for addressing the diverse aspects of OSA treatment and effectively managing the side effects associated with MAD use (Cistulli, et al., 2004).

4.3. Preventive measures

As previously cited, long-term use of mandibular advancement devices (MAD) for Obstructive Sleep Apnea (OSA) treatment can lead to various side effects. The side effects can be better managed by applying some preventive measures to maintain patient comfort and treatment adherence.

An essential preventive strategy in the long-term management of MAD therapy is titration. This process involves the gradual adjustment of the mandibular advancement to achieve optimal efficacy while minimizing adverse effects. According to Pliska and Almeida (2012), the MAD is initially set at about 50-66% of the patient's maximum protrusion (Pliska & Almeida, 2012). Sampol Rubio et al. (2018) recommend that during the titration phase, which usually spans from 4 to 12 weeks, advancements ranges from 50-75% of maximum

protrusion (Sampol Rubio, et al., 2018). This gradual approach allows muscles and joints to adapt slowly, thereby reducing initial discomfort and pain (Pileggi, et al., 2020). The titration procedure is personalized, considering factors such as anatomic and neuromuscular evaluation, periodontal and TMJ assessment, parafunction levels, and the severity of OSA (Barewal & Hagen, 2014). It involves regular follow-ups with dental specialists to adjust the device based on subjective improvements in symptoms, objective measurements like polysomnography results, and patient tolerability (Vecchierini, et al., 2016; Vigié du Cayla, et al., 2019). Some studies have explored more advanced titration methods, such as remotely controlled mandibular positioners during overnight polysomnography, aiming to optimize the process objectively (Verbraecken, et al., 2022). To Pliska & Almeida (2012), proper titration is essential for maximizing MAD efficacy, especially in moderate to severe OSA cases (Pliska & Almeida, 2012). It helps prevent potential side effects like changes in occlusion or reduction in overjet. The studies by Ghazal et al. (2018) and Markun & Sampat (2020) concluded that preventive measures during titration include using appliances with built-in proclination of maxillary incisors, wearing corrective daytime splints, or can even include utilizing chewing gum as part of a regimen to maintain jaw mobility and muscle tone (Ghazal, et al., 2008; Markun & Sampat, 2020). The importance of careful, gradual titration is marked by findings suggesting that some cases of excessive advancement can sometimes exacerbate airway obstruction rather than alleviate it. The titration process in MAD therapy for OSA is a delicate balance between achieving therapeutic efficacy and minimizing long-term side effects, requiring ongoing monitoring and adjustment to ensure optimal patient outcomes (Verbraecken, et al., 2022).

Recent advancements in diagnostic techniques have introduced novel approaches to optimize the use of mandibular advancement devices (MAD) in treating Obstructive Sleep Apnea (OSA). One such innovation is drug-induced sleep endoscopy (DISE), which offers real-time visualization of airway behavior under conditions analogous to natural sleep. During DISE, clinicians can employ a modified Esmarch maneuver to replicate the effects of a MAD, allowing them to gauge the potential efficacy of this treatment modality for individual patients. This maneuver involves gently pulling the mandible forward with an interincisive distance of about 5 mm to mimic both the advancement and thickness of a MAD. This

personalized assessment aids in identifying suitable candidates for MAD therapy and guides the fine-tuning process. Some practitioners have even experimented with conducting DISE while patients wear their custom-fitted devices, providing direct insight into the MAD impact on airway patency. This tailored approach to MAD therapy, informed by detailed airway analysis, holds promise for enhancing treatment outcomes and potentially mitigating long-term complications associated with mandibular repositioning. By aligning device adjustments more closely with each patient's unique airway characteristics, DISE represents a significant step towards precision medicine in OSA management (Carrasco-Llatas, et al., 2019).

The dentist plays a key role in DISE for MAD therapy. They pre-measure the patient's jaw protrusion using a gauge ruler, calculating an average position. The pre-registered ruler is used by the otolaryngologist (who usually performs the DISE procedure) to verify effective airway deobstruction. The ruler allows for minor adjustments while the patient is sedated, determining the minimum advancement needed. This collaboration between dentists and sleep specialists during DISE is crucial and enables precise, patient-specific MAD optimization (Fernández-Sanjuán, et al., 2022).

4.4. Treatment options for side effects

While preventive measures are important, it is equally essential to address side effects that may arise despite precautions. There is a range of treatment options available to manage and alleviate the various side effects associated with long-term MAD use. Specific exercises aimed at strengthening jaw muscles and improving temporomandibular joint (TMJ) mobility can effectively reduce pain and stiffness. Aarab et al. (2011) demonstrated in their study that exercises such as controlled mandibular protrusion, retraction, and opening/closing movements, have been shown to significantly decrease pain and enhance joint function in MAD users (Aarab, et al., 2011).

The choice of device is pivotal in minimizing side effects. Technological advancements such as 3D printing and computer-aided design (CAD)/computer-aided manufacturing (CAM) enable the customization of MAD. Custom-made devices, particularly those utilizing CAD/CAM technology, are typically better tolerated and more effective than standard models. Continuous innovations in MAD design and materials are essential for reducing long-term complications (Vecchierini, et al., 2016).

Maintaining proper oral hygiene and device maintenance is fundamental in preventing dental caries and gingival diseases that can exacerbate dental and gingival pain. To mitigate potential negative impacts on periodontal health, regular professional dental cleanings and careful monitoring of periodontal status are crucial for long-term MAD users. Patient education on proper oral hygiene techniques specific to MAD use is essential, with some clinicians recommending the use of interdental brushes or water flossers to maintain gingival health in areas prone to plaque retention (Umalkar, et al., 2023).

Management strategies for persistent dry mouth and salivation issues include regular oral health assessments, use of saliva substitutes, and modifications to device design to minimize oral dryness or excessive salivation. Some clinicians recommend the use of xylitol-containing products to stimulate salivary flow and provide additional protection against caries in patients experiencing dry mouth (Mhatre, et al., 2024).

Regular evaluation of dental occlusion is necessary to address potential changes and prevent permanent malocclusions and TMJ pain. According to Dioguardi & Al-Halawani (2016), this monitoring is particularly important for avoiding long-term changes in teeth and jaw alignment (Dioguardi & Al-Halawani, 2016).

Pharmacological interventions can also play a role in managing side effects. George (2001) recommended non-steroidal anti-inflammatory drugs (NSAID) like ibuprofen have proven effective in reducing pain and inflammation associated with MAD use (George, 2001). Ferguson et al. (2006) suggested that for severe muscle pain, muscle relaxants may be prescribed to reduce muscle tension (Ferguson, et al., 2006). In cases where NSAID are insufficient, Cistulli et al. (2004) recommended considering corticosteroids like prednisone

for their potent anti-inflammatory effects, although their use should be strictly controlled due to potential side effects (Cistulli, et al., 2004).

Physical interventions such as physiotherapy and massage are frequently used to treat TMJ pain and dysfunction related to MAD use (Giannasi, et al., 2009). Osteopathy, focusing on gentle manipulation of soft tissues and bone structures, can improve mobility and reduce pain (Cuccia, et al., 2011). Osteopathic techniques have been particularly beneficial for patients suffering from chronic pain related to MAD use.

By implementing these preventive measures and treatment options, the long-term side effects of MAD use in OSA treatment can be effectively managed, improving patient comfort and treatment adherence. It's crucial for clinicians to regularly assess patients for these issues and adjust treatment plans accordingly to ensure long-term comfort and efficacy of MAD therapy (Doff et al., 2013).

5. CONCLUSION

This narrative review has explored the long-term effects of mandibular advancement devices (MAD) used in treating Obstructive Sleep Apnea (OSA). This narrative review has explored the long-term side effects associated with MAD used in treating Obstructive Sleep Apnea (OSA). The findings highlight a complex relationship between the therapeutic benefits of MAD and their potential long-term impacts on oral health and craniofacial structures. MAD have shown significant efficacy in managing OSA symptoms and enhancing the quality of life for many patients, especially those with mild to moderate OSA or who cannot tolerate CPAP therapy. The prolonged use of MAD has been associated with sustained improvements in sleep parameters, daytime functioning, and overall well-being. However, this positive outcome needs to be weighed against the potential development of adverse effects over time.

The most significant long-term side effects include changes in dental occlusion, skeletal alterations, and effects on the temporomandibular joint. These effects typically mild and often unnoticed by patients, can occasionally lead to significant changes such as decreased overjet and overbite, anterior crossbites, and alterations in dental arch dimensions. Skeletal changes, although less consistently reported, may involve adjustments in jaw positioning and facial height. Moreover, effects on soft tissues, including persistent dry mouth or excessive salivation, myofascial pain, and muscle fatigue are also notable side effects. The potential for periodontal health complications, such as increased tooth mobility and gingival recession, further emphasizes the need for vigilant monitoring and management.

Despite these potential side effects, it is important to recognize that many patients experience minimal discomfort, and the benefits of treating OSA often outweigh the risks associated with MAD use. It is also worth noting that alternative treatments such as CPAP therapy also come with their own set of side effects, underscoring that no single approach is without potential drawbacks. Furthermore, with proper monitoring, timely interventions, and preventive measures, many of these side effects can be mitigated or effectively managed. Successful long-term MAD therapy hinges on individualized treatment approaches, regular follow-ups, and a multidisciplinary team involving sleep specialists, dentists, and other

healthcare professionals. Treatment options range from specific exercises and physical therapies to pharmacological interventions and device adjustments. Regular follow-ups, including cephalometric analysis and polysomnography, are crucial for monitoring treatment efficacy and detecting early signs of adverse effects. Advancements in technology and diagnostic techniques offer new avenues for optimizing MAD therapy. The integration of computer-aided design and manufacturing (CAD/CAM) in device production allows for more precise and comfortable appliances. Novel approaches like drug-induced sleep endoscopy (DISE) provide valuable insights into individual airway dynamics, potentially improving treatment outcomes and reducing long-term complications.

Looking forward, several areas warrant further investigation. Long-term studies with larger cohorts are needed to fully understand the implications of extended MAD use, particularly regarding its effects on soft tissues and periodontal health. Research into improving device design, refining patient selection criteria, and developing more effective strategies for managing side effects should be prioritized. Exploring combination therapies and integrating MAD with other treatment modalities may offer new avenues for enhancing long-term efficacy and patient outcomes. While MAD therapy presents challenges in long-term management, it remains a valuable treatment option for many OSA patients. The key to successful outcomes lies in balancing the therapeutic benefits against potential side effects through personalized care, regular monitoring, and proactive management strategies.

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